The British National Formulary (BNF) is aimed at health professionals involved with prescribing, monitoring, supplying and administering medicines.

Organised for rapid access, the BNF provides essential information on the selection of safe and effective medicines for individual patients. It includes an overview of the drug management of common conditions together with details of the medicines used. The BNF is issued every six months; it is available in print and digital formats.

Latest information from clinical literature, regulatory authorities and professional bodies is used to construct the BNF knowledge base.

▼ Yellow Cards
A vital means of identifying adverse drug reactions, see page 11.
Medicines information services

Information on any aspect of drug therapy can be obtained from Regional and District Medicines Information Services. Details regarding the local services provided within your Region can be obtained by telephoning the following numbers.

**England**
- Birmingham: (0121) 311 1974
- Bristol: (0117) 342 2867
- Ipswich: (01473) 704 431
- Leeds: (0113) 392 3547
- Leicester: (0116) 255 5779
- Liverpool: (0151) 794 8113/4/5/7 (0151) 794 8206

**London**
- Guy’s Hospital: (020) 7188 8750
- Northwick Park Hospital: (020) 8869 3973
- Newcastle: (0191) 260 6198
- Southampton: (023) 8079 6908/9

**Wales**
- Cardiff: (029) 2074 2979 (029) 2074 2251

**Scotland**
- Aberdeen: (01224) 552 316
- Dundee: (01382) 632 351 (01382) 660 111 Ext 32351
- Edinburgh: (0131) 242 2920
- Glasgow: (0141) 211 4407

**Northern Ireland**
- Belfast: (028) 9063 2032 (028) 9063 3847

**Republic of Ireland**
- Dublin: Dublin 473 0589 Dublin 453 7941 Ext 2348

**Information on drug therapy relating to dental treatment can be obtained by telephoning:**
- Liverpool: (0151) 794 8206

**DIAL: Paediatric Drug (Medicine) Information Advisory Line**
- Tel: (0151) 252 5837
- Fax: (0151) 220 3885
- info@dial.org.uk
- www.dial.org.uk

**Driver and Vehicle Licensing Agency (DVLA)**
- Information on the national medical guidelines of fitness to drive is available from: www.dvla.gov.uk/medical.aspx

**Patient Information Lines**
- NHS Direct: 0845 4647

**Poisons Information Services**
- UK National Poisons Information Service (directs caller to relevant local centre)
  - 0844 892 0111

**Sport**
- Information on substances currently permitted or prohibited is provided in a card supplied by UK Sport.
- Further information regarding medicines in sport is available from: www.uksport.gov.uk
- The status of a particular medicine may be checked using the Drug Information Line
  - Tel: 0800 528 0004

**Travel Immunisation**
- Up-to-date information on travel immunisation requirements may be obtained from:
  - National Travel Health Network and Centre (for healthcare professionals only)
    - 0845 602 6712 (09.00–12.00 and 14.00–16.30 hours weekdays)
  - Travel Medicine Team, Health Protection Scotland (0141) 300 1100 (14.00–16.00 hours weekdays)
    - www.travax.nhs.uk (for registered users of the NHS website Travax only)
  - Welsh Assembly Government (029) 2082 5397 (09.00–17.30 hours weekdays)
  - Department of Health and Social Services (Belfast) (028) 9052 0000 (weekdays)

**United Kingdom Medicines Information Pharmacists Group (UKMIPG) website**
- www.ukmi.nhs.uk

Addresses, telephone and fax numbers of manufacturers and suppliers are shown in the Index of Manufacturers.
Material published in the British National Formulary may not be used for any form of advertising, sales or publicity without prior written permission. Each of the classification and the text are protected by copyright and/or database right.
Preface

The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society of Great Britain. It is published biannually under the authority of a Joint Formulary Committee which comprises representatives of the two professional bodies and of the UK Health Departments. The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the Group includes representatives of the British Dental Association. The Nurse Prescribers’ Advisory Group advises on the content relevant to nurses.

The BNF aims to provide prescribers, pharmacists and other healthcare professionals with sound up-to-date information about the use of medicines.

The BNF includes key information on the selection, prescribing, dispensing and administration of medicines. Medicines generally prescribed in the UK are covered and those considered less suitable for prescribing are clearly identified. Little or no information is included on medicines promoted for purchase by the public.

Information on drugs is drawn from the manufacturers’ product literature, medical and pharmaceutical literature, UK health departments, regulatory authorities, and professional bodies. Advice is constructed from clinical literature and reflects, as far as possible, an evaluation of the evidence from diverse sources. The BNF also takes account of authoritative national guidelines and emerging safety concerns. In addition, the editorial team receives advice on all therapeutic areas from expert clinicians; this ensures that the BNF’s recommendations are relevant to practice.

The BNF is designed as a digest for rapid reference and it may not always include all the information necessary for prescribing and dispensing. Also, less detail is given on areas such as obstetrics, malignant disease, and anaesthesia since it is expected that those undertaking treatment will have specialist knowledge and access to specialist literature. *BNF for Children* should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialised publications and by reference to the product literature. Information is also available from medicines information services (see inside front cover).

It is vital to use the most recent edition of the BNF for making clinical decisions. The more important changes for this edition are listed on p. xi.

The BNF on the internet (bnf.org) includes additional information of relevance to healthcare professionals dealing with medicines. Other digital versions of the BNF—including intranet and personal digital assistant (PDA) versions—are produced in parallel with the paper version.

The BNF welcomes comments from healthcare professionals. Comments and constructive criticism should be sent to:
British National Formulary,
Royal Pharmaceutical Society of Great Britain,
1 Lambeth High Street, London SE1 7JN.
Email: editor@bnf.org

Contents

Preface iii
Acknowledgements iv
How to use the BNF ix
Changes for this edition xi
Significant changes xi
Dose changes xi
Classification changes xii
Discontinued preparations xii
New preparations included in this edition xii
Late additions xii
Name changes xiii
Guidance on prescribing 1
General guidance 1
Prescription writing 4
Emergency supply of medicines 6
Controlled Drugs and drug dependence 7
Adverse reactions to drugs 11
Prescribing for children 13

For detailed advice on medicines used for children consult *BNF for Children*

Prescribing in palliative care 15
Prescribing for the elderly 19
Prescribing in dental practice 21
Drugs and sport 26
Emergency treatment of poisoning 27

Notes on drugs and Preparations

1: Gastro-intestinal system 37
2: Cardiovascular system 71
3: Respiratory system 148
4: Central nervous system 183
5: Infections 283
6: Endocrine system 367
7: Obstetrics, gynaecology, and urinary-tract disorders 429
8: Malignant disease and immunosuppression 459
9: Nutrition and blood 504
10: Musculoskeletal and joint diseases 551
11: Eye 582
12: Ear, nose, and oropharynx 600
13: Skin 615
14: Immunological products and vaccines 660
15: Anaesthesia 686

Appendixes and indices

Appendix 1: Interactions 708
Appendix 2: Liver disease 790
Appendix 3: Renal impairment 801
Appendix 4: Pregnancy 817
Appendix 5: Breast-feeding 838
Appendix 6: Intravenous additives 853
Appendix 7: Borderline substances 865
Appendix 8: Wound management products and elastic hosiery 883
Appendix 9: Cautionary and advisory labels for dispensed medicines 902
Dental Practitioners’ Formulary 917
Nurse Prescribers’ Formulary 919
Non-medical prescribing 923
Index of manufacturers 924
Index 941
Acknowledgements

The Joint Formulary Committee is grateful to individuals and organisations that have provided advice and information to the BNF.

The principal contributors for this edition were:

Expert advice on the management of oral and dental conditions was kindly provided by M. Addy, P. Coulthard, A. Crichton, M.A.O. Lewis, J.G. Meechan, N.D. Robb, R.A. Seymour, R. Welbury, and J.M. Zakrzewska. S. Kaur provided valuable advice on dental prescribing policy.

Members of the British Association of Dermatologists Therapy Guidelines Subcommittee, H.K. Bell, L.C. Fuller, J. Hughes, S. Lawton, J. Lear, N.J. Levell, A.J. McDonagh, M.J. Tidman, P.D. Yesudian, and M.F.M. Mustapa (Secretariat) have provided valuable advice.


The Joint British Societies’ Coronary Risk Prediction Charts have been reproduced with the kind permission of P.N. Durrington who has also provided the BNF with access to the computer program for assessing coronary and stroke risk.

R. Suvarna and colleagues at the MHRA have provided valuable assistance.

Correspondents in the pharmaceutical industry have provided information on new products and commented on products in the BNF. The Prescription Pricing Division has supplied the prices of products in the BNF.

Numerous doctors, pharmacists, nurses and others have sent comments and suggestions.

The BNF has valuable access to the Martindale data banks by courtesy of S. Sweetman and staff.

J.E. Macintyre and staff provided valuable technical assistance.


Xpage have provided technical assistance with the editorial database and typesetting software.

Owen Lyndon Wade

The BNF would like to acknowledge the valued contribution of Professor Owen Lyndon Wade, the first Chair of the JFC and founding father of the modern British National Formulary, who died on December 10, 2008.
Editorial Staff

Managing Editor: Knowledge Creation
John Martin BPharm, PhD, MRPharmS

Assistant Editors
Leigh Anne Claase BSc, PhD, MRPharmS
Bryony Jordan BSc, DipPharmPract, MRPharmS
Colin R. Macfarlane BPharm, MSc, MRPharmS
Allison F. Patterson BPharm, MRPharmS
Rachel S. M. Ryan BPharm, MRPharmS
Shama M. S. Wagle BPharm, DipPharmPract, MRPharmS

Staff Editors
Onatefe Akporobaro-Iwudibia MPharm, MRPharmS
Sejal Amin BPharm, MSc, MRPharmS
Susan E. Clarke BPharm, DipClinPharm, MRPharmS
Julia A. Dickin MPharm, MRPharmS
Manjula Halai BScChem, MPharm, MRPharmS
Emma E. Harris MPharm, DipPharmPract, MRPharmS
Amy E. Harvey MPharm, PGDipCommPharm, MRPharmS
Belén Granell Villen BSc, PGDipClinPharm, MRPharmS
Paul S. Maycock MPharm, DipClinPharm, MRPharmS
Elizabeth Nix DipPharm(NZ), MRPharmS
Claire L. Preston BPharm, MRPharmS
Shaista J. Qureshi MPharm, MRPharmS
Vinaya K. Sharma BPharm, MSc, PGDipPIM, MRPharmS

Editorial Assistant
Jennifer L. Palmer

Senior BNF Administrator
Heidi Homar BA

Administrative Assistant
Cristina Lopez-Bueno BA

Managing Editor: Digital Development and Delivery
Cornelia Schnelle MPhil

Knowledge Systems
Robert C. Buckingham BSc
Digital Development Assistant
Philip D. Lee BSc, PhD
Digital Development Editor
Sarah Peck BSc
Terminologist

Head of Publishing Services
John Wilson

BNF Publishing Director
Duncan S. T. Enright MA, PGCE, MInstP, FIDM

Managing Director, RPS Publishing
Charles Fry

Joint Formulary Committee
2008–2009

Chairman
Derek G. Waller
BSc, MB, BS, DM, FRCP
(from January 2009)
Martin J. Kendall
OBE, MD, FRCP, FFPM
(_until December 2008)

Deputy Chairman
Alison Blenkinsopp
PhD, BPharm, FRPharmS

Committee Members
Jeffrey K. Aronson
MA, MB ChB, DPhil, FRCP, FBPharmacolS, FFPM
Anthony J. Avery
BMedSci, MB ChB, DM, FRCGP
Tawfique K. Daneshmend
MB ChB, MD, FRCP
Beth Hird
BPharm, MSc, MRPharmS, SP, IP
W. Moira Kinnear
BSc, MSc, MRPharmS
Gul Root
BSc(Pharm), MRPharmS, DMS
Rafe Suvarna
MBBS, BSc, FFPM, DAvMed, DipIMC
Carwen Wynne Howells
BPharm, FRPharmS

Executive Secretary
Heidi Homar
BA
Dental Advisory Group 2008–2009

Chairman
David Wray
MD, BDS, MB ChB, FDSRCPS, FDSRCS Ed, F MedSci

Committee Members
Christine Arnold
BDS, DDPHRCS, MCDH
Simon J. Carruthers
LDSRCS, BDS, MFGDP(UK)
(untl October 2008)
Barry Cockcroft
BDS, FDSRCS (Eng)
Duncan S.T. Enright
MA, PGCE, MinstP, FIDM
Amy E. Harvey
MPharm, PGDipCommPharm, MRPharmS
Martin J. Kendall
OBE, MD, FRCP, FFPM
Lesley P. Longman
BSc, BDS, FDSRCS Ed, PhD
John Martin
BPharm, PhD, MRPharmS
Michelle Moffat
BDS, MFDS RCS Ed, M Paed Dent RCPS, FDS (Paed Dent)
RCS Ed
Richard J. Oliver
BDS, BSc, PhD, FDSRCP, FDS (OS) RCPS
Rachel S.M. Ryan
BPharm, MRPharmS

Secretary
Richard Clifford
BA, MA

Executive Secretary
Heidi Homar
BA

Advice on dental practice
The British Dental Association has contributed to the advice on medicines for dental practice through its representatives on the Dental Advisory Group.

Nurses Prescribers’ Advisory Group 2008–2009

Chairman
Nicky A. Cullum
PhD, RGN

Committee Members
Una J. Adderley
MSc, BA, RGN, DN
Michele L. Cossey
BPharm, MSc, MRPharmS
Molly Courtenay
PhD, MSc, Cert Ed, BSc, RGN
Duncan S.T. Enright
MA, PGCE, MinstP, FIDM
Margaret F. Helliwell
MB, BS, BSc, MFPHM, FRCP (Edin)
Bryony Jordan
BSc, DipPharmPract, MRPharmS
Martin J. Kendall
OBE, MD, FRCP Pract, FFPM
Fiona Lynch
BSc, MSc, RGN, RSCN
John Martin
BPharm, PhD, MRPharmS
Paul S. Maycock
MPharm, DipPharmPract, MRPharmS
Maureen P. Morgan
RN, RHV, MBA
Elizabeth J. Plastow
RMN, RGN, RSCPHN(HV), MSc, PGDipEd
Paul G.H. Robinson
Gul Root
BSc, MRPharmS, DMS
Jill M. Shearer
BSc, RGN, RM
Rabina Tindale
RGN, RSCN, BSc, DipAEN, PGCE
Vicky Vidler
MA, RGN, RSCN

Executive Secretary
Heidi Homar
BA
How the BNF is constructed

The BNF is unique in bringing together authoritative, independent guidance on best practice with clinically validated drug information, enabling healthcare professionals to select safe and effective medicines for individual patients.

Information in the BNF has been validated against emerging evidence, best-practice guidelines, and advice from a network of clinical experts.

Hundreds of changes are made between editions, and the most clinically significant changes are listed at the front of each edition (pp. xi–xii).

Joint Formulary Committee

The Joint Formulary Committee (JFC) is responsible for the content of the BNF. The JFC includes doctors appointed by the BMJ Publishing Group, pharmacists appointed by the Royal Pharmaceutical Society of Great Britain, and representatives from the Medicines and Healthcare products Regulatory Agency (MHRA) and the UK health departments. The JFC decides on matters of policy and reviews amendments to the BNF in the light of new evidence and expert advice. The Committee meets quarterly and each member also receives proofs of all BNF chapters for review before publication.

Editorial team

BNF staff editors are pharmacists with a sound understanding of how drugs are used in clinical practice. Each staff editor is responsible for editing, maintaining, and updating specific chapters of the BNF. During the publication cycle the staff editors review information in the BNF against a variety of sources (see below).

Amendments to the text are drafted when the editors are satisfied that any new information is reliable and relevant. The draft amendments are passed to expert advisers for comment and then presented to the Joint Formulary Committee for consideration. Additionally, for each edition, sections are chosen from every chapter for thorough review. These planned reviews aim to verify all the information in the selected sections and to draft any amendments to reflect the current best practice.

Staff editors prepare the text for publication and undertake a number of checks on the knowledge at various stages of the production.

Expert advisers

The BNF uses about 60 expert clinical advisers (including doctors, pharmacists, nurses, and dentists) throughout the UK to help with the production of each edition. The role of these expert advisers is to review existing text and to comment on amendments drafted by the staff editors. These clinical experts help to ensure that the BNF remains reliable by:

- checking draft amendments for appropriate interpretation of any new evidence;
- providing expert opinion in areas of controversy or when reliable evidence is lacking;
- advising on areas where the BNF diverges from summaries of product characteristics;
- providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breast-feeding, children, the elderly, palliative care, and the emergency treatment of poisoning.

In addition to consulting with regular advisers, the BNF calls on other clinical specialists for specific developments when particular expertise is required.

The BNF also works closely with a number of expert bodies that produce clinical guidelines. Drafts or pre-publication copies of guidelines are routinely received for comment and for assimilation into the BNF.

Sources of BNF information

The BNF uses a variety of sources for its information; the main ones are shown below.

Summaries of product characteristics The BNF receives summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are the principal source of product information and are carefully processed, despite the ever-increasing volume of information being issued by the pharmaceutical industry. Such processing involves:

- verifying the approved names of all relevant ingredients including 'non-active' ingredients (the BNF is committed to using approved names and descriptions as laid down by the Medicines Act);
- comparing the indications, cautions, contra-indications, and side-effects with similar existing drugs. Where these are different from the expected pattern, justification is sought for their inclusion or exclusion;
- seeking independent data on the use of drugs in pregnancy and breast-feeding;
- incorporating the information into the BNF using established criteria for the presentation and inclusion of the data;
- checking interpretation of the information by two staff editors before submitting to a senior editor; changes relating to doses receive an extra check;
- identifying potential clinical problems or omissions and seeking further information from manufacturers or from expert advisers;
- careful validation of any areas of divergence of the BNF from the SPC before discussion by the Committee (in the light of supporting evidence);
- constructing, with the help of expert advisers, a comment on the role of the drug in the context of similar drugs.

Much of this processing is applicable to the following sources as well.

Expert advisers The role of expert clinical advisers in providing the appropriate clinical context for all BNF information is discussed above.
Literature  Staff editors monitor core medical and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in the BNF and the paper is noted, the new information is assessed for reliability and relevance to UK clinical practice. If necessary, new text is drafted and discussed with expert advisers and the Joint Formulary Committee. The BNF enjoys a close working relationship with a number of national information providers.

Systematic reviews  The BNF has access to various databases of systematic reviews (including the Cochrane Library and various web-based resources). These are used for answering specific queries, for reviewing existing text and for constructing new text. Staff editors receive training in critical appraisal, literature evaluation, and search strategies. Reviews published in Clinical Evidence are used to validate BNF advice.

Consensus guidelines  The advice in the BNF is checked against consensus guidelines produced by expert bodies. A number of bodies make drafts or pre-publication copies of the guidelines available to the BNF; it is therefore possible to ensure that a consistent message is disseminated. The BNF routinely processes guidelines from the National Institute for Health and Clinical Excellence (NICE), the Scottish Medicines Consortium (SMC), and the Scottish Intercollegiate Guidelines Network (SIGN).

Reference sources  Textbooks and reference sources are used to provide background information for the review of existing text or for the construction of new text. The BNF team works closely with the editorial team that produces Martindale: The Complete Drug Reference. The BNF has access to Martindale information resources and each team keeps the other informed of significant developments and shifts in the trends of drug usage.

Statutory information  The BNF routinely processes relevant information from various Government bodies including Statutory Instruments and regulations affecting the Prescription only Medicines Order. Official compendia such as the British Pharmacopoeia and its addenda are processed routinely to ensure that the BNF complies with the relevant sections of the Medicines Act. The BNF itself is named as an official compendium in the Medicines Act.

The BNF maintains close links with the Home Office (in relation to controlled drug regulations) and the Medicines and Healthcare products Regulatory Agency (including the British Pharmacopoeia Commission). Safety warnings issued by the Commission on Human Medicines (CHM) and guidelines on drug use issued by the UK health departments are processed as a matter of routine.

Relevant professional statements issued by the Royal Pharmaceutical Society of Great Britain are included in the BNF as are guidelines from bodies such as the Royal College of General Practitioners.

The BNF reflects information from the Drug Tariff, the Scottish Drug Tariff, and the Northern Ireland Drug Tariff.

Pricing information  The Prescription Pricing Division provides information on prices of medicinal products and appliances in the BNF. The BNF also receives and processes price lists from product suppliers.

Comments from readers  Readers of the BNF are invited to send in comments. Numerous letters and emails are received during the preparation of each edition. Such feedback helps to ensure that the BNF provides practical and clinically relevant information. Many changes in the presentation and scope of the BNF have resulted from comments sent in by users.

Comments from industry  Each manufacturer is provided with a complimentary copy of the BNF and invited to comment on it. Close scrutiny of the BNF by the manufacturers provides an additional check and allows them an opportunity to raise issues about the BNF’s presentation of the role of various drugs; this is yet another check on the balance of the BNF’s advice. All comments are looked at with care and, where necessary, additional information and expert advice are sought.

Virtual user groups  The BNF has set up virtual user groups across various healthcare professions (e.g. doctors, pharmacists, nurses, dentists). The aim of these groups will be to provide feedback to the editors and publishers to ensure that BNF publications continue to serve the needs of its users.

Market research  Market research is conducted at regular intervals to gather feedback on specific areas of development, such as drug interactions or changes to the way information is presented in digital formats.

The BNF is an independent professional publication that is kept up-to-date and addresses the day-to-day prescribing information needs of healthcare professionals. Use of this resource throughout the health service helps to ensure that medicines are used safely, effectively, and appropriately.
How to use the BNF

Notes on conditions, drugs and preparations

The main text consists of classified notes on clinical conditions, drugs and preparations. These notes are divided into 15 chapters, each of which is related to a particular system of the body or to an aspect of medical care. Each chapter is then divided into sections which begin with appropriate notes for prescribers. These notes are intended to provide information to doctors, dental surgeons, pharmacists, nurses, and other healthcare professionals to facilitate the selection of suitable treatment. Guidance on dental and oral conditions is identified by means of a relevant heading (e.g. Dental and Orofacial pain) in the appropriate sections of the BNF. The notes are followed by details of relevant drugs and preparations which can be prescribed by dental surgeons using NHS form FP10D (GP14 in Scotland, WP10D in Wales) are identified within the BNF by means of a note headed Dental Prescribing on NHS.

For information available since publication of this edition see bnf.org

Guidance on prescribing

This part includes information on prescription writing, controlled drugs and dependence, prescribing for children and the elderly, and prescribing in palliative care. Advice is given on the reporting of adverse reactions. The BNF also includes advice on medical emergencies

Drugs

Drugs appear under pharmacopoeial or other non-proprietary titles. When there is an appropriate current monograph (Medicines Act 1968, Section 65) preference is given to a name at the head of that monograph; otherwise a British Approved Name (BAN), if available, is used (see also Name changes). The symbol \( \hat{U} \) is used to denote those preparations that are considered by the Joint Formulary Committee to be less suitable for prescribing. Although such preparations may not be considered as drugs of first choice, their use may be justifiable in certain circumstances.

Prescription-only medicines \( \hat{P} \)

This symbol has been placed against those preparations that are available only on a prescription issued by an appropriate practitioner. For more detailed information see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available).

The symbol \( \hat{C} \) indicates that the preparation is subject to the prescription requirements of the Misuse of Drugs Act. For regulations governing prescriptions for such preparations see p. 7.

Preparations not available for NHS prescription \( \hat{D} \)

This symbol has been placed against those preparations included in the BNF that are not prescribable under the NHS. Those prescribable only for specific disorders have a footnote specifying the condition(s) for which the preparation remains available. Some preparations which are not prescribable by brand name under the NHS may nevertheless be dispensed using the brand name providing that the prescription shows an appropriate non-proprietary name.

Prices

Prices have been calculated from the basic cost used in pricing NHS prescriptions dispensed in November 2008, see also Prices in the BNF p. x for details.
and other medical problems in dental practice, together with a review of the oral side-effects of drugs. An index of conditions relevant to dental surgeons is included.

Emergency treatment of poisoning

This chapter provides information on the management of acute poisoning when first seen in the home, although aspects of hospital-based treatment are mentioned.

Appendixes and indexes

The appendixes include information on interactions, liver disease, renal impairment, pregnancy, breast-feeding, intravenous additives, borderline substances, wound management products, and cautionary and advisory labels for dispensed medicines. They are designed for use in association with the main body of the text. The Dental Practitioners’ List and the Nurse Prescribers’ List are also included in this section. The indexes consist of the Index of Manufacturers and the Main Index.

Patient packs

Directive 92/27/EEC specifies the requirements for the labelling of medicines and outlines the format and content of patient information leaflets to be supplied with every medicine; the directive also requires the use of Recommended International Non-proprietary Names for drugs (see p. xiii).

All medicines have approved labelling and patient information leaflets; anyone who supplies a medicine is responsible for providing the relevant information to the patient (see also Appendix 9).

Many medicines are available in manufacturers’ original packs complete with patient information leaflets. Where patient packs are available, the BNF shows the number of dose units in the packs. In particular clinical circumstances, where patient packs need to be split or medicines are provided in bulk dispensing packs, manufacturers will provide additional supplies of patient information leaflets on request.

During the revision of each edition of the BNF careful note is taken of the information that appears on the patient information leaflets. Where it is considered appropriate to alert a prescriber to some specific limitation appearing on the patient information leaflet (for example, in relation to pregnancy) this advice now appears in the BNF.

The patient information leaflet also includes details of all inactive ingredients in the medicine. A list of common E numbers and the inactive ingredients to which they correspond is now therefore included in the BNF (see inside back cover).

PACT and SPA

PACT (Prescribing Analyses and Cost) and SPA (Scottish Prescribing Analysis) provide prescribers with information about their prescribing.

The PACT Standard Report, or in Scotland SPA Level 1 Report, is sent to all general practitioners on a quarterly basis. The PACT Standard Report contains an analysis of the practitioner’s prescribing and the practice prescribing over the last 3 months, and gives comparisons with the local Primary Care Trust equivalent practice and with a national equivalent. The report also contains details of the practice prescribing for a specific topic; a different topic is chosen each quarter.

The PACT Catalogue, or in Scotland SPA Level 2 Report, provides a full inventory of the prescriptions issued by a prescriber. The PACT catalogue is available on request for periods between 1 and 24 months. To allow the prescriber to target specific areas of prescribing, a Catalogue may be requested to cover individual preparations, BNF sections, or combinations of BNF chapters.

PACT is also available electronically (ePACT:net). This system gives users on-line access through NHSnet to the 3 years’ prescribing data held on the Prescription Pricing Division’s database; tools for analysing the data are also provided.

Prices in the BNF

Basic net prices are given in the BNF to provide an indication of relative cost. Where there is a choice of suitable preparations for a particular disease or condition the relative cost may be used in making a selection. Cost-effective prescribing must, however, take into account other factors (such as dose frequency and duration of treatment) that affect the total cost. The use of more expensive drugs is justified if it will result in better treatment of the patient or a reduction of the length of an illness or the time spent in hospital.

Prices have generally been calculated from the net cost used in pricing NHS prescriptions dispensed in November 2008. Unless an original pack is available these prices are based on the largest pack size of the preparation in use in community pharmacies. The price for an extemporaneously prepared preparation has been omitted where the net cost of the ingredients used to make it would give a misleadingly low impression of the final price. In Appendix 8 prices stated are per dressing or bandage.

The unit of 20 is still sometimes used as a basis for comparison, but where suitable original packs or patient packs are available these are priced instead.

Gross prices vary as follows:
1. Costs to the NHS are greater than the net prices quoted and include professional fees and overhead allowances;
2. Private prescription charges are calculated on a separate basis;
3. Over-the-counter sales are at retail price, as opposed to basic net price, and include VAT.

BNF prices are NOT, therefore, suitable for quoting to patients seeking private prescriptions or contemplating over-the-counter purchases.

A fuller explanation of costs to the NHS may be obtained from the Drug Tariff. Separate drug tariffs are applicable to England and Wales, Scotland, and Northern Ireland; prices in the different tariffs may vary.
Significant changes

The BNF is revised twice yearly and numerous changes are made between issues. All copies of BNF No. 56 (September 2008) should therefore be withdrawn and replaced by BNF No. 57 (March 2009). Significant changes have been made in the following sections for BNF No. 57:

- Salicylate poisoning [updated advice], Emergency treatment of poisoning
- Heavy metal poisoning [updated advice], Emergency treatment of poisoning
- Fistulating Crohn's disease, section 1.5
- Irritable bowel syndrome, section 1.5
- Aminosalicylates [monitoring of renal function], section 1.5
- Cardiovascular risk charts [change to estimated risk for non-diabetic men aged 50–59 years who are non-smokers], inside back cover
- Chronic obstructive pulmonary disease [oxygen alert card], section 3.1
- Oxygen [new text], section 3.6
- Antipsychotic drugs [prescribing for elderly], section 4.2.1
- Clostridium difficile infection, section 5.1, Table 1
- Throat infections, sinusitis, otitis media, section 5.1, Table 1
- Tendon damage with quinolones [updated advice], section 5.1.12
- HIV infection [updated advice], section 5.3.1
- Entecavir and telbivudine for chronic hepatitis B [NICE guidance], section 5.3.3
- Prophylaxis of influenza [NICE guidance], section 5.3.4
- Continuous subcutaneous insulin infusion [NICE guidance], section 6.1.1
- Use of oral hypoglycaemic drugs for type 2 diabetes during pregnancy and breast-feeding, section 6.1.2
- Use of metformin in renal impairment and risk of lactic acidosis, section 6.1.2.2
- Primary prevention of osteoporotic fractures in postmenopausal women [NICE guidance], section 6.6
- Secondary prevention of osteoporotic fractures in postmenopausal women [NICE guidance updated], section 6.6
- Reasons to stop combined hormonal contraceptives immediately [amendment to blood pressure bullet point], section 7.3.1
- Risk factors for venous thromboembolism [addition of age and smoking as risk factors], section 7.3.1
- Risk factors for arterial disease [amendment to blood pressure bullet point], section 7.3.1
- Tacrolimus [MHRA/CHM advice], section 8.2.2
- Management of hyperkalaemia [updated advice], section 9.2.1.1
- Management of severe acute hypocalcaemia [updated advice], section 9.5.1
- Management of osteoarthritis, section 10.1
- Adalimumab, etanercept, and infliximab for the treatment of ankylosing spondylitis [NICE guidance], section 10.1.3
- Abatacept for the treatment of rheumatoid arthritis [NICE guidance], section 10.1.3
- Glucosamine [less suitable for prescribing], section 10.1.5
- Ranibizumab and pegaptanib for the treatment of wet age-related macular degeneration [NICE guidance], section 11.8.2
- Acitretin [duration of contraception after stopping treatment], section 13.5.2
- Active immunity [reorganised and updated], section 14.1
- Immunisation schedule [table], section 14.1
- Vaccines and antiserum [reformatted and updated], section 14.4
- Anti-D (Rh ) immunoglobulin [NICE guidance], section 14.5
- Risk of neurological and haematological toxic effects with nitrous oxide, section 15.1.2
- Advice on reducing the risk of overdose with midazolam, section 15.1.4.1
- Adjustment of drug dosages in renal impairment [updated advice], appendix 3

Dose changes

Changes in dose statements introduced into BNF No. 57:

- Aciclovir [herpes simplex, prevention of recurrence], p. 344
- Adenosine, p. 81
- Betaine, p. 549
- Bromocriptine, p. 265
- Buprenorphine [opioid dependence], p. 279
- Cabergoline, p. 265
- Chloroquine [treatment of benign malaria], p. 354 and [prophylaxis of malaria], p. 357
- Doxycycline [syphilis], p. 304
- EMLA®, p. 704
- Etanercept [plaque psoriasis], p. 637
- Fentanyl injection, p. 696
- Flixotide® Accuhaler, p. 166
- Flixotide® Diskhaler, p. 166
- Flixotide® Evohaler, p. 166
- Lisinopril [renal complications of diabetes mellitus], p. 103
- Memantine, p. 282
- Methotrexate [psoriasis], p. 636
- Midazolam [premedication by intravenous injection and dose for induction of anaesthesia], p. 694
- Naloxone hydrochloride [overdose with opioids], p. 31
- Omeprazole [severe peptic ulcer bleeding], p. 49
- Pergolide, p. 265
- Phosphate infusion, p. 535
- Prednisolone [inflammatory bowel disease], p. 57
- Propofol [maintenance of anaesthesia], p. 689
- Rufinamide, p. 256
- Trimethoprim, p. 316
Classification changes
Classification changes have been made in the following sections for BNF No. 57:
Section 1.5.1 Aminosalicylates [new sub-section]
Section 1.5.2 Corticosteroids [new sub-section]
Section 1.5.3 Drugs affecting the immune response [new sub-section]
Section 1.5.4 Food allergy [new sub-section]
Section 1.6.6 Peripheral opioid-receptor antagonist [new sub-section]
Section 3.4.3 Allergic emergencies [section re-organised]
Section 5.1.2 Cephalosporins, carbapenems, and other beta-lactams [title change]
Section 5.1.2.1 Cephalosporins [new sub-section]
Section 5.1.2.2 Carbapenems [new sub-section]
Section 5.1.2.3 Other beta-lactam antibiotics [new subsection]
Section 6.1.6 Oral glucose tolerance test [sub-section title change]

Discontinued preparations
Preparations discontinued during the compilation of BNF No. 57:
Aerobec® preparations
Agenerase®
Amprenavir
Benztropine
Clinoril®
Daclizumab
Dynepo®
Efcortelan®
Epoetin delta
Fletchers’® enemas
Graneodin®
Gyno-Daktarin® pessaries
Idrolax®
Intal® spincaps
Kloref®
Locoid C®
Navoban®
Nilopress® Retard
Nisolipine
Nystan® cream and ointment
Procainamide
Pulmicort® LS aerosol inhaler
Senokot® granules
Syscor MR®
Tri-Adcortyl® cream and ointment
Tropisetron
Volmax®
Zenapax®

New preparations included in this edition
Preparations included in the relevant sections of BNF No. 57:
Bolamyn® SR, p. 378
Bridion®, p. 701
Bumetanide oral solution, p. 76
Clasteon®, p. 420
Clinitas®, p. 596
Doribax®, p. 301
Ethidine XL®, p. 75
Ferinject®, p. 507
Ferriprox® oral solution, p. 514
Frazy®, p. 176
Flexbumin®, p. 524
Hycamtin® capsules, p. 484
Intal® aerosol inhalation, p. 168
Intelen®®, p. 342
Isoplex®, p. 525
Mucoclear®, p. 179
Mycamine®, p. 332
Nutriflex® basal, p. 528
Nutriflex® peri, p. 528
Nutriflex® plus, p. 528
Nutriflex® special, p. 528
Oxusan®, p. 596
Optichamber®, p. 160
Optive®, p. 595
Oxyal®, p. 596
Personal Best®, p. 159
Ratiogristin®, p. 517
Relistor®, p. 66
Retacrit®, p. 512
Rosiced®, p. 649
Seroquel® XL, p. 201
Tetraspan®, p. 526
Thalidomide Pharmion®, p. 495
Thymoglobulin®, p. 488
Toctino®, p. 630
Torisel®, p. 483
Tyverb®, p. 482
Vimpat®, p. 253
Vismed®, p. 596
Vismed® Multi, p. 596
Volibris®, p. 94
Xamlo®, p. 632
Xarelto®, p. 131
Yaz®, p. 442

Late additions
Siklos® (Nordic) ▼ [HRA]
Tablets, f/c, hydroxycarbamide 1 g, net price 30-tab pack = £500.00
BNF section 9.1.3. For prophylaxis of recurrent painful vaso-occlusive crises including acute chest syndrome in patients with sickle-cell disease
Name changes

European Law requires use of the Recommended International Non-proprietary Name (rINN) for medicinal substances. In most cases the British Approved Name (BAN) and rINN were identical. Where the two differed, the BAN was modified to accord with the rINN.

The following list shows those substances for which the former BAN has been modified to accord with the rINN. Former BANs have been retained as synonyms in the BNF.

**Adrenaline and noradrenaline** Adrenaline and noradrenaline are the terms used in the titles of monographs in the European Pharmacopoeia and are thus the official names in the member states. For these substances, BP 2008 shows the European Pharmacopoeia names and the rINNs at the head of the monographs; the BNF has adopted a similar style.

<table>
<thead>
<tr>
<th>Former BAN</th>
<th>New BAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>adrenaline</td>
<td>tetracaine</td>
</tr>
<tr>
<td>methoxamine</td>
<td>see above</td>
</tr>
<tr>
<td>aminacrine</td>
<td>aminoacridine</td>
</tr>
<tr>
<td>amylocin</td>
<td>amoxicillin</td>
</tr>
<tr>
<td>amphetamine</td>
<td>amfetamine</td>
</tr>
<tr>
<td>amylorubatone sodium</td>
<td>amobarbital sodium</td>
</tr>
<tr>
<td>beclometasone</td>
<td>beclometasone</td>
</tr>
<tr>
<td>bendroflumethiazide</td>
<td>trihexyphenidyl</td>
</tr>
<tr>
<td>benzhexol</td>
<td>benzetamine</td>
</tr>
<tr>
<td>bezpethamine</td>
<td>busulfan</td>
</tr>
<tr>
<td>butobarbitone</td>
<td>butobarbital</td>
</tr>
<tr>
<td>carticine</td>
<td>articaine</td>
</tr>
<tr>
<td>cephalaxin</td>
<td>cefalexin</td>
</tr>
<tr>
<td>cephradine</td>
<td>cefradine</td>
</tr>
<tr>
<td>chloral betaine</td>
<td>cloral betaine</td>
</tr>
<tr>
<td>chlorbutol</td>
<td>chlorbutanol</td>
</tr>
<tr>
<td>chlormethiazole</td>
<td>clomethiazole</td>
</tr>
<tr>
<td>chlorpheniramine</td>
<td>chlorphenamine</td>
</tr>
<tr>
<td>chlorthalidone</td>
<td>chlortalidone</td>
</tr>
<tr>
<td>cholecalciferol</td>
<td>cocolciferol</td>
</tr>
<tr>
<td>cholestyramine</td>
<td>coleystyramine</td>
</tr>
<tr>
<td>clomiphene</td>
<td>clomifene</td>
</tr>
<tr>
<td>colistin sulphamate sodium</td>
<td>colistimethate sodium</td>
</tr>
<tr>
<td>sodium corticotrophin</td>
<td>corticotropin</td>
</tr>
<tr>
<td>cycloporin</td>
<td>ciclosporin</td>
</tr>
<tr>
<td>cysteamine</td>
<td>mercaptamine</td>
</tr>
<tr>
<td>danthron</td>
<td>dantron</td>
</tr>
<tr>
<td>dexamphetamine</td>
<td>dexamfetamine</td>
</tr>
<tr>
<td>dibromopropamidine</td>
<td>dibromopropamidine</td>
</tr>
<tr>
<td>dicycloxine</td>
<td>dicyclevorine</td>
</tr>
<tr>
<td>dienoestrol</td>
<td>dienestrol</td>
</tr>
<tr>
<td>dimethicon(s)</td>
<td>dimeticone</td>
</tr>
<tr>
<td>dimethyl sulphoxide</td>
<td>dimethyl sulfoxide</td>
</tr>
<tr>
<td>dothepip</td>
<td>dosulepin</td>
</tr>
<tr>
<td>doxyxycycline hydrochloride (hemihydrate hemi-ethanolate)</td>
<td>doxyxycycline hyclate</td>
</tr>
<tr>
<td>eformoterol</td>
<td>formoterol</td>
</tr>
<tr>
<td>Former BAN</td>
<td>ethamsylate</td>
</tr>
<tr>
<td>ethyloestradiol</td>
<td>ethyloestradiol</td>
</tr>
<tr>
<td>ethynodiol</td>
<td>ethynodiol</td>
</tr>
<tr>
<td>flumethasone</td>
<td>flumethasone</td>
</tr>
<tr>
<td>flupentixol</td>
<td>flupentixol</td>
</tr>
<tr>
<td>flurazolene</td>
<td>flurazolene</td>
</tr>
<tr>
<td>frusemide</td>
<td>frusemide</td>
</tr>
<tr>
<td>guaiphenesin</td>
<td>guaiphenesin</td>
</tr>
<tr>
<td>hexachlorophophone</td>
<td>hexachlorophosphate</td>
</tr>
<tr>
<td>hexaméxic hippurate</td>
<td>hydroxyurea</td>
</tr>
<tr>
<td>indomethacin</td>
<td>indomethacin</td>
</tr>
<tr>
<td>lignocaine</td>
<td>lignocaine</td>
</tr>
<tr>
<td>methotrepineprazine</td>
<td>methyl cysteine</td>
</tr>
<tr>
<td>methyl blue</td>
<td>methylene blue</td>
</tr>
<tr>
<td>New BAN</td>
<td>etamsylate</td>
</tr>
<tr>
<td>ethyloestradiol</td>
<td>etyloestradiol</td>
</tr>
<tr>
<td>ethynodiol</td>
<td>ethynodiol</td>
</tr>
<tr>
<td>flumethasone</td>
<td>flumethasone</td>
</tr>
<tr>
<td>flupentixol</td>
<td>flupentixol</td>
</tr>
<tr>
<td>fludroxyxycortic</td>
<td>fludroxyxycortic</td>
</tr>
<tr>
<td>furosemide</td>
<td>furosemide</td>
</tr>
<tr>
<td>guaiphenesin</td>
<td>guaiphenesin</td>
</tr>
<tr>
<td>hexachlorophosphate</td>
<td>hexachlorophosphate</td>
</tr>
<tr>
<td>methenamine hippurate</td>
<td>hydroxyuramicamide</td>
</tr>
<tr>
<td>indometacin</td>
<td>indometacin</td>
</tr>
<tr>
<td>lidocaine</td>
<td>lidocaine</td>
</tr>
<tr>
<td>levomepromazine</td>
<td>levomepromazine</td>
</tr>
<tr>
<td>mecyasteine</td>
<td>mecyasteine</td>
</tr>
<tr>
<td>methylthioninium chloride</td>
<td>metichelin</td>
</tr>
<tr>
<td>micoxantrone</td>
<td>micoxantrone</td>
</tr>
<tr>
<td>nicoumalone</td>
<td>nicoumalone</td>
</tr>
<tr>
<td>noradrenaline</td>
<td>see above</td>
</tr>
<tr>
<td>oestradiol</td>
<td>estradiol</td>
</tr>
<tr>
<td>oestriol</td>
<td>estrone</td>
</tr>
<tr>
<td>oestrone</td>
<td>estrone</td>
</tr>
<tr>
<td>oxpentifyline</td>
<td>oxpentifyline</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>phenobarbital</td>
</tr>
<tr>
<td>pipotiazine</td>
<td>pipotiazine</td>
</tr>
<tr>
<td>poliexanide</td>
<td>poliexanide</td>
</tr>
<tr>
<td>pramocaine</td>
<td>pramocaine</td>
</tr>
<tr>
<td>procaine benzylpenicillin</td>
<td>protoniamide</td>
</tr>
<tr>
<td>secoxbartil</td>
<td>secoxbartil</td>
</tr>
<tr>
<td>riboflavin</td>
<td>riboflavine</td>
</tr>
<tr>
<td>calcitonin</td>
<td>calcitonin (salmon)</td>
</tr>
<tr>
<td>sodium calciumedetate</td>
<td>sodium cromoglycate</td>
</tr>
<tr>
<td>sodium cromoglycate</td>
<td>sodium ironedetate</td>
</tr>
<tr>
<td>sodium picosulphate</td>
<td>sodium monostearate</td>
</tr>
<tr>
<td>stibocaprate</td>
<td>stibocaprate</td>
</tr>
<tr>
<td>stilboestrol</td>
<td>stilboestrol</td>
</tr>
<tr>
<td>sulphacetamide</td>
<td>sulphacetamide</td>
</tr>
<tr>
<td>sulphadiazine</td>
<td>sulphadiazine</td>
</tr>
<tr>
<td>sulphamethoxazole</td>
<td>sulphamethoxazole</td>
</tr>
<tr>
<td>sulphapyridine</td>
<td>sulphapyridine</td>
</tr>
<tr>
<td>sulphasalazine</td>
<td>sulphasalazine</td>
</tr>
<tr>
<td>sulphathiazole</td>
<td>sulphathiazole</td>
</tr>
<tr>
<td>sulphirpyrazone</td>
<td>sulphirpyrazone</td>
</tr>
<tr>
<td>tetracosactacin</td>
<td>tetracosactacin</td>
</tr>
<tr>
<td>thibendazole</td>
<td>thibendazole</td>
</tr>
<tr>
<td>thioguanine</td>
<td>thioguanine</td>
</tr>
<tr>
<td>thiopenteone</td>
<td>thiopenteone</td>
</tr>
<tr>
<td>thymoxamine</td>
<td>thymoxamine</td>
</tr>
<tr>
<td>thyroxine sodium tribavirin</td>
<td>thyroxine sodium tribavirin</td>
</tr>
<tr>
<td>trimeprazine</td>
<td>trimeprazine</td>
</tr>
<tr>
<td>urofollitropin</td>
<td>urofollitropin</td>
</tr>
</tbody>
</table>
Guidance on prescribing

General guidance

Medicines should be prescribed only when they are necessary, and in all cases the benefit of administering the medicine should be considered in relation to the risk involved. This is particularly important during pregnancy, when the risk to both mother and fetus must be considered (for further details see Prescribing in Pregnancy, Appendix 4).

It is important to discuss treatment options carefully with the patient to ensure that the patient is content to take the medicine as prescribed (see also Taking Medicines to Best Effect, below). In particular, the patient should be helped to distinguish the adverse effects of prescribed drugs from the effects of the medical disorder. When the beneficial effects of the medicine are likely to be delayed, the patient should be advised of this.

Taking medicines to best effect Difficulties in compliance with drug treatment occur regardless of age. Factors contributing to poor compliance with prescribed medicines include:

- prescription not collected or not dispensed;
- purpose of medicine not clear;
- perceived lack of efficacy;
- real or perceived side-effects;
- patients’ perception of the risk and severity of side-effects may differ from that of the prescriber;
- instructions for administration not clear;
- physical difficulty in taking medicines (e.g. with swallowing the medicine, with handling small tablets, or with opening medicine containers);
- unattractive formulation (e.g. unpleasant taste);
- complicated regimen.

The prescriber and the patient should agree on the health outcomes that the patient desires and on the strategy for achieving them (‘concordance’). The prescriber should be sensitive to religious, cultural, and personal beliefs that can affect patients’ acceptance of medicines.

Taking the time to explain to the patient (and relatives) the rationale and the potential adverse effects of treatment may improve compliance. Reinforcement and elaboration of the physician’s instructions by the pharmacist also helps. Advising the patient of the possibility of alternative treatments may encourage the patient to seek advice rather than merely abandon unacceptable treatment.

Simplifying the drug regimen may help; the need for frequent administration may reduce compliance, although there appears to be little difference in compliance between once-daily and twice-daily administration. Combination products reduce the number of drugs taken but this may be at the expense of the ability to titrate individual doses.

Biosimilar medicines A biosimilar medicine is a new biological product that is similar to a medicine that has already been authorised to be marketed (the biological reference medicine) in the European Union. The active substance of a biosimilar medicine is similar, but not identical, to the biological reference medicine. Biological products are different from standard chemical products in terms of their complexity and although theoretically there should be no important differences between the biosimilar and the biological reference medicine in terms of safety or efficacy, when prescribing biological products, it is good practice to use the brand name. This will ensure that substitution of a biosimilar medicine does not occur when the medicine is dispensed.

Biosimilar medicines have black triangle status (▼) at the time of initial marketing. It is important to report suspected adverse reactions to biosimilar medicines using the Yellow Card Scheme (p. 11). For biosimilar medicines, adverse reaction reports should clearly state the brand name of the suspected medicine.

Complementary and alternative medicine An increasing amount of information on complementary and alternative medicine is becoming available. The scope of the BNF is restricted to the discussion of conventional medicines but reference is made to complementary treatments if they affect conventional therapy (e.g. interactions with St John’s wort—see Appendix 1). Further information on herbal medicines is available at www.mhra.gov.uk.

Abbreviation of titles In general, titles of drugs and preparations should be written in full. Unofficial abbreviations should not be used as they may be misinterpreted.

Non-proprietary titles Where non-proprietary (‘generic’) titles are given, they should be used in prescribing. This will enable any suitable product to be dispensed, thereby saving delay to the patient and sometimes expense to the health service. The only exception is where bioavailability problems are so important that the patient should always receive the same brand; in such cases, the brand name or the manufacturer should be stated. Non-proprietary titles should not be invented for the purposes of prescribing generically since this can lead to confusion, particularly in the case of compound and modified-release preparations.

Titles used as headings for monographs may be used freely in the United Kingdom but in other countries may be subject to restriction.

Many of the non-proprietary titles used in this book are titles of monographs in the European Pharmacopoeia, British Pharmacopoeia, or British Pharmaceutical Codex 1973. In such cases the preparations must comply with the standard (if any) in the appropriate publication, as required by the Medicines Act (Section 65).

Proprietary titles Names followed by the symbol® are or have been used as proprietary names in the United Kingdom. These names may in general be applied only to products supplied by the owners of the trade marks.

Marketing authorisation and BNF advice In general the doses, indications, cautions, contra-indications, and side-effects in the BNF reflect those in the manufacturers’ data sheets or Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). The BNF does not generally include propri-
Summary of Product Characteristics or when the marketing authorisation holder has not been able to supply essential information. When a preparation is available from more than one manufacturer, the BNF reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisations. Unlicensed products can be obtained from ‘special-order’ manufacturers or specialist importing companies, see p. 939.

Where an unlicensed drug is included in the BNF, this is indicated in square brackets after the entry. Where the BNF suggests a use (or route) that is outside the licensed indication of a product (‘off-label’ use), this too is indicated. Unlicensed use of medicines becomes necessary if the clinical need cannot be met by licensed medicines; such use should be supported by appropriate evidence and experience.

The doses stated in the BNF are intended for general guidance and represent, unless otherwise stated, the usual range of doses that are generally regarded as being suitable for adults.

**Prescribing medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber’s professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.**

**Oral syringes** An oral syringe is supplied when oral liquid medicines are prescribed in doses other than multiples of 5 mL. The oral syringe is marked in 0.5-mL divisions from 1 to 5 mL to measure doses of less than 5 mL. (other sizes of oral syringe may also be available). It is provided with an adaptor and an instruction leaflet. The 5-mL spoon is used for doses of 5 mL (or multiples thereof).

To avoid inadvertent intravenous administration of oral liquid medicines, only an appropriate oral or enteral syringe should be used to measure an oral liquid medicine (if a medicine spoon or graduated measure cannot be used); these syringes should not be compatible with intravenous or other parenteral devices. Oral or enteral syringes should be clearly labelled ‘Oral’ or ‘Enteral’ in a large font size; it is the healthcare practitioner’s responsibility to label the syringe with this information if the manufacturer has not done so.

**Strengths and quantities** The strength or quantity to be contained in capsules, lozenges, tablets, etc. should be stated by the prescriber.

If a pharmacist receives an incomplete prescription for a systemically administered preparation and considers it would not be appropriate for the patient to return to the doctor, the following procedures will apply:

(a) an attempt must always be made to contact the prescriber to ascertain the intention;

(b) if the attempt is successful the pharmacist must, where practicable, subsequently arrange for details of quantity, strength where applicable, and dosage to be inserted by the prescriber on the incomplete form;

(c) where, although the prescriber has been contacted, it has not proved possible to obtain the written intention regarding an incomplete prescription, the pharmacist may endorse the form ‘p.c.’ (prescriber contacted) and add details of the quantity and strength where applicable of the preparation supplied, and of the dose indicated. The endorsement should be initialed and dated by the pharmacist;

(d) where the prescriber cannot be contacted and the pharmacist has sufficient information to make a professional judgement the preparation may be dispensed. If the quantity is missing the pharmacist may supply sufficient to complete up to 5 days’ treatment, except that where a combination pack (i.e. a proprietary pack containing more than one medicinal product) or oral contraceptive is prescribed by name only, the smallest pack shall be dispensed. In all cases the prescription must be endorsed ‘p.n.c.’ (prescriber not contacted), the quantity, the dose, and the strength (where applicable) of the preparation supplied must be indicated, and the endorsement must be initialed and dated;

(e) if the pharmacist has any doubt about exercising discretion, an incomplete prescription must be referred back to the prescriber.

**Excipients** Branded oral liquid preparations that do not contain fructose, glucose, or sucrose are described as ‘sugar-free’ in the BNF. Preparations containing hydro-génated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked ‘sugar-free’ since there is evidence that they do not cause dental caries. Patients receiving medicines containing cariogenic sugars should be advised of appropriate dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible.

Where information on the presence of aspartame, gluten, sulphites, tartrazine, arachis (peanut) oil or sesame oil is available, this is indicated in the BNF against the relevant preparation. Information is provided on selected excipients in skin preparations (section 13.1.3), in vaccines (section 14.1), and on selected preservatives and excipients in eye drops and injections. Pressurised metered aerosols containing chlorofluorocarbons (CFCs) have also been identified throughout the BNF (see section 3.1.1.1).

The presence of benzyl alcohol and polyoxyl castor oil (polyethoxylated castor oil) in injections is indicated in the BNF. Benzyl alcohol has been associated with a fatal toxic syndrome in preterm neonates, and therefore, parenteral preparations containing the preservative should not be used in neonates. Polyoxyl castor oils, used as vehicles in intravenous injections, have been associated with severe anaphylactoid reactions.

The presence of propylene glycol in oral or parenteral medicines is indicated in the BNF; it can cause adverse effects if its elimination is impaired, e.g. in renal failure, in neonates and young children, and in slow metabolisers of the substance. It may interact with disulphiram and metronidazole.

**In the absence of information on excipients in the BNF and in the product literature, contact the manufacturer (see Index of Manufacturers) if it is essential to check details.**

**Extemporaneous preparation** A product should be dispensed extemporaneously only when no product with a marketing authorisation is available.

The BP direction that a preparation must be freshly prepared indicates that it must be made not more than 24 hours before it is issued for use. The direction that a
Non-proprietary names of compound preparations

Which appear in the BNF are those that have been compiled by the British Pharmacopoeia Commission or another recognised body; whenever possible they reflect the names of the active ingredients.

Prescribers should avoid creating their own compound names for the purposes of generic prescribing: such names do not have an approved definition and can be misinterpreted.

Special care should be taken to avoid errors when prescribing compound preparations; in particular the hyphen in the prefix 'co-' should be retained. Special care should also be taken to avoid creating generic names for modified-release preparations where the use of these names could lead to confusion between formulations with different lengths of action.

Security and validity of prescriptions

The Council of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions. In particular, prescription forms should:

- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

Patient group direction (PGD)

In most cases, the most appropriate clinical care will be provided on an individual basis by a prescriber to a specific individual patient. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit patient care without compromising safety.

A Patient Group Direction is a written direction relating to the supply and administration (or administration only) of a licensed prescription-only medicine by certain prescribers. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

BNF 57 General guidance

General guidance

Preparation should be recently prepared indicates that deterioration is likely if the preparation is stored for longer than about 4 weeks at 15–25 °C.

The term water used without qualification means either potable water freshly drawn direct from the public supply and suitable for drinking or freshly boiled and cooled purified water. The latter should be used if the public supply is from a local storage tank or if the potable water is unsuitable for a particular preparation (Water for injections, section 9.2.2).

Drugs and driving

Prescribers should advise patients if treatment is likely to affect their ability to drive motor vehicles. This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol. General information about a patient’s fitness to drive is available from the Driver and Vehicle Licensing Agency at www.dvla.gov.uk (see also Appendix 9).

Patents

In the BNF, certain drugs have been included notwithstanding the exercise of actual or potential patent rights. In so far as such substances are protected by Letters Patent, their inclusion in this Formulary neither conveys, nor implies, licence to manufacture.

Health and safety

When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Substances such as corticosteroids, some antmicrobials, phenothiazines, and many cytotoxics, are irritant or very potent and should be handled with caution. Contact with the skin and inhalation of dust should be avoided.

Safety in the home

Patients must be warned to keep all medicines out of the reach of children. All solid dose and all oral and external liquid preparations must be dispensed in a reclosable child-resistant container unless:

- the medicine is in an original pack or patient pack such as to make this inadvisable;
- the patient will have difficulty in opening a child-resistant container;
- a specific request is made that the product shall not be dispensed in a child-resistant container;
- no suitable child-resistant container exists for a particular liquid preparation.

All patients should be advised to dispose of unwanted medicines by returning them to a supplier for destruction.

Name of medicine

The name of the medicine should appear on the label unless the prescriber indicates otherwise.

(a) The strength is also stated on the label in the case of tablets, capsules, and similar preparations that are available in different strengths.

(b) If it is the wish of the prescriber that a description such as ‘The Sedative Tablets’ should appear on the label, the prescriber should write the desired description on the prescription form.

(c) The arrangement will extend to approved names, proprietary names or titles given in the BP, BPC, BNF, DPF, or NPF.

(d) The name written on the label is that used by the prescriber on the prescription.

(e) When a prescription is written other than on an NHS prescription form the name of the prescribed preparation will be stated on the label of the dispensed medicine unless the prescriber indicates otherwise.

(f) The Council of the Royal Pharmaceutical Society advises that the labels of dispensed medicines should indicate the total quantity of the product dispensed in the container to which the label refers. This requirement applies equally to solid, liquid, internal, and external preparations. If a product is dispensed in more than one container, the reference should be to the amount in each container.

Security and validity of prescriptions

The Councils of the British Medical Association and the Royal Pharmaceutical Society have issued a joint statement on the security and validity of prescriptions. In particular, prescription forms should:

- not be left unattended at reception desks;
- not be left in a car where they may be visible; and
- when not in use, be kept in a locked drawer within the surgery and at home.

Where there is any doubt about the authenticity of a prescription, the pharmacist should contact the prescriber. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.

Patient group direction (PGD)

In most cases, the most appropriate clinical care will be provided on an individual basis by a prescriber to a specific individual patient. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit patient care without compromising safety.

A Patient Group Direction is a written direction relating to the supply and administration (or administration only) of a licensed prescription-only medicine by certain prescribers. If this is done by telephone, the number should be obtained from the directory rather than relying on the information on the prescription form, which may be false.
Prescription writing

Shared care
In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription.

Prescriptions should be written legibly in ink or otherwise so as to be indelible, should be dated, should state the full name and address of the patient, and should be signed in ink by the prescriber. The age and the date of birth of the patient should preferably be stated, and it is a legal requirement in the case of prescription-only medicines to state the age for children under 12 years.

The following should be noted:
(a) The unnecessary use of decimal points should be avoided, e.g. 3 mg, not 3.0 mg.

Quantities of 1 gram or more should be written as 1 g etc.
Quantities less than 1 gram should be written in milligrams, e.g. 500 mg, not 0.5 g.
Quantities less than 1 mg should be written in micrograms, e.g. 100 micrograms, not 0.1 mg.

When decimals are unavoidable a zero should be written in front of the decimal point where there is no other figure, e.g. 0.5 mL, not .5 mL.
(b) ‘Micrograms’ and ‘nanograms’ should not be abbreviated. Similarly ‘units’ should not be abbreviated.

(c) The term ‘millilitre’ (ml or mL) is used in medicine and pharmacy, and cubic centimetre, c.c., or cm should not be used.

(d) Dose and dose frequency should be stated; in the case of preparations to be taken ‘as required’ a minimum dose interval should be specified.

When doses other than multiples of 5 mL are prescribed for oral liquid preparations the dose-volume will be provided by means of an oral syringe, see p. 2 (except for preparations intended to be measured with a pipette).

Suitable quantities:
- Elixirs, Linctuses, and Paediatric Mixtures (5-mL dose), 50, 100, or 150 mL
- Adult Mixtures (10-mL dose), 200 or 300 mL
- Ear Drops, Eye drops, and Nasal Drops, 10 mL (or the manufacturer’s pack)
- Eye Lotions, Gargles, and Mouthwashes, 200 mL

For suitable quantities of dermatological preparations, see section 13.1.2.

(f) The names of drugs and preparations should be written clearly and not abbreviated, using approved titles only (see also advice in box on p. 3 to avoid creating generic titles for modified-release preparations).

(g) The quantity to be supplied may be stated by indicating the number of days of treatment required in the box provided on NHS forms. In most cases the exact amount will be supplied. This does not apply to items directed to be used as required—if the dose and frequency are not given then the quantity to be supplied needs to be stated.

When several items are ordered on one form the box can be marked with the number of days of treatment provided the quantity is added for any item for which the amount cannot be calculated.

(h) Although directions should preferably be in English without abbreviation, it is recognised that some Latin abbreviations are used (for details see Inside Back Cover).

(i) Medical and dental practitioners may prescribe unlicensed medicines (i.e. those without marketing authorisation) or withdrawn medicines. The prescriber should inform the patient or the patient’s carer that the product does not have a marketing authorisation.

Prescribing by dental surgeons
Until new prescribing arrangements are in place for NHS prescriptions, dental surgeons should use form FP10D (GP14 in Scotland, WP10D in Wales) to prescribe only those items listed in the Dental Practitioners’ Formulary.

1. These recommendations are acceptable for prescription-only medicines (POM). For items marked (R) see also Controlled Drugs and Drug Dependence, p. 7.
2. It is permissible to issue carbon copies of NHS prescriptions as long as they are signed in ink.
3. Computer-generated facsimile signatures do not meet the legal requirement.
4. The use of capital ‘L’ in mL is a printing convention throughout the BNF; both ‘mL’ and ‘ml’ are recognised SI abbreviations.
The Act and Regulations do not set any limitations upon the number and variety of substances which the dental surgeon may administer to patients in the surgery or may order by private prescription—provided the relevant legal requirements are observed the dental surgeon may use or order whatever is required for the clinical situation. There is no statutory requirement for the dental surgeon to communicate with a patient’s medical practitioner when prescribing for dental use. There are, however, occasions when this would be in the patient’s interest and such communication is to be encouraged.

For legal requirements relating to prescriptions for Controlled Drugs, see p. 7.

### Computer-issued prescriptions

For computer-issued prescriptions the following advice, based on the recommendations of the Joint GP Information Technology Committee, should also be noted:

1. The computer must print out the date, the patient’s surname, one forename, other initials, and address, and may also print out the patient’s title and date of birth. The age of children under 12 years and of adults over 60 years must be printed in the box available; the age of children under 5 years should be printed in years and months. A facility may also exist to print out the age of patients between 12 and 60 years.

2. The doctor’s name must be printed at the bottom of the prescription form; this will be the name of the doctor responsible for the prescription (who will normally sign it). The doctor’s surgery address, reference number, and Primary Care Trust (PCT) are also necessary. In addition, the surgery telephone number should be printed.

3. When prescriptions are to be signed by general practitioner registrars, assistants, locums, or depu-tising doctors, the name of the doctor printed at the bottom of the form must still be that of the responsible principal.

4. Names of medicines must come from a dictionary held in the computer memory, to provide a check on the spelling and to ensure that the name is written in full. The computer can be programmed to recognise both the non-proprietary and the proprietary name of a particular drug and to print out the preferred choice, but must not print out both names. For medicines not in the dictionary, separate checks are required—the user must be warned that no check was possible and the entire prescription must be entered in the lexicon.

5. The dictionary may contain information on the usual doses, formulations, and pack sizes to produce standard predetermined prescriptions for common preparations, and to provide a check on the validity of an individual prescription on entry.

6. The prescription must be printed in English without abbreviation; information may be entered or stored in abbreviated form. The dose must be in numbers, the frequency in words, and the quantity in numbers in brackets, thus: 40 mg four times daily (112). It must also be possible to prescribe by indicating the length of treatment required, see (h) above.

7. The BNF recommendations should be followed as in (a), (b), (c), (d), and (e) above.

8. Checks may be incorporated to ensure that all the information required for dispensing a particular drug has been filled in. For instructions such as ‘as directed’ and ‘when required’, the maximum daily dose should normally be specified.

9. Numbers and codes used in the system for organising and retrieving data must never appear on the form.

10. Supplementary warnings or advice should be written in full, should not interfere with the clarity of the prescription itself, and should be in line with any warnings or advice in the BNF; numerical codes should not be used.

11. A mechanism (such as printing a series of non-specific characters) should be incorporated to cancel out unused space, or wording such as ‘no more items on this prescription’ may be added after the last item. Otherwise the doctor should delete the space manually.

12. To avoid forgery the computer may print on the form the number of items to be dispensed (somewhere separate from the box for the pharmacist). The number of items per form need be limited only by the ability of the printer to produce clear and well-demarcated instructions with sufficient space for each item and a spacer line before each fresh item.

13. Handwritten alterations should only be made in exceptional circumstances—it is preferable to print out a new prescription. Any alterations must be made in the doctor’s own handwriting and countersigned; computer records should be updated to fully reflect any alteration. Prescriptions for drugs used for contraceptive purposes (but which are not promoted as contraceptives) may need to be marked in handwriting with the symbol \( \text{‡} \) (or endorsed in another way to indicate that the item is prescribed for contraceptive purposes).

14. Prescriptions for controlled drugs can be printed from the computer, but the prescriber’s signature must be handwritten^2^.

15. The strip of paper on the side of the FP10SS may be used for various purposes but care should be taken to avoid including confidential information. It may be advisable for the patient’s name to appear at the top, but this should be preceded by ‘confidential’.

16. In rural dispensing practices prescription requests (or details of medicines dispensed) will normally be entered in one surgery. The prescriptions (or dispensed medicines) may then need to be delivered to another surgery or location; if possible the computer should hold up to 10 alternatives.

17. Prescription forms that are reprinted or issued as a duplicate should be labelled clearly as such.

---

1. Health Board in Scotland, Local Health Board in Wales.
2. See Controlled Drugs and Drug Dependence p. 7; the prescriber may use a date stamp.
3. GP10SS in Scotland, WP10SS in Wales.
Emergency supply of medicines

Emergency supply requested by member of the public

Pharmacists are sometimes called upon by members of the public to make an emergency supply of medicines. The Prescription Only Medicines (Human Use) Order 1997 allows exemptions from the Prescription Only requirements for emergency supply to be made by a person lawfully conducting a retail pharmacy business provided:

(a) that the pharmacist has interviewed the person requesting the prescription-only medicine and is satisfied:
   (i) that there is immediate need for the prescription-only medicine and that it is impracticable in the circumstances to obtain a prescription without undue delay;
   (ii) that treatment with the prescription-only medicine has on a previous occasion been prescribed by a doctor, a supplementary prescriber, a community practitioner nurse prescriber (formerly a district nurse or health visitor prescriber), a nurse independent prescriber, or a pharmacist independent prescriber, for the person requesting it;
   (iii) as to the dose that it would be appropriate for the person to take;
(b) that no greater quantity shall be supplied than will provide 5 days' treatment except when the prescription-only medicine is:
   (i) insulin, an ointment or cream, or a preparation for the relief of asthma in an aerosol dispenser when the smallest pack can be supplied;
   (ii) an oral contraceptive when a full cycle may be supplied;
   (iii) an antibiotic in liquid form for oral administration when the smallest quantity that will provide a full course of treatment can be supplied;
(c) that an entry shall be made by the pharmacist in the prescription book stating:
   (i) the date of supply;
   (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   (iii) the name and address of the patient;
   (iv) the nature of the emergency;
(d) that the container or package must be labelled to show:
   (i) the date of supply;
   (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   (iii) the name of the patient;
   (iv) the words 'Emergency supply';
   (v) the words 'Keep out of the reach of children' (or similar warning);
(e) that the prescription-only medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital or phenobarbital sodium for the treatment of epilepsy: for details see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available).

Emergency supply requested by prescriber

Emergency supply of a prescription-only medicine may also be made at the request of a doctor, a supplementary prescriber, a community practitioner nurse prescriber (formerly a district nurse or health visitor prescriber), a nurse independent prescriber, or a pharmacist independent prescriber provided:

(a) that the pharmacist is satisfied that the prescriber by reason of some emergency is unable to furnish a prescription immediately;
(b) that the prescriber has undertaken to furnish a prescription within 72 hours;
(c) that the medicine is supplied in accordance with the directions of the prescriber requesting it;
(d) that the medicine is not a substance specifically excluded from the emergency supply provision, and does not contain a Controlled Drug specified in Schedules 1, 2, or 3 to the Misuse of Drugs Regulations 2001 except for phenobarbital or phenobarbital sodium for the treatment of epilepsy: for details see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available);
(e) that an entry shall be made in the prescription book stating:
   (i) the date of supply;
   (ii) the name, quantity and, where appropriate, the pharmaceutical form and strength;
   (iii) the name and address of the practitioner requesting the emergency supply;
   (iv) the name and address of the patient;
   (v) the date on the prescription;
   (vi) when the prescription is received the entry should be amended to include the date on which it is received.

Royal Pharmaceutical Society's Guidelines

1. The pharmacist should consider the medical consequences of not supplying a medicine in an emergency.
2. If the pharmacist is unable to make an emergency supply of a medicine the pharmacist should advise the patient how to obtain essential medical care.

For conditions that apply to supplies made at the request of a patient see Medicines, Ethics and Practice, No. 32, London Pharmaceutical Press, 2008 (and subsequent editions).
Controlled Drugs and drug dependence

The Misuse of Drugs Act, 1971 prohibits certain activities in relation to 'Controlled Drugs', in particular their manufacture, supply, and possession. The penalties applicable to offences involving the different drugs are graded broadly according to the harmfulness attributable to a drug when it is misused and for this purpose the drugs are defined in the following three classes:

Class A includes: alfentanil, cocaine, diamorphine (heroin), dipipanone, lysergide (LSD), methadone, methylenedioxymethamphetamine (MDMA, 'ecstasy'), morphine, opium, pethidine, phenylcyclidine, remifentanil, and class B substances when prepared for injection

Class B includes: oral amphetamines, barbiturates, cannabis, cannabis resin, codeine, ethylmorphine, glutethimide, pentazocine, phentemazine, and pholcodine

Class C includes: certain drugs related to the anabolics such as benzotriamidone and chlorphentermine, buprenorphine, diethylpropion, mazindol, meprobamate, pemoline, pipradrol, most benzodiazepines, zolpidem, androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin

The Misuse of Drugs Regulations 2001 define the classes of person who are authorised to supply and possess controlled drugs while acting in their professional capacities and lay down the conditions under which these activities may be carried out. In the regulations drugs are divided into five schedules each specifying the requirements governing such activities as import, export, production, supply, possession, prescribing, and record keeping which apply to them.

Schedule 1 includes drugs such as cannabis and lysergide which are not used medicinally. Possession and supply are prohibited except in accordance with Home Office authority.

Schedule 2 includes drugs such as diamorphine (heroin), morphine, remifentanil, pethidine, seco-barbital, glutethimide, amfetamine, and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for seco-barbital), the need to keep registers, etc. (unless exempted in Schedule 5).

Schedule 3 includes the barbiturates (except seco-barbital, now Schedule 2), buprenorphine, diethylpropion, mazindol, meprobamate, midazolam, pentazocine, pethidine, and temazepam. They are subject to the special prescription requirements (except for temazepam) but not to the safe custody requirements (except for buprenorphine, diethylpropion, and temazepam) nor to the need to keep registers (although there are requirements for the retention of invoices for 2 years).

Schedule 4 includes in Part I benzodiazepines (except temazepam and midazolam, which are in Schedule 3) and zolpidem, which are subject to minimal control. Part II includes androgenic and anabolic steroids, clenbuterol, chorionic gonadotrophin (HCG), non-human chorionic gonadotrophin, somatotropin, somatrem, and somatropin. Controlled drug prescription requirements do not apply and Schedule 4 Controlled Drugs are not subject to safe custody requirements.

Schedule 5 includes those preparations which, because of their strength, are exempt from virtually all Controlled Drug requirements other than retention of invoices for two years.

Prescriptions Preparations in Schedules 2 and 3 of the Misuse of Drugs Regulations 2001 (and subsequent amendments) are identified throughout the BNF by the symbol (©) (Controlled Drug). The principal legal requirements relating to medical prescriptions are listed below (see also Department of Health Guidance, p. 8).

Prescription requirements

Prescriptions for Controlled Drugs that are subject to prescription requirements must be indelible, and must be signed by the prescriber, be dated, and specify the prescriber’s address. The prescription must always state:

- the name and address of the patient;
- in the case of a preparation, the form and where appropriate the strength of the preparation;
- either the total quantity (in both words and figures) of the preparation, or the number (in both words and figures) of dosage units, as appropriate, to be supplied; in any other case, the total quantity (in both words and figures) of the Controlled Drug to be supplied;
- the dose;
- the words 'for dental treatment only' if issued by a dentist.

A pharmacist is not allowed to dispense a Controlled Drug unless all the information required by law is given on the prescription. In the case of a prescription for a Controlled Drug in Schedule 2 or 3, a pharmacist can amend the prescription if it specifies the total quantity only in words or in figures or if it contains minor typographical errors, provided that such amendments are indelible and clearly attributable to the pharmacist. Failure to comply with the regulations concerning the writing of prescriptions will result in inconvenience to patients and delay in supplying the necessary medicine.

1. All preparations in Schedules 2 and 3, except temazepam.
2. A machine-written prescription is acceptable. The prescriber’s signature must be handwritten.
3. The dosage form (e.g. tablets) must be included on a Controlled Drugs prescription irrespective of whether it is implicit in the proprietary name (e.g. MST Continus) or whether only one form is available.
4. When more than one strength of a preparation exists the strength required must be specified.
5. The Home Office has advised that quantities of liquid preparations, such as methadone oral solution, should be written in millilitres.
6. The instruction 'one as directed' constitutes a dose but ‘as directed’ does not.
Instalments and ‘repeats’ A prescription may order a Controlled Drug to be dispensed by instalments; the amount of instalments and the intervals to be observed must be specified. Prescriptions ordering ‘repeats’ on the same form are not permitted for Controlled Drugs in Schedules 2 or 3. A prescription for a Controlled Drug in Schedules 2, 3, or 4 is valid for 28 days from the date stated thereon.

Private prescriptions Private prescriptions for Controlled Drugs in Schedules 2 and 3 must be written on specially designated forms provided by Primary Care Trusts in England, Health Boards in Scotland, Local Health Boards in Wales, or the Northern Ireland Central Services Agency; in addition, prescriptions must specify the prescriber’s identification number. Prescriptions to be supplied by a pharmacist in hospital are exempt from the requirements for private prescriptions.

Department of Health guidance Guidance (June 2006) issued by the Department of Health in England on prescribing and dispensing of Controlled Drugs requires:

- In general, prescriptions for Controlled Drugs in Schedules 2, 3, and 4 to be limited to a supply of up to 30 days’ treatment; exceptionally, to cover a justifiable clinical need and after consideration of any risk, a prescription can be issued for a longer period, but the reasons for the decision should be recorded on the patient’s notes;

- the patient’s identifier to be shown on NHS and private prescriptions for Controlled Drugs in Schedules 2 and 3.

Further information is available at www.dh.gov.uk/controlleddrugs.

Dependence and misuse The most serious drugs of addiction are cocaine, diamorphine (heroin), morphine, and the synthetic opioids. For arrangements for prescribing of diamorphine, dipipanone, or cocaine for addicts, see p. 10.

Despite marked reduction in the prescribing of amphetamines there is concern that abuse of illicit amphetamine and related compounds is widespread.

The benzodiazepine temazepam has commonly been associated with misuse. The misuse of barbiturates is now less common, in line with declining prescription numbers.

Cannabis (Indian hemp) has no approved medicinal use and cannot be prescribed by doctors. Its use is illegal but has become widespread. Cannabis is a mild hallucinogen seldom accompanied by a desire to increase the dose; withdrawal symptoms are unusual.

Lysergide (lysergic acid diethylamide, LSD) is a much more potent hallucinogen; its use can lead to severe psychotic states which can be life-threatening.

Prescribing drugs likely to cause dependence or misuse The prescriber has three main responsibilities:

- To avoid creating dependence by introducing drugs to patients without sufficient reason. In this context, the proper use of the morphine-like drugs is well understood. The dangers of other Controlled Drugs are less clear because recognition of dependence is not easy and its effects, and those of withdrawal, are less obvious.

- To see that the patient does not gradually increase the dose of a drug, given for good medical reasons, to the point where dependence becomes more likely. This tendency is seen especially with hypnotics and anxiolytics (for CSM advice see section 4.1). The prescriber should keep a close eye on the amount prescribed to prevent patients from accumulating stocks. A minimal amount should be prescribed in the first instance, or when seeing a new patient for the first time.

- To avoid being used as an unwitting source of supply for addicts. Methods include visiting more than one doctor, fabricating stories, and forging prescriptions.

Patients under temporary care should be given only small supplies of drugs unless they present an unequivocal letter from their own doctors. Doctors should also remember that their own patients may be attempting to collect prescriptions from other prescribers, especially in hospitals. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if it is apparent that dependence is occurring.
The stealing and misuse of prescription forms could be minimised by the following precautions:

- do not leave unattended if called away from the consulting room or at reception desks; do not leave in a car where they may be visible; when not in use, keep in a locked drawer within the surgery and at home;
- draw a diagonal line across the blank part of the form under the prescription;
- write the quantity in words and figures when prescribing drugs prone to abuse; this is obligatory for controlled drugs (see Prescriptions, above);
- alterations are best avoided but if any are made they should be clear and unambiguous; add initials against altered items;
- if prescriptions are left for collection they should be left in a safe place in a sealed envelope.

Travelling abroad
Prescribed drugs listed in Schedule 4 Part II (CD Anab) and Schedule 5 of the Misuse of Drugs Regulations 2001 are not subject to export or import licensing. However, patients intending to travel abroad for more than 3 months carrying any amount of drugs listed in Schedules 2, 3, or 4 Part I (CD Benz) will require a personal export/import licence. Further details can be obtained at www.drugs.homeoffice.gov.uk/drugs-laws/licensing/personal, or from the Home Office by contacting the Home Office, Drugs Licensing, Peel Building, 2 Marsham Street, London, SW1P 4DF. Alternatively, completed application forms can be emailed to licensing_enquiry.aadu@homeoffice.gsi.gov.uk with a scanned copy of the covering letter from the prescriber. A minimum of two weeks should be allowed for processing the application.

Patients travelling for less than 3 months do not require a personal export/import licence for carrying Controlled Drugs, but are advised to carry a letter from the prescribing doctor. Those travelling for more than 3 months are advised to make arrangements to have their medication prescribed by a practitioner in the country they are visiting.

Doctors who want to take Controlled Drugs abroad while accompanying patients may similarly be issued with licences. Licences are not normally issued to doctors who want to take Controlled Drugs abroad solely in case a family emergency should arise.

Personal export/import licences do not have any legal status outside the UK and are issued only to comply with the Misuse of Drugs Act and to facilitate passage through UK Customs and Excise control. For clearance in the country to be visited it is necessary to approach that country’s consulate in the UK.

Notification of drug misusers
Doctors should report cases of drug misuse to their regional or national drug misuse database or centre—see below for contact telephone numbers. The National Drugs Treatment Monitoring System (NDTMS) was introduced in England in April 2001; regional (NDTMS) centres replace the Regional Drug Misuse Databases. A similar system has been introduced in Wales.

Notification to regional (NDTMS) or national centre should be made when a patient starts treatment for drug misuse. All types of problem drug misuse should be reported including opioid, benzodiazepine, and CNS stimulant.

The regional (NDTMS) or national centres are now the only national and local source of epidemiological data on people presenting with problem drug misuse; they provide valuable information to those working with drug misusers and those planning services for them. The databases cannot, however be used as a check on multiple prescribing for drug addicts because the data are anonymised.

Enquiries about the regional (NDTMS) or national centres (including information on how to submit data) can be made to one of the centres listed below:

**ENGLAND**

- **Eastern**
  - Tel: (01223) 767 904
  - Fax: (01223) 597 601
- **South East**
  - Tel: (01865) 334 725
  - Fax: (01865) 334 733
- **London**
  - Tel: (020) 7261 8820
  - Fax: (020) 7261 8883
- **North West**
  - Tel: (0151) 231 4533
  - Fax: (0151) 231 4515
- **North East**
  - Tel: (0191) 334 0372
  - Fax: (0191) 334 0391
- **Yorkshire and the Humber**
  - Tel: (0113) 295 3714
  - Fax: (0113) 295 3720
- **South Western**
  - Tel: (0117) 970 6474 ext 311
  - Fax: (0117) 970 7021
- **East Midlands**
  - Tel: (0115) 971 2738
  - Fax: (0115) 971 2740
- **West Midlands**
  - Tel: (021) 415 8556
  - Fax: (021) 414 8197

**SCOTLAND**

- Tel: (0131) 275 6655
  - Fax: (0131) 275 7511

**WALES**

- Tel: (029) 2050 3343
  - Fax: (029) 2050 2330

In **Northern Ireland**, the Misuse of Drugs (Notification of and Supply to Addicts) (Northern Ireland) Regulations 1973 require doctors to send particulars of persons whom they consider to be addicted to certain controlled...
Prescribing of diamorphine (heroin), dipipanone, and cocaine for addicts

The Misuse of Drugs (Supply to Addicts) Regulations 1997 require that only medical practitioners who hold a special licence issued by the Home Secretary may prescribe, administer, or supply diamorphine, dipipanone (*Diconal*®), or cocaine in the treatment of drug addiction; other practitioners must refer any addict who requires these drugs to a treatment centre. Whenever possible the addict will be introduced by a member of staff from the treatment centre to a pharmacist whose agreement has been obtained and whose pharmacy is conveniently sited for the patient. Prescriptions for weekly supplies will be sent to the pharmacy by post and will be dispensed on a daily basis as indicated by the doctor. If any alterations of the arrangements are requested by the addict, the portion of the prescription affected must be represcribed and not merely altered.

General practitioners and other doctors do not require a special licence for prescribing diamorphine, dipipanone, and cocaine for patients (including addicts) for relieving pain from organic disease or injury.

For guidance on prescription writing, see p. 7.
Adverse reactions to drugs

Any drug may produce unwanted or unexpected adverse reactions. Rapid detection and recording of adverse reactions is of vital importance so that recognised hazards are identified promptly and appropriate regulatory action is taken to ensure that medicines are used safely. Doctors, dentists, coroners, pharmacists, and nurses (see also self-reporting below) are urged to report suspected adverse reactions directly to the Medicines and Healthcare products Regulatory Agency (MHRA) through the Yellow Card Scheme using the electronic form at www.yellowcard.gov.uk. Alternatively, prepay Yellow Cards for reporting are available from the address below and are also bound in this book (inside back cover).

Meditines and Healthcare products Regulatory Agency
CHM
Freepost
London SW8 5BR
Tel: 0800 731 6789

Suspected adverse reactions to any therapeutic agent should be reported, including drugs (self-medication as well as those prescribed), blood products, vaccines, radiographic contrast media, complementary and herbal products.

A 24-hour Freephone service is available to all parts of the UK for advice and information on suspected adverse drug reactions; contact the National Yellow Card Information Service at the MHRA on 0800 731 6789. Outside office hours a telephone-answering machine will take messages.

The following Yellow Card Centres may follow up reports:

Yellow Card Centre Mersey
Freepost
Liverpool L3 3AB
Tel: (0151) 794 8206

Yellow Card Centre Wales
Freepost
Cardiff CF4 1ZZ
Tel: (029) 2074 4181
(direct line)

Yellow Card Centre Northern & Yorkshire
Freepost
Newcastle upon Tyne NE1 1BR
Tel: (0191) 232 1525
(direct line)

Yellow Card Centre Scotland
CARDS
Freepost NAT3271
Edinburgh EH16 4BR
Tel: (0131) 242 2919

The MHRA’s database facilitates the monitoring of adverse drug reactions.

More detailed information on reporting and a list of products currently under intensive monitoring can be found on the MHRA website: www.mhra.gov.uk.

Self-reporting

Patients, parents, and carers can also report suspected adverse reactions to the MHRA. Reports can be submitted directly to the MHRA through the Yellow Card Scheme using the electronic form at www.yellowcard.gov.uk or by telephone on 0800 100 3352. Alternatively, patient Yellow Cards are available from pharmacies.

Prescription-event monitoring

In addition to the MHRA’s Yellow Card Scheme, an independent scheme monitors the safety of new medicines using a different approach. The Drug Safety Research Unit identifies patients who have been prescribed selected new medicines and collects data on clinical events in these patients. The data are submitted on a voluntary basis by general practitioners on green forms. More information about the scheme and the Unit’s educational material is available from www.dsru.org.

Newer drugs and vaccines

Only limited information is available from clinical trials on the safety of new medicines. Further understanding about the safety of medicines depends on the availability of information from routine clinical practice.

The black triangle symbol (▼) identifies newly licensed medicines that are monitored intensively by the MHRA. Such medicines include new active substances, biosimilar medicines, medicines that have been licensed for administration by a new route or drug delivery system, or for significant new indications which may alter the established risks and benefits of that drug, or that contain a new combination of active substances. There is no standard time for which products retain a black triangle; safety data are usually reviewed after 2 years.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. For medicines showing the black triangle symbol, the MHRA asks that all suspected reactions (including those considered not to be serious) are reported through the Yellow Card Scheme. An adverse reaction should be reported even if it is not certain that the drug has caused it, or if the reaction is well recognised. Exam- ples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions.

Established drugs and vaccines

Doctors, dentists, coroners, pharmacists and nurses are asked to report all serious suspected reactions, including those that are fatal, life-threatening, disabling, incapacitating, or which result in or prolong hospitalisation; they should be reported even if the effect is well recognised. Examples include anaphylaxis, blood disorders, endocrine disturbances, effects on fertility, haemorrhage from any site, renal impairment, jaundice, ophthalmic disorders, severe CNS effects, severe skin reactions, reactions in pregnant women, and any drug interactions. Reports of serious adverse reactions are required to enable comparison with other drugs of a similar class. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

For established drugs there is no need to report well-known, relatively minor side-effects, such as dry mouth with tricyclic antidepressants or constipation with opioids.
Adverse reactions to medical devices

Suspected adverse reactions to medical devices including dental or surgical materials, intra-uterine devices, and contact lens fluids should be reported. Information on reporting these can be found at: www.mhra.gov.uk.

Side-effects in the BNF

The BNF includes clinically relevant side-effects for most drugs; an exhaustive list is not included for drugs that are used by specialists (e.g. cytotoxic drugs and drugs used in anaesthesia). Where causality has not been established, side-effects in the manufacturers’ literature may be omitted from the BNF.

Recognising that hypersensitivity reactions can occur with virtually all medicines, this effect is not generally listed, unless the drug carries an increased risk of such reactions. The BNF also omits effects that are likely to have little clinical consequence (e.g. transient increase in liver enzymes).

Side-effects are generally listed in order of frequency and arranged broadly by body systems. Occasionally a rare side-effect might be listed first if it is considered to be particularly important because of its seriousness.

In the product literature the frequency of side-effects is generally described as follows:

- **Very common**: greater than 1 in 10
- **Common**: 1 in 100 to 1 in 10
- **Uncommon** (‘less commonly’ in BNF): 1 in 1000 to 1 in 100
- **Rare**: 1 in 10 000 to 1 in 1000
- **Very rare**: less than 1 in 10 000

### Special problems

#### Delayed drug effects

Some reactions (e.g. cancers, chloroquine retinopathy, and retroperitoneal fibrosis) may become manifest months or years after exposure. Any suspicion of such an association should be reported directly to the MHRA through the Yellow Card Scheme.

#### The elderly

Particular vigilance is required to identify adverse reactions in the elderly.

#### Congenital abnormalities

When an infant is born with a congenital abnormality or there is a malformed aborted fetus doctors are asked to consider whether this might be an adverse reaction to a drug and to report all drugs (including self-medication) taken during pregnancy.

#### Children

Particular vigilance is required to identify and report adverse reactions in children, including those resulting from the unlicensed use of medicines; all suspected reactions should be reported directly to the MHRA through the Yellow Card Scheme.

### Prevention of adverse reactions

Adverse reactions may be prevented as follows:

- never use any drug unless there is a good indication. If the patient is pregnant do not use a drug unless the need for it is imperative;
- allergy and idiosyncrasy are important causes of adverse drug reactions. Ask if the patient had previous reactions;
- ask if the patient is already taking other drugs including self-medication drugs, health supplements, complementary and alternative therapies; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, so that much smaller doses may be needed. Genetic factors may also be responsible for variations in metabolism, notably of isoniazid and the tricyclic antidepressants;
- prescribe as few drugs as possible and give very clear instructions to the elderly or any patient likely to misunderstand complicated instructions;
- whenever possible use a familiar drug; with a new drug, be particularly alert for adverse reactions or unexpected events;
- warn the patient if serious adverse reactions are liable to occur.

### Oral side-effects of drugs

Drug-induced disorders of the mouth may be due to a local action on the mouth or to a systemic effect manifested by oral changes. In the latter case urgent referral to the patient’s medical practitioner may be necessary.

#### Oral mucosa

Medicaments left in contact with or applied directly to the oral mucosa can lead to inflammation or ulceration; the possibility of allergy should also be borne in mind. 

Aspirin tablets allowed to dissolve in the sulcus for the treatment of toothache can lead to a white patch followed by ulceration.

Flavouring agents, particularly essential oils, may sensitise the skin, but mucosal swelling is not usually prominent.

The oral mucosa is particularly vulnerable to ulceration in patients treated with cytotoxic drugs, e.g. methotrexate. Other drugs capable of causing oral ulceration include captopril (and other ACE inhibitors), gold, nicorandil, NSAIDs, pancreatic, penicillamine, proguanil, and protease inhibitors.

*Erythema multiforme* (including Stevens-Johnson syndrome) may follow the use of a wide range of drugs including antibiotics, antiretrovirals, sulphamamide derivatives, and anticonvulsants; the oral mucosa may be extensively ulcerated, with characteristic target lesions on the skin. Oral lesions of toxic epidermal necrolysis (Lyell’s syndrome) have been reported with a similar range of drugs.

Lichenoid eruptions are associated with ACE inhibitors, NSAIDs, methyldopa, chloroquine, oral anti-diabetics, thiazide diuretics, and gold.

*Candidiasis* can complicate treatment with antibiotics and immunosuppressants and is an occasional side-effect of corticosteroid inhalers, see also p. 163.

### Teeth and Jaw

Brown staining of the teeth frequently follows the use of chlorhexidine mouthwash, spray or gel, but can readily be removed by polishing. Iron salts in liquid form can stain the enamel black. Superficial staining has been reported rarely with co-amoxiclav suspension.
**Intrinsic staining** of the teeth is most commonly caused by **tetracyclines**. They will affect the teeth if given at any time from about the fourth month *in utero* until the age of twelve years; they are contra-indicated in pregnancy, breast-feeding women, and in children under 12 years. All tetracyclines can cause permanent, unsightly staining in children, the colour varying from yellow to grey.

Excessive ingestion of **fluoride** leads to *dental fluorosis* with mottling of the enamel and areas of hypoplasia or pitting; fluoride supplements occasionally cause mild mottling (white patches) if the dose is too large for the child's age (taking into account the fluoride content of the local drinking water and of toothpaste).

**Gingival overgrowth** (gingival hyperplasia) is a side-effect of **phenytoin** and sometimes of **ciclosporin** or of **nifedipine** (and some other calcium-channel blockers). **Thrombocytopenia** may be drug related and may cause bleeding at the gingival margins, which may be spontaneous or may follow mild trauma (such as toothbrushing).

**Salivary glands**

The most common effect that drugs have on the salivary glands is to *reduce flow* (xerostomia). Patients with a persistently dry mouth may have poor oral hygiene; they are at an increased risk of dental caries and oral infections (particularly candidiasis). Many drugs have been implicated in xerostomia, particularly **antimuscarinics** (anticholinergics), **antidepressants** (including tricyclic antidepressants, and selective serotonin re-uptake inhibitors), **alpha-blockers**, **antihistamines**, **antipsychotics**, **baclofen**, **bupropion**, **clonidine**, **SHT agonists**, **opioids**, **sibutramine**, and **tizanidine**. Excessive use of **diuretics** can also result in xerostomia.

Some drugs (e.g. clozapine, neostigmine) can *increase saliva production* but this is rarely a problem unless the patient has associated difficulty in swallowing.

Pain in the salivary glands has been reported with some **antihypertensives** (e.g. clonidine, methyldopa) and with **vinca alkaloids**.

Swelling of the salivary glands can occur with **iodides**, **antithyroid drugs**, **phenothiazines**, **ritodrine**, and **sulphonamides**.

**Taste**

There can be decreased taste acuity or alteration in taste sensation. Drugs implicated include **amiodarone**, **calcitonin**, **captopril** (and other ACE inhibitors), **carbamazepine**, **clarithromycin**, **gold**, **griseofulvin**, **lithium salts**, **metformin**, **metronidazole**, **penicillamine**, **phenindione**, **propafenone**, **protease inhibitors**, **terbinafine**, and **zopiclone**.

**Defective medicines**

During the manufacture or distribution of a medicine an error or accident may occur whereby the finished product does not conform to its specification. While such a defect may impair the therapeutic effect of the product and could adversely affect the health of a patient, it should not be confused with an *Adverse Drug Reaction* where the product conforms to its specification.

The Defective Medicines Report Centre assists with the investigation of problems arising from licensed medicinal products thought to be defective and co-ordinates any necessary protective action. Reports on suspect defective medicinal products should include the brand or the non-proprietary name, the name of the manufacturer or supplier, the strength and dosage form of the product, the product licence number, the batch number or numbers of the product, the nature of the defect, and an account of any action already taken in consequence. The Centre can be contacted at:

The Defective Medicines Report Centre
Medicines and Healthcare products Regulatory Agency
Room 18–159
1 Nine Elms Lane
London SW8 5NQ
(020) 7084 2574 (weekdays 9.00 am–5.00 pm)
or (020) 7210 3000 (outside office hours)

---

**Prescribing for children**

For detailed advice on medicines used for children, consult *BNF for Children*

Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 30 days of life) and doses should always be calculated with care. At this age, the risk of toxicity is increased by reduced drug clearance and differing target organ sensitivity.

Whenever possible, intramuscular injections should be **avoided** in children because they are painful.

Where possible, medicines for children should be prescribed within the terms of the marketing authorisation (product licence). However, many children may require medicines not specifically licensed for paediatric use.

Although medicines cannot be promoted outside the limits of the licence, the Medicines Act does not prohibit the use of unlicensed medicines. It is recognised that the informed use of unlicensed medicines or of licensed medicines for unlicensed applications (‘off-label’ use) is often necessary in paediatric practice.
Prescribing for children

Dosage in children

Children's doses in the BNF are stated in the individual drug entries as far as possible, except where paediatric use is not recommended, information is not available, or there are special hazards.

Doses are generally based on body-weight (in kilograms) or the following age ranges:

- first month (neonate)
- up to 1 year (infant)
- 1–5 years
- 6–12 years

Unless the age is specified, the term ‘child’ in the BNF includes persons aged 12 years and younger.

Dose calculation

Many children’s doses are standardised by weight (and therefore require multiplying by the body-weight in kilograms to determine the child’s dose); occasionally, the doses have been standardised by body-surface area (in m²). These methods should be used rather than attempting to calculate a child’s dose on the basis of doses used in adults.

For most drugs the adult maximum dose should not be exceeded. For example if the dose is stated as 8 mg/kg (max. 300 mg), a child weighing 10 kg should receive 80 mg but a child weighing 40 kg should receive 300 mg (rather than 320 mg).

Young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Other problems need to be considered. For example, calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases, dose should be calculated from an ideal weight, related to height and age (see inside back cover).

Body-surface area (BSA) estimates are more accurate for calculation of paediatric doses than body-weight since many physiological phenomena correlate better with body-surface area. Body-surface area can be estimated from weight by means of a table. For more information, refer to BNF for Children.

Where the dose for children is not stated, prescribers should consult BNF for Children or seek advice from a medicines information centre.

Dose frequency

Antibacterials are generally given at regular intervals throughout the day. Some flexibility should be allowed in children to avoid waking them during the night. For example, the night-time dose may be given at the parent’s bedtime.

Where new or potentially toxic drugs are used, the manufacturers’ recommended doses should be carefully followed.

Adverse drug reactions in children

The reporting of all suspected adverse drug reactions in children is strongly encouraged through the Yellow Card Scheme (see p. 11) even if the intensive monitoring symbol (▼) has been removed, because experience in children may still be limited.

The identification and reporting of adverse reactions to drugs in children is particularly important because:

- the action of the drug and its pharmacokinetics in children (especially in the very young) may be different from that in adults;
- drugs are not extensively tested in children;
- many drugs are not specifically licensed for use in children and are used ‘off-label’;
- suitable formulations may not be available to allow precise dosing in children;
- the nature and course of illnesses and adverse drug reactions may differ between adults and children.

Prescription writing

Prescriptions should be written according to the guidelines in Prescription Writing (p. 4). Inclusion of age is a legal requirement in the case of prescription-only medicines for children under 12 years of age, but it is preferable to state the age for all prescriptions for children.

It is particularly important to state the strengths of capsules or tablets. Although liquid preparations are particularly suitable for children, they may contain sugar which encourages dental decay. Sugar-free medicines are preferred for long-term treatment.

Many children are able to swallow tablets or capsules and may prefer a solid dose form; involving the child and parents in choosing the formulation is helpful.

When a prescription for a liquid oral preparation is written and the dose ordered is smaller than 5 mL an oral syringe will be supplied (for details, see p. 2). Parents should be advised not to add any medicines to the infant’s feed, since the drug may interact with the milk or other liquid in it; moreover the ingested dosage may be reduced if the child does not drink all the contents.

Parents must be warned to keep all medicines out of reach of children, see Safety in the Home, p. 3.

Rare paediatric conditions

Information on substances such as biotin and sodium benzoate used in rare metabolic conditions is included in BNF for Children; further information can be obtained from:

Alder Hey Children’s Hospital
Drug Information Centre
Liverpool L12 2AP
Tel: (0151) 252 5381

Great Ormond Street Hospital for Children
Pharmacy
Great Ormond St
London WC1N 3JH
Tel: (020) 7405 9200
Prescribing in palliative care

Palliative care is the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems, is paramount to provide the best quality of life for patients and their families. Careful assessment of symptoms and needs of the patient should be undertaken by a multidisciplinary team.

Specialist palliative care is available in most areas as day hospice care, home-care teams (often known as Macmillan teams), in-patient hospice care, and hospital teams. Many acute hospitals and teaching centres now have consultative, hospital-based teams.

Hospice care of terminally ill patients has shown the importance of symptom control and psychosocial support of the patient and family. Families should be included in the care of the patient if they wish.

Many patients wish to remain at home with their families. Although some families may at first be afraid of caring for the patient at home, support can be provided by community nursing services, social services, voluntary agencies and hospices together with the general practitioner. The family may be reassured by the knowledge that the patient will be admitted to a hospital or hospice if the family cannot cope.

Drug treatment The number of drugs should be as few as possible, for even the taking of medicine may be an effort. Oral medication is usually satisfactory unless there is severe nausea and vomiting, dysphagia, weakness, or coma, when parenteral medication may be necessary.

Pain Analgesics are more effective in preventing pain than in the relief of established pain; it is important that they are given regularly.

The non-opioid analgesic paracetamol (section 4.7.1) or a NSAID (section 10.1.1) given regularly will often make the use of opioids unnecessary. A NSAID may also control the pain of bone secondaries; if necessary, flurbiprofen or indomethacin can be given rectally. Radiotherapy, bisphosphonates (section 6.6.2), and radioactive isotopes of strontium (Metastron® available from GE Healthcare) may also be useful for pain due to bone metastases.

An opioid analgesic (section 4.7.2) such as codeine (p. 235), alone or in combination with a non-opioid analgesic at adequate dosage, may be helpful in the control of moderate pain if non-opioids alone are not sufficient. Alternatively, tramadol (p. 241) can be considered for moderate pain. If these preparations do not control the pain, morphine (p. 238) is the most useful opioid analgesic. Alternatives to morphine, including hydrocodone (p. 238), methadone (p. 238), oxycodone (p. 240), and transdermal fentanyl (see below and p. 236) are best initiated by those with experience in palliative care. Initiation of an opioid analgesic should not be delayed by concern over a theoretical likelihood of psychological dependence (addiction).

Prescribing in palliative care

Equivalent single doses of opioid analgesics

These equivalences are intended only as an approximate guide; patients should be carefully monitored after any change in medication and dose titration may be required.

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine salts (oral)</td>
<td>10 mg</td>
</tr>
<tr>
<td>Diamorphine hydrochloride</td>
<td>3 mg</td>
</tr>
<tr>
<td>Hydrodromorphine hydrochloride</td>
<td>1.3 mg</td>
</tr>
<tr>
<td>Oxycodone (oral)</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Oral route Morphine (p. 238) is given by mouth as an oral solution or as standard (‘immediate release’) tablets every 4 hours, the initial dose depending largely on the patient’s previous treatment. A dose of 5–10 mg is enough to replace a weaker analgesic (such as paracetamol), but 10–20 mg or more is required to replace a strong one (comparable to morphine itself). If the first dose of morphine is no more effective than the previous analgesic, the next dose should be increased by 50%, the aim being to choose the lowest dose that prevents pain. The dose should be adjusted with careful assessment of the pain, and the use of adjuvant analgesics (such as NSAIDs) should also be considered. Although morphine in a dose of 5–20 mg is usually adequate there should be no hesitation in increasing it stepwise according to response to 100 mg or occasionally up to 500 mg or higher if necessary. It may be possible to omit the overnight dose if double the usual dose is given at bedtime.

If pain occurs between regular doses of morphine (‘breakthrough pain’), an additional dose (‘rescue dose’) should be given. An additional dose should also be given 30 minutes before an activity that causes pain (e.g. wound dressing). Fentanyl lozenges are also licensed for breakthrough pain.

When the pain is controlled and the patient’s 24-hour morphine requirement is established, the daily dose can be given as a modified-release preparation in a single dose or in two divided doses.

Preparations suitable for twice-daily administration include Morphgesic® SR tablets (p. 239), MST Continus® tablets or suspension (p. 239), and Zomorph® capsules (p. 239). MXI® capsules (p. 239) allow administration of the total daily morphine requirement as a single dose. The starting dose of modified-release morphine preparations designed for twice daily administration is usually 10–20 mg every 12 hours if no other analgesic (or only paracetamol) has been taken previously, but to replace a weaker opioid analgesic (such as co-codamol) the starting dose is usually 20–30 mg every 12 hours. Increments should be made to the dose, not to the frequency of administration, which should remain at every 12 hours.

The effective dose of modified-release preparations can alternatively be determined by giving the oral solution of morphine every 4 hours in increasing doses until the pain has been controlled, and then transferring the patient to the same total 24-hour dose of morphine given as the modified-release preparation (divided into two portions for 12-hourly administration). The first
Prescribing in palliative care

Dose of the modified-release preparation is given 4 hours after the last dose of the oral solution. Morphine, as oral solution or standard formulation tablets, should be prescribed for breakthrough pain; the dose should be about one-sixth of the total daily dose of oral morphine repeated every 4 hours if necessary (review pain management if analgesic required more frequently).

Oxycodone (p. 240) can be used in patients who require an opioid but cannot tolerate morphine. If the patient is already receiving an opioid, oxycodone should be started at a dose equivalent to the current analgesic (see Equivalent Single Doses of Opioid Analgesics table, p. 15).

Levomepromazine (methotrimeprazine, p. 195) is licensed to treat pain in palliative care, and may be of benefit in some patients. It should be reserved for use in conjunction with strong opioid analgesics in distressed patients with severe pain unresponsive to other measures.

Parenteral route If the patient becomes unable to swallow, the equivalent intramuscular dose of morphine is half the oral solution dose; in the case of the modified-release tablets it is half the total 24-hour dose (which is then divided into 6 portions to be given every 4 hours). Diamorphine is preferred for injection because, being more soluble, it can be given in a smaller volume. The equivalent intramuscular (or subcutaneous) dose is approximately a third of the oral dose of morphine. Subcutaneous infusion of diamorphine via syringe driver can be useful (for details, see p. 17).

If the patient can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous or intramuscular injection in a dose of 200 micrograms every 4 hours. Alternatively glycopyrronium can be given by subcutaneous or intramuscular injection in a dose of 0.2 mg every 4 hours. Must be taken to avoid the discomfort of dry mouth.

Gastro-intestinal pain The pain of bowel colic may be reduced by loperamide 2–4 mg 4 times daily. Hyoscine hydrobromide (section 4.6) may also be helpful, given sublingually at a dose of 300 micrograms 3 times daily as Kwell® tablets. For the dose by subcutaneous infusion using a syringe driver, see p. 18).

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (section 1.1.1) and by domperidone 10 mg 3 times daily before meals.

Muscle spasm The pain of muscle spasm can be helped by a muscle relaxant such as diazepam 5–10 mg daily or baclofen 5–10 mg 3 times daily.

Neuropathic pain Patients with neuropathic pain (section 4.7.3) may benefit from a trial of a tricyclic antidepressant for several weeks. An anticonvulsant may be added or substituted if pain persists; gabapentin and pregabalin (both section 4.8.1) are licensed for neuropathic pain.

Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone 8 mg daily, which reduces oedema around the tumour, thus reducing compression. Nerve blocks can be considered when pain is localised to a specific area. Transcutaneous electrical nerve stimulation (TENS) may also help.

Miscellaneous conditions

Unlicensed indications or routes
Several recommendations in this section involve unlicensed indications or routes.

Raised intracranial pressure Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone 16 mg daily for 4 to 5 days, subsequently reduced to 4–6 mg daily if possible; dexamethasone should be given before 6 p.m. to reduce the risk of insomnia.

Intractable cough Intractable cough may be relieved by moist inhalations or by regular administration of oral morphine in an initial dose of 5 mg every 4 hours. Methadone linctus should be avoided because it has a long duration of action and tends to accumulate.

Dyspnoea Breathlessness at rest may be relieved by regular oral morphine in carefully titrated doses, starting at 5 mg every 4 hours. Diazepam 5–10 mg daily may be helpful for dyspnoea associated with anxiety. A corticosteroid, such as dexamethasone 4–8 mg daily, may also be helpful if there is bronchospasm or partial obstruction.

Excessive respiratory secretion Excessive respiratory secretion (death rattle) may be reduced by subcutaneous injection of hyoscine hydrobromide 400–600 micrograms every 4 to 8 hours; however, care must be taken to avoid the discomfort of dry mouth. Alternatively glycopyrronium can be given by subcutaneous or intramuscular injection in a dose of 200 micrograms every 4 hours. For the dose by subcutaneous infusion using a syringe driver, see p. 18.

Restlessness and confusion Restlessness and confusion may require treatment with haloperidol 1–3 mg by mouth every 8 hours. Levomepromazine (methotrimeprazine) is also used occasionally for restlessness. For the dose by subcutaneous infusion using a syringe driver, see p. 18.

Reference

1. Studies have indicated that administration of the last dose of the oral solution with the first dose of the modified-release tablets is not necessary.
Hiccups Hiccups due to gastric distension may be helped by a preparation incorporating an antacid with an anti-flatulent (section 1.1.1). If this fails, metoclopramide 10 mg every 6 to 8 hours by mouth or by subcutaneous or intramuscular injection can be added; if this also fails, baclofen 5 mg twice daily, or nifedipine 10 mg three times daily, or chlorpromazine 10–25 mg every 6 to 8 hours can be tried.

Anorexia Anorexia may be helped by prednisolone 15–30 mg daily or dexamethasone 2–4 mg daily.

Constipation Constipation is a very common cause of distress and is almost invariably after administration of an opioid. It should be prevented if possible by the regular administration of laxatives; a faecal softener with a peristaltic stimulant (e.g. co-danthramer) or lactulose solution with a senna preparation should be used (section 1.6.2 and section 1.6.3). Methyl-naltrexone (section 1.6.6) is licensed for the treatment of opioid-induced constipation.

Fungating tumours Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole (section 5.11) is often required but topical metronidazole (section 13.10.1.2) is also used.

Capillary bleeding Capillary bleeding can be treated with tranexamic acid (section 2.11) by mouth; treatment is usually discontinued one week after the bleeding has stopped, or, if necessary, it can be continued at a reduced dose. Alternatively, gauze soaked in tranexamic acid 100 mg/mL or adrenaline (epinephrine) solution 1 mg/mL (1 in 1000) can be applied to the affected area.

Dry mouth Dry mouth may be relieved by good mouth care and measures such as the sucking of ice or pine-apple chunks or the use of artificial saliva (section 12.3.5); dry mouth associated with candidiasis can be treated by oral preparations of nystatin or miconazole (section 12.3.2); alternatively, fluconazole can be given by mouth (section 5.2). Dry mouth may be caused by certain medications including opioids, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antileukemic; if possible, an alternative preparation should be considered.

Pruritus Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients (section 13.2.1). In the case of obstructive jaundice, further measures include administration of colchicine (section 1.9.2).

Convulsions Patients with cerebral tumours or uraemia may be susceptible to convulsions. Prophylactic treatment with phenytoin or carbamazepine (section 4.8.1) should be considered. When oral medication is no longer possible, diazepam as suppositories 10–20 mg every 4 to 8 hours, or phenobarbital by injection 50–200 mg twice daily is continued as prophylaxis. For the use of midazolam by a preparation incorporating an antacid with an anti-flatulent (section 1.9.2). If this fails, metoclopramide 10 mg every 6 to 8 hours can be tried.

Dysphagia A corticosteroid such as dexamethasone 8 mg daily may help, temporarily, if there is an obstruction due to tumour. See also under Dry Mouth.

Nausea and vomiting Nausea and vomiting are common in patients with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic (section 4.6) is started. Nausea and vomiting may occur with opioid therapy particularly in the initial stages but can be prevented by giving an antiemetic such as haloperidol or metoclopramide. An antiemetic is usually necessary only for the first 4 or 5 days and therefore combined preparations containing an opioid with an antiemetic are not recommended because they lead to unnecessary antiemetic therapy (and associated side-effects when used long-term). Metoclopramide has a prokinetic action and is used in a dose of 10 mg 3 times daily by mouth for nausea and vomiting associated with gastritis, gastric stasis, and functional bowel obstruction. Drugs with antimuscarinic effects antagonise prokinetic drugs and, if possible, should not be used concurrently.

Haloperidol is used by mouth in an initial dose of 1.5 mg once or twice daily (can be increased if necessary to 5–10 mg daily in divided doses) for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure).

Cyclizine is given in a dose of 50 mg up to 3 times daily by mouth. It is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness.

Antiemetic therapy should be reviewed every 24 hours; it may be necessary to substitute the antiemetic or to add another one.

Levomepromazine (methotrimeprazine) can be used if first-line antiemetics are inadequate; it is given by mouth in a dose of 6–50 mg daily (6-mg tablets available from ‘special-order’ manufacturers or specialist importing companies; see p. 939) in 1–2 divided doses. For the dose by subcutaneous infusion, see p. 18. Dexamethasone 8–16 mg daily by mouth can be used as an adjunct.

For the administration of antiemetics by subcutaneous infusion using a syringe driver, see below.

For the treatment of nausea and vomiting associated with cancer chemotherapy, see section 8.1.

Insomnia Patients with advanced cancer may not sleep because of discomfort, cramps, night sweats, joint stiffness, or fear. There should be appropriate treatment of these problems before hypnotics are used. Benzodiazepines, such as temazepam (section 4.1.1), may be useful.

Hypercalcaemia See section 9.5.1.2.

Syringe drivers

Although drugs can usually be administered by mouth to control the symptoms of advanced cancer, the parenteral route may sometimes be necessary. Repeated administration of intramuscular injections can be difficult in a cachectic patient. This has led to the use of a portable syringe driver to give a continuous subcutaneous infusion, which can provide good control of symptoms with little discomfort or inconvenience to the patient.

Syringe driver rate settings Staff using syringe drivers should be adequately trained and different rate settings should be clearly identified and differentiated; incorrect use of syringe drivers is a common cause of drug errors.
Indications for the parenteral route are:

- the patient is unable to take medicines by mouth owing to nausea and vomiting, dysphagia, severe weakness, or coma;
- there is malignant bowel obstruction in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- occasionally when the patient does not wish to take regular medication by mouth.

Nausea and vomiting

Diamorphine is the preferred opioid of choice for stopped. Midazolam is the benzodiazepine antiepileptic medication should not be
uraemia) antiepileptic medication should not be used in patients for whom further surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube).

Midazolam is a sedative and an antiepileptic that may

Cyclizine is particularly likely to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility, below); it is given in a subcutaneous infusion dose of 150 mg/24 hours.

Metoclopramide can cause skin reactions; it is given in a subcutaneous infusion dose of 30–100 mg/24 hours.

Hyoscine butylbromide is effective in bowel colic, is less sedative than hyoscine hydrobromide, but is not always adequate for the control of respiratory secretions; it is given in a subcutaneous infusion dose of 20–60 mg/24 hours (important: this dose of hyoscine butylbromide must not be confused with the much lower dose of hyoscine hydrobromide, above).

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL, either water for injections or physiological saline (sodium chloride 0.9%) is a suitable diluent—above that strength only water for injections is used to avoid precipitation.

The following can be mixed with diamorphine:

- Cyclizine
- Dexamethasone
- Haloperidol
- Hyoscine butylbromide
- Midazolam

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.

Problems encountered with syringe drivers

The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs too quickly check the rate setting and the calculation;
- if the subcutaneous infusion runs too slowly check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an injection site reaction make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.

- if a patient has previously been receiving an antiepileptic drug or has a primary or secondary cerebral tumour or is at risk of convulsion (e.g. owing to uraemia) antiepileptic medication should not be stopped. Midazolam is the benzodiazepine antiepileptic of choice for continuous subcutaneous infusion, and it is given initially in a dose of 20–40 mg/24 hours.

Pain control

Diamorphine is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility, below). The table on p. 19 shows approximate equivalent doses of morphine and diamorphine.

Mixing and compatibility

The general principle that injections should be given into separate sites (and should not be mixed) does not apply to the use of syringe drivers in palliative care. Provided that there is evidence of compatibility, selected injections can be mixed in syringe drivers. Not all types of medication can be used in a subcutaneous infusion. In particular, chlorpromazine, prochlorperazine, and diazepam are contra-indicated as they cause skin reactions at the injection site; to a lesser extent cyclizine and levomepromazine (methotrimeprazine) also sometimes cause local irritation.

In theory injections dissolved in water for injections are more likely to be associated with pain (possibly owing to their hypotonicity). The use of physiological saline (sodium chloride 0.9%) however increases the likelihood of precipitation when more than one drug is used; moreover subcutaneous infusion rates are so slow (0.1–0.3 mL/hour) that pain is not usually a problem when water is used as a diluent.

Diamorphine can be given by subcutaneous infusion in a strength of up to 250 mg/mL; up to a strength of 40 mg/mL, either water for injections or physiological saline (sodium chloride 0.9%) is a suitable diluent—above that strength only water for injections is used (to avoid precipitation).

Subcutaneous infusion solution should be monitored regularly both to check for precipitation (and discoloration) and to ensure that the infusion is running at the correct rate.

Problems encountered with syringe drivers

The following are problems that may be encountered with syringe drivers and the action that should be taken:

- if the subcutaneous infusion runs too quickly check the rate setting and the calculation;
- if the subcutaneous infusion runs too slowly check the start button, the battery, the syringe driver, the cannula, and make sure that the injection site is not inflamed;
- if there is an injection site reaction make sure that the site does not need to be changed—firmness or swelling at the site of injection is not in itself an indication for change, but pain or obvious inflammation is.

1. Cyclizine may precipitate at concentrations above 10 mg/mL or in the presence of sodium chloride 0.9% or as the concentration of diamorphine relative to cyclizine increases; mixtures of diamorphine and cyclizine are also likely to precipitate after 24 hours.
2. Special care is needed to avoid precipitation of dexamethasone when preparing it.
3. Mixtures of haloperidol and diamorphine are likely to precipitate after 24 hours if haloperidol concentration is above 2 mg/mL.
4. Under some conditions infusions containing metoclopramide become discoloured; such solutions should be discarded.
Prescribing for the elderly

Old people, especially the very old, require special care and consideration from prescribers. Medicines for Older People, a component document of the National Service Framework for Older People, describes how to maximise the benefits of medicines and how to avoid excessive, inappropriate, or inadequate consumption of medicines by older people.

Appropriate prescribing Elderly patients often receive multiple drugs for their multiple diseases. This greatly increases the risk of drug interactions as well as adverse reactions, and may affect compliance (see Taking medicines to best effect under General guidance).

The balance of benefit and harm of some medicines may be altered in the elderly. Therefore, elderly patients’ medicines should be reviewed regularly and medicines which are not of benefit should be stopped.

Non-pharmacological measures may be more appropriate for symptoms such as headache, sleeplessness, and lightheadedness when associated with social stress as in widowhood, loneliness, and family dispersal.

In some cases prophylactic drugs are inappropriate if they are likely to complicate existing treatment or introduce unnecessary side-effects, especially in elderly patients with poor prognosis or with poor overall health. However, elderly patients should not be denied medicines which may help them, such as anticoagulants or antiplatelet drugs for atrial fibrillation, anti-hypertensives, statins, and drugs for osteoporosis.

Form of medicine Frail elderly patients may have difficulty swallowing tablets; if left in the mouth, ulceration may develop. They should always be encouraged to take their tablets or capsules with enough fluid, and whilst in an upright position to avoid the possibility of oesophageal ulceration. It can be helpful to discuss with the patient the possibility of taking the drug as a liquid if available.

Manifestations of ageing In the very old, manifestations of normal ageing may be mistaken for disease and lead to inappropriate prescribing. In addition, age-related muscle weakness and difficulty in maintaining balance should not be confused with neurological disease. Disorders such as lightheadedness not associated with postural or postprandial hypotension are unlikely to be helped by drugs.

Sensitivity The nervous system of elderly patients is more sensitive to many commonly used drugs, such as opioid analgesics, benzodiazepines, antipsychotics, and antiparkinsonian drugs, all of which must be used with caution. Similarly, other organs may also be more susceptible to the effects of drugs such as antihypertensives and NSAIDs.

---

**Equivalent doses of morphine sulphate and diamorphine hydrochloride**

These equivalences are approximate only and should be adjusted according to response.

<table>
<thead>
<tr>
<th>Morphine sulphate oral solution or standard tablets</th>
<th>Morphine sulphate by subcutaneous infusion</th>
<th>Diamorphine hydrochloride by intramuscular injection</th>
<th>Diamorphine hydrochloride by subcutaneous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>every 4 hours</td>
<td>every 24 hours</td>
<td>every 4 hours</td>
<td>every 24 hours</td>
</tr>
<tr>
<td>5 mg</td>
<td>15 mg</td>
<td>1.25–2.5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>10 mg</td>
<td>30 mg</td>
<td>2.5–5 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>15 mg</td>
<td>45 mg</td>
<td>5 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>20 mg</td>
<td>60 mg</td>
<td>7.5 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>30 mg</td>
<td>90 mg</td>
<td>10 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>40 mg</td>
<td>120 mg</td>
<td>12.5 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>60 mg</td>
<td>180 mg</td>
<td>20 mg</td>
<td>120 mg</td>
</tr>
<tr>
<td>80 mg</td>
<td>240 mg</td>
<td>27.5 mg</td>
<td>160 mg</td>
</tr>
<tr>
<td>100 mg</td>
<td>300 mg</td>
<td>35 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>130 mg</td>
<td>390 mg</td>
<td>42.5 mg</td>
<td>260 mg</td>
</tr>
<tr>
<td>160 mg</td>
<td>480 mg</td>
<td>55 mg</td>
<td>320 mg</td>
</tr>
<tr>
<td>200 mg</td>
<td>600 mg</td>
<td>65 mg</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

If breakthrough pain occurs give a subcutaneous (preferable) or intramuscular injection equivalent to one-sixth of the total 24-hour subcutaneous infusion dose. It is kinder to give an intermittent bolus injection subcutaneously—absorption is smoother so that the risk of adverse effects at peak absorption is avoided (an even better method is to use a subcutaneous butterfly needle).

To minimise the risk of infection no individual subcutaneous infusion solution should be used for longer than 24 hours.
Pharmacokinetics
Pharmacokinetic changes can markedly increase the tissue concentration of a drug in the elderly, especially in debilitated patients. The most important effect of age is reduced renal clearance. Many aged patients thus excrete drugs slowly, and are highly susceptible to nephrotoxic drugs. Acute illness can lead to rapid reduction in renal clearance, especially if accompanied by dehydration. Hence, a patient stabilised on a drug with a narrow margin between the therapeutic and the toxic dose (e.g. digoxin) can rapidly develop adverse effects in the aftermath of a myocardial infarction or a respiratory-tract infection. The metabolism of some drugs is reduced in the elderly.

Adverse reactions
Adverse reactions often present in the elderly in a vague and non-specific fashion. Confusion is often the presenting symptom (caused by almost any of the commonly used drugs). Other common manifestations are constipation (with antimuscarinics and many tranquillisers) and postural hypotension (with diuretics and many psychotropics).

Hypnotics Many hypnotics with long half-lives have serious hangover effects, including drowsiness, unsteady gait, slurred speech, and confusion. Hypnotics with short half-lives should be used but they too can present problems (section 4.1.1). Short courses of hypnotics are occasionally useful for helping a patient through an acute illness or some other crisis but every effort must be made to avoid dependence. Benzodiazepines impair balance, which can result in falls.

Diuretics Diuretics are overprescribed in old age and should not be used on a long-term basis to treat simple gravitational oedema which will usually respond to increased movement, raising the legs, and support stockings. A few days of diuretic treatment may speed the clearing of the oedema but it should rarely need continued drug therapy.

NSAIDs Bleeding associated with aspirin and other NSAIDs is more common in the elderly who are more likely to have a fatal or serious outcome. NSAIDs are also a special hazard in patients with cardiac disease or renal impairment which may again place older patients at particular risk.

Owing to the increased susceptibility of the elderly to the side-effects of NSAIDs the following recommendations are made:

- for osteoarthritis, soft-tissue lesions, and back pain, first try measures such as weight reduction (if obese), warmth, exercise, and use of a walking stick;
- for osteoarthritis, soft-tissue lesions, back pain, and pain in rheumatoid arthritis, paracetamol should be used first and can often provide adequate pain relief;
- alternatively, a low-dose NSAID (e.g. ibuprofen up to 1.2 g daily) may be given;
- for pain relief when either drug is inadequate, paracetamol in a full dose plus a low-dose NSAID may be given;
- if necessary, the NSAID dose can be increased or an opioid analgesic given with paracetamol;
- do not give two NSAIDs at the same time.

For advice on prophylaxis of NSAID-induced peptic ulcers if continued NSAID treatment is necessary, see section 1.3.

Other drugs Other drugs which commonly cause adverse reactions are antiparkinsonian drugs, anti-hypertensives, psychotropics, and digoxin. The usual maintenance dose of digoxin in very old patients is 125 micrograms daily (62.5 micrograms in those with renal disease); lower doses are often inadequate but toxicity is common in those given 250 micrograms daily. Drug-induced blood disorders are much more common in the elderly. Therefore drugs with a tendency to cause bone marrow depression (e.g. co-trimoxazole, mianserin) should be avoided unless there is no acceptable alternative.

The elderly generally require a lower maintenance dose of warfarin than younger adults; once again, the outcome of bleeding tends to be more serious.

Guidelines
Always consider whether a drug is indicated at all.

Limit range It is a sensible policy to prescribe from a limited range of drugs and to be thoroughly familiar with their effects in the elderly.

Reduce dose Dosage should generally be substantially lower than for younger patients and it is common to start with about 50% of the adult dose. Some drugs (e.g. long-acting anti-diabetic drugs such as glibenclamide and chlorpropamide) should be avoided altogether.

Review regularly Review repeat prescriptions regularly. In many patients it may be possible to stop some drugs, provided that clinical progress is monitored. It may be necessary to reduce the dose of some drugs as renal function declines.

Simplify regimens Elderly patients benefit from simple treatment regimens. Only drugs with a clear indication should be prescribed and whenever possible given once or twice daily. In particular, regimens which call for a confusing array of dosage intervals should be avoided.

Explain clearly Write full instructions on every prescription (including repeat prescriptions) so that containers can be properly labelled with full directions. Avoid imprecisions like ‘as directed’. Child-resistant containers may be unsuitable.

Repeats and disposal Instruct patients what to do when drugs run out, and also how to dispose of any that are no longer necessary. Try to prescribe matching quantities.

If these guidelines are followed most elderly people will cope adequately with their own medicines. If not then it is essential to enrol the help of a third party, usually a relative or a friend.
Prescribing in dental practice

The following is a list of topics of particular relevance to dental surgeons.

Advice on the drug management of dental and oral conditions has been integrated into the BNF. For ease of access, guidance on such conditions is usually identified by means of a relevant heading (e.g. Dental and Orofacial Pain) in the appropriate sections of the BNF.

General guidance
Prescribing by dental surgeons, p. 4
Oral side-effects of drugs, p. 12
Medical emergencies in dental practice, below
Medical problems in dental practice, p. 23

Drug management of dental and oral conditions
Dental and orofacial pain, p. 229
Neuropathic pain, p. 242
Non-opioid analgesics, p. 229
Opioid analgesics, p. 234
Non-steroidal anti-inflammatory drugs, p. 553

Oral infections
Bacterial infections, p. 284
Phenoxymethylpenicillin, p. 291
Broad-spectrum penicillins (amoxicillin and ampicillin), p. 293
Cephalosporins (cefalexin and cefradine), p. 297
Tetracyclines, p. 303
Macrolides (erythromycin and azithromycin), p. 307
Clindamycin, p. 310
Metronidazole, p. 322
Fusidic acid p. 649
Fungal infections, p. 610
Local treatment, p. 610
Systemic treatment, p. 327

Viral infections
Herpetic gingivostomatitis, local treatment, p. 611
Herpetic gingivostomatitis, systemic treatment, p. 343 and p. 611
Herpes labialis, p. 652

Anaesthetics, anxiolytics and hypnotics
Anaesthesia, sedation, and resuscitation in dental practice, p. 687
Hypnotics, p. 184
Peri-operative anxiolytics, p. 693
Local anaesthesia, p. 703

Oral ulceration and inflammation, p. 608
Mouthwashes, gargles and dentifrices, p. 612
Dry mouth, p. 613

Vitamins and minerals
Fluorides, p. 536
Aromatic inhalations, p. 179
Nasal decongestants, p. 607

Dental Practitioners’ Formulary, p. 917
Changes to Dental Practitioners’ Formulary, p. 918

Medical emergencies in dental practice
This section provides guidelines on the management of the more common medical emergencies which may arise in dental practice. Dental surgeons and their staff should be familiar with standard resuscitation procedures, but in all circumstances it is advisable to summon medical assistance as soon as possible. For an algorithm of the procedure for cardiopulmonary resuscitation, see inside back cover.

The drugs referred to in this section include:
Adrenaline Injection (Epinephrine Injection), adrenaline 1 in 1000, (adrenaline 1 mg/mL as acid tartrate), 1-mL amps
Aspirin Dispersible Tablets 300 mg
Glucagon Injection, glucagon (as hydrochloride), 1-unit vial (with solvent)
Glucose (for administration by mouth)
Glyceryl Trinitrate Spray
Midazolam Buccal Liquid, midazolam 10 mg/mL or Midazolam Injection, midazolam (as hydrochloride) 2 mg/mL, 5-mL amps, or 5 mg/mL, 2-mL amps
Oxygen
Salbutamol Aerosol Inhalation, salbutamol 100 micrograms/metered inhalation

Adrenal insufficiency
Adrenal insufficiency may follow prolonged therapy with corticosteroids and can persist for years after stopping. A patient with adrenal insufficiency may become hypotensive under the stress of a dental visit (important: see also p. 390 for details of corticosteroid cover before dental surgical procedures under general anaesthesia).

Management
• Lay the patient flat
• Give oxygen (see section 3.6)
• Transfer patient urgently to hospital

Anaphylaxis
A severe allergic reaction may follow oral or parenteral administration of a drug. Anaphylactic reactions in dentistry may follow the administration of a drug or contact with substances such as latex in surgical gloves. In general, the more rapid the onset of the reaction the more profound it tends to be. Symptoms may develop within minutes and rapid treatment is essential.

Anaphylactic reactions may also be associated with additives and excipients in foods and medicines (see Excipients, p. 2). Refined arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergenic fats or oils (including those for topical application, particularly if they are intended for use in the mouth or for application to the nasal mucosa).
**Symptoms and signs**
- Paraesthesia, flushing, and swelling of face
- Generalised itching, especially of hands and feet
- Bronchospasm and laryngospasm (with wheezing and difficulty in breathing)
- Rapid weak pulse together with fall in blood pressure and pallor; finally cardiac arrest

**Management**
First-line treatment includes securing the airway, restoration of blood pressure (laying the patient flat and raising the feet, or in the recovery position if unconscious or nauseous and at risk of vomiting), and administration of adrenaline (epinephrine) injection. This is given intramuscularly in a dose of 500 micrograms (0.5 mL adrenaline injection 1 in 1000); a preparation delivering a dose of 300 micrograms (0.3 mL adrenaline injection 1 in 1000) is available for immediate intramuscular injection also increases the risk of local bleeding. Oxygen administration is also of primary importance (see section 3.6). Arrangements should be made to transfer the patient to hospital urgently.

**Asthma**
Patients with asthma may have an attack while at the dental surgery. Most attacks will respond to 2 puffs of the patient’s short-acting beta agonist inhaler such as salbutamol 100 micrograms/puff; further puffs are required if the patient does not respond rapidly. If the patient is unable to use the inhaler effectively, further puffs should be given through a large-volume spacer device (or, if not available, through a plastic or paper cup with a hole in the bottom for the inhaler mouthpiece). If the response remains unsatisfactory, or if further deterioration occurs, then the patient should be transferred urgently to hospital. Whilst awaiting transfer, oxygen (section 3.6) should be given with salbutamol 2.5–5 mg by nebuliser. If a nebuliser is unavailable, then 4–10 puffs of salbutamol 100 micrograms/metered inhalation should be given (preferably by a large-volume spacer), and repeated every 10–20 minutes if necessary. If asthma is part of a more generalised anaphylactic reaction, an intramuscular injection of adrenaline (as detailed under Anaphylaxis above) should be given. For a table describing the management of Acute Asthma, see p. 150

Patients with severe chronic asthma or whose asthma has deteriorated previously during a dental procedure may require an increase in their prophylactic medication before a dental procedure. This should be discussed with the patient’s medical practitioner and may include increasing the dose of inhaled or oral corticosteroid.

**Cardiac emergencies**
If there is a history of angina the patient will probably carry glyceryl trinitrate spray or tablets (or isosorbide dinitrate tablets) and should be allowed to use them. Hospital admission is not necessary if symptoms are mild and resolve rapidly with the patient’s own medication. See also Coronary Artery Disease on p. 24.

**Symptoms and signs of myocardial infarction**
- Progressive onset of severe, crushing pain across front of chest; pain may radiate towards the shoulder and down arm, or into neck and jaw
- Skin becomes pale and clammy
- Nausea and vomiting are common
- Pulse may be weak and blood pressure may fall
- Breathlessness

**Initial management of myocardial infarction**
Call immediately for medical assistance and an ambulance, as appropriate.

Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. Oxygen may be administered (see section 3.6). Sublingual glyceryl trinitrate may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug. Reassure the patient as much as possible to relieve further anxiety. If available, aspirin in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see p. 135.

If the patient collapses and loses consciousness attempt standard resuscitation measures. For an algorithm of the procedure for cardiopulmonary resuscitation, see inside back cover.

**Epileptic seizures**
Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

**Symptoms and signs**
- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while

**Arrhythmias** may lead to a sudden reduction in cardiac output with loss of consciousness. Medical assistance should be summoned. For advice on pacemaker interference, see also Pacemakers, p. 24.

The pain of myocardial infarction is similar to that of angina but generally more severe and more prolonged. For general advice see also Coronary Artery Disease on p. 24

**Initial management of myocardial infarction**
Call immediately for medical assistance and an ambulance, as appropriate.

Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. Oxygen may be administered (see section 3.6).

Sublingual glyceryl trinitrate may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug.

Reassure the patient as much as possible to relieve further anxiety. If available, aspirin in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see p. 135.

If the patient collapses and loses consciousness attempt standard resuscitation measures. For an algorithm of the procedure for cardiopulmonary resuscitation, see inside back cover.

**Epileptic seizures**
Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

**Symptoms and signs**
- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while

**Arrhythmias** may lead to a sudden reduction in cardiac output with loss of consciousness. Medical assistance should be summoned. For advice on pacemaker interference, see also Pacemakers, p. 24.

The pain of myocardial infarction is similar to that of angina but generally more severe and more prolonged. For general advice see also Coronary Artery Disease on p. 24

**Initial management of myocardial infarction**
Call immediately for medical assistance and an ambulance, as appropriate.

Allow the patient to rest in the position that feels most comfortable; in the presence of breathlessness this is likely to be sitting position, whereas the syncopal patient should be laid flat; often an intermediate position (dictated by the patient) will be most appropriate. Oxygen may be administered (see section 3.6).

Sublingual glyceryl trinitrate may relieve pain. Intramuscular injection of drugs should be avoided because absorption may be too slow (particularly when cardiac output is reduced) and pain relief is inadequate. Intramuscular injection also increases the risk of local bleeding into the muscle if the patient is given a thrombolytic drug.

Reassure the patient as much as possible to relieve further anxiety. If available, aspirin in a single dose of 300 mg should be given. A note (to say that aspirin has been given) should be sent with the patient to the hospital. For further details on the initial management of myocardial infarction, see p. 135.

If the patient collapses and loses consciousness attempt standard resuscitation measures. For an algorithm of the procedure for cardiopulmonary resuscitation, see inside back cover.

**Epileptic seizures**
Patients with epilepsy must continue with their normal dosage of anticonvulsant drugs when attending for dental treatment. It is not uncommon for epileptic patients not to volunteer the information that they are epileptic but there should be little difficulty in recognising a tonic-clonic (grand mal) seizure.

**Symptoms and signs**
- There may be a brief warning (but variable)
- Sudden loss of consciousness, the patient becomes rigid, falls, may give a cry, and becomes cyanotic (tonic phase)
- After 30 seconds, there are jerking movements of the limbs; the tongue may be bitten (clonic phase)
- There may be frothing from mouth and urinary incontinence
- The seizure typically lasts a few minutes; the patient may then become flaccid but remain unconscious. After a variable time the patient regains consciousness but may remain confused for a while
Management
During a convulsion try to ensure that the patient is not at risk from injury but make no attempt to put anything in the mouth or between the teeth (in mistaken belief that this will protect the tongue). Give oxygen (section 3.6) to support respiration if necessary.

Do not attempt to restrain convulsive movements.

After convulsive movements have subsided place the patient in the coma (recovery) position and check the airway.

After the convulsion the patient may be confused (‘post-ictal confusion’) and may need reassurance and sympathy. The patient should not be sent home until fully recovered. Seek medical attention or transfer the patient to hospital if it was the first episode of epilepsy, or if the convulsion was atypical, prolonged (or repeated), or if injury occurred.

Medication should only be given if convulsive seizures are prolonged (convulsive movements lasting 5 minutes or longer) or repeated rapidly.

Either midazolam buccal liquid or midazolam injection solution can be given by the buccal route [unlicensed use] in a single dose of 10 mg. For further details on the management of status epilepticus, including details of paediatric doses of midazolam, see p. 263.

Partial seizures similarly need very little active management (in an automatism only a minimum amount of restraint should be applied to prevent injury). Again, the patient should be observed until post-ictal confusion has completely resolved.

Hypoglycaemia
Insulin-treated diabetic patients attending for dental treatment under local anaesthesia should inject insulin and eat meals as normal. If food is omitted the blood glucose will fall to an abnormally low level (hypoglycaemia). Patients can often recognise the symptoms themselves and this state responds to sugar in water (or a cup of sweet tea).

Symptoms and signs
- Shaking and trembling
- Sweating
- ‘Pins and needles’ in lips and tongue
- Hunger
- Palpitation
- Headache (occasionally)
- Double vision
- Difficulty in concentration
- Slurring of speech
- Confusion
- Change of behaviour; truculence
- Convulsions
- Unconsciousness

Management
Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Glucose 10 g is available from 2 teaspoons sugar, 3 sugar lumps, GlucoGel® (formerly known as Hypostop® Gel; glucose 10 g/25 g tube, available from BBI Healthcare), and non-diet versions of Lucozade® Energy Original 55 mL, Coca-Cola® 90 mL, Ribena® Original 15 mL (to be diluted). If necessary this may be repeated in 10–15 minutes.

If glucose cannot be given by mouth, if it is ineffective, or if the hypoglycaemia causes unconsciousness, glucagon 1 mg (1 unit) should be given by intramuscular (or subcutaneous) injection; a child under 8 years or of body-weight under 25 kg should be given 500 micrograms. Once the patient regains consciousness oral glucose should be administered as above. If glucagon is ineffective or contra-indicated, the patient should be transferred urgently to hospital. The patient must also be admitted to hospital if hypoglycaemia is caused by an oral antidiabetic drug.

Syncope
Insufficient blood supply to the brain results in loss of consciousness. The commonest cause is a vasovagal attack or simple faint (syncope) due to emotional stress.

Symptoms and signs
- Patient feels faint
- Low blood pressure
- Pallor and sweating
- Yawning and slow pulse
- Nausea and vomiting
- Dilated pupils
- Muscular twitching

Management
- Lay the patient as flat as is reasonably comfortable and, in the absence of associated breathlessness, raise the legs to improve cerebral circulation
- Loosen any tight clothing around the neck
- Once consciousness is regained, give sugar in water or a cup of sweet tea

Other possible causes
Postural hypotension can be a consequence of rising abruptly or of standing upright for too long; antihypertensive drugs predispose to this. When rising, susceptible patients should take their time. Management is as for a vasovagal attack.

Under stressful circumstances, some patients hyperventilate. This gives rise to feelings of faintness but does not usually result in syncope. In most cases reassurance is all that is necessary; rebreathing from cupped hands or a bag may be helpful but calls for careful supervision.

Adrenal insufficiency or arrhythmias are other possible causes of syncope, see p. 21 and p. 24.

Medical problems in dental practice
Individuals presenting at the dental surgery may also suffer from an unrelated medical condition; this may require modification to the management of their dental condition. If the patient has systemic disease or is taking other medication, the matter may need to be discussed with the patient’s general practitioner or hospital consultant.

For advice on adrenal insufficiency, anaphylaxis, asthma, cardiac emergencies, epileptic seizures, hypoglycaemia and syncope see under Medical Emergencies in Dental Practice.
Allergy
Patients should be asked about any history of allergy; those with a history of atopic allergy (asthma, eczema, hay fever, etc.) are at special risk. Those with a history of a severe allergy or of anaphylactic reactions are at high risk—it is essential to confirm that they are not allergic to any medication, or to any dental materials or equipment (including latex gloves). See also Anaphylaxis on p. 703.

Arrhythmias
Patients, especially those who suffer from heart failure or who have sustained a myocardial infarction, may have irregular cardiac rhythm. Atrial fibrillation is a common arrhythmia even in patients with normal hearts and is of little concern except that dental surgeons should be aware that such patients may be receiving anticoagulant therapy. The patient's medical practitioner should be asked whether any special precautions are necessary. Premedication (e.g. with temazepam) may be useful in some instances for very anxious patients.

See also Cardiac emergencies, p. 22 and Dental Anaesthesia, p. 703.

Cardiac prostheses
For an account of the risk of infective endocarditis in patients with prosthetic heart valves, see Infective Endocarditis, below. For advice on patients receiving anticoagulants, see Thromboembolic disease, below.

Coronary artery disease
Patients are vulnerable for at least 4 weeks following a myocardial infarction or following any sudden increase in the symptoms of angina. It would be advisable to check with the patient's medical practitioner before commencing treatment. See also Cardiac Emergencies on p. 22.

Treatment with low-dose aspirin (75 mg daily), clopidogrel, or dipyridamole should not be stopped routinely nor should the dose be altered before dental procedures.

A Working Party of the British Society for Antimicrobial Chemotherapy has not recommended antibiotic prophylaxis for patients following coronary artery bypass surgery.

Cyanotic heart disease
Patients with cyanotic heart disease are at risk in the dental chair, particularly if they have pulmonary hypertension. In such patients a syncopal reaction increases the shunt away from the lungs, causing more hypoxia which worsens the syncopal reaction—a vicious circle that may prove fatal. The advice of the cardiologist should be sought on any patient with congenital cyanotic heart disease. Treatment in hospital is more appropriate for some patients with this condition.

Hypertension
Patients with hypertension are likely to be receiving antihypertensive drugs such as those described in section 2.5. Their blood pressure may fall dangerously low under general anaesthesia, see also under Dental Anaesthesia on p. 703.

Immunosuppression and indwelling intraperitoneal catheters
See Table 2, section 5.1

Infective endocarditis
While almost any dental procedure can cause bacteraemia, there is no clear association with the development of infective endocarditis. Routine daily activities such as tooth brushing also produce a bacteraemia and may present a greater risk of infective endocarditis than a single dental procedure.

Antibacterial prophylaxis and chlorhexidine mouthwash are not recommended for the prevention of endocarditis in patients undergoing dental procedures. Such prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Reduction of oral bacteraemia
Patients at risk of endocarditis should be advised to maintain the highest possible standards of oral hygiene in order to reduce the:
- need for dental extractions or other surgery;
- chances of severe bacteraemia if dental surgery is needed;
- possibility of ‘spontaneous’ bacteraemia.

Postoperative care
Patients at risk of endocarditis should be warned to report to the doctor or dental surgeon any unexplained illness that develops after dental treatment. Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

Patients on anticoagulant therapy
For general advice on dental surgery in patients receiving oral anticoagulant therapy see Thromboembolic Disease, below.

Joint prostheses
See Table 2, section 5.1

Liver disease
Liver disease may alter the response to drugs and drug prescribing should be kept to a minimum in patients with severe liver disease. Problems are likely mainly in patients with jaundice, ascites, or evidence of encephalopathy.

For a table of drugs to be avoided or used with caution in liver disease see Appendix 2.

Pacemakers
Pacemakers prevent asystole or severe bradycardia. Some ultrasonic scalers, electronic apex locators, electro-analgesic devices, and electrocautery devices interfere with the normal function of pacemakers (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis.

1. Patients at risk of endocarditis include those with valve replacement, acquired valvar heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis.
manufacturer’s literature should be consulted whenever possible. If severe bradycardia occurs in a patient fitted with a pacemaker, electrical equipment should be switched off and the patient placed supine with the legs elevated. If the patient loses consciousness and the pulse remains slow or is absent, cardiopulmonary resuscitation (see inside back cover) may be needed. Call immediately for medical assistance and an ambulance, as appropriate.


**Pregnancy**

Drugs taken during pregnancy can be harmful to the fetus and should be prescribed only if the expected benefit to the mother is thought to be greater than the risk to the fetus; all drugs should be avoided if possible during the first trimester.

Appendix 4 includes information on drug treatment during pregnancy.

**Breast-feeding**

Some drugs taken by the mother whilst breast-feeding can be transferred to the breast milk, and may affect the infant.

Appendix 5 includes information on drug treatment during breast-feeding.

**Renal impairment**

The use of drugs in patients with reduced renal function can give rise to many problems. Many of these problems can be avoided by reducing the dose or by using alternative drugs.

Special care is required in renal transplantation and immunosuppressed patients; if necessary such patients should be referred to specialists.

For a table of drugs to be avoided or used with caution in renal impairment see Appendix 3.

**Thromboembolic disease**

Patients receiving **heparin** or oral anticoagulants such as **warfarin**, **acenocoumarol** (nicoumalone), **phenindione**, **dabigatran etexilate**, or **rivaroxaban** may be liable to excessive bleeding after extraction of teeth or other dental surgery. Often dental surgery can be delayed until the anticoagulant therapy has been completed.

For a patient requiring long-term therapy with warfarin, the patient’s medical practitioner should be consulted and the International Normalised Ratio (INR) should be assessed 72 hours before the dental procedure. This allows sufficient time for dose modification if necessary. In those with an unstable INR (including those who require weekly monitoring of their INR, or those who have had some INR measurements greater than 4.0 in the last 2 months), the INR should be assessed within 24 hours of the dental procedure. Patients requiring minor dental procedures (including extractions) who have an INR below 4.0 may continue warfarin without dose adjustment. There is no need to check the INR for a patient requiring a non-invasive dental procedure.

If possible, a single extraction should be done first; if this goes well further teeth may be extracted at subsequent visits (two or three at a time). Measures should be taken to minimise bleeding during and after the procedure. This includes the use of sutures and a haemostatic such as oxidised cellulose, collagen sponge or resorbable gelatin sponge. Scaling and root planing should initially be restricted to a limited area to assess the potential for bleeding.

For a patient on long-term warfarin, the advice of the clinician responsible for the patient’s anticoagulation should be sought if:
- the INR is unstable, or if the INR is greater than 4.0;
- the patient has thrombocytopenia, haemophilia, or other disorders of haemostasis, or suffers from liver impairment, alcoholism, or renal failure;
- the patient is receiving antiplatelet drugs, cytotoxic drugs or radiotherapy.

Intramuscular injections are **contra-indicated** in patients on anticoagulant therapy, and in those with any disorder of haemostasis.

A local anaesthetic containing a vasoconstrictor should be given by infiltration, or by intraligamentary or mental nerve injection if possible. If regional nerve blocks cannot be avoided the local anaesthetic should be given cautiously using an aspirating syringe.

Drugs which have potentially serious interactions with anticoagulants include aspirin and other NSAIDs, carbamazepine, imidazole and triazole antifungals (including miconazole), erythromycin, clarithromycin, and metronidazole; for details of these and other interactions with anticoagulants, see Appendix 1 (dabigatran etexilate, heparin, phenindione, rivaroxaban, and coumarins).

Although studies have failed to demonstrate an interaction, common experience in anticoagulant clinics is that the INR can be altered following a course of an oral broad-spectrum antibiotic, such as ampicillin or amoxicillin.

Information for dental patients who take anticoagulants is available at www.npsa.nhs.uk/patientsafety/alerts-and-directives/alerts/anticoagulant.
Drugs and sport

UK Sport advises that athletes are personally responsible should a prohibited substance be detected in their body. Information and advice, including the status of specific drugs in sport, can be obtained from UK Sport’s Drug Information Database at www.didglobal.com. An advice card listing examples of permitted and prohibited substances is available from:

Drug-Free Sport
UK Sport
40 Bernard Street
London WC1N 1ST
Tel: 0800 528 0004
drug-free@uksport.gov.uk
www.uksport.gov.uk

A similar card detailing classes of drugs and doping methods prohibited in football is available from the Football Association.

General Medical Council’s advice

Doctors who prescribe or collude in the provision of drugs or treatment with the intention of improperly enhancing an individual’s performance in sport contravene the GMC’s guidance, and such actions would usually raise a question of a doctor’s continued registration. This does not preclude the provision of any care or treatment where the doctor’s intention is to protect or improve the patient’s health.
Emergency treatment of poisoning

These notes provide only an overview of the treatment of poisoning, and it is strongly recommended that either TOXBASE or the UK National Poisons Information Service (see below) be consulted when there is doubt about the degree of risk or about management.

Hospital admission Patients who have features of poisoning should generally be admitted to hospital. Patients who have taken poisons with delayed action should also be admitted, even if they appear well. Delayed-action poisons include aspirin, iron, paracetamol, tricyclic antidepressants, and co-phenotrope (diphenoxylate with atropine, Lomotil®): the effects of modified-release preparations are also delayed. A note of all relevant information, including what treatment has been given, should accompany the patient to hospital.

Further information and advice

TOXBASE, the primary clinical toxicology database of the National Poisons Information Service, is available on the internet to registered users at www.toxbase.org. It provides information about routine diagnosis, treatment, and management of patients exposed to drugs, household products, and industrial and agricultural chemicals.

Specialist information and advice on the treatment of poisoning is available day and night from the UK National Poisons Information Service on the following number:
Tel: 0844 892 0111

Advice on laboratory analytical services can be obtained from TOXBASE or from the National Poisons Information Service.
Help with identifying capsules or tablets may be available from a regional medicines information centre (see inside front cover).

General care

It is often impossible to establish with certainty the identity of the poison and the size of the dose. Fortunately this is not usually important because only a few poisons (such as opioids, paracetamol, and iron) have specific antidotes; few patients require active removal of the poison. In most patients, treatment is directed at managing symptoms as they arise. Nevertheless, knowledge of the type and timing of poisoning can help in anticipating the course of events. All relevant information should be sought from the poisoned individual and from carers or parents. However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses and patients should be assessed carefully. Accidents may involve domestic and industrial products (the contents of which are not generally known). The National Poisons Information Service should be consulted when there is doubt about any aspect of suspected poisoning.

Respiration

Respiration is often impaired in unconscious patients. An obstructed airway requires immediate attention. In the absence of trauma, the airway should be opened with simple measures such as chin lift or jaw thrust. An oropharyngeal or nasopharyngeal airway may be useful in patients with reduced consciousness to prevent obstruction, provided ventilation is adequate. Intubation and ventilation should be considered in patients whose airway cannot be protected or who have respiratory acidosis because of inadequate ventilation; such patients should be monitored in a critical care area. Most poisons that impair consciousness also depress respiration. Assisted ventilation (either mouth-to-mouth or using a bag-valve-mask device) may be needed. Oxygen is not a substitute for adequate ventilation, although it should be given in the highest concentration possible in poisoning with carbon monoxide and irritant gases.

Respiratory stimulants do not help and should be avoided.

Blood pressure

Hypotension is common in severe poisoning with central nervous system depressants. A systolic blood pressure of less than 70 mmHg may lead to irreversible brain damage or renal tubular necrosis. Hypotension should be corrected initially by tilting down the head of the bed and administration of either sodium chloride intravenous infusion or a colloidal infusion. Vasconstrictor sympathomimetics (section 2.7.2) are rarely required and their use may be discussed with the National Poisons Information Service.

Fluid depletion without hypotension is common after prolonged coma and after aspirin poisoning due to vomiting, sweating, and hyperpnoea. Hypertension, often transient, occurs less frequently than hypotension in poisoning: it may be associated with sympathomimetic drugs such as amphetamines, phencyclidine, and cocaine.

Heart

Cardiac conduction defects and arrhythmias can occur in acute poisoning, notably with tricyclic antidepressants, some antipsychotics, and some antihistamines. Arrhythmias often respond to correction of underlying hypoxia, acidosis, or other biochemical abnormalities. Ventricular arrhythmias that cause serious hypotension require treatment. If the QT interval is prolonged, specialist advice should be sought because the use of some anti-arrhythmic drugs may be inappropriate. Supraventricular arrhythmias are seldom life-threatening and drug treatment is best withheld until the patient reaches hospital.
Body temperature

Hyperthermia may develop in patients of any age who have been deeply unconscious for some hours, particularly following overdose with barbiturates or phenothiazines. It may be missed unless core temperature is measured using a low-reading rectal thermometer or by some other means. Hyperthermia is best treated by wrapping the patient (e.g. in a ‘space blanket’) to conserve body heat.

Hyperthermia can develop in patients taking CNS stimulants; children and the elderly are also at risk when taking therapeutic doses of drugs with antimuscarinic properties. Hyperthermia is initially managed by removing all unnecessary clothing and using a fan. Sponging with tepid water will promote evaporation; iced water should not be used. Advice should be sought from the National Poisons Information Service on the management of severe hyperthermia resulting from conditions such as the serotonin syndrome.

Both hyperthermia and hyperthermia require urgent hospitalisation for assessment and supportive treatment.

Convulsions

Single short-lived convulsions do not require treatment. If convulsions are protracted or recur frequently, lorazepam 4 mg or diazepam (preferably as emulsion) 10 mg should be given by slow intravenous injection into a large vein (section 4.8.2). Benzodiazepines should not be given by the intramuscular route for convulsions. If the intravenous route is not readily available, diazepam can be administered as a rectal solution or midazolam (unlicensed use) can be given by the buccal route (section 4.8.2).

Removal and elimination

Prevention of absorption

Given by mouth, activated charcoal can bind many poisons in the gastro-intestinal system, thereby reducing their absorption. The sooner it is given the more effective it is, but it may still be effective up to 1 hour after ingestion of the poison—longer in the case of modified-release preparations or of drugs with antimuscarinic (anticholinergic) properties. It is relatively safe and is particularly useful for the prevention of absorption of poisons that are toxic in small amounts, such as antidepressants.

For the use of charcoal in active elimination techniques, see below.

Active elimination techniques

Repeated doses of activated charcoal by mouth enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with:

- Carbamazepine
- Dapsone
- Phenobarbital

The usual dose of activated charcoal in adults and children over 12 years of age is 50 g initially then 50 g every 4 hours. Vomiting should be treated (e.g. with an antiemetic drug) since it may reduce the efficacy of charcoal treatment. In cases of intolerance, the dose may be reduced and the frequency increased (e.g. 25 g every 2 hours or 12.5 g every hour) but this may compromise efficacy.

In children under 12 years of age, activated charcoal is given in a dose of 1 g/kg (max. 50 g) every 4 hours; the dose may be reduced and the frequency increased if not tolerated.

Other techniques intended to enhance the elimination of poisons after absorption are only practicable in hospital and are only suitable for a small number of severely poisoned patients. Moreover, they only apply to a limited number of poisons. Examples include:

- haemodialysis for salicylates, phenobarbital, methyl alcohol (methanol), ethylene glycol, and lithium;
- alkalisation of the urine for salicylates and phenoxycetate herbicides (e.g. 2,4-dichloro-phenoxycetic acid). Forced diuresis is potentially harmful and no longer recommended.

Removal from the gastro-intestinal tract

Gastric lavage is rarely required; for substances that cannot be removed effectively by other means (e.g. iron), it should be considered only if a life-threatening amount has been ingested within the previous hour. It should be carried out only if the airway can be protected adequately. Gastric lavage is contra-indicated if a corrosive substance or a petroleum distillate has been ingested, but it may occasionally be considered in patients who have ingested drugs that are not adsorbed by charcoal, such as iron or lithium. Induction of emesis (e.g. with ipecacuanha) is not recommended because there is no evidence that it affects absorption and it may increase the risk of aspiration.

Whole bowel irrigation (by means of a bowel cleansing solution) has been used in poisoning with certain modified-release or enteric-coated formulations, in severe poisoning with iron and lithium salts, and if illicit drugs are carried in the gastro-intestinal tract (‘body-packing’). However, it is not clear that the procedure improves outcome and advice should be sought from the National Poisons Information Service.
Acetone is a painkiller and is often used in the treatment of pain. It is known to have serious side effects, including respiratory depression, hypotension, and cardiac arrest. Aspirin is a non-steroidal anti-inflammatory drug (NSAID) that is commonly used to relieve pain, reduce inflammation, and lower fever. It is known to have serious side effects, including gastrointestinal bleeding, ulceration, and perforation. NSAIDs are commonly used to relieve pain, reduce inflammation, and lower fever. They are known to have serious side effects, including gastrointestinal bleeding, ulceration, and perforation.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.

**Analgesics (non-opioid)**

**Aspirin** The chief features of salicylate poisoning are hyperventilation, tinnitus, deafness, vasodilatation, and sweating. Coma is uncommon but indicates very severe poisoning. The associated acid-base disturbances are complex.

Treatment must be in hospital where plasma salicylate, pH, and electrolytes can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement of plasma-salicylate concentration. Plasma-salicylate concentration may not correlate with clinical severity in the young and the elderly, and clinical and biochemical assessment is necessary. Generally, the clinical severity of poisoning is low below a plasma-salicylate concentration of 500 mg/litre (3.6 mmol/litre). Activated charcoal can be given within 1 hour of ingesting more than 125 mg/kg of aspirin. Fluid losses should be replaced and intravenous sodium bicarbonate may be given to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5).

Haemodialysis is the treatment of choice for severe salicylate poisoning and should be considered when the plasma-salicylate concentration exceeds 700 mg/litre (5.1 mmol/litre) or in the presence of severe metabolic acidosis.

**NSAIDs** Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent require treatment, see p. 28.

Overdosage with ibuprofen may cause nausea, vomiting, epigastric pain, and tinnitus, but more serious toxicity is very uncommon. Activated charcoal followed by symptomatic measures are indicated if more than 400 mg/kg has been ingested within the preceding hour.

**Paracetamol** Single or repeated doses totalling as little as 10–15 g (20–30 tablets) or 150 mg/kg of paracetamol taken within 24 hours may cause severe hepato-cellular necrosis and, much less frequently, renal tubular necrosis. Patients at high-risk of liver damage, including those taking enzyme-inducing drugs or who are malnourished (see below), may develop liver toxicity with as little as 75 mg/kg of paracetamol (equivalent to approx. 5 g (10 tablets) in a 70-kg patient) taken within 24 hours. Nausea and vomiting, the only early features of poisoning, usually settle within 24 hours. Persistence beyond this time, often associated with the onset of right subcostal pain and tediumness, usually indicates development of hepatic necrosis. Liver damage is maximal 3–4 days after ingestion and may lead to encephalopathy, haemorrhage, hypoglycaemia, cerebral oedema, and death.

Therefore, despite a lack of significant early symptoms, patients who have taken an overdose of paracetamol should be transferred to hospital urgently. Administration of activated charcoal should be considered if paracetamol in excess of 150 mg/kg or 12 g, whichever is the smaller, is thought to have been ingested within the previous hour.

Acetylcysteine protects the liver if infused within 24 hours of ingesting paracetamol. It is most effective if given within 8 hours of ingestion, after which effectiveness declines sharply; if more than 24 hours have elapsed advice should be sought from the National Poisons Information Service or from a liver unit on the management of serious liver damage. In remote areas, methionine by mouth is an alternative if acetylcysteine cannot be given promptly. Once the patient reaches hospital the need to continue treatment with the antidote will be assessed from the plasma-paracetamol concentration (related to the time from ingestion).

Patients at risk of liver damage and therefore requiring treatment can be identified from a single measurement of the plasma-paracetamol concentration, related to the time from ingestion, provided this time interval is not less than 4 hours; earlier samples may be misleading. The concentration is plotted on a paracetamol treatment graph, with a reference line (‘normal treatment line’) joining plots of 200 mg/litre (1.32 mmol/litre) at 4 hours and 6.25 mg/litre (0.04 mmol/litre) at 24 hours (see p. 30). Those whose plasma-paracetamol concentration is above the normal treatment line are treated with acetylcysteine by intravenous infusion (or, if acetylcysteine is not available, with methionine by mouth, provided the overdose has been taken within 10–12 hours and the patient is not vomiting).

Patients taking enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, and St John’s wort), or who are malnourished (e.g. in anorexia, in alcoholism, or those who are HIV-positive), or following a few days of acute starvation, may develop toxicity at lower plasma-paracetamol concentration and should be treated if the concentration is above the high-risk treatment line (which joins plots that are at 50% of the plasma-paracetamol concentrations of the normal treatment line).

The prognostic accuracy of plasma-paracetamol concentration taken after 15 hours is uncertain, but a concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage. The plasma-paracetamol concentration may be difficult to interpret when paracetamol has been ingested over
several hours. If there is doubt about timing or the need for treatment then the patient should be treated with an antidote.

**ACETYLCYSTEINE**

**Indications** paracetamol overdosage, see notes above  
**Cautions** asthma (see side-effects below but do not delay acetylcysteine treatment)  
**Side-effects** hypersensitivity-like reactions managed by reducing infusion rate or suspending until reaction settled—contact the National Poisons Information Service if reaction severe (rash also managed by giving antihistamine; acute asthma managed by giving nebulised short-acting beta agonist)

**Dose**  
- By intravenous infusion, **ADULT** and **CHILD**, initially 150 mg/kg (max. 16.5 g) over 15 minutes, then 50 mg/kg (max. 5.5 g) over 4 hours then 100 mg/kg (max. 11 g) over 16 hours  
**Administration** Dilute requisite dose in glucose intravenous infusion 5% as follows: **ADULT** and **CHILD** over 12 years, initially 200 mL given over 15 minutes, then 500 mL over 4 hours, then 1 litre over 16 hours; **CHILD** under 12 years, body-weight over 20 kg, initially 100 mL given over 15 minutes, then 250 mL over 4 hours, then 500 mL over 16 hours; **CHILD** body-weight under 20 kg, initially 3 mL/kg given over 15 minutes, then 7 mL/kg over 4 hours, then 14 mL/kg over 16 hours  
**Note** Manufacturer also recommends other infusion fluids, but glucose 5% is preferable

Patients whose plasma-paracetamol concentrations are above the **normal treatment line** should be treated with acetylcysteine by intravenous infusion (or, if acetylcysteine cannot be used, with methionine by mouth, provided the overdose has been taken within 10–12 hours and the patient is not vomiting).

Patients on enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, and St John’s wort) or who are malnourished (e.g. in anorexia, in alcoholism, or those who are HIV-positive) should be treated if their plasma-paracetamol concentration is above the **high-risk treatment line**.

The prognostic accuracy after 15 hours is uncertain but a plasma-paracetamol concentration above the relevant treatment line should be regarded as carrying a serious risk of liver damage.

Graph reproduced courtesy of University of Wales College of Medicine Therapeutics and Toxicology Centre
Emergency treatment of poisoning

**Analgesics (opioid)**

Opioids (narcotic analgesics) cause coma, respiratory depression, and pinpoint pupils. The specific antidote naloxone is indicated if there is coma or bradypnoea. Since naloxone has a shorter duration of action than many opioids, close monitoring and repeated injections are necessary according to the respiratory rate and depth of coma. When repeated administration of naloxone is required, it can be given by continuous intravenous infusion instead and the rate of infusion adjusted according to response (see above) and infused over 1 hour.

**Indications**

overdose with opioids; postoperative respiratory depression (section 15.1.7)

**Cautions**

- physical dependence on opioids
- cardiac failure, cardiac conduction defects, and arrhythmias.

**Dose**

- By intravenous injection, 0.4–2 mg repeated at intervals of 2–3 minutes to a max. of 10 mg if respiratory function does not improve (then question diagnosis); CHILD 10 micrograms/kg; if no response give subsequent dose of 100 micrograms/kg (then question diagnosis), further doses may be required if respiratory function deteriorates
- By subcutaneous or intramuscular injection, ADULT and CHILD dose as for intravenous injection but use only if intravenous route not feasible (onset of action slower)
- By continuous intravenous infusion using an infusion pump, 4 mg diluted in 20 mL intravenous infusion solution [unlicensed concentration] at a rate adjusted according to response (initial rate may be set at 60% of initial intravenous injection dose (see above) and infused over 1 hour). Important Doses used in acute opioid overdose may not be appropriate for the management of opioid-induced respiratory depression and sedation in those receiving palliative care and in chronic opioid use; see also section 15.1.7 for management of postoperative respiratory depression

**Antidepressants**

Tricyclic and related antidepressants Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hyperreflexia, extensor plantar responses, convulsions, respiratory failure, cardiac conduction defects, and arrhythmias. Dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery.

Transfer to hospital is strongly advised in case of poisoning by tricyclic and related antidepressants but symptomatic treatment and activated charcoal can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or intravenous diazepam (preferably in emulsion form) may be required to treat convulsions. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

**Selective serotonin re-uptake inhibitors (SSRIs)**

Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic disturbances.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

**NALOXONE HYDROCHLORIDE**

**Indications**

overdose with opioids; postoperative respiratory depression (section 15.1.7)

**Cautions**

physical dependence on opioids; cardiac irritability; naloxone is short-acting, see notes above

**Dose**

- By intravenous injection, 0.4–2 mg repeated at intervals of 2–3 minutes to a max. of 10 mg if respiratory function does not improve (then question diagnosis); CHILD 10 micrograms/kg; if no response give subsequent dose of 100 micrograms/kg (then question diagnosis), further doses may be required if respiratory function deteriorates
- By subcutaneous or intramuscular injection, ADULT and CHILD dose as for intravenous injection but use only if intravenous route not feasible (onset of action slower)
- By continuous intravenous infusion using an infusion pump, 4 mg diluted in 20 mL intravenous infusion solution [unlicensed concentration] at a rate adjusted according to response (initial rate may be set at 60% of initial intravenous injection dose (see above) and infused over 1 hour).

**METHIONINE**

**Indications**

paracetamol overdose, see notes above

**Cautions**

hepatic impairment (Appendix 2)

**Side-effects**

- nausea, vomiting, drowsiness, irritability
- dilated pupils and urinary retention also occur. Metabolic acidosis may complicate severe poisoning; delirium with confusion, agitation, and visual and auditory hallucinations are common during recovery.

Transfer to hospital is strongly advised in case of poisoning by tricyclic and related antidepressants but symptomatic treatment and activated charcoal can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or intravenous diazepam (preferably in emulsion form) may be required to treat convulsions. Although arrhythmias are worrying, some will respond to correction of hypoxia and acidosis. The use of anti-arrhythmic drugs is best avoided, but intravenous infusion of sodium bicarbonate can arrest arrhythmias or prevent them in those with an extended QRS duration. Diazepam given by mouth is usually adequate to sedate delirious patients but large doses may be required.

**Selective serotonin re-uptake inhibitors (SSRIs)**

Symptoms of poisoning by selective serotonin re-uptake inhibitors include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic disturbances.

1. Restrictions do not apply where administration is for saving life in emergency
Emergency treatment of poisoning

Activated charcoal should be considered if the patient presents within 1 hour of overdose with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved. In patients with significant features of poisoning, calcium chloride or calcium gluconate (section 9.5.1.1) is given by injection; atropine is given to correct symptomatic bradyarrhythmias. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vaso-dilatation or to myocardial depression and advice should be sought from the National Poisons Information Service.

Antimalarials

Overdose with quinine, chloroquine, or hydroxychloroquine is extremely hazardous and difficult to treat. Urgent advice from the National Poisons Information Service is essential. Life-threatening features include arrhythmias (which can have a very rapid onset) and convulsions (which can be intractable).

Beta-blockers

Therapeutic overdosages with beta-blockers may cause lightheadedness, dizziness, and possibly syncope as a result of bradycardia and hypotension; heart failure may be precipitated or exacerbated. These complications are most likely in patients with conduction system disorders or impaired myocardial function. Bradyarrhythmia is the most common arrhythmia caused by beta-blockers, but sotalol may induce ventricular tachyarrhythmias (sometimes of the torsade de pointes type). The effects of massive overdose can vary from one beta-blocker to another; propranolol overdose in particular may cause coma and convulsions.

Acute massive overdose must be managed in hospital and expert advice should be obtained. Maintenance of a clear airway and adequate ventilation is mandatory. An intravenous injection of atropine is required to treat bradycardia and hypotension (3 mg for an adult, 40 micrograms/kg (max. 3 mg) for a child). Cardiogenic shock unresponsive to atropine is probably best treated with an intravenous injection of glucagon 2–10 mg (CHILD 50–150 micrograms/kg) [unlicensed indication (section 9.1.3)] is given by injection; atropine is given to correct symptomatic bradyarrhythmias. If glucagon is not available, intravenous isoprenaline (available from ‘special-order’ manufacturers or specialist importing companies, see p. 28) should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour.

Mortality is reduced by intensive and specific therapy with desferrioxamine, which chelates iron. The serum-iron concentration is measured as an emergency and intravenous desferrioxamine given to chelate absorbed iron in excess of the expected iron binding capacity. In severe toxicity intravenous desferrioxamine should be given immediately without waiting for the result of the serum-iron measurement.

Iron salts

Iron poisoning is commonest in childhood and is usually accidental. The symptoms are nausea, vomiting, abdominal pain, diarrhoea, haematemesis, and rectal bleeding. Hypotension, coma, and hepatocellular necrosis can occur later.

Advice should be sought from the National Poisons Information Service if a significant quantity of iron has been ingested within the previous hour.

Mortality is reduced by intensive and specific therapy with desferrioxamine, which chelates iron. The serum-iron concentration is measured as an emergency and intravenous desferrioxamine given to chelate absorbed iron in excess of the expected iron binding capacity. In severe toxicity intravenous desferrioxamine should be given immediately without waiting for the result of the serum-iron measurement.

Calcium-channel blockers

Features of calcium-channel blocker poisoning include nausea, vomiting, dizziness, agitation, confusion, and coma in severe poisoning. Metabolic acidosis and hyperglycaemia may occur. Verapamil and diltiazem have a profound cardiac depressant effect causing hypotension and arrhythmias, including complete heart block and asystole. The dihydropyridine calcium-channel blockers cause severe hypotension secondary to profound peripheral vasodilatation.
Lithium

Most cases of lithium intoxication occur as a complication of long-term therapy and are caused by reduced excretion of the drug due to a variety of factors including dehydration, deterioration of renal function, infections, and co-administration of diuretics or NSAIDs (or other drugs that interact). Acute deliberate overdoses may also occur with delayed onset of symptoms (12 hours or more) owing to slow entry of lithium into the tissues and continuing absorption from modified-release formulations.

The early clinical features are non-specific and may include apathy and restlessness which could be confused with mental changes arising from the patient’s depressed illness. Vomiting, diarrhoea, ataxia, weakness, dystarthis, muscle twitching, and tremor may follow. Severe poisoning is associated with convulsions, coma, renal failure, electrolyte imbalance, dehydration, and hypotension.

Therapeutic lithium concentrations are within the range of 0.4–1.0 mmol/litre; concentrations in excess of 2.0 mmol/litre are usually associated with serious toxicity and such cases may need treatment with haemodialysis if neurological symptoms or renal failure are present. In acute overdosage much higher serum-lithium concentrations may be present without features of toxicity and all that is usually necessary is to take measures to increase urine output (e.g. by increasing fluid intake but avoiding diuretics). Otherwise, treatment is supportive with special regard to electrolyte balance, renal function, and control of convulsions. The stomach should be emptied by gastric lavage if it can be performed within 1 hour of ingesting significant quantities of lithium. Whole-bowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service, p. 27.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night.

Phenothiazines and related drugs

Phenothiazines cause less depression of consciousness and respiration than other sedatives. Hypotension, hypothermia, sinus tachycardia, and arrhythmias may complicate poisoning. Dystonic reactions can occur with therapeutic doses (particularly with prochlorperazine and trifluoperazine), and convulsions may occur in severe cases. Arrhythmias may respond to correction of hypoxia, acidosis, and other biochemical abnormalities, but specialist advice should be sought if arrhythmias result from a prolonged QT interval; the use of some anti-arrhythmic drugs can worsen such arrhythmias. Dystonic reactions are rapidly abolished by injection of drugs such as procyclidine (section 4.9.2) or diazepam (section 4.8.2, emulsion preferred).

Atypical antipsychotic drugs

Features of poisoning by atypical antipsychotic drugs include drowsiness, convulsions, extrapyramidal symptoms, hypotension, and ECG abnormalities (including prolongation of the QT interval). Management is supportive. Activated charcoal can be given within 1 hour of ingesting a significant quantity of atypical antipsychotic drug.

Stimulants

Amphetamines These cause wakefulness, excessive activity, paranoia, hallucinations, and hypertension followed by exhaustion, convulsions, hyperthermia, and coma. The early stages can be controlled by diazepam or lorazepam; advice should be sought from the National Poisons Information Service (p. 27) on the management of hypertension. Later, tepid sponging, anticonvulsants, and artificial respiration may be needed.

Cocaine Cocaine stimulates the central nervous system, causing agitation, dilated pupils, tachycardia, hypertension, hallucinations, hyperthermia, hypertonia, and hyperreflexia; cardiac effects include chest pain, myocardial infarction, and arrhythmias.

Initial treatment of cocaine poisoning involves intravenous administration of diazepam to control agitation and cooling measures for hyperthermia (see Body temperature, p. 28); hypertension and cardiac effects require specific treatment and expert advice should be sought.

Ecstasy Ecstasy (methylenthiolxymethamphetamine, MDMA) may cause severe reactions, even at doses that were previously tolerated. The most serious effects are delirium, coma, convulsions, ventricular arrhythmias, hyperthermia, rhabdomyolysis, acute renal failure, acute hepatitis, disseminated intravascular coagulation, adult respiratory distress syndrome, myocardial infarction, and arrhythmias. Severe hypokalemia has also been associated with ecstasy use.

Treatment of methylenthiolxymethamphetamine poisoning is supportive, with diazepam to control severe agitation or persistent convulsions and close monitoring including ECG. Self-induced water intoxication should be considered in patients with ecstasy poisoning.

‘Liquid ecstasy’ is a term used for sodium oxybate (gamma-hydroxybutyrate, GHB), which is a sedative.

Theophylline

Theophylline and related drugs are often prescribed as modified-release formulations and toxicity can therefore be delayed. They cause vomiting (which may be severe and intractable), agitation, restlessness, dilated pupils, sinus tachycardia, and hyperglycaemia. More serious effects are haematemesis, convulsions, and supraventricular and ventricular arrhythmias. Severe hypokalaemia may develop rapidly.

Repeated doses of activated charcoal can be used to eliminate theophylline even if more than 1 hour has elapsed after ingestion and especially if a modified-release preparation has been taken (see also under Active Elimination Techniques, p. 28). Ondansetron (section 4.6) may be effective for severe vomiting that is resistant to other antiemetics [unlicensed indication]. Hypokalaemia is corrected by intravenous infusion of potassium chloride and may be so severe as to require 60 mmol/hour (high doses require ECG monitoring). Convulsions should be controlled by intravenous administration of lorazepam or diazepam (emulsion pre-
Emergency treatment of poisoning

Indications

Poisoning with cyanides (used in conjunction with sodium thiosulphate)

Side-effects

flushing and headache due to vasodilatation

Dose

- By intravenous injection over 5–20 minutes (as sodium nitrite injection 30 mg/mL), 300 mg; CHILD 4–10 mg/kg (max. 300 mg)

1 Sodium Nitrite (RM)

Injection, sodium nitrite 3% (30 mg/mL) in water for injections

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 939

Other poisons

Consult either the National Poisons Information Service day and night or TOXBASE, see p. 27.

The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night

Cyanides

Oxygen should be administered to patients with cyanide poisoning. The choice of antidote depends on the severity of poisoning, certainty of diagnosis, and the cause. Dicobalt edetate is the antidote of choice when there is a high clinical suspicion of severe cyanide poisoning. Dicobalt edetate itself is toxic, associated with anaphylactic reactions, and is potentially fatal if administered in the absence of cyanide poisoning. A regimen of sodium nitrite followed by sodium thiosulphate is an alternative if dicobalt edetate is not available.

Hydroxocobalamin can be considered for victims of smoke inhalation who show signs of significant cyanide poisoning. The usual dose is 5 g (70 mg/kg in children) by intravenous infusion (given once or twice according to severity). Cyanokit® provides hydroxocobalamin 2.5 g/bottle—contact the National Poisons Information Service for advice.

Dicobalt edetate

Indications

severe poisoning with cyanides

Cautions

owing to toxicity to be used only for definite cyanide poisoning when patient tending to lose, or has lost, consciousness; not to be used as a precautionary measure

Side-effects

hypotension, tachycardia, and vomiting; anaphylactic reactions including facial and laryngeal oedema and cardiac abnormalities

Dose

- By intravenous injection, ADULT 300 mg over 1 minute (5 minutes if condition less serious) followed immediately by 50 mL of glucose intravenous infusion 50%; if response inadequate a second dose of both may be given, but risk of cobalt toxicity; CHILD consult the National Poisons Information Service

1 Dicobalt Edetate (Cambridge) (RM)

Injection, dicobalt edetate 15 mg/mL, net price 20 mL (300 mg) amp = £13.75

Sodium nitrite

Indications

poisoning with cyanides (used in conjunction with sodium thiosulphate)

1. RM restriction does not apply where administration is for saving life in emergency

Ethylene glycol and methanol

Ethanol (by mouth or by intravenous infusion) is used for the treatment of ethylene glycol or methanol (methyl alcohol) poisoning. Fomepizole (available from ‘special-order’ manufacturers or specialist importing companies, see p. 939) has also been used for the treatment of ethylene glycol or methanol poisoning. Advice on the treatment of ethylene glycol or methanol poisoning should be obtained from the National Poisons Information Service.

Heavy metals

Heavy metal antidotes include dimercaprol and sodium calcium edetate. Other antidotes include succimer (DMSA) and unithiol (DMPS) [both unlicensed]; they may be useful in certain cases of heavy metal poisoning but the advice of the National Poisons Information Service should be sought.

Dimercaprol

Indications

poisoning by antimony, arsenic, bismuth, gold, mercury

Cautions

hypertension, renal impairment (discontinue or use with extreme caution if impairment develops during treatment), elderly, pregnancy and breastfeeding; interactions: Appendix 1 (dimercaprol)

Contra-indications

not indicated for iron, cadmium, or selenium poisoning; severe hepatic impairment (unless due to arsenic poisoning)

Side-effects

hypertension, tachycardia, malaise, nausea, vomiting, salivation, laceration, sweating, burning sensation (mouth, throat, and eyes), feeling of constriction of throat and chest, headache, muscle
spasm, abdominal pain, tingling of extremities; pyrexia in children; local pain and abscess at injection site

**Dose**

- **By intramuscular injection, ADULT** and **CHILD** 2.5–3 mg/kg every 4 hours for 2 days, 2–4 times on the third day, then 1–2 times daily for 10 days or until recovery

**Dimercaprol** (Sovereign) (PHN)

**Injection**, dimercaprol 50 mg/mL. Net price 2-mL amp = £42.73

**Note** Contains arachis (peanut) oil as solvent

---

**SODIUM CALCIUM EDETATE**

(Sodium Calciumedetate)

**Indications** lead poisoning

**Cautions** renal impairment

**Side-effects** nausea, diarrhoea, abdominal pain, pain at site of injection, thrombophlebitis if given too rapidly, renal damage particularly in overdosage; hypotension, lacerimation, myalgia, nasal congestion, sneezing, malaise, thirst, fever, chills, headache also reported

**Dose**

- **By intravenous infusion, ADULT** and **CHILD** 40 mg/kg twice daily for up to 5 days; if necessary, a second course can be given at least 7 days after the first course, a third course can be given at least 7 days after the second course

**Ledclair** (Durbin) (PHN)

**Injection**, sodium calcium edetate 200 mg/mL, net price 5-mL amp = £7.29

---

**Noxious gases**

**Carbon monoxide** Carbon monoxide poisoning is usually due to inhalation of smoke, car exhaust, or fumes caused by blocked flues or incomplete combustion of fuel gases in confined spaces.

Immediate treatment of carbon monoxide poisoning is essential. The person should be moved to fresh air, the airway cleared, and oxygen 100% administered through a tight-fitting mask with an inflated face seal. Artificial respiration should be given as necessary and continued until adequate spontaneous breathing starts, or stopped only after persistent and efficient treatment of cardiac arrest has failed. The patient should be admitted to hospital because complications may arise after a delay of hours or days. Cerebral oedema should be anticipated in severe poisoning and is treated with an intravenous infusion of mannitol (section 2.2.5). Referral for hyperbaric oxygen treatment should be discussed with the National Poisons Information Service if the victim is or has been unconscious, or has psychiatric or neurological features other than a headache, or has myocardial ischaemia or an arrhythmia, or has a blood carboxyhaemoglobin concentration of more than 20%, or is pregnant.

**Sulphur dioxide, chlorine, phosgene, ammonia**

All of these gases can cause upper respiratory tract and conjunctival irritation. Pulmonary oedema, with severe breathlessness and cyanosis may develop suddenly up to 36 hours after exposure. Death may occur. Patients are kept under observation and those who develop pulmonary oedema are given oxygen. Assisted ventilation may be necessary in the most serious cases.

---

**CS Spray**

CS spray, which is used for riot control, irritates the eyes (hence ‘tear gas’) and the respiratory tract; symptoms normally settle spontaneously within 15 minutes. If symptoms persist, the patient should be removed to a well-ventilated area, and the exposed skin washed with soap and water after removal of contaminated clothing. Contact lenses should be removed and rigid ones washed (soft ones should be discarded). Eye symptoms should be treated by irrigating the eyes with physiological saline (or water if saline is not available) and advice sought from an ophthalmologist. Patients with features of severe poisoning, particularly respiratory complications, should be admitted to hospital for symptomatic treatment.

---

**Nerve agents**

Treatment of nerve agent poisoning is similar to organophosphorus insecticide poisoning (see below), but advice must be sought from the National Poisons Information Service. The risk of cross-contamination is significant; adequate decontamination and protective clothing for healthcare personnel are essential. In emergencies involving the release of nerve agents, kits (‘NAAS pods’) containing pralidoxime can be obtained through the Ambulance Service from the National Blood Service (or the Welsh Blood Service in South Wales or designated hospital pharmacies in Northern Ireland and Scotland—see TOXBASE for list of designated centres).

---

**Pesticides**

**Organophosphorus insecticides** Organophosphorus insecticides are usually supplied as powders or dissolved in organic solvents. All are absorbed through the bronchi and intact skin as well as through the gut and inhibit cholinesterase activity, thereby prolonging and intensifying the effects of acetylcholine. Toxicity between different compounds varies considerably, and onset may be delayed after skin exposure.

Anxiety, restlessness, dizziness, headache, miosis, nausea, hypersalivation, vomiting, abdominal colic, diarrhoea, bradycardia, and sweating are common features of organophosphorus poisoning. Muscle weakness and fasciculation may develop and progress to generalised flaccid paralysis, including the ocular and respiratory muscles. Convulsions, coma, pulmonary oedema with copious bronchial secretions, hypopxia, and arrhythmias occur in severe cases. Hyperglycaemia and glycosuria without ketonuria may also be present.

Further absorption of the organophosphorus insecticide should be prevented by moving the patient to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear
Emergency treatment of poisoning

Emergency treatment of poisoning

Airway, frequent removal of bronchial secretions, and adequate ventilation and oxygenation; gastric lavage may be considered provided that the airway is protected. **Atropine** will reverse the muscarinic effects of acetylcholine and is given in a dose of 2 mg (20 micrograms/kg (max. 2 mg) in a child) as atropine sulphate (intramuscularly or intravenously according to the severity of poisoning) every 5 to 10 minutes until the skin becomes flushed and dry, the pupils dilate, and tachycardia develops.

**Pralidoxime chloride**, a cholinesterase reactivator, is used as an adjunct to atropine in moderate or severe poisoning. It improves muscle tone within 30 minutes of administration. Pralidoxime chloride is continued until the patient has not required atropine for 12 hours. Pralidoxime chloride can be obtained from designated centres, the names of which are held by the National Poisons Information Service (see p. 27).

### Pralidoxime Chloride

**Indications** adjacent to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent

**Cautions** renal impairment, myasthenia gravis

**Contra-indications** poisoning with carbamates or with organophosphorus compounds without anti-cholinesterase activity

**Side-effects** drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness

**Dose**

- By intravenous infusion, **ADULT** and **CHILD** initially 30 mg/kg over 20 minutes, followed by 8 mg/kg/hour; usual max. 12 g in 24 hours

**Note** The loading dose may be administered by intravenous injection (diluted to a concentration of 50 mg/mL with water for injections) over at least 5 minutes if pulmonary oedema is present or if it is not practical to administer an intravenous infusion; pralidoxime chloride doses in BNF may differ from those in product literature

1. **Pralidoxime chloride**

   **Injection**, powder for reconstitution, pralidoxime chloride 1 g/vial

   Available as Prostigmin (from designated centres for organophosphorus insecticide poisoning or from the National Blood Service and the Welsh Blood Service for nerve agent poisoning—see TOXBASE for list of designated centres)

   **Note** restriction does not apply where administration is for saving life in emergency

Early anaphylactoid symptoms should be treated with **adrenaline** (epinephrine) (section 3.4.3). Indications for antivenom treatment include systemic envenoming, especially hypotension (see above), ECG abnormalities, vomiting, haemostatic abnormalities, and marked local envenoming such that after bites on the hand or foot, swelling extends beyond the wrist or ankle within 4 hours of the bite. For both adults and children, the contents of one vial (10 mL) of **European viper venom antiserum** (available from Movianto) is given by intravenous injection over 10–15 minutes or by intravenous infusion over 30 minutes after diluting in sodium chloride intravenous infusion 0.9% (use 5 mL diluent/kg bodyweight). The dose can be repeated in 1–2 hours if symptoms of systemic envenoming persist. Adrenaline (epinephrine) injection must be immediately to hand for treatment of anaphylactoid reactions to the antivenom (for the management of anaphylaxis, see section 3.4.3). Antivenom is available for bites by certain foreign snakes and spiders, stings by scorpions and fish. For information on identification, management, and for supply in an emergency, telephone:

- Liverpool (School of Tropical Medicine) (0151) 708 9393
- Liverpool (Royal Liverpool University Hospital) (emergency supply only) (0151) 706 2096
- London (emergency supply only) (020) 7771 5394

### Insect stings

Stings from ants, wasps, hornets, and bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time. If the sting is in the mouth or on the tongue local swelling may threaten the upper airway. The stings from these insects are usually treated by cleaning the area with a topical antiseptic. Bee stings should be removed as quickly as possible. Anaphylactic reactions require immediate treatment with intramuscular adrenaline (epinephrine): self-administered intramuscular adrenaline (e.g. EpiPen®) is the best first-aid treatment for patients with severe hypersensitivity. An inhaled bronchodilator should be used for asthmatic reactions. For the management of anaphylaxis, see section 3.4.3. A short course of an oral antihistamine or a topical corticosteroid may help to reduce inflammation and relieve itching. A vaccine containing extracts of bee and wasp venom can be used to reduce the risk of anaphylaxis and systemic reactions in patients with systemic hypersensitivity to bee or wasp stings (section 3.4.2).

### Marine stings

The severe pain of weeverfish (**Trachinus draco**) and Portuguese man-o’-war stings can be relieved by immersing the stung area immediately in uncomfortably hot, but not scalding, water (not more than 45°C). People stung by jellyfish and Portuguese man-o’-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater. Alcoholic solutions, including suntan lotions, should not be applied because they can cause further discharge of stinging hairs. Ice packs will reduce pain and a slurry of baking soda (sodium bicarbonate), but not vinegar, may be useful for treating stings from UK species.

### Snake bites and animal stings

**Snake bites** Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (*Vipera berus*). The bite may cause local and systemic effects. Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Systemic effects include early anaphylactoid symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhoea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure. Fatal envenoming is rare but the potential for severe envenoming must not be underestimated.

**Marine stings** The severe pain of weeverfish (*Trachinus draco*) and Portuguese man-o’-war stings can be relieved by immersing the stung area immediately in uncomfortably hot, but not scalding, water (not more than 45°C). People stung by jellyfish and Portuguese man-o’-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater. Alcoholic solutions, including suntan lotions, should not be applied because they can cause further discharge of stinging hairs. Ice packs will reduce pain and a slurry of baking soda (sodium bicarbonate), but not vinegar, may be useful for treating stings from UK species.

**Snakes**

- Bees cause local pain and swelling but seldom cause severe direct toxicity unless many stings are inflicted at the same time. If the sting is in the mouth or on the tongue local swelling may threaten the upper airway. The stings from these insects are usually treated by cleaning the area with a topical antiseptic. Bee stings should be removed as quickly as possible. Anaphylactic reactions require immediate treatment with intramuscular adrenaline (epinephrine): self-administered intramuscular adrenaline (e.g. EpiPen®) is the best first-aid treatment for patients with severe hypersensitivity. An inhaled bronchodilator should be used for asthmatic reactions. For the management of anaphylaxis, see section 3.4.3. A short course of an oral antihistamine or a topical corticosteroid may help to reduce inflammation and relieve itching. A vaccine containing extracts of bee and wasp venom can be used to reduce the risk of anaphylaxis and systemic reactions in patients with systemic hypersensitivity to bee or wasp stings (section 3.4.2).

**Marine stings** The severe pain of weeverfish (*Trachinus draco*) and Portuguese man-o’-war stings can be relieved by immersing the stung area immediately in uncomfortably hot, but not scalding, water (not more than 45°C). People stung by jellyfish and Portuguese man-o’-war around the UK coast should be removed from the sea as soon as possible. Adherent tentacles should be lifted off carefully (wearing gloves or using tweezers) or washed off with seawater. Alcoholic solutions, including suntan lotions, should not be applied because they can cause further discharge of stinging hairs. Ice packs will reduce pain and a slurry of baking soda (sodium bicarbonate), but not vinegar, may be useful for treating stings from UK species.

**Snake bites** Envenoming from snake bite is uncommon in the UK. Many exotic snakes are kept, some illegally, but the only indigenous venomous snake is the adder (*Vipera berus*). The bite may cause local and systemic effects. Local effects include pain, swelling, bruising, and tender enlargement of regional lymph nodes. Systemic effects include early anaphylactoid symptoms (transient hypotension with syncope, angioedema, urticaria, abdominal colic, diarrhoea, and vomiting), with later persistent or recurrent hypotension, ECG abnormalities, spontaneous systemic bleeding, coagulopathy, adult respiratory distress syndrome, and acute renal failure. Fatal envenoming is rare but the potential for severe envenoming must not be underestimated.
Dyspepsia and gastro-oesophageal reflux disease

1.1 Antacids and simeticone

1.2 Compound alginates and proprietary indigestion preparations

1.3 Antispasmodics and other drugs altering gut motility

1.4 Acute diarrhoea

1.5 Chronic bowel disorders

1.6 Laxatives

1.7 Local preparations for anal and rectal disorders

1.8 Stoma care

1.9 Drugs affecting intestinal secretions

1.9.2 Bile acid sequestrants

1.9.3 Aprotinin

1.9.4 Pancreatin

Dyspepsia

Dyspepsia covers pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration (section 1.3) and gastric cancer but most commonly it is of uncertain origin.

Urgent endoscopic investigation is required if dyspepsia is accompanied by ‘alarm features’ (e.g. bleeding, dysphagia, recurrent vomiting, or weight loss). Urgent investigation should also be considered for patients over 55 years with unexplained dyspepsia that has not responded to treatment.

Patients with dyspepsia should be advised about lifestyle changes (see Gastro-oesophageal reflux disease, below). Some medications may cause dyspepsia—these should be stopped, if possible. Antacids may provide some symptomatic relief.

If symptoms persist in uninvestigated dyspepsia, treatment involves a proton pump inhibitor (section 1.3) for 4 weeks. A proton pump inhibitor can be used intermittently to control symptoms long-term. Patients with uninvestigated dyspepsia, who do not respond to an initial trial with a proton pump inhibitor, should be tested for Helicobacter pylori and given eradication therapy (section 1.3) if H. pylori is present. Alternatively, particularly in populations where H. pylori infection is more likely, the ‘test and treat’ strategy for H. pylori can be used before a trial with a proton pump inhibitor.
If *H. pylori* is present in patients with functional (investigated, non-ulcer) dyspepsia, eradication therapy should be provided. However, most patients with functional dyspepsia do not benefit symptomatically from *H. pylori* eradication. If symptoms persist, treatment with either a proton pump inhibitor (section 1.3.5) or a histamine H*-receptor antagonist* (section 1.3.1) can be given for 4 weeks. These antisecretory drugs can be used intermittently to control symptoms long-term.

### Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (including non-erosive gastro-oesophageal reflux and erosive oesophagitis) is associated with heartburn, acid regurgitation, and sometimes, difficulty in swallowing (dysphagia); oesophageal inflammation (oesophagitis), ulceration, and stricture formation may occur and there is an association with asthma.

The management of gastro-oesophageal reflux disease includes drug treatment, lifestyle changes and, in some cases, surgery. Initial treatment is guided by the severity of symptoms and treatment is then adjusted according to response. The extent of healing depends on the severity of the disease, the treatment chosen, and the duration of therapy.

Patients with gastro-oesophageal reflux disease should be advised about lifestyle changes (avoidance of excess alcohol and of aggravating foods such as fats); other measures include weight reduction, smoking cessation, and raising the head of the bed.

For mild symptoms of gastro-oesophageal reflux disease, initial management may include the use of antacids and alginites. Alginate-containing antacids can form a ‘raft’ that floats on the surface of the stomach contents to reduce reflux and protect the oesophageal mucosa.

**Histamine H*-receptor antagonists** (section 1.3.1) may relieve symptoms and permit reduction in antacid consumption. However, proton pump inhibitors (section 1.3.5) provide more effective relief of symptoms than H*-receptor antagonists. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by giving treatment intermittently).

For severe symptoms of gastro-oesophageal reflux disease or for patients with a proven or severe pathology (e.g. oesophagitis, oesophageal ulceration, oesophagopharyngeal reflux, Barrett’s oesophagus), initial management involves the use of a proton pump inhibitor (section 1.3.5); patients need to be reassessed if symptoms persist despite treatment for 4–6 weeks with a proton pump inhibitor. When symptoms abate, treatment is titrated down to a level which maintains remission (e.g. by reducing the dose of the proton pump inhibitor or by giving it intermittently, or by substituting treatment with a histamine H*-receptor antagonist). However, for endoscopically confirmed erosive, ulcerative, or strictureting disease, as Barrett’s oesophagus, treatment with a proton pump inhibitor usually needs to be maintained at the minimum effective dose.

A prokinetic drug such as metoclopramide (section 4.6) may improve gastro-oesophageal sphincter function and accelerate gastric emptying.

**Children** Gastro-oesophageal reflux disease is common in infancy but most symptoms resolve without treatment between 12 and 18 months of age. In infants, mild or moderate reflux without complications can be managed initially by changing the frequency and volume of feed; a feed thickener or thickened formula feed can be used (with advice of a dietitian—see Appendix 7 for suitable products). If necessary, a suitable alginate-containing preparation can be used instead of thickened feeds. For older children, life-style changes similar to those for adults (see above) may be helpful followed if necessary by treatment with an alginate-containing preparation.

Children who do not respond to these measures or who have problems such as respiratory disorders or suspected oesophagitis need to be referred to hospital; an H*-receptor antagonist (section 1.3.1) may be needed to reduce acid secretion. If the oesophagitis is resistant to H*-receptor blockade, the proton pump inhibitor omeprazole (section 1.3.5) can be tried.

### 1.1.1 Antacids and simeticone

Antacids (usually containing aluminium or magnesium compounds) can often relieve symptoms in ulcer dyspepsia and in non-erosive gastro-oesophageal reflux (see also section 1.1); they are also sometimes used in functional (non-ulcer) dyspepsia but the evidence of benefit is uncertain. Antacids are best given when symptoms occur or are expected, usually between meals and at bedtime, 4 or more times daily; additional doses may be required up to once an hour. Conventional doses e.g. 10 mL 3 or 4 times daily of liquid magnesium–aluminium antacids promote ulcer healing, but less well than antisecretory drugs (section 1.3); proof of a relationship between healing and neutralising capacity is lacking. Liquid preparations are more effective than tablet preparations.

**Aluminium- and magnesium-containing** antacids (e.g. aluminium hydroxide, and magnesium carbonate, hydroxide and trisilicate), being relatively insoluble in water, are long-acting if retained in the stomach. They are suitable for most antacid purposes. Magnesium-containing antacids tend to be laxative whereas aluminium-containing antacids may be constipating; antacids containing both magnesium and aluminium may reduce these colonic side-effects. Aluminium accumulation does not appear to be a risk if renal function is normal (see also Appendix 3). The acid-neutralising capacity of preparations that contain more than one antacid may be the same as simpler preparations. Complexes such as hydrotalcite confer no special advantage.

**Sodium bicarbonate** should no longer be prescribed alone for the relief of dyspepsia but it is present as an ingredient in many indigestion remedies. However, it retains a place in the management of urinary-tract disorders (section 7.4.3) and acidosis (section 9.2.1.3 and section 9.2.2). Sodium bicarbonate should be avoided in patients on salt-restricted diets.

**Bismuth-containing** antacids (unless chelates) are not recommended because absorbed bismuth can be neurotoxic, causing encephalopathy; they tend to be constipating. **Calcium-containing** antacids (section 1.1.2) can induce rebound acid secretion; with modest doses the clinical significance is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis, and can precipitate the milk-alkali syndrome.
Simeticone (activated dimeticone) is added to an antacid as an antifoaming agent to relieve flatulence. These preparations may be useful for the relief of hiccup in palliative care. Alginates, added as protectants, may be useful in gastro-oesophageal reflux disease (section 1.1 and section 1.1.2). The amount of additional ingredient or antacid in individual preparations varies widely, as does their sodium content, so that preparations may not be freely interchangeable.

See also section 1.3 for drugs used in the treatment of peptic ulceration.

**Interactions** Antacids should preferably not be taken at the same time as other drugs since they may impair absorption. Antacids may also damage enteric coatings at the same time as other drugs since they may impair absorption. Antacids may also damage enteric coatings at the same time as other drugs since they may impair absorption.

**Aluminium- and magnesium-containing antacids**

### Aluminium Hydroxide

**Indications** dyspepsia; hyperphosphataemia (section 9.5.2.2)

**Cautions** see notes above; renal impairment (Appendix 3); interactions: Appendix 1 (antacids)

**Contra-indications** hypophosphataemia

**Side-effects** diarrhoea; belching due to liberated carbon dioxide

#### Aluminium-only preparations

**Aluminium Hydroxide** (Non-proprietary)

- **Tablets**, dried aluminium hydroxide 500 mg. Net price $20 = $28p
- **Dose** 1–2 tablets chewed 4 times daily and at bedtime or as required

Altacite

#### Alu-Cap

- **Capsules**, green/red, dried aluminium hydroxide 475 mg (low Na⁺). Net price £2.75
- **Dose** 1 capsule 4 times daily and at bedtime; **CHILD** not recommended for antacid therapy

**Co-magaldrox**

Co-magaldrox is a mixture of aluminium hydroxide and magnesium hydroxide; the proportions are expressed in the form x/y where x and y are the strengths in milligrams per unit dose of magnesium hydroxide and aluminium hydroxide respectively.

- **Maalox®** (Sanofi-Aventis)
  - **Suspension**, sugar-free, co-magaldrox 195/220 (magnesium hydroxide 195 mg, dried aluminium hydroxide 220 mg/5 mL (low Na⁺)). Net price 500 mL = £2.79
  - **Dose** **ADULT** and **CHILD** over 14 years, 10–20 mL 20–60 minutes after meals, and at bedtime or when required

- **Mucogel®** (Chemidex)
  - **Suspension**, sugar-free, co-magaldrox 195/220 (magnesium hydroxide 195 mg, dried aluminium hydroxide 220 mg/5 mL (low Na⁺)). Net price 500 mL = £1.71
  - **Dose** **ADULT** and **CHILD** over 12 years, 10–20 mL 3 times daily, 20–60 minutes after meals, and at bedtime or when required

**Magnesium Carbonate**

**Indications** dyspepsia

**Cautions** renal impairment (Appendix 3); see also notes above; interactions: Appendix 1 (antacids)

**Contra-indications** hypophosphataemia

**Side-effects** diarrhoea; belching due to liberated carbon dioxide

### Magnesium Trisilicate

**Indications** dyspepsia

**Cautions** see under Magnesium Carbonate

**Contra-indications** see under Magnesium Carbonate

**Side-effects** diarrhoea; belching due to liberated carbon dioxide; silica-based renal stones reported on long-term treatment

**Magnesium Trisilicate Tablets, Compound, BP**

#### Tablets, magnesium trisilicate 250 mg, dried aluminium hydroxide 120 mg

- **Dose** 1–2 tablets chewed when required

**Magnesium Trisilicate Mixture, BP**

#### (Magnesium Trisilicate Oral Suspension)

**Indications** dyspepsia

**Cautions** see under Magnesium Carbonate

**Contra-indications** see under Magnesium Carbonate

**Side-effects** diarrhoea; belching due to liberated carbon dioxide; silica-based renal stones reported on long-term treatment

**Magnesium Trisilicate Mixture Tablets, Compound, BP**

- **Dose** 10–20 mL in water 3 times daily or as required; **CHILD** 5–12 years, 5–10 mL in water 3 times daily or as required

For preparations also containing aluminium, see above and section 1.1.2.

**Aluminium-magnesium complexes**

### Hydropticarbonate

**Indications** dyspepsia

**Cautions** see notes above; interactions: Appendix 1 (antacids)

**Side-effects** see notes above

**Hydrotalcite**

**Indications** dyspepsia

**Cautions** see notes above; interactions: Appendix 1 (antacids)

**Side-effects** see notes above

**Hydrotalcite Suspension**, hydrotalcite 500 mg/5 mL (low Na⁺). Net price 500-mL pack = £1.96

- **Dose** **ADULT** and **CHILD** over 12 years, 10–20 mL 3 times daily, 20–60 minutes after meals, and at bedtime or when required

**Note** The brand name Altacite® is used for hydrotalcite suspension; for Altacite Plus suspension, see below
1 Gastro-intestinal system

Alginate Raft-forming Oral Suspension, BP

... contains sodium alginate, sodium bicarbonate, and calcium carbonate in a suitable flavoured vehicle, and conform to the specification for Alginate Raft-forming Oral Suspension, BP.

**Antacid preparations containing simeticone**

**Alalcite Plus®** (Peckforton)

**Suspension**, sugar-free, co-simalcicte 125/500 (simeticone 125 mg, hydrocortisone 500 mg)/5 mL (low Na+).

Net price 500 mL = £1.96

**Dose** 10 mL between meals and at bedtime when required; CHILD 8–12 years 5 mL between meals and at bedtime when required

**Asilone®** (Thornton & Ross)

**Suspension**, sugar-free, dried aluminium hydroxide 420 mg, simeticone 135 mg, light magnesium oxide 70 mg/5 mL (low Na+).

Net price 500 mL = £1.95

**Dose** ADULT over 12 years, 5–10 mL after meals and at bedtime or when required up to 4 times daily

**Maalox Plus®** (Sanofi-Aventis)

**Suspension**, sugar-free, dried aluminium hydroxide 220 mg, simeticone 25 mg, magnesium hydroxide 195 mg/5 mL (low Na+).

Net price 500 mL = £2.79

**Dose** 5–10 mL 4 times daily (after meals and at bedtime) or when required, CHILD under 5 years 5 mL 3 times daily, over 5 years appropriate proportion of adult dose

**Simeticone alone**

Simeticone (activated dimeticone) is an antifoaming agent. It is licensed for infantile colic but evidence of benefit is uncertain.

**Dentinox®** (DDD)

**Colic drops** (= emulsion), simeticone 21 mg/2.5-mL dose.

Net price 100 mL = £1.73

**Dose** colic or wind pains, NEONATE and INFANT 2.5 mL with or after each feed (max. 6 doses in 24 hours); may be added to bottle feed

**Note** The brand name Dentinox is also used for other preparations including teething gel

**Infacol®** (Forest)

**Liquid**, sugar-free, simeticone 40 mg/mL (low Na+).

Net price 50 mL = £2.26. Counselling, use of dropper

**Dose** colic or wind pains, NEONATE and INFANT 0.5–1 mL before feeds

**Acidex®** (Pinewood)

**Liquid**, sugar-free, sodium alginate 250 mg, sodium bicarbonate 133.5 mg, calcium carbonate 80 mg/5 mL. Contains about 3 mmol Na+/5 mL. Net price 500 mL (aniseed- or peppermint-flavour) = £1.70

**Dose** 10–20 mL after meals and at bedtime; CHILD 6–12 years 5–10 mL after meals and at bedtime

**Peptac®** (IVAX)

**Suspension**, sugar-free, sodium bicarbonate 133.5 mg, sodium alginate 250 mg, calcium carbonate 80 mg/5 mL. Contains 3.1 mmol Na+/5 mL. Net price 500 mL (aniseed- or peppermint-flavoured) = £2.16

**Dose** 10–20 mL after meals and at bedtime; CHILD 6–12 years 5–10 mL after meals and at bedtime

**Other compound alginate preparations**

**Gastrocote®** (Actavis)

**Tablets**, alginic acid 200 mg, dried aluminium hydroxide 80 mg, magnesium trisilicate 40 mg, sodium bicarbonate 70 mg. Contains about 1 mmol Na+/tablet.

Net price 100-tablet pack = £3.51

**Cautions** diabetes mellitus (high sugar content)

**Dose** ADULT and CHILD over 6 years, 1–2 tablets chewed 4 times daily (after meals and at bedtime)

**Liquid**, sugar-free, peach-coloured, dried aluminium hydroxide 80 mg, magnesium trisilicate 40 mg, sodium alginate 220 mg, sodium bicarbonate 70 mg/5 mL. Contains 2.13 mmol Na+/5 mL. Net price 500 mL = £2.67

**Dose** ADULT and CHILD over 6 years, 5–15 mL 4 times daily (after meals and at bedtime)

**Gaviscon® Advance** (R&C)

**Tablets**, sugar-free, sodium alginate 500 mg, potassium bicarbonate 100 mg. Contains 2.25 mmol Na+,

1 mmol K+/tablet.

Net price 60-tab pack (peppermint-flavoured) = £3.24

**Excipients** include aspartame (section 9.4.1)

**Dose** ADULT and CHILD over 12 years, 1–2 tablets to be chewed after meals and at bedtime; CHILD 6–12 years, 1 tablet to be chewed after meals and at bedtime (under medical advice only)

**Suspension**, sugar-free, aniseed- or peppermint flavour, sodium alginate 500 mg, potassium bicarbonate 100 mg/5 mL. Contains 2.3 mmol Na+, 1 mmol K+/5 mL.

Net price 250 mL = £2.70, 500 mL = £5.40

**Dose** ADULT and CHILD over 12 years, 5–10 mL after meals and at bedtime; CHILD 2–12 years, 2.5–5 mL after meals and at bedtime (under medical advice only)

**Gaviscon Infant®** (R&C)

**Oral powder**, sugar-free, sodium alginate 225 mg, magnesium alginate 87.5 mg, with colloidal silica and mannitol/dose (half dual-sachet). Contains 0.92 mmol Na+/dose.

Net price 15 dual-sachets (30 doses) = £2.46

**Dose** INFANT body-weight under 4.5 kg, 1 ‘dose’ (half dual-sachet) mixed with feeds (or water in breast-fed infants) when required (max. 6 times in 24 hours); body-weight over 4.5 kg, 2 ‘doses’ (1 dual-sachet) mixed with feeds (or water in breast-fed infants) when required (max. 6 times in 24 hours); CHILD 2 ‘doses’ (1 dual-sachet) in water after each meal (max. 6 times in 24 hours)

**Note** Not to be used in preterm neonates, or where excessive water loss likely (e.g. fever, diarrhoea, vomiting, high room temperature), or if intestinal obstruction. Not to be used with other preparations containing thickeners agents

**Important** Each half of the dual-sachet is identified as ‘one dose’. To avoid errors prescribe as ‘dual-sachet’ with directions in terms of ‘dose’
1.2 Antispasmodics and other drugs altering gut motility

Drugs in this section include antimuscarinic compounds and drugs believed to be direct relaxants of intestinal smooth muscle. The smooth muscle relaxant properties of antimuscarinic and other antispasmodic drugs may be useful in irritable bowel syndrome and in diverticular disease.

The dopamine-receptor antagonists metoclopramide and domperidone (section 4.6) stimulate transit in the gut.

Antimuscarinics

Antimuscarinics (formerly termed ‘anticholinergics’) reduce intestinal motility. They are used for the management of irritable bowel syndrome and diverticular disease. However, their value has not been established and response varies. Other indications for antimuscarinic drugs include arthritides (section 2.3.1), asthma and airways disease (section 3.1.2), motion sickness (section 4.6), parkinsonism (section 4.9.2), urinary incontinence (section 7.4.2), mydriasis and cycloplegia (section 11.5), premedication (section 15.1.3) and as an antidote to organophosphorus poisoning (p. 36).

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amines atropine sulphate and dicycloverine hydrochloride (dicyclomine hydrochloride) and the quaternary ammonium compounds propantheline bromide and hyoscyamine butylbromide. The quaternary ammonium compounds are less lipid soluble than atropine and may also have antimuscarinic action than atropine and may also have antimuscarinic action than atropine and may also have reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin. Side-effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting, and giddiness; very rarely, angle-closure glaucoma may occur.

Contra-indications Antimuscarinics are contra-indicated in myasthenia gravis (but may be used to decrease muscarinic side-effects of anticholinesterases—section 10.2.1), paralytic ileus, pyloric stenosis and prostatic enlargement.

Side-effects Side-effects of antimuscarinics include constipation, transient bradycardia (followed by tachycardia, palpitation and arrhythmias), reduced bronchial secretions, urinary urgency and retention, dilatation of the pupils with loss of accommodation, photophobia, dry mouth, flushing and dryness of the skin. Side-effects that occur occasionally include confusion (particularly in the elderly), nausea, vomiting, and giddiness; very rarely, angle-closure glaucoma may occur.

Antimuscarinics should be used with caution in Down’s syndrome, in children and in the elderly; they should also be used with caution in gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, pregnancy (Appendix 4), and in individuals susceptible to angle-closure glaucoma. Interactions: Appendix 1 (antimuscarinics).

Antimuscarinics are less well absorbed from the gastro-intestinal tract. Dicycloverine hydrochloride has a much less marked antimuscarinic action than atropine and may also have some direct action on smooth muscle. Hyoscine butylbromide is advocated as a gastro-intestinal antispasmodic, but it is poorly absorbed; the injection is useful in endoscopy and radiology. Atropine and the belladonna alkaloids are outmoded treatments, any clinical virtues being outweighed by atropinic side-effects.

Excipients include propylene glycol

Cautions Antimuscarinics should be used with caution in Down’s syndrome, in children and in the elderly; they should also be used with caution in gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, acute myocardial infarction, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, pregnancy (Appendix 4), and in individuals susceptible to angle-closure glaucoma. Interactions: Appendix 1 (antimuscarinics).
Gastro-intestinal system

1.2 Antispasmodics and other drugs altering gut motility

**HYOSCINE BUTYLBROMIDE**

**Indications** symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm; bowel colic and excessive respiratory secretions (see Prescribing in Palliative Care, p. 18)

**Cautions** see notes above; also breast-feeding (Appendix 5)

**Contra-indications** see notes above; also hepatic and renal impairment; pregnancy (Appendix 4); avoid in acute porphyria (section 9.8.2.)

**Side-effects** rarely allergic reactions (including rash, urticaria, angioedema)

**Dose**
- **ADULT** over 12 years 10–20 mg 1–3 times daily
- **CHILD** over 12 years 5 mg 1–3 times daily

**Buscopan** (Boehringer Ingelheim)

- **Tablets**, coated, hyoscine butylbromide 10 mg. Net price 56-tab pack = £2.59
  - Note Hyoscine butylbromide tablets can be sold to the public provided single dose does not exceed 20 mg, daily dose does not exceed 80 mg, and pack does not contain a total of more than 240 mg

- **Injection**, hyoscine butylbromide 20 mg/mL. Net price 1 mL amp = 20p

**PROPANThELINE BROMIDE**

**Indications** symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm; urinary frequency (section 7.4.2); gustatory sweating (section 6.1.5)

**Cautions** see notes above; also hepatic and renal impairment; breast-feeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- **ADULT** and **CHILD** over 12 years, 15 mg 3 times daily at least 1 hour before meals and 30 mg at night, max. 120 mg daily
- **CHILD** 6–18 years, 2–10 mg 4 times daily

**Mebeverine Hydrochloride**

**Indications** adjunct in gastro-intestinal disorders characterised by smooth muscle spasm

**Cautions** pregnancy (Appendix 4); avoid in acute porphyria (section 9.8.2.)

**Contra-indications** paralytic ileus

**Side-effects** nausea; headache; dizziness; pruritus; rash; hepatitis also reported

**Dose**
- **ADULT** and **CHILD** over 12 years 10–20 mg 4 times daily

**Spasmonal** (Norgine)

- **Capsules**, alverine citrate 60 mg (blue/grey), net price 100-cap pack = £11.95; 120 mg (Spasmonal® Forte, blue/grey), 60-cap pack = £13.80

**ALVERINE CITRATE**

**Indications** adjunct in gastro-intestinal disorders characterised by smooth muscle spasm; dysmenorrhoea

**Cautions** pregnancy; breast-feeding (Appendix 5)

**Contra-indications** paralytic ileus

**Side-effects** nausea; headache; dizziness; pruritus; rash; hepatitis also reported

**Dose**
- **ADULT** and **CHILD** over 12 years, 60–120 mg 1–3 times daily

**Colofac** (Solvay)

- **Tablets**, mebeverine hydrochloride 135 mg. Net price 20 = £2.21

**Oral suspension**, mebeverine hydrochloride (as mebeverine embonate) 50 mg/5 mL, net price 300 mL = £107.00

**Compound preparations**

**1. Fybogel® Mebeverine** (R&C)

- **Granules**, buff, effervescent, ispaghula husk 3.5 g, mebeverine hydrochloride 135 mg/sachet. Contains 2.5 mmol K+/sachet, net price 10 sachets = £2.50. Label: 13, 22, counselling, see below

**Excipients** include aspartame (section 9.4.1)

**Dose**
- **ADULT** and **CHILD** over 12 years, 1 sachet in water, morning and evening 30 minutes before food, an additional sachet may also be taken before the midday meal if necessary

**Counselling** Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

- **1. 10-sachet pack can be sold to the public**

**Other antispasmodics**

Alverine, mebeverine, and peppermint oil are believed to be direct relaxants of intestinal smooth muscle and may relieve pain in *irritable bowel syndrome* and *diverticular disease*. They have no serious adverse effects but, like all antispasmodics, should be avoided in paralytic ileus. Peppermint oil occasionally causes heartburn.
Peptic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma.

**Indications** relief of abdominal colic and distension, particularly in irritable bowel syndrome

**Cautions** sensitivity to menthol

**Side-effects** heartburn, perianal irritation; rarely, allergic reactions (including rash, headache, bradycardia, muscle tremor, ataxia)

**Local irritation** Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus

**Dose**
- See preparations

Colpermin® (McNeil)

Capsules, m/r, e/c, light blue/dark blue, blue band, peppermint oil 0.2 mL. Net price 100-cap pack = £12.05. Label: 5, 22, 25

Excipients include arachis (peanut) oil

Dose: ADULT over 15 years, 1–2 capsules, swallowed whole with water, 3 times daily for up to 3 months if necessary

Mintec® (Shire)

Capsules, e/c, green/ivory, peppermint oil 0.2 mL. Net price 84-cap pack = £7.04. Label: 5, 22, 25

Dose: ADULT over 15 years, 1–2 capsules swallowed whole with water, 3 times daily before meals for up to 2–3 months if necessary

**Motility stimulants**

Metoclopramide and domperidone (section 4.6) are dopamine receptor antagonists which stimulate gastric emptying and small intestinal transit, and enhance the strength of oesophageal sphincter contraction. They are used in some patients with functional dyspepsia that has not responded to a proton pump inhibitor or a H₂-receptor antagonist. Metoclopramide is also used to speed the transit of barium during intestinal follow-through examination, and as accessory treatment for gastro-oesophageal reflux disease. For the management of gastroparesis in patients with diabetes, see section 6.1.5. Metoclopramide and domperidone are useful in non-specific and in cytotoxic-induced nausea and vomiting. Metoclopramide and occasionally domperidone can cause acute dystonic reactions, particularly in young women and children—for further details of this and other side-effects, see section 4.6.

**Helicobacter pylori infection**

Eradication of Helicobacter pylori reduces recurrence of gastric and duodenal ulcers and the risk of rebleeding. The presence of H. pylori should be confirmed before starting eradication treatment. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of H. pylori; reinfection is rare. Antibiotic-induced colitis is an uncommon risk.

For initial treatment, a one-week triple-therapy regimen that comprises a proton pump inhibitor, clarithromycin, and either amoxicillin or metronidazole can be used. However, if a patient has been treated with metronidazole for other infections, a regimen containing a proton pump inhibitor, amoxicillin and clarithromycin is preferred for initial therapy. If a patient has been treated with clarithromycin for other infections, a regimen containing a proton pump inhibitor, amoxicillin and metronidazole is preferred for initial therapy. These regimens eradicate H. pylori in about 85% of cases. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H₂-receptor antagonist), however, if the ulcer is large, or complicated by haemorrhage or perforation, then antisecretory treatment is continued for a further 3 weeks. Treatment failure usually indicates antibacterial resistance or poor compliance. Resistance to amoxicillin is rare. However, resistance to clarithromycin and metronidazole is common and can develop during treatment.

Two-week triple-therapy regimens offer the possibility of higher eradication rates compared to one-week regimens, but adverse effects are common and poor compliance is likely to offset any possible gain.

Two-week dual-therapy regimens using a proton pump inhibitor and a single antibacterial are licensed, but produce low rates of H. pylori eradication and are not recommended.

Tinidazole is also used occasionally for H. pylori eradication as an alternative to metronidazole; tinidazole should be combined with antisecretory drugs and other antibacterials.

A two-week regimen comprising a proton pump inhibitor (e.g. omeprazole 20 mg twice daily) plus tripotassium dicitratobismuthate 120 mg four times daily, plus tetracycline 500 mg four times daily, plus metronidazole 400 mg three times daily can be used for eradication failure. Alternatively, the patient can be referred for endoscopy and treatment based on the results of culture and sensitivity testing.

For the role of H. pylori eradication therapy in patients starting or taking a NSAID, see NSAID-associated Ulcers, p. 44. For H. pylori eradication in patients with dyspepsia, see also section 1.1.
### Recommended regimens for *Helicobacter pylori* eradication in adults

<table>
<thead>
<tr>
<th>Acid suppressant</th>
<th>Antibacterial</th>
<th>Price for 7-day course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Amoxicillin</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td><strong>Esomeprazole</strong></td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>20 mg twice daily</td>
<td>— 250 mg twice daily</td>
<td>400 mg twice daily</td>
</tr>
<tr>
<td><strong>Lansoprazole</strong></td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>30 mg twice daily</td>
<td>— 400 mg twice daily</td>
<td>—</td>
</tr>
<tr>
<td><strong>Omeprazole</strong></td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>20 mg twice daily</td>
<td>500 mg 3 times daily</td>
<td>400 mg 3 times daily</td>
</tr>
<tr>
<td>— 250 mg twice daily</td>
<td>400 mg twice daily</td>
<td>—</td>
</tr>
<tr>
<td><strong>Pantoprazole</strong></td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>40 mg twice daily</td>
<td>400 mg twice daily</td>
<td>—</td>
</tr>
<tr>
<td><strong>Rabeprazole</strong></td>
<td>1 g twice daily</td>
<td>500 mg twice daily</td>
</tr>
<tr>
<td>20 mg twice daily</td>
<td>— 400 mg twice daily</td>
<td>—</td>
</tr>
</tbody>
</table>

### Test for *Helicobacter pylori*

C-Urea breath test kits are available for the diagnosis of gastro-duodenal infection with *Helicobacter pylori*. The test involves collection of breath samples before and after ingestion of an oral solution of C-urea; the samples are sent for analysis by an appropriate laboratory. The test should not be performed within 4 weeks of treatment with an antibacterial or within 2 weeks of treatment with an antisecretory drug. A specific C-urea breath test kit for children (Helicobacter Test INFAI for children of the age 3–11) is available. However, the appropriateness of testing for *H. pylori* infection in children has not been established.

**diabact UBT® (MDE)**

- **Tablets**, C-urea 50 mg, net price 1 kit (including 1 tablet, 4 breath-sample containers, straws) = £19.95 (analysis included), 10-kit pack (hosp. only) = £74.50 (analysis not included)

**Helicobacter Test INFAI® (Infai)**

- **Oral powder**, C-urea 75 mg, net price 1 kit (including 4 breath-sample containers, straws) = £19.20 (spectrometric analysis included), 1 kit (including 2 breath bags) = £14.20 (spectrometric analysis not included), 50-test set = £855.00 (spectrometric analysis included); 45 mg (*Helicobacter Test INFAI for children of the age 3–11*), 1 kit (including 4 breath-sample containers, straws) = £19.20 (spectrometric analysis included)

**Pylobactell® (Torbet)**

- **Soluble tablets**, C-urea 100 mg, net price 1 kit (including 6 breath-sample containers, 30-mL mixing and administration vial, straws) = £20.75 (analysis included)

### NSAID-associated ulcers

Gastro-intestinal bleeding and ulceration can occur with NSAID use (section 10.1.1). The risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs (see CSM advice, p. 554). Wherever possible, the NSAID should be withdrawn if an ulcer occurs.

Patients at high risk of developing gastro-intestinal complications include those aged over 65 years, those with a history of peptic ulcer disease or serious gastro-intestinal complication, those taking other medicines that increase the risk of gastro-intestinal side-effects, or those with serious co-morbidity. In those at risk of ulceration, a proton pump inhibitor can be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs; a H₂-receptor antagonist such as ranitidine given at twice the usual dose or misoprostol are alternatives. Colic and diarrhoea may limit the dose of misoprostol.

NSAID use and *H. pylori* infection are independent risk factors for gastro-intestinal bleeding and ulceration. In patients already taking a NSAID, eradication of *H. pylori* is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in patients with dyspepsia or a history of gastric or duodenal ulcer, who are *H. pylori* positive, and who are about to start long-term treatment with a non-selective NSAID, eradication of *H. pylori* may reduce the overall risk of ulceration. If the NSAID can be discontinued in a patient who has developed an ulcer, a proton pump inhibitor usually produces the most rapid healing, but the ulcer can be treated with a H₂-receptor antagonist or misoprostol.

If treatment with a non-selective NSAID needs to continue, the following options are suitable:

- Treat ulcer with a proton pump inhibitor and on healing continue the proton pump inhibitor (dose not normally reduced because asymptomatic ulcer recurrence may occur);
- Treat ulcer with a proton pump inhibitor and on healing switch to misoprostol for maintenance therapy (colic and diarrhoea may limit the dose of misoprostol);
- Treat ulcer with a proton pump inhibitor and switch non-selective NSAID to a cyclo-oxygenase-2 selective inhibitor, but see NSAIDs and Cardiovascular Events, p. 553; on healing, continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.
If treatment with a cyclo-oxygenase-2 selective inhibitor needs to continue, treat ulcer with a proton pump inhibitor; on healing continuation of the proton pump inhibitor in patients with a history of upper gastro-intestinal bleeding may provide further protection against recurrence.

1.3.1 H₂-receptor antagonists

Histamine H₂-receptor antagonists heal gastric and duodenal ulcers by reducing gastric acid output as a result of histamine H₂-receptor blockade; they are also used to relieve symptoms of gastro-oesophageal reflux disease (section 1.1). H₂-receptor antagonists should not normally be used for Zollinger–Ellison syndrome because proton pump inhibitors (section 1.3.5) are more effective.

Maintenance treatment with low doses for the prevention of peptic ulcer disease has largely been replaced in Helicobacter pylori positive patients by eradication regimens (section 1.3). H₂-receptor antagonists are used for the treatment of functional dyspepsia (section 1.1). Treatment of uninvestigated dyspepsia with H₂-receptor antagonists used regularly or on an intermittent basis, may be acceptable in younger patients but care is required in older people because of the possibility of gastric cancer in these patients.

H₂-receptor antagonist therapy can promote healing of NSAID-associated ulcers (particularly duodenal) (section 1.3).

Treatment with a H₂-receptor antagonist has not been shown to be beneficial in haematemeses and melena, but prophylactic use reduces the frequency of bleeding from gastroduodenal erosions in hepatic coma, and possibly in other conditions requiring intensive care. H₂-receptor antagonists also reduce the risk of acid aspiration in obstetric patients at delivery (Mendelson’s syndrome).

Cautions H₂-receptor antagonists should be used with caution in renal impairment (Appendix 3), pregnancy (Appendix 4), and in breast-feeding (Appendix 5). H₂-receptor antagonists might mask symptoms of gastric cancer; particular care is required in those whose symptoms change and in those who are middle-aged or older.

Side-effects Side-effects of the H₂-receptor antagonists include diarrhoea and other gastro-intestinal disturbances, altered liver function tests (rarely liver damage), headache, dizziness, rash, and tiredness. Rare side-effects include acute pancreatitis, bradycardia, AV block, confusion, depression, and hallucinations particularly in the elderly or the very ill, hypersensitivity reactions (including fever, arthralgia, myalgia, anaphylaxis), blood disorders (including agranulocytosis, leucopenia, pancycopenia, thrombocytopenia), and skin reactions (including erythema multiforme and toxic epidermal necrolysis). There have been occasional reports of gynaecomastia and impotence.

Interactions Cimetidine retards oxidative hepatic drug metabolism by binding to microsomal cytochrome P450. It should be avoided in patients stabilised on warfarin, phenytoin, and theophylline (or aminophylline), but other interactions (see Appendix 1) may be of less clinical relevance. Famotidine, nizatidine, and ranitidine do not share the drug metabolism inhibitory properties of cimetidine.

Cimetidine

Indications benign gastric and duodenal ulceration, stomal ulcer, reflux oesophagitis, Zollinger–Ellison syndrome, other conditions where gastric acid reduction is beneficial (see notes above and section 1.9.4)

Cautions see notes above; also hepatic impairment (Appendix 2); interactions: Appendix 1 (histamine H₂-antagonists) and notes above

Side-effects see notes above; also alopecia; very rarely tachycardia, interstitial nephritis

Dose
- 400 mg twice daily (with breakfast and at night) or 800 mg at night (benign gastric and duodenal ulceration) for at least 4 weeks (6 weeks in gastric ulceration, 8 weeks in NSAID-associated ulceration); when necessary the dose may be increased to 400 mg 4 times daily; INFANT under 1 year 20 mg/kg daily in divided doses has been used; CHILD 1–12 years, 25–30 mg/kg daily in divided doses; max. 400 mg 4 times daily
- Maintenance, 400 mg at night or 400 mg morning and night
- Reflux oesophagitis, 400 mg 4 times daily for 4–8 weeks
- Zollinger–Ellison syndrome (but see notes above), 400 mg 4 times daily or occasionally more (max. 2.4 g daily)
- Prophylaxis of stress ulceration, 200–400 mg every 4–6 hours
- Gastric acid reduction (prophylaxis of acid aspiration; do not use syrup), obstetrics 400 mg at start of labour, then up to 400 mg every 4 hours if required (max. 2.4 g daily); surgical procedures 400 mg 90–120 minutes before induction of general anaesthesia
- Short-bowel syndrome, 400 mg twice daily (with breakfast and at bedtime) adjusted according to response
- To reduce degradation of pancreatic enzyme supplements, 0.8–1.6 g daily in 4 divided doses 1–1½ hours before meals

1 Cimetidine (Non-proprietary) Tablets, cimetidine 200 mg, net price 60-tab pack = £1.48; 400 mg, 60-tab pack = £1.61; 800 mg, 30-tab pack = £1.88 Oral solution, cimetidine 200 mg/5 mL, net price 300 mL = £14.24 Excipients may include propylene glycol (see Excipients, p. 2)

1. Cimetidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity (max. single dose 200 mg, max. daily dose 800 mg), and for the prophylactic management of nocturnal heartburn (single night-time dose 100 mg)

Tagamet® (Chemidex) Tablets, all green, f/c, cimetidine 200 mg, net price 120-tab pack = £19.58; 400 mg, 60-tab pack = £22.62; 800 mg, 30-tab pack = £22.62

Syrup, orange, cimetidine 200 mg/5 mL. Net price 600 mL = £28.49 Excipients include propylene glycol 10% (see Excipients, p. 2)
FAMOTIDINE

Indications  see under Dose

Cautions  see notes above; interactions: Appendix 1 (histamine H-antagonists) and notes above

Side-effects  see notes above; also very rarely anorexia, cholestatic jaundice, interstitial pneumonia, anxiety, paraesthesia, insomnia, decreased libido, dry mouth, and taste disturbances

Dose
- Benign gastric and duodenal ulceration, treatment, 40 mg at night for 4–8 weeks; maintenance (duodenal ulceration), 20 mg at night
- Reflux oesophagitis, 20–40 mg twice daily for 6–12 weeks; maintenance, 20 mg twice daily
- Zollinger–Ellison syndrome (but see notes above), 20 mg every 6 hours (higher dose in those who have previously been receiving another H-receptor antagonist); up to 800 mg daily in divided doses has been used
- CHILD not recommended

Famotidine (Non-proprietary)  
Tablets, famotidine 20 mg, net price 28-tab pack = £4.11; 40 mg, 28-tab pack = £5.20

1. Famotidine can be sold to the public for adults and children over 16 years (provided packs do not contain more than 2 weeks’ supply) for the short-term symptomatic relief of heartburn, dyspepsia, and hyperacidity, and for the prevention of these symptoms when associated with consumption of food or drink including when they cause sleep disturbance (max. single dose 10 mg, max. daily dose 20 mg)

NIZATIDINE

Indications  see under Dose

Cautions  see notes above; also avoid rapid intravenous injection (risk of arrhythmias and postural hypotension); hepatic impairment (Appendix 2); interactions: Appendix 1 (histamine H-antagonists) and notes above

Side-effects  see notes above; also sweating; rarely hyperuricaemia

Dose
- By mouth, benign gastric, duodenal or NSAID-associated ulceration, treatment, 300 mg in the evening or 150 mg twice daily for 4–8 weeks; maintenance, 150 mg at night
- Gastro-oesophageal reflux disease, 150–300 mg twice daily for up to 12 weeks
- By intravenous infusion, for short-term use in peptic ulcer as alternative to oral route (for hospital inpatients), by intermittent intravenous infusion over 15 minutes, 100 mg 3 times daily, or by continuous intravenous infusion, 10 mg/hour, max. 480 mg daily
- CHILD not recommended

1. Nizatidine (Non-proprietary)  
Capsules, nizatidine 150 mg, net price 30-cap pack = £3.82; 300 mg, 30-cap pack = £6.18

1. Nizatidine can be sold to the public for the prevention and treatment of symptoms of food-related heartburn and meal-induced indigestion in adults and children over 16 years; max. single dose 75 mg, max. daily dose 150 mg for max. 14 days

Axid® (Flynn)  
Capsules, nizatidine 150 mg (pale yellow/dark yellow), net price 28-cap pack (hosp. only) = £6.87, 30-cap pack = £7.97; 300 mg (pale yellow/brown), 30-cap pack = £15.80

Injection, nizatidine 25 mg/mL. For dilution and use as an intravenous infusion. Net price 4-mL amp = £1.14

RANITIDINE

Indications  see under Dose, other conditions where reduction of gastric acidity is beneficial (see notes above and section 1.9.4)

Cautions  see notes above; also acute porphyria; interactions: Appendix 1 (histamine H-antagonists) and notes above

Side-effects  see notes above; also rarely tachycardia, agitation, visual disturbances, alopecia, vasculitis; very rarely interstitial nephritis

Dose
- By mouth, benign gastric and duodenal ulceration, chronic episodic dyspepsia, ADULT and CHILD over 12 years, 150 mg twice daily or 300 mg at night for 4–8 weeks in benign gastric and duodenal ulceration, up to 6 weeks in chronic episodic dyspepsia, and up to 8 weeks in NSAID-associated ulceration (in duodenal ulcer 300 mg can be given twice daily for 4 weeks to achieve a higher healing rate); CHILD 3–12 years, (benign gastric and duodenal ulceration) 2–4 mg/kg (max. 150 mg) twice daily for 4–8 weeks Prophylaxis of NSAID-associated gastric or duodenal ulcer (unlicensed dose), ADULT and CHILD over 12 years, 300 mg twice daily
- Gastro-oesophageal reflux disease, ADULT and CHILD over 12 years, 150 mg twice daily or 300 mg at night for up to 8 weeks or if necessary 12 weeks (moderate to severe, 600 mg daily in 2–4 divided doses for up to 12 weeks); long-term treatment of healed gastro-oesophageal reflux disease, 150 mg twice daily; CHILD 3–12 years, 2.5–5 mg/kg (max. 300 mg) twice daily Zollinger–Ellison syndrome (but see notes above), ADULT and CHILD over 12 years, 150 mg 3 times daily; doses up to 6 g daily in divided doses have been used Gastric acid reduction (prophylaxis of acid aspiration) in obstetrics, ADULT and CHILD over 12 years, by mouth, 150 mg at onset of labour, then every 6 hours; surgical procedures, by intramuscular or slow intravenous injection, 50 mg 45–60 minutes before induction of anaesthesia (intravenous injection diluted to 20 mL and given over at least 2 minutes), or by mouth, 150 mg 2 hours before induction of anaesthesia and also when possible on the preceding evening
- By intramuscular injection, 50 mg every 6–8 hours
- By slow intravenous injection, ADULT and CHILD over 12 years, 50 mg diluted to 20 mL and given over at least 2 minutes; may be repeated every 6–8 hours
- By intravenous infusion, 25 mg/hour for 2 hours; may be repeated every 6–8 hours
- Prophylaxis of stress ulceration, ADULT and CHILD over 12 years, initial slow intravenous injection of 50 mg (as above) then continuous infusion, 125–250 micrograms/kg/hour (may be followed by 150 mg twice daily by mouth when oral feeding commences)
1.3.2 Selective antimuscarinics

Pirenzepine is a selective antimuscarinic drug which was used for the treatment of gastric and duodenal ulcers. It has been discontinued.

1.3.3 Chelates and complexes

Tripotassium dicitratobismuthate is a bismuth chelate effective in healing gastric and duodenal ulcers. For the role of tripotassium dicitratobismuthate in a Helicobacter pylori eradication regimen for those who have not responded to first-line regimens, see section 1.3.

The bismuth content of tripotassium dicitratobismuthate is low but absorption has been reported; encephalopathy (described with older high-dose bismuth preparations) has not been reported.

Sucralfate may act by protecting the mucosa from acid-pepsin attack in gastric and duodenal ulcers. It is a complex of aluminium hydroxide and sulphated sucrose but has minimal antacid properties. It should be used with caution in patients under intensive care (important: reports of bezoar formation, see CSM advice below).

TRIPOTASSIUM DICRATOBISMUTHATE

Indications benign gastric and duodenal ulceration; see also Helicobacter pylori infection, section 1.3

Cautions see notes above; interactions: Appendix 1 (tripotassium dicitratobismuthate)

Contra-indications renal impairment (avoid if creatinine clearance less than 10 mL/minute); pregnancy (Appendix 4)

Side-effects may darken tongue and blacken faeces; less commonly nausea, vomiting, diarrhoea, constipation, rash, and pruritus reported

De-Noltab® (Astellas)

Tablets, £/c, tripotassium dicitratobismuthate 120 mg. Contains 2 mmol K+ /tablet. Net price 112-tab pack = £7.27. Counselling, see below

Dose 2 tablets twice daily or 1 tablet 4 times daily, taken for 28 days followed by further 28 days if necessary; maintenance not indicated but course may be repeated after interval of 1 month; CHILD not recommended

Counselling To be swallowed with half a glass of water; twice-daily dosage to be taken 30 minutes before breakfast and main evening meal, four-times-daily dosage to be taken as follows: one dose 30 minutes before breakfast, midday meal and main evening meal, and one dose 2 hours after main evening meal; milk should not be drunk by itself during treatment but small quantities may be taken in tea or coffee or on cereal; antacids, fruit, or fruit juice should not be taken half an hour before or after a dose; may darken tongue and blacken faeces

SUCRALFATE

Indications see under Dose

Cautions renal impairment (Appendix 3); pregnancy and breast-feeding; administration of sucralfate and enteral feeds should be separated by 1 hour; interactions: Appendix 1 (sucralfate)

Bezoar formation Following reports of bezoar formation associated with sucralfate, the CSM has advised caution in seriously ill patients, especially those receiving concomitant enteral feeds or those with predisposing conditions such as delayed gastric emptying

Side-effects constipation; less frequently diarrhoea, nausea, indigestion, flatulence, gastric discomfort, back pain, dizziness, headache, drowsiness, bezoar formation (see above), dry mouth and rash

Dose
• Benign gastric and duodenal ulceration and chronic gastritis, ADULT and CHILD over 15 years, 2 g twice daily (on rising and at bedtime) or 1 g 4 times daily 1 hour before meals and at bedtime, taken for 4–6 weeks or in resistant cases up to 12 weeks; max. 8 g daily
• Prophylaxis of stress ulceration, ADULT and CHILD over 15 years, 1 g 6 times daily; max. 8 g daily
• CHILD under 15 years, see BNF for Children

Antepsin® (Chugai) (FR)

Tablets, scored, sucralfate 1 g, net price 50-tab pack = £4.81. Label: 5

Note Crushed tablets may be dispersed in water

Suspension, sucralfate 1 g/5 mL, net price 250 mL (aniseed- and caramel-flavoured) = £4.81. Label: 5

1.3.4 Prostaglandin analogues

Misoprostol, a synthetic prostaglandin analogue has antisecretory and protective properties, promoting healing of gastric and duodenal ulcers. It can prevent NSAID-associated ulcers, its use being most appropriate for the frail or very elderly from whom NSAIDs cannot be withdrawn.

For comment on the use of misoprostol to induce abortion or labour [unlicensed indications], see section 7.1.1.
1.3.5 Proton pump inhibitors

Proton pump inhibitors inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell. Proton pump inhibitors are effective short-term treatments for gastritis and duodenal ulcers; they are also used in combination with antibacterials for the eradication of *Helicobacter pylori* (see eradication regimens on p. 43). Following endoscopic treatment of severe peptic ulcer bleeding, an intravenous, high-dose proton pump inhibitor reduces the risk of rebleeding and the need for surgery (unlicensed use). Proton pump inhibitors can be used for the treatment of dyspepsia and gastro-oesophageal reflux disease (section 1.1).

Proton pump inhibitors are also used for the prevention and treatment of NSAID-associated ulcers (see p. 44). In patients who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should normally not be reduced because asymptomatic ulcer deterioration may occur.

A proton pump inhibitor can be used to control excessive secretion of gastric acid in Zollinger–Ellison syndrome; high doses are often required.

**Cautions** Proton pump inhibitors should be used with caution in patients with liver disease (Appendix 2), in pregnancy (Appendix 4) and in breast-feeding (Appendix 5). Proton pump inhibitors may mask the symptoms of gastric cancer; particular care is required in those presenting with ‘alarm features’ (see p. 37), in such cases gastric malignancy should be ruled out before treatment.

**Side-effects** Side-effects of the proton pump inhibitors include gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, flatulence, diarrhoea, constipation), and headache. Less frequent side-effects include dry mouth, peripheral oedema, dizziness, sleep disturbances, fatigue, paraesthesia, arthralgia, myalgia, rash, and pruritus. Other side-effects reported rarely or very rarely include taste disturbance, stomatitis, hepatitis, jaundice, hypersensitivity reactions (including anaphylaxis, bronchospasm), fever, depression, hallucinations, confusion, gynaecomastia, interstitial nephritis, haemoptoama, blood disorders (including leucopenia, leucocytosis, pancytopenia, thrombocytopenia), visual disturbances, sweating, photosensitivity, alopecia, Stevens–Johnson syndrome, and toxic epidermal necrolysis. By decreasing gastric acidity, proton pump inhibitors may increase the risk of gastro-intestinal infections (including *Clostridium difficile* infection).

**ESOMEPROZOLE**

**Indications** see under Dose

**Cautions** see notes above; renal impairment (Appendix 3); interactions: Appendix 1 (proton pump inhibitors)

**Side-effects** see notes above

**Dose**

- *By mouth* duodenal ulcer associated with *Helicobacter pylori*, see eradication regimens on p. 43 NSAID-associated gastric ulcer, *ADULT* over 18 years, 20 mg once daily for 4–8 weeks; prophylaxis in patients with an increased risk of gastroduodenal complications who require continued NSAID treatment, 20 mg daily
- *Gastro-oesophageal reflux disease, ADULT* and *CHILD* over 12 years, 40 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed or symptoms persist; maintenance 20 mg daily; symptomatic treatment in the absence of oesophagitis, 20 mg daily for up to 4 weeks, then in *ADULTS* over 18 years 20 mg daily when required
- Zollinger–Ellison syndrome, *ADULT* over 18 years, initially 40 mg twice daily, adjusted according to response; usual range 80–160 mg daily (above 80 mg in 2 divided doses)

**Counselling** Do not chew or crush tablets, swallow whole or disperse in water

- *By intravenous injection* over at least 3 minutes or by intravenous infusion, *ADULT* over 18 years, gastro-oesophageal reflux disease, 40 mg once daily; symptomatic reflux disease without oesophagitis, treatment of NSAID-associated gastric ulcer, prevention of NSAID-associated gastric or duodenal ulcer, 20 mg daily; continue until oral administration possible

**Nexium®** *(AstraZeneca)*

**Tablets, f/c, esomeprazole (as magnesium trihydrate) 20 mg (light pink)*, net price 28-tab pack = £18.50 (also 7-tab pack, hosp. only); 40 mg (pink), 28-tab pack =
£25.19 (also 7-tab pack, hosp. only). Counselling, administration

Injection, powder for reconstitution, esomeprazole (as sodium salt), net price 40-mg vial = £5.21

### LANSOPRAZOLE

**Indications** see under Dose

**Cautions** see notes above; interactions: Appendix 1 (proton pump inhibitors)

**Side-effects** see notes above; also glossitis, pancreatitis, anorexia, restlessness, tremor, impotence, petechiae, and purpura; very rarely colitis, raised serum cholesterol or triglycerides

**Dose**

- Benign gastric ulcer, 30 mg daily in the morning for 8 weeks
- Duodenal ulcer, 30 mg daily in the morning for 4 weeks; maintenance 15 mg daily
- NSAID-associated duodenal or gastric ulcer, 30 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; prophylaxis, 15–30 mg once daily
- Eradication of *Helicobacter pylori* associated with duodenal ulcer or ulcer-like dyspepsia, see eradication regimens on p. 43
- Zollinger–Ellison syndrome (and other hypersecretory conditions), initially 60 mg once daily adjusted according to response; daily doses of 120 mg or more given in two divided doses
- Gastro-oesophageal reflux disease, 30 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed; maintenance 15–30 mg daily
- Acid-related dyspepsia, 15–30 mg daily in the morning for 2–4 weeks
- **CHILD** under 18 years, see *BNF for Children*

**Note** Lansoprazole doses in BNF may differ from those in product literature

### Lansoprazole

#### (Non-proprietary) *OMEPRAZOLE*

**Capsules,** enclosing e/c granules, lansoprazole 15 mg, net price 28-cap pack = £1.71; 30 mg, 28-cap pack = £3.06. Label: 5, 22, 25

**Dental prescribing on NHS** Lansoprazole capsules may be prescribed

#### Zoton® (Wyeth) *OMEPRAZOLE*

**Capsules** utilise MUPS® technology, lansoprazole 15 mg, net price 28-cap pack = £5.97; 30 mg, 7-cap pack = £2.74, 14-cap pack = £5.47, 28-cap pack = £11.00. Label: 5, 22, counselling, administration

**Excipients** include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to disperse and swallowed, or may be swallowed whole with a glass of water. Alternatively, tablets can be dispersed in a small amount of water and administered by an oral syringe or nasogastric tube

### OMEPRAZOLE

**Indications** see under Dose

**Cautions** see notes above; interactions: Appendix 1 (proton pump inhibitors)

**Side-effects** see notes above; also agitation and impotence

**Dose**

- **By mouth,** benign gastric and duodenal ulcers, 20 mg once daily for 4 weeks in duodenal ulceration or 8 weeks in gastric ulceration; in severe or recurrent cases increase to 40 mg daily; maintenance for recurrent duodenal ulcer, 20 mg once daily; prevention of relapse in duodenal ulcer, 10 mg daily increasing to 20 mg once daily if symptoms return
- NSAID-associated duodenal or gastric ulcer and gastroduodenal erosions, 20 mg once daily for 4 weeks, continued for further 4 weeks if not fully healed; prophylaxis in patients with a history of NSAID-associated duodenal or gastric ulcers, gastroduodenal lesions, or dyspeptic symptoms who require continued NSAID treatment, 20 mg once daily
- Duodenal or benign gastric ulcer associated with *Helicobacter pylori*, see eradication regimens on p. 43
- Zollinger–Ellison syndrome, initially 60 mg once daily; usual range 20–120 mg daily (above 80 mg in 2 divided doses)
- Gastric acid reduction during general anaesthesia (prophylaxis of acid aspiration), 40 mg on the preceding evening then 40 mg 2–6 hours before surgery
- Gastro-oesophageal reflux disease, 20 mg once daily for 4 weeks, continued for further 4–8 weeks if not fully healed; 40 mg once daily has been given for 8 weeks in gastro-oesophageal reflux disease refractory to other treatment; maintenance 20 mg once daily
- Acid reflux disease (long-term management), 10 mg daily increasing to 20 mg once daily if symptoms return
- Acid-related dyspepsia, 10–20 mg once daily for 2–4 weeks according to response
- Severe ulcerating reflux oesophagitis, **CHILD** over 1 year, body-weight 10–20 kg, 10 mg once daily increased if necessary to 20 mg once daily for 4–12 weeks; body-weight over 20 kg, 20 mg once daily increased if necessary to 40 mg once daily for 4–12 weeks; to be initiated by hospital paediatrician
- **By intravenous injection** over 5 minutes or **by intravenous infusion** over 20–30 minutes, prophylaxis of acid aspiration, 40 mg completed 1 hour before surgery
- Benign gastric ulcer, duodenal ulcer and gastro-oesophageal reflux, 40 mg once daily until oral administration possible
- Severe peptic ulcer bleeding [unlicensed indication], initial intravenous infusion of 80 mg then by continuous intravenous infusion, 8 mg/hour for 72 hours (then change to oral therapy)

**Counselling** Swallow whole, or disperse MUPS® tablets in water, or oral suspension, or MUPS® tablets with fruit juice or yoghurt. Preparations consisting of an e/c tablet within a capsule should not be opened

### Omeprazole

#### (Non-proprietary) *OMEPRAZOLE*

**Capsules** utilise MUPS® technology, omeprazole 10 mg, net price 28-cap pack = £1.87; 20 mg, 28-cap pack = £1.75; 40 mg, 7-cap pack = £2.04, 28-cap pack = £5.08. Counselling, administration

**Note** Some preparations consist of an e/c tablet within a capsule; brands include Mepradec

**Dental prescribing on NHS** Gastro-resistant omeprazole capsules may be prescribed

Tablets, e/c, omeprazole 10 mg, net price 28-tab pack = £5.13; 20 mg, 28-tab pack = £5.37; 40 mg, 7-tab pack = £5.08. Label: 25

**Intravenous infusion,** powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial = £5.21

1. Omeprazole 10 mg tablets can be sold to the public for the short-term relief of reflux-like symptoms (e.g. heartburn) in adults over 18 years, max. daily dose 20 mg for max. 4 weeks, and a pack size of 28 tablets
1.4 Acute diarrhoea

Losec® (AstraZeneca) [PHI]  
Pants® [multiple-unit pellet system = dispersible tablets], 1/c, omeprazole 10 mg (light pink), net price 28-tab pack = £19.34; 20 mg (pink), 28-tab pack = £29.22; 40 mg (red-brown), 7-tab pack = £14.61. Counselling, administration
Capsules, enclosing e/c granules, omeprazole 10 mg (pink), net price 28-cap pack = £19.34; 20 mg (pink/brown), 28-cap pack = £29.22; 40 mg (brown), 7-cap pack = £14.61. Counselling, administration
Intravenous infusion, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial = £5.41
Injection, powder for reconstitution, omeprazole (as sodium salt), net price 40-mg vial (with solvent) = £5.41

1.4 Antimotility drugs

RABEPRAZOLE SODIUM  
Indications see under Dose  
Cautions see notes above; interactions: Appendix 1 (proton pump inhibitors)  
Side-effects see notes above; also cough, influenza-like syndrome, and rhinitis; less commonly chest pain and nervousness; rarely anorexia and weight gain

Dose
- Benign gastric ulcer; 20 mg daily in the morning for 6 weeks, continued for further 6 weeks if not fully healed  
- Duodenal ulcer, 20 mg daily in the morning for 4 weeks, continued for further 4 weeks if not fully healed  
- Gastro-oesophageal reflux disease, 20 mg once daily for 4–8 weeks; maintenance 10–20 mg daily; symptomatic treatment in the absence of oesophagitis, 10 mg daily for up to 4 weeks, then 10 mg daily when required  
- Duodenal and benign gastric ulcer associated with Helicobacter pylori, see eradication regimens on p. 43  
- Zollinger–Ellison syndrome, initially 60 mg once daily adjusted according to response (max. 120 mg daily); doses above 100 mg daily given in 2 divided doses  
- CHILD not recommended

Pariet® (Janssen-Cilag, Eisai) [PHI]  
Tablets, e/c, rabeprazole sodium 10 mg (pink), net price 28-tab pack = £11.56; 20 mg (yellow), 28-tab pack = £21.16. Label: 25

1.4.1 Adsorbents and bulk-forming drugs

1.4.2 Antimotility drugs

The priority in acute diarrhoea, as in gastro-enteritis, is the prevention or reversal of fluid and electrolyte depletion. This is particularly important in infants and in frail and elderly patients. For details of oral rehydration preparations, see section 9.2.1.2. Severe depletion of fluid and electrolytes requires immediate admission to hospital and urgent replacement.

Antimotility drugs (section 1.4.2) relieve symptoms of acute diarrhoea. They are used in the management of uncomplicated acute diarrhoea in adults; fluid and electrolyte replacement may be necessary in case of dehydration. However, antimotility drugs are not recommended for acute diarrhoea in young children. Antispasmodics (section 1.2) are occasionally of value in treating abdominal cramp associated with diarrhoea but they should not be used for primary treatment. Antispasmodics and antiemetics should be avoided in young children with gastro-enteritis because they are rarely effective and have troublesome side-effects.

Antibacterial drugs are generally unnecessary in simple gastro-enteritis because the complaint usually resolves quickly without them, and infective diarrhoeas in the UK often have a viral cause. Systemic bacterial infection does, however, need appropriate systemic treatment; for drugs used in campylobacter enteritis, shigellosis, and salmonellosis, see Table 1, section 5.1. Ciprofloxacin is occasionally used for prophylaxis against travellers' diarrhoea, but routine use is not recommended. Lacto-
bacillus preparations have not been shown to be effective.

Colestyramine (cholestyramine, section 1.9.2), binds unabsorbed bile salts and provides symptomatic relief of diarrhoea following ileal disease or resection.

1.4.1 Adsorbents and bulk-forming drugs

Adsorbents such as kaolin are not recommended for acute diarrhoea. Bulk-forming drugs, such as ispaghula, methylcellulose, and sterculia (section 1.6.1) are useful in controlling diarrhoea associated with diverticular disease.

KAOLIN, LIGHT

Indications diarrhoea but see notes above

Cautions interactions: Appendix 1 (kaolin)

Kaolin Mixture, BP

(Kaolin Oral Suspension)

Oral suspension, light kaolin or light kaolin (natural) 20%, light magnesium carbonate 5%, sodium bicarbonate 5% in a suitable vehicle with a peppermint flavour.

Dose 10–20 mL every 4 hours

1.4.2 Antimotility drugs

Antimotility drugs have a role in the management of uncomplicated acute diarrhoea in adults but not in young children; see also section 1.4. However, in severe cases, fluid and electrolyte replacement (section 9.2.1.2) are of primary importance.

For comments on the role of antimotility drugs in chronic bowel disorders see section 1.5. For their role in stoma care see section 1.8.

Loperamide can be used for faecal incontinence [unlicensed indication] after the underlying cause of incontinence has been addressed.

CODEINE PHOSPHATE

Indications see notes above; cough suppression (section 3.9.1); pain (section 4.7.2)

Cautions see section 4.7.2; tolerance and dependence may occur with prolonged use; interactions: Appendix 1 (opioid analgesics)

Contra-indications see section 4.7.2; also conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic-associated colitis

Side-effects see section 4.7.2

Dose

- See preparations

Codeine Phosphate (Non-proprietary) Tablets, codeine phosphate 15 mg, net price 28 = £1.08; 30 mg, 28 = £1.24; 60 mg, 28 = £1.73. Label: 2

Dose ADULT and CHILD over 12 years, acute diarrhoea, 30 mg 3–4 times daily (range 15–60 mg)

Note As for schedule 2 controlled drugs, travellers needing to take codeine phosphate tablets abroad may require a doctor’s letter explaining why codeine is necessary.

CO-PHENOTROPE

A mixture of diphenoxylate hydrochloride and atropine sulphate in the mass proportions 100 parts to 1 part respectively

Indications adjunct to rehydration in acute diarrhoea (but see notes above); control of faecal consistency after colostomy or ileostomy (section 1.8)

Cautions see under Codeine Phosphate (section 4.7.2); also young children are particularly susceptible to overdosage and symptoms may be delayed and observation is needed for at least 48 hours after ingestion; presence of subclinical doses of atropine may give rise to atropine side-effects in susceptible individuals or in overdosage (section 1.2); interactions: Appendix 1 (antimuscarinics, opioid analgesics)

Contra-indications see under Antimuscarinics (section 1.2) and Codeine Phosphate (section 4.7.2); also jaundice

Side-effects see under Antimuscarinics (section 1.2) and Codeine Phosphate (section 4.7.2); also fever

Dose

- See preparations

Co-phenotrope (Non-proprietary) Tablets, co-phenotrope 2.5/0.025 (diphenoxylate hydrochloride 2.5 mg, atropine sulphate 25 micrograms), net price 20 = £1.79

Brands include Lomotil

Dose initially 4 tablets, followed by 2 tablets every 6 hours until diarrhoea controlled, CHILD under 4 years see BNF for Children, 4–9 years 1 tablet 3 times daily, 9–12 years 1 tablet 4 times daily, 12–16 years 2 tablets 3 times daily, but see also notes above

Note Co-phenotrope 2.5/0.025 can be sold to the public for adults and children over 16 years (provided packs do not contain more than 20 tablets) as an adjunct to rehydration in acute diarrhoea (max. daily dose 10 tablets)

LOPERAMIDE HYDROCHLORIDE

Indications symptomatic treatment of acute diarrhoea; adjunct to rehydration in acute diarrhoea in adults and children over 4 years (but see notes above); chronic diarrhoea in adults only

Cautions see notes above; also liver disease; pregnancy (Appendix 4); interactions: Appendix 1 (loperamide)

Contra-indications conditions where inhibition of peristalsis should be avoided, where abdominal distension develops, or in conditions such as active ulcerative colitis or antibiotic-associated colitis

Side-effects abdominal cramps, dizziness, drowsiness, and skin reactions including urticaria; paralytic ileus and abdominal bloating also reported

Dose

- Acute diarrhoea, 4 mg initially followed by 2 mg after each loose stool for up to 5 days; usual dose 6–8 mg daily; max. 16 mg daily; CHILD under 4 years not recommended; 4–8 years, 1 mg 3–4 times daily for up to 3 days only; 8–12 years, 2 mg 4 times daily for up to 5 days

- Chronic diarrhoea in adults, initially, 4–8 mg daily in divided doses, subsequently adjusted according to response and given in 2 divided doses for maintenance; max. 16 mg daily; CHILD under 18 years see BNF for Children

- Faecal incontinence [unlicensed indication], initially 500 micrograms daily, adjusted according to response; max. 16 mg daily in divided doses
Loperamide (Non-proprietary) ( council compliance)
Capsules, loperamide hydrochloride 2 mg, net price 30- cap pack = £1.07
Tablets, loperamide hydrochloride 2 mg, net price 30- tab pack = £2.15

Brands include Norimode

Note Loperamide can be sold to the public, for adults and children over 12 years, provided it is licensed and labelled for the treatment of acute diarrhoea

Imodium® (Janssen-Cilag) ( PH)
Capsules, green/grey, loperamide hydrochloride 2 mg. Net price 30-cap pack = £1.13
Syrup, red, sugar-free, loperamide hydrochloride 1 mg/5 mL. Net price 100 mL = 98p

Compound preparations
Imodium Plus (McNeil)
Caplets (= tablets), loperamide hydrochloride 2 mg, simeticone 125 mg, net price 6-tab pack = £2.14, 12- tab pack = £3.40

Dose acute diarrhoea with abdominal colic; initially 2 tablets or caplets (CHILD 12–18 years 1 tablet or caplet) then 1 tablet or caplet after each loose stool; max. 4 tablets or caplets daily for up to 2 days; CHILD under 12 years not recommended

MORPHINE

Indications see notes above; cough in terminal disease (section 3.9.1); pain (section 4.7.2)

Cautions see notes above and under Morphine Salts (section 4.7.2)

Contra-indications see notes above and under Morphine Salts (section 4.7.2)

Side-effects see notes above and under Morphine Salts (section 4.7.2); sedation and the risk of dependence are greater

Dose
• See preparation

Kaolin and Morphine Mixture, BP (Kaolin and Morphine Oral Suspension)
Oral suspension, light kaolin or light kaolin (natural) 20%, sodium bicarbonate 5%, and chloroform and morphine tincture 4% in a suitable vehicle. Contains anhydrous morphine 550–800 micrograms/10 mL.
Dose 10 mL every 6 hours in water

1.5 Chronic bowel disorders

Once tumours are ruled out individual symptoms of chronic bowel disorders need specific treatment including dietary manipulation as well as drug treatment and the maintenance of a liberal fluid intake.

Inflammatory bowel disease

Chronic inflammatory bowel diseases include ulcerative colitis and Crohn’s disease. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

Aminosalicylates (balsalazide, mesalazaine, olsalazine, and sulfasalazine), and corticosteroids (hydrocortisone, budesonide, and prednisolone) form the basis of drug treatment.

Treatment of acute ulcerative colitis and Crohn’s disease

Acute mild to moderate disease affecting the rectum (proctitis) or the recto-sigmoid (distal colitis) is treated initially with local application of an aminosalicylate; alternatively, a local corticosteroid can be used but it is less effective. Foam preparations and suppositories are especially useful when patients have difficulty retaining liquid enemas.

Diffuse inflammatory bowel disease or disease that does not respond to local therapy requires oral treatment. Mild disease affecting the colon can be treated with an oral aminosalicylate alone; a combination of a local and an oral aminosalicylate may be used in distal colitis. Refractory or moderate inflammatory bowel disease usually requires adjunctive use of an oral corticosteroid such as prednisolone (section 1.5.2) for 4–8 weeks. Modified-release budesonide is licensed for Crohn’s disease affecting the ileum and the ascending colon; it causes fewer systemic side-effects than oral prednisolone but may be less effective. Beclometasone dipropionate by mouth is licensed as an adjunct to mesalazine for mild to moderate ulcerative colitis, but it is not known whether it is as effective as other corticosteroids.

Severe inflammatory bowel disease calls for hospital admission and treatment with an intravenous corticosteroid (such as hydrocortisone or methylprednisolone, section 6.3.2); other therapy may include intravenous fluid and electrolyte replacement, and possibly parenteral nutrition. Specialist supervision is required for patients who fail to respond adequately to these measures. Patients with severe ulcerative colitis that has not responded to intravenous corticosteroids, may benefit from a short course of intravenous ciclosporin [unlicensed indication] (section 1.5.3). Patients with unre sponsive or chronically active Crohn’s disease may benefit from azathioprine (section 1.5.3), mercaptopurine (section 1.5.3), or once-weekly methotrexate (section 1.5.3) [all unlicensed indications].

Infliximab is licensed for the management of severe active Crohn’s disease and moderate to severe ulcerative colitis in patients whose condition has not responded adequately to treatment with a corticosteroid and a conventional immunosuppressant or who are intolerant of them.

NICE guidance

Infliximab for Crohn’s disease (April 2002)
Infliximab is recommended for the treatment of severe active Crohn’s disease (with or without fistulae) when treatment with immunomodulating drugs and corticosteroids has failed or is not tolerated and when surgery is inappropriate. Treatment may be repeated if the condition responded to the initial course but relapsed subsequently. Infliximab should be prescribed only by a gastroenterologist.

NICE guidance

Infliximab for subacute manifestations of ulcerative colitis (April 2008)
Infliximab is not recommended for the treatment of subacute manifestations of moderate to severe active ulcerative colitis that would normally be managed in an outpatient setting.

Adalimumab is licensed for the treatment of severe active Crohn’s disease in patients whose condition has
not responded adequately to treatment with a cortisone and a conventional immunosuppressant, or who are intolerant of them. For inducing remission, adalimumab should be used in combination with a corticosteroid, but it may be given alone if a corticosteroid is inappropriate or is not tolerated. Adalimumab may also be used for Crohn’s disease in patients who have relapsed while taking infliximab or who cannot tolerate infliximab because of hypersensitivity reactions.

**Maintenance of remission of acute ulcerative colitis and Crohn’s disease** Smoking cessation (section 4.10) may reduce the risk of relapse in Crohn’s disease. Aminosalicylates are of great value in the maintenance of remission of ulcerative colitis. They are of less value in the maintenance of remission of Crohn’s disease; an oral formulation of mesalazine is licensed for the long-term management of ileal disease. Corticosteroids are not suitable for maintenance treatment because of their side-effects. In resistant or frequently relapsing cases either azathioprine (section 1.5.3) [unlicensed indication] or mercaptopurine (section 1.5.3) [unlicensed indication], given under close supervision may be helpful. Methotrexate (section 1.5.3) is tried in Crohn’s disease if azathioprine or mercaptopurine cannot be used [unlicensed indication]. Maintenance therapy with infliximab should be considered for patients with Crohn’s disease or ulcerative colitis who respond to the initial induction course of infliximab; fixed-interval dosing is superior to intermittent dosing. Adalimumab is licensed for maintenance therapy in Crohn’s disease.

**Fistulating Crohn’s disease** Treatment may not be necessary for simple, asymptomatic perianal fistulas. Metronidazole (section 5.1.11) or ciprofloxacin (section 5.1.12) may be beneficial for the treatment of fistulating Crohn’s disease [unlicensed indication]. Metronidazole by mouth is used at a dose of 10–20 mg/kg daily in divided doses (usual dose 400–500 mg 3 times daily); it is usually given for 1 month but no longer than 3 months because of concerns about developing peripheral neuropathy. Ciprofloxacin by mouth is given at a dose of 500 mg twice daily, usually for 2–3 weeks. Other antibacterials should be given if specifically indicated (e.g. sepis associated with fistulas and perianal disease) and for managing bacterial overgrowth in the small bowel. Fistulas may also require surgical exploration and local drainage.

Either azathioprine or mercaptopurine is used as a second-line treatment for fistulating Crohn’s disease and continued for maintenance [unlicensed indication]. Infliximab is used for fistulating Crohn’s disease refractory to conventional treatments and it can be continued as maintenance therapy. Adalimumab can be used if there is intolerance to infliximab [unlicensed indication].

**Adjunctive treatment of inflammatory bowel disease** Due attention should be paid to diet; high-fibre or low-residue diets should be used as appropriate. Irritable bowel syndrome during remission of ulcerative colitis calls for avoidance of a high-fibre diet and possible treatment with an antispasmodic (section 1.2). Antimotility drugs such as codeine and loperamide, and antispasmodic drugs may precipitate paralytic ileus and megacolon in active ulcerative colitis; treatment of the inflammation is more logical. Laxatives may be required in proctitis. Diarrhoea resulting from the loss of bile-salt absorption (e.g. in terminal ileal disease or bowel resection) may improve with colestyramine (section 1.9.2), which binds bile salts.

**Clostridium difficile infection** Antibiotic-associated colitis is caused by colonisation of the colon with *Clostridium difficile* which may follow antibiotic therapy. It is usually of acute onset, but may run a chronic course; it is a particular hazard of clindamycin but few antibiotics are free of this side-effect. Oral metronidazole (see section 5.1.11) or oral vancomycin (see section 5.1.7) are used as specific treatment; vancomycin may be preferred for very sick patients. Metronidazole can be given by intravenous infusion if oral treatment is inappropriate.

**Diverticular disease** Diverticular disease is treated with a high-fibre diet, bran supplements, and bulk-forming drugs (section 1.6.1). Antispasmodics may provide symptomatic relief when colic is a problem (section 1.2). Antibacterials are used only when the diverticula in the intestinal wall become infected (specialist referral). Antimotility drugs which slow intestinal motility, e.g. codeine, diphenoxylate, and loperamide could possibly exacerbate the symptoms of diverticular disease and are contra-indicated.

**Irritable bowel syndrome** Irritable bowel syndrome can present with pain, constipation, or diarrhea. In some patients there may be important psychological aggravating factors which respond to reassurance and possibly specific treatment e.g. with an antidepressant.

The fibre intake of patients with irritable bowel syndrome should be reviewed. If an increase in dietary fibre is required, soluble fibre (e.g. ispaghula husk, sterculia, or oats) is recommended; insoluble fibre (e.g. bran) should be avoided. A laxative (section 1.6) can be used to treat constipation. An osmotic laxative, such as a macrogol, is preferred; lactulose may cause bloating. Loperamide (section 1.4.2) may relieve diarrhoea and antispasmodic drugs (section 1.2) may relieve pain. Opioids with a central action, such as codeine, are better avoided because of the risk of dependence.

A tricyclic antidepressant (section 4.3.1) can be used for abdominal pain or discomfort [unlicensed indication] in patients who have not responded to laxatives, loperamide, or antispasmodics. Low doses of a tricyclic antidepressant are used (e.g. amitriptyline, initially 5–10 mg each night, increased if necessary in steps of 10 mg at intervals of at least 2 weeks to max. 30 mg each night). A selective serotonin reuptake inhibitor (section 4.3.3) may be considered in those who do not respond to a tricyclic antidepressant [unlicensed indication].

**Malabsorption syndromes** Individual conditions need specific management and also general nutritional consideration. Coeliac disease (gluten enteropathy) usually needs a gluten-free diet and pancreatic insufficiency needs pancreatin supplements (section 1.9.4)

For further information on foods for special diets (ACBS), see Appendix 7.
1.5.1 Aminosalicylates

Sulfasalazine is a combination of 5-aminosalicylic acid (‘5-ASA’) and sulfapyridine; sulfapyridine acts only as a carrier to the colonic site of action but still causes side-effects. In the newer aminosalicylates, mesalazine (5-aminosalicylic acid), balsalazide (a prodrug of 5-aminosalicylic acid) and olsalazine (a dimer of 5-aminosalicylic acid) which cleaves in the lower bowel), the sulfonamide-related side-effects of sulfasalazine are avoided, but 5-aminosalicylic acid alone can still cause side-effects including blood disorders (see recommendation below) and lupus-like syndrome also seen with sulfasalazine.

Cautions Renal function should be monitored before starting an oral aminosalicylate, at 3 months of treatment, and then annually during treatment (more frequently in renal impairment). Aminosalicylates should be used with caution in renal impairment (Appendix 3); blood disorders can occur (see recommendation below) and during pregnancy (Appendix 4) and breast-feeding (Appendix 5); blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinemia, peripheral neuropathy, blood disorders (including eosinophilia and fibrosing alveolitis), peripheral neuropathy, blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinemia, neutropenia, and thrombocytopenia—see also recommendation above), renal dysfunction (interstitial nephritis, nephrotic syndrome), myalgia, arthralgia, skin reactions (including lupus erythematosus-like syndrome, Stevens-Johnson syndrome), alopecia.

Contra-indications Aminosalicylates should be avoided in salicylate hypersensitivity.

Side-effects Side-effects of the aminosalicylates include diarrhoea, nausea, vomiting, abdominal pain, exacerbation of symptoms of colitis, headache, hypersensitivity reactions (including rash and urticaria); side-effects that occur rarely include acute pancreatitis, hepatitis, myocarditis, pericarditis, lung disorders (including eosinophilia and fibrosing alveolitis), peripheral neuropathy, blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinemia, neutropenia, and thrombocytopenia—see also recommendation above), renal dysfunction (interstitial nephritis, nephrotic syndrome), myalgia, arthralgia, skin reactions (including lupus erythematosus-like syndrome, Stevens-Johnson syndrome), alopecia.

Blood disorders Patients receiving aminosalicylates should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise that occurs during treatment. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Contra-indications Aminosalicylates should be avoided in salicylate hypersensitivity.

Side-effects Side-effects of the aminosalicylates include diarrhoea, nausea, vomiting, abdominal pain, exacerbation of symptoms of colitis, headache, hypersensitivity reactions (including rash and urticaria); side-effects that occur rarely include acute pancreatitis, hepatitis, myocarditis, pericarditis, lung disorders (including eosinophilia and fibrosing alveolitis), peripheral neuropathy, blood disorders (including agranulocytosis, aplastic anaemia, leucopenia, methaemoglobinemia, neutropenia, and thrombocytopenia—see also recommendation above), renal dysfunction (interstitial nephritis, nephrotic syndrome), myalgia, arthralgia, skin reactions (including lupus erythematosus-like syndrome, Stevens-Johnson syndrome), alopecia.

BALSALAZIDE SODIUM

Indications treatment of mild to moderate ulcerative colitis and maintenance of remission

Cautions see notes above; also history of asthma; interactions: Appendix 1 (aminosalicylates)

Blood disorders See recommendation above

Contra-indications see notes above; also severe hepatic impairment

Side-effects see notes above; also severe hepatic impairment

Dose

- Acute attack, 2.25 g 3 times daily until remission occurs or for up to max. 12 weeks
- Maintenance, 1.5 g twice daily, adjusted according to response (max. 6 g daily)
- CHILD under 18 years, see BNF for Children

Colazide® (Shire) Tablets, beige, balsalazide sodium 750 mg. Net price 130-cap pack = £39.00. Label: 21, 25, counselling, blood disorder symptoms (see recommendation above)

MESALAZINE

Indications treatment of mild to moderate ulcerative colitis and maintenance of remission; see also under preparations

Cautions see notes above; elderly; interactions: Appendix 1 (aminosalicylates)

Blood disorders See recommendation above

Contra-indications see notes above; also severe hepatic impairment (Appendix 2)

Side-effects see notes above

Dose

- See under preparations, below

Note The delivery characteristics of oral mesalazine preparations may vary; these preparations should not be considered interchangeable

Asacol® (Procter & Gamble Pharm.) Foam enema, mesalazine 1 g/ metered application, net price 14-application canister with disposable applicators and plastic bags = £28.37. Counselling, blood disorder symptoms (see recommendation above)

Excipients include disodium edetate, hydroxybenzoates (parabens), polysorbate 20, sodium metabisulphite

Dose acute attack affecting the rectosigmoid region, 1 metered application (mesalazine 1 g) into the rectum daily for 4–6 weeks; acute attack affecting the descending colon, 2 metered applications (mesalazine 2 g) once daily for 4–6 weeks; CHILD 12–18 years, see BNF for Children

Suppositories, mesalazine 250 mg, net price 20-suppos pack = £5.12; 500 mg, 10-suppos pack = £5.12. Counselling, blood disorder symptoms (see recommendation above)

Dose acute attack or maintenance, by rectum 0.75–1.5 g daily in divided doses, with last dose at bedtime; CHILD 12–18 years, see BNF for Children

Asacol® MR (Procter & Gamble Pharm.) Tablets, red, e/c, mesalazine 400 mg, net price 90-tab pack = £31.22, 120-tab pack = £41.62. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ulcerative colitis, acute attack, 2.4 g daily in divided doses; maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis, 1.2–2.4 g daily in divided doses; CHILD 12–18 years, see BNF for Children

Suppositories, red-brown, e/c, mesalazine 800 mg, net price 180-tab pack = £124.86. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ADULT over 18 years, ulcerative colitis, acute attack, 2.4–4.8 g daily in divided doses; maintenance of remission of ulcerative colitis and Crohn’s ileo-colitis, up to 2.4 g daily in divided doses

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Ipolcol® (Sandoz) Tablets, e/c, mesalazine 400 mg, net price 120-tab pack = £41.62. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose acute attack, 2.4 g daily in divided doses; maintenance, 1.2–2.4 g daily in divided doses; CHILD 12–18 years, see BNF for Children

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine
Mesren® MR (IvAX) Tablets, red-brown, e/c, mesalazine 400 mg; net price 90-tab pack = £20.29, 120-tab pack = £27.05. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ADULT and CHLD over 12 years, acute attack, 2.4 g daily in divided doses, maintenance, 1.2–2.4 g daily in divided doses

Mezavant® XL (Shire) Tablets, m/r, red-brown, e/c, mesalazine 1.2 g; net price 60-tab pack = £62.44. Label: 21, 25, counselling, blood disorder symptoms (see recommendations above)

Dose ADULT over 18 years, acute attack, 2.4 g once daily, increase if necessary to 4.8 g once daily (review treatment at 8 weeks); maintenance, 2.4 g once daily

Pentasa® (Ferring) Tablets, m/r, scored, mesalazine 500 mg (grey), net price 100-tab pack = £25.48. Counselling, administration, see dose, blood disorder symptoms (see recommendation above)

Dose ADULT and CHILD over 15 years, acute attack, up to 4 g daily in 2–3 divided doses; maintenance, 1.5 g daily in 2–3 divided doses; tablets may be dispersed in water, but should not be chewed; CHILD 5–15 years see BNF for Children

Granules, m/r, pale brown, mesalazine 1 g/sachet, net price 50-sachet pack = £30.02; 2 g/sachet, 60-sachet pack = £72.05. Counselling, administration, see dose, blood disorder symptoms (see recommendation above)

Dose acute attack, up to 4 g daily in 2–4 divided doses; maintenance, 2 g once daily; granules should be placed on tongue and washed down with water or orange juice without chewing; CHILD 5–12 years see BNF for Children

Retention enema, mesalazine 1 g in 100-mL pack. Net price 7 enemas = £18.09. Counselling, blood disorder symptoms (see recommendation above)

Dose by rectum 1 enema at bedtime; CHILD not recommended

Suppositories, mesalazine 1 g. Net price 28-suppos pack = £41.55. Counselling, blood disorder symptoms (see recommendation above)

Dose by rectum ulcerative proctitis, ADULT and CHILD over 15 years, acute attack, 1 g daily for 2–4 weeks; maintenance, 1 g daily; CHILD 12–15 years see BNF for Children

Salofalk® (Dr Falk) Tablets, e/c, yellow, mesalazine 250 mg. Net price 100-tab pack = £17.40. Label: 5, 25, counselling, blood disorder symptoms (see recommendation above)

Dose ADULT and CHILD over 15 years, acute attack, 1.5 g daily in 3 divided doses; maintenance, 0.75–1.5 g daily in divided doses

Granules, m/r, grey, e/c, vanilla-flavoured, mesalazine 500 mg/sachet, net price 100-sachet pack = £29.30; 1 g/sachet, 50-sachet pack = £29.30; 1.5 g/sachet, 60-sachet pack = £49.80. Label: 25, counselling, administration, see dose, blood disorder symptoms (see recommendation above)

Suppositories, mesalazine 500 mg. Net price 30-suppos pack = £15.90. Counselling, blood disorder symptoms (see recommendation above)

Dose ADULT and CHILD over 15 years, acute attack, by rectum, 0.5–1 g 2–3 times daily adjusted according to response; CHILD 12–15 years, see BNF for Children

Enema, mesalazine 2 g in 59-mL pack. Net price 7 enemas = £31.20. Counselling, blood disorder symptoms (see recommendation above)

Dose acute attack or maintenance, by rectum, 2 g daily at bedtime; CHILD 12–18 years, see BNF for Children

Rectal foam, mesalazine 1 g/metered application, net price 14-application canister with disposable applicators and plastic bags = £31.10. Counselling, blood disorder symptoms (see recommendation above)

Excipients include cetostearyl alcohol, disodium edetate, polysorbate 60, propylene glycol, sodium metabisulphate

Dose mild ulcerative colitis affecting sigmoid colon and rectum, ADULT and CHILD over 12 years, 2 metered applications (mesalazine 2 g) into the rectum at bedtime increased if necessary to 2 metered applications (mesalazine 2 g) twice daily

Olsalazine Sodium

Indications treatment of mild ulcerative colitis and maintenance of remission

Cautions see notes above; interactions: Appendix 1 (aminosalicylates)

Blood disorders See recommendation above

Contra-indications see notes above

Side-effects see notes above; also watery diarrhoea

Dose
- ADULT and CHILD over 12 years, acute attack, 1 g daily in divided doses after meals increased if necessary over 1 week to max. 3 g daily (max. single dose 1 g); maintenance, 500 mg twice daily after meals
- CHILD under 12 years see BNF for Children

Dipentum® (UCB Pharma) Capsules, brown, olsalazine sodium 250 mg. Net price 112-cap pack = £20.57. Label: 21, counselling, blood disorder symptoms (see recommendation above)

Tablets, yellow, scored, olsalazine sodium 500 mg. Net price 60-tab pack = £22.04. Label: 21, counselling, blood disorder symptoms (see recommendation above)

Sulfasalazine (Sulphasalazine)

Indications treatment of mild to moderate and severe ulcerative colitis and maintenance of remission; active Crohn's disease; rheumatoid arthritis (section 10.1.3)

Cautions see notes above; also history of allergy; hepatic impairment; G6PD deficiency (section 9.1.5); slow acetylator status; risk of haematological and hepatic toxicity (differential white cell, red cell and platelet counts initially and at monthly intervals for first 3 months); liver function tests at monthly intervals for first 3 months); upper gastro-intestinal side-effects common over 4 g daily; acute porphyria (section 9.8.2); interactions: Appendix 1 (aminosalicylates)

Blood disorders See recommendation above

Contra-indications see notes above; also sulphasalazine and olsalazine

Side-effects see notes above; also loss of appetite; fever; blood disorders (including Heinz body anaemia, megaloblastic anaemia); hypersensitivity reactions (including exfoliative dermatitis, epidermal necrolysis, pruritus, photosensitisation, anaphylaxis, serum sickness); ocular complications (including peri-orbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, insomnia, depression, hallucinations; kidney reactions (including proteinur-
ia, crystalluria, haematuria); oligosperma; urine may be coloured orange; some soft contact lenses may be stained

**Dose**

- **By mouth**, acute attack 1–2 g 4 times daily (but see **cautions** until remission occurs (if necessary corticosteroids may also be given), reducing to a maintenance dose of 500 mg 4 times daily; **CHILD** over 2 years, acute attack 40–60 mg/kg daily, maintenance dose 20–30 mg/kg daily
- **By rectum**, in suppositories, alone or in conjunction with oral treatment 0.5–1 g morning and night after a bowel movement

**Sulfasalazine** (Non-proprietary) *(Non-proprietary)*

- **Tablets**, sulfasalazine 500 mg. Net price 112 = £9.21. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained
- **Tablets**, e/c, sulfasalazine 500 mg. **NET** price 112-tab pack = £21.52. Label: 5, 14, 25, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

**Brands include** Salazine EC

**Salazopyrin** *(Pharmacia)* *(Pharmacia)*

- **Tablets**, yellow, scored, sulfasalazine 500 mg. Net price 112-tab pack = £8.97. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained
- **EN-Tabs** *(= tablets e/c)*, yellow, f/c, sulfasalazine 500 mg. **NET** price 112-tab pack = £8.43. Label: 5, 14, 25, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained
- **Suspension**, yellow, sulfasalazine 250 mg/5 mL. **NET** price 500 mL = £18.84. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained
- **Suppositories**, yellow, sulfasalazine 500 mg. **NET** price 10 = £3.30. Label: 14, counselling, blood disorder symptoms (see recommendation above), contact lenses may be stained

**BUDESONIDE**

**Indications** see preparations

**Cautions** section 6.3.2; **interactions**: Appendix 1 (corticosteroids)

**Contra-indications** section 6.3.2

**Side-effects** section 6.3.2

**Dose**

- See preparations

**Budenofalk** *(Dr Falk)* *(Dr Falk)*

- **Capsules**, pink, enclosing e/c pellets, budesonide 3 mg, **NET** price 100-cap pack = £76.70. Label: 5, 10, steroid card, 22, 25
- **Dose** mild to moderate Crohn’s disease affecting ileum or ascending colon, chronic diarrhoea due to collagenous colitis, **ADULT** over 18 years, 3 mg 3 times daily for up to 8 weeks; reduce dose for the last 2 weeks of treatment (see also section 6.3.2), **CHILD** 12–18 years, see **BNF for Children**

**Rectal foam**, budesonide 2 mg/metered application, net price 14-application canister with disposable applicators and plastic bags = £58.22

**Excipients** include cetyl alcohol, disodium edetate, propylene glycol, sorbic acid
- **Dose** ulcerative colitis affecting sigmoid colon and rectum, **by rectum**; **ADULT** over 18 years, 1 metered application (budesonide 2 mg) once daily for up to 8 weeks

**Entocort** *(AstraZeneca)* *(AstraZeneca)*

- **CR Capsules**, grey/pink, enclosing e/c pellets, m/r granules, budesonide 3 mg, **NET** price 100-cap pack = £99.00. Label: 5, 10, steroid card, 25
- **Note** Dispense in original container (contains desiccant)
- **Dose** mild to moderate Crohn’s disease affecting the ileum or ascending colon, 9 mg once daily in the morning for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment (see also section 6.3.2), **CHILD** 12–18 years, see **BNF for Children**

**Enema**, budesonide 2 mg/100 mL when dispersible tablet reconstituted in isotonic saline vehicle, net price pack of 7 dispersible tablets and bottles of vehicle = £33.00
- **Dose** ulcerative colitis involving rectal and recto-sigmoid disease, **by rectum**; 1 enema at bedtime for 4 weeks; **CHILD** 12–18 years, see **BNF for Children**

**HYDROCORTISONE**

**Indications** ulcerative colitis, proctitis, proctosigmoiditis

**Cautions** section 6.3.2; systemic absorption may occur; prolonged use should be avoided

**Contra-indications** intestinal obstruction, bowel perforation, recent intestinal anastomoses, extensive fistulas; untreated infection

**Side-effects** section 6.3.2; also local irritation

**Dose**

- **By rectum** see preparations

**Colifoam** *(Meda)* *(Meda)*

- **Foam** in aerosol pack, hydrocortisone acetate 10%, net price 14-application canister with applicator = £8.21
- **Excipients** include cetyl alcohol, hydroxybenzoates (parabens), propylene glycol
- **Dose** initially 1 metered application (125 mg hydrocortisone acetate) inserted into the rectum once or twice daily for 2–3 weeks, then once on alternate days, **CHILD** 2–18 years, see **BNF for Children**

**1.5.2 Corticosteroids**

For the role of corticosteroids in acute ulcerative colitis and Crohn’s disease, see Inflammatory Bowel Disease, p. 52.

**BECLOMETASONE DIPROPIONATE**

**Indications** adjunct to aminosalicylates in acute mild to moderate ulcerative colitis; asthma (section 3.2); allergic and vasomotor rhinitis (section 12.2.1); oral ulceration [unlicensed indication] (section 12.3.1)

**Cautions** section 6.3.2; **interactions**: Appendix 1 (corticosteroids)

**Contra-indications** section 6.3.2

**Side-effects** section 6.3.2; also nausea, constipation, headache, and drowsiness

**Dose**

- 5 mg in the morning; max. duration of treatment 4 weeks; **CHILD** safety and efficacy not established

**Clipper** *(Trinity-Chiesi)* *(Trinity-Chiesi)*

- **Tablets**, m/r, ivory, beclometasone dipropionate 5 mg, **NET** price 30-tab pack = £60.00. Label: 25
**PREDNISOLONE**

**Indications** ulcerative colitis, and Crohn’s disease; other indications, see section 6.3.2, see also preparations

**Cautions** section 6.3.2; systemic absorption may occur with rectal preparations; prolonged use should be avoided

**Contra-indications** section 6.3.2; intestinal obstruction, bowel perforation, recent intestinal anastomoses, extensive fistulas; untreated infection

**Side-effects** section 6.3.2

**Dose**
- **By mouth**, initially 20–40 mg daily (or up to 1 mg/kg daily) preferably taken in the morning after breakfast; continued until remission occurs, followed by reducing doses
- **By rectum**, see preparations

**Oral preparations** Section 6.3.2

**Rectal preparations**

**Predenema®** (Forest)
- **Retention enema**, prednisolone 20 mg (as sodium metasulphobenzoate) in 100-mL single-dose disposable pack. Net price 1 (standard tube) = £1.21

**Dose** ulcerative colitis, by rectum, **ADULT** and **CHILD** over 12 years, initially 20 mg at bedtime for 2–4 weeks, continued if good response

**Predfoam®** (Forest)
- **Foam** in aerosol pack, prednisolone 20 mg (as metasulphobenzoate sodium)/metered application, net price 14-application canister with disposable applicators = £6.32

**Excipients** include cetostearyl alcohol, disodium edetate, polysorbate 20, sorbic acid

**Dose** proctitis and distal ulcerative colitis, 1 metered application (20 mg prednisolone) inserted into the rectum once or twice daily for 2 weeks, continued for further 2 weeks if good response; **CHILD** not recommended

**Predsol®** (UCB Pharma)
- **Retention enema**, prednisolone 20 mg (as sodium phosphate) in 100-mL single-dose disposable packs fitted with a nozzle. Net price 7 = £7.50

**Dose** rectal and rectosigmoidal ulcerative colitis and Crohn’s disease, **by rectum**, initially 20 mg at bedtime for 2–4 weeks, continued if good response; **CHILD** not recommended

**Suppositories**, prednisolone 5 mg (as sodium phosphate). Net price 10 = £1.40

**Dose** **ADULT** and **CHILD** proctitis and rectal complications of Crohn’s disease, **by rectum**, 5 mg inserted night and morning after a bowel movement

---

**AZATHIOPRINE**

**Indications** see under Inflammatory Bowel Disease, p. 52; autoimmune conditions and prophylaxis of transplant rejection (section 8.2.1); rheumatoid arthritis (section 10.1.3)

**Cautions** section 8.2.1

**Contra-indications** section 8.2.1

**Side-effects** section 8.2.1; also severe diarrhoea

**Dose**
- Severe acute Crohn’s disease, maintenance of remission of Crohn’s disease or ulcerative colitis [unlicensed indications], **ADULT** over 18 years, **by mouth**, 2–2.5 mg/kg daily; some patients may respond to lower doses

**Preparations** Section 8.2.1

---

**CICLOSPORIN** (Cyclosporin)

**Indications** severe acute ulcerative colitis refractory to corticosteroid treatment [unlicensed indication]; transplantation and graft-versus-host disease, nephrotic syndrome (section 8.2.2); rheumatoid arthritis (section 10.1.3); atopic dermatitis and psoriasis (section 13.5.3)

**Cautions** section 8.2.2

**Contra-indications** section 8.2.2

**Side-effects** section 8.2.2

**Dose**
- **By continuous intravenous infusion**, **ADULT** over 18 years, 2 mg/kg daily over 24 hours; dose adjusted according to blood-ciclosporin concentration and response

**Preparations** Section 8.2.2

---

**MERCAPTOPURINE**

**Indications** see under Inflammatory Bowel disease, p. 52; acute leukaemias and chronic myeloid leukaemia (section 8.1.3)

**Cautions** section 8.1.3

**Contra-indications** section 8.1.3

**Side-effects** section 8.1.3

**Dose**
- Severe acute Crohn’s disease, maintenance of remission of Crohn’s disease or ulcerative colitis [unlicensed indications], **ADULT** over 18 years, **by mouth**, 1–1.5 mg/kg daily; some patients may respond to lower doses

**Preparations** Section 8.1.3

---

**METHOTREXATE**

**Indications** see under Inflammatory Bowel Disease, p. 52; malignant disease (section 8.1.3); rheumatoid arthritis (section 10.1.3); psoriasis (section 13.5.3)

**Cautions** section 10.1.3

**Contra-indications** section 10.1.3

**Side-effects** section 10.1.3

---

1.5.3 Drugs affecting the immune response

For the role of azathioprine, ciclosporin, mercaptopurine, and methotrexate in the treatment of inflammatory bowel disease, see p. 52.
Dose

- Severe Crohn's disease [unlicensed indication], ADULT over 18 years, by intramuscular injection, induction of remission, 25 mg once weekly; maintenance, 15 mg once weekly

Important
Note that the above dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:

- the patient is carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

Preparations
Section 10.1.3

Cytokine modulators

Infliximab and adalimumab are monoclonal antibodies which inhibit the pro-inflammatory cytokine, tumour necrosis factor alpha. They should be used under specialist supervision. Adequate resuscitation facilities must be available when infliximab is used.

ADALIMUMAB

Indications see under Inflammatory Bowel Disease, p. 52; ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, juvenile idiopathic arthritis, (section 10.1.3); psoriasis (section 13.5.3)

Cautions section 10.1.3

Contra-indications section 10.1.3

Side-effects section 10.1.3

Dose

- By subcutaneous injection, severe active Crohn's disease, ADULT over 18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks after initial dose; then if the condition has responded, maintenance either 5 mg/kg 6 weeks after initial dose, then 5 mg/kg every 8 weeks or further dose of 5 mg/kg if signs and symptoms recur; CHILD 6–18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then 5 mg/kg every 8 weeks; interval between maintenance doses adjusted according to response; discontinue if no response within 10 weeks of initial dose

Fistulating Crohn's disease, ADULT over 18 years, initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then if condition has responded, consult product literature for guidance on further doses; CHILD under 18 years, see BNF for Children

SODIUM CROMOGLICATE (sodium cromoglycate) may be helpful as an adjunct to dietary avoidance.

Preparations
Section 10.1.3

1.5.4 Food allergy

Allergy with classical symptoms of vomiting, colic and diarrhoea caused by specific foods such as shellfish should be managed by strict avoidance. The condition should be distinguished from symptoms of occasional food intolerance in those with irritable bowel syndrome.

Preparations
Section 10.1.3

SODIUM CROMOGLICATE

(Sodium cromoglycate)

Indications food allergy (in conjunction with dietary restriction); asthma (section 3.3); allergic conjunctivitis (section 11.4.2); allergic rhinitis (section 12.2.1)

Side-effects occasional nausea, rashes, and joint pain

Dose

- 200 mg 4 times daily before meals; may be increased if necessary after 2–3 weeks to a max. of 40 mg/kg daily and then reduced according to response; CHILD 2–14 years 100 mg 4 times daily before meals; may be increased if necessary after 2–3 weeks to a max. of 40 mg/kg daily and then reduced according to response

Counselling Capsules may be swallowed whole or the contents dissolved in hot water and diluted with cold water before taking

Nalcrom® (Sanofi-Aventis) ™
Capsules, sodium cromoglicate 100 mg. Net price 100-cap pack = £62.17. Label: 22, counselling, see dose above
Before prescribing laxatives it is important to be sure that the patient is constipated and that the constipation is not secondary to an underlying undiagnosed complaint.

It is also important for those who complain of constipation to understand that bowel habit can vary considerably in frequency without doing harm. Some people tend to consider themselves constipated if they do not have a bowel movement each day. A useful definition of constipation is the passage of hard stools less frequently than the patient’s own normal pattern and this can be explained to the patient.

Misconceptions about bowel habits have led to excessive laxative use. Abuse may lead to hypokalaemia. Thus, laxatives should generally be avoided except where straining will exacerbate a condition (such as angina) or increase the risk of rectal bleeding as in haemorrhoids. Laxatives are also of value in drug-induced constipation, for the expulsion of parasites after anthelmintic treatment, and to clear the alimentary tract before surgery and radiological procedures. Prolonged treatment of constipation is sometimes necessary.

Children Laxatives should be prescribed by a healthcare professional experienced in the management of constipation in children. Delays of greater than 3 days between stools may increase the likelihood of pain on passing hard stools leading to anal fissure, anal spasm and eventually to a learned response to avoid defaecation.

If increased fluid and fibre intake is insufficient, an osmotic laxative containing macrogol or lactulose (section 1.6.4) can be used. If there is evidence of minor faecal retention, the addition of a stimulant laxative (section 1.6.2) may overcome withholding but may lead to colic or, in the presence of faecal impaction in the rectum, an increase of faecal overflow.

In children with faecal impaction, an oral preparation containing macrogol is used to clear faecal mass and to establish and maintain soft well-formed stools. Rectal administration of laxatives may be effective but this route is frequently distressing for the child and may lead to persistent withholding. If the impacted mass is not expelled following treatment with macrogol, referral to hospital may be necessary. Enemas may be administered under heavy sedation in hospital or alternatively, a bowel cleansing solution (section 1.6.5) may be tried. In severe cases or where the child is afraid, a manual evacuation under anaesthetic may be appropriate.

Long-term regular use of laxatives is essential to maintain well-formed stools and prevent recurrence of faecal impaction; intermittent use may provoke relapses.

For children with chronic constipation, it may be necessary to exceed the licensed doses of some laxatives. Parents and carers of children should be advised to adjust the dose of laxative in order to establish a regular pattern of bowel movements in which stools are soft, well-formed, and passed without discomfort.

Pregnancy If dietary and lifestyle changes fail to control constipation in pregnancy, moderate doses of poorly absorbed laxatives may be used. A bulk-forming laxative should be tried first. An osmotic laxative, such as lactulose, can also be used. Bisacodyl or senna may be suitable, if a stimulant effect is necessary.

The laxatives that follow have been divided into 5 main groups (sections 1.6.1–1.6.5). This simple classification disguises the fact that some laxatives have a complex action.

### 1.6.1 Bulk-forming laxatives

Bulk-forming laxatives relieve constipation by increasing faecal mass which stimulates peristalsis; patients should be advised that the full effect may take some days to develop.

Bulk-forming laxatives are of particular value in those with small hard stools, but should not be required unless fibre cannot be increased in the diet. A balanced diet, including adequate fluid intake and fibre is of value in preventing constipation.

Bulk-forming laxatives are useful in the management of patients with colostomy, ileostomy, haemorrhoids, anal fissure, chronic diarrhoea associated with diverticular disease, irritable bowel syndrome, and as adjuncts in ulcerative colitis (section 1.5). Adequate fluid intake must be maintained to avoid intestinal obstruction. Unprocessed wheat bran, taken with food or fruit juice, is a most effective bulk-forming preparation. Finely ground bran, though more palatable, has poorer water-retaining properties, but can be taken as bran bread or biscuits in appropriately increased quantities. Oat bran is also used.

Methylcellulose, ispaghula, and ster culia are useful in patients who cannot tolerate bran. Methylcellulose also acts as a faecal softener.

#### ISPAGHULA HUSK

**Indications** see notes above

**Cautions** adequate fluid intake should be maintained to avoid intestinal obstruction—it may be necessary to supervise elderly or debilitated patients or those with intestinal narrowing or decreased motility

**Contra-indications** difficulty in swallowing, intestinal obstruction, colonic atony, faecal impaction

**Side-effects** flatulence, abdominal distension, gastrointestinal obstruction or impaction; hypersensitivity reported

**Dose**

• See preparations below

**Counselling** Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed
1.6.2 Stimulant laxatives

Stimulant laxatives include bisacodyl and members of the anthraquinone group, senna and dantron (danthon). The indications for dantron are limited (see below) by its potential carcinogenicity (based on rodent carcinogenicity studies) and evidence of genotoxicity. Powerful stimulants such as cascara (an anthraquinone) and castor oil are obsolete. Docusate sodium probably acts both as a stimulant and as a softening agent.

Stimulant laxatives increase intestinal motility and often cause abdominal cramp; they should be avoided in intestinal obstruction. Excessive use of stimulant laxatives can cause diarrhoea and related effects such as hypokalaemia; however, prolonged use may be justifiable in some circumstances (see section 1.6 for the use of stimulant laxatives in children).

Glycerol suppositories act as a rectal stimulant by virtue of the mildly irritant action of glycerol. The parasymphathomimetics bethanechol, distigmine, neostigmine, and pyridostigmine (see section 7.4.1 and section 10.2.1) enhance parasympathetic activity in the gut and increase intestinal motility. They are rarely used for their gastro-intestinal effects. Organic obstruction of the gut must first be excluded and they should not be used shortly after bowel anastomosis.

### METHYCELLULOSE

**Indications** see notes above; adjunct in obesity (but see section 4.5.1)

**Cautions** see under Ispaghula Husk

**Contra-indications** see under Ispaghula Husk; also infective bowel disease

**Side-effects** see under Ispaghula Husk

**Dose**

- See preparations below

  **Counselling** Preparations that swell in contact with liquid should always be carefully swallowed with water and should not be taken immediately before going to bed

---

**BISACODYL**

**Indications** see under Dose

**Cautions** see notes above; pregnancy, see p. 59

**Contra-indications** see notes above, acute surgical abdominal conditions, acute inflammatory bowel disease, severe dehydration

**Side-effects** see notes above; tablets, griping; suppositories, local irritation
### Dose

- **Constipation. by mouth;** 5–10 mg at night; **CHILD** (but see section 1.6) 4–10 years (on medical advice only) 5 mg at night, over 10 years, adult dose

**By rectum** in suppositories, 10 mg in the morning; **CHILD** (but see section 1.6) under 10 years (on medical advice only) 5 mg, over 10 years, adult dose

- Before radiological procedures and surgery, **by mouth,** 10–20 mg the night before procedure and **by rectum** in suppositories, 10 mg the following morning; **CHILD** 4–10 years **by mouth,** 5 mg the night before procedure and **by rectum** in suppositories, 5 mg the following morning; over 10 years, adult dose

**Note** tablets act in 10–12 hours; suppositories act in 20–60 minutes

### Bisacodyl (Non-proprietary)

**Tablets,** e/c, bisacodyl 5 mg. Net price 20 = 65p. Label: 5, 25

**Suppositories,** bisacodyl 10 mg. Net price 12 = 89p

**Paediatric suppositories,** bisacodyl 5 mg. Net price 5 = 94p

**Note** The brand name Dulcolax (Boehringer Ingelheim) is used for bisacodyl tablets. Net price 10-tab pack = 74p; suppositories (10 mg), 10 = £1.57; paediatric suppositories (5 mg), 5 = 94p.

The brand names Dulcolax, Liquid and Dulcolax Perles are used for sodium picosulfate preparations

### DANTRON (Danthron)

**Indications** only for constipation in terminally ill patients of all ages

**Cautions** see notes above; rodent studies indicate potential carcinogenic risk; avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies)—risk of irritation and excoriation; pregnancy (Appendix 4) and breastfeeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above; urine may be coloured red

**Dose**

- See under preparations

**With poloxamer ‘188’ (as co-danthramer)**

**Note** Co-danthramer suspension 5 mL = one co-danthramer capsule, but strong co-danthramer suspension 5 mL = two strong co-danthramer capsules

**Co-danthramer (Non-proprietary)**

**Capsules,** co-danthramer 25/200 (dantron 25 mg, poloxamer ‘188’ 200 mg). Net price 60-cap pack = £12.86. Label: 14, (urine red)

**Dose** 1–2 capsules at bedtime; **CHILD** 1 capsule at bedtime (restricted indications, see notes above)

**Strong capsules,** co-danthramer 37.5/500 (dantron 37.5 mg, poloxamer ‘188’ 500 mg). Net price 60-cap pack = £15.55. Label: 14, (urine red)

**Dose** **ADULT** and **CHILD** over 12 years, 1–2 capsules at bedtime (restricted indications, see notes above)

**Suspension,** co-danthramer 25/200 in 5 mL (dantron 25 mg, poloxamer ‘188’ 200 mg/5 mL). Net price 300 mL = £11.27, 1 litre = £37.57. Label: 14, (urine red)

**Dose** 5–10 mL at night; **CHILD** 2.5–5 mL (restricted indications, see notes above)

**Brands include** Codalax, Danlax

**With docusate sodium (as co-danthrusate)**

**Co-danthrusate (Non-proprietary)**

**Capsules,** co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg). Net price 63-cap pack = £14.50. Label: 14, (urine red)

**Dose** 1–3 capsules at night; **CHILD** 6–12 years 1 capsule at night (restricted indications, see notes above)

**Brands include** Normax

**Suspension,** yellow, co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg/5 mL). Net price 200 mL = £8.75. Label: 14, (urine red)

**Dose** 5–15 mL at night; **CHILD** 6–12 years 5 mL at night (restricted indications, see notes above)

**Brands include** Normax

### Docusate Sodium (Dicetyl sodium sulphosuccinate)

**Indications** constipation, adjunct in abdominal radiological procedures

**Cautions** see notes above; do not give with liquid paraffin; rectal preparations not indicated if haemorrhoids or anal fissure; pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- **By mouth,** chronic constipation, up to 500 mg daily in divided doses; **CHILD** (but see section 1.6) 6 months–2 years 12.5 mg 3 times daily, 2–12 years 12.5–25 mg 3 times daily (use paediatric oral solution only)

**Note** Oral preparations act within 1–2 days

With barium meal, **ADULT** and **CHILD** over 12 years, 400 mg

**Dicolyt** (UCB Pharma)

**Capsules,** yellow/white, docusate sodium 100 mg, net price 30-cap pack = £2.40, 100-cap pack = £8.00

**Docusol** (Typharm)

**Adult oral solution,** sugar-free, docusate sodium 50 mg/5 mL, net price 300 mL = £2.48

**Paediatric oral solution,** sugar-free, docusate sodium 12.5 mg/5 mL, net price 300 mL = £1.63

**Rectal preparations**

**Norgalax Micro-enema** (Norgine)

**Enema,** docusate sodium 120 mg in 10-g single-dose disposable packs. Net price 10-g unit = 60p

**Dose** **ADULT** and **CHILD** (but see section 1.6) over 12 years, 10-g unit

### Glycerol (Glycerin)

**Indications** constipation

**Dose**

- See below
Glycerol Suppositories, BP (Glycerin Suppositories)

Suppositories, gelatin 140 mg, glycerol 700 mg, purified water to 1 g. Net price 12 = £1.07 (infant), £1.03 (child), £1.54 (adult)

Dose 1 suppository moistened with water before use, when required. The usual sizes are for INFANT under 1 year, small (1-g mould), CHILD 1–12 years medium (2-g mould), ADULT and CHILD over 12 years, large (4-g mould)

Indications constipation; bowel evacuation before abdominal radiological and endoscopic procedures on the colon, and surgery (section 1.6.5); acts within 6–12 hours

Cautions see notes above; active inflammatory bowel disease (avoid if fulminant); pregnancy, see p. 59; breastfeeding (Appendix 5)

Side-effects see notes above; severe dehydration

Contra-indications see notes above; pregnancy, see p. 59

Bowel cleansing solutions

Section 1.6.5

Other stimulant laxatives

Unstandardised preparations of cascara, frangula, rhubarb, and senna should be avoided as their laxative action is unpredictable. Aloeis, colocynth, and jalap should be avoided as they have a drastic purgative action.

Sodium Picosulfate (Non-proprietary)

Elixir, sodium picosulfate 5 mg/5 mL, net price 100 mL = £1.85

Note The brand name Dulcolax Liquid (Boehringer Ingelheim) is used for sodium picosulfate elixir 5 mg/5 mL.

Dulcolax® (Boehringer Ingelheim)

Perles® (= capsules), sodium picosulfate 2.5 mg, net price 20-cap pack = £1.93, 50-cap pack = £2.73

Note The brand name Dulcolax is also used for bisacodyl tablets and suppositories

ARACHIS OIL

Enema, arachis (peanut) oil in 130-mL single-dose disposable packs. Net price 130 mL = £7.98

Note The brand name Arachis Oil Enema is also used for bisacodyl tablets and suppositories

LIQUID PARAFFIN

Indications constipation; bowel evacuation after abdominal radiological and endoscopic procedures on the colon, and surgery (section 1.6.5); acts within 6–12 hours

Cautions see notes above; active inflammatory bowel disease (avoid if fulminant); pregnancy, see p. 59; breastfeeding (Appendix 5)

Contra-indications see notes above; severe dehydration

Side-effects anal seepage of paraffin and consequent anal irritation after prolonged use, granulomatous reactions caused by absorption of small quantities of liquid paraffin (especially from the emulsion), lipid pneumonia, and interference with the absorption of fat-soluble vitamins

Dose See under preparation
1.6.4 Osmotic laxatives

Osmotic laxatives increase the amount of water in the large bowel, either by drawing fluid from the body into the bowel or by retaining the fluid they were administered with.

**Lactulose** is a semi-synthetic disaccharide which is not absorbed from the gastro-intestinal tract. It produces an osmotic diarrhoea of low faecal pH, and discourages the proliferation of ammonia-producing organisms. It is therefore useful in the treatment of hepatic encephalopathy.

**Macrogols** are inert polymers of ethylene glycol which sequester fluid in the bowel; giving fluid with macrogols may reduce the dehydrating effect sometimes seen with osmotic laxatives.

Saline purgatives such as magnesium hydroxide are commonly abused but are satisfactory for occasional use; adequate fluid intake should be maintained.

**Magnesium salts** are useful where rapid bowel evacuation is required. **Sodium salts** should be avoided as they may give rise to sodium and water retention in susceptible individuals. **Phosphate enemas** are useful in bowel clearance before radiology, endoscopy, and surgery.

---

**LACTULOSE**

**Indications** constipation (may take up to 48 hours to act), hepatic encephalopathy (portal systemic encephalopathy)

**Cautions** lactose intolerance; interactions: Appendix 1 (lactulose)

**Contra-indications** galactosaemia, intestinal obstruction

**Side-effects** flatulence, cramps, and abdominal discomfort

**Dose**

- See under preparations below

**Lactulose** (Non-proprietary)

**Solution**, lactulose 3.1–3.7 g/5 mL with other ketoses. Net price 300–mL pack = £2.51, 500–mL pack = £2.90

**Dose** constipation, initially 15 mL twice daily, adjusted according to patient’s needs; CHILD (adjusted according to response but see section 1.6) under 1 year 2.5 mL twice daily, 1–5 years 5 mL twice daily, 5–10 years 10 mL twice daily

Hepatic encephalopathy, 30–50 mL 3 times daily, subsequently adjusted to produce 2–3 soft stools daily

**Brands** include Daphlac, Lactugal, Regulose

**MACROGOLS** (Polyethylene glycols)

**Indications** see preparations below

**Cautions** pregnancy (Appendix 4); breast-feeding (Appendix 5); discontinue if symptoms of fluid and electrolyte disturbance; see also preparations below

**Laxido®** (Galen)

**Oral powder**, orange-flavoured, macrogol ‘3350’ (polyethylene glycol ‘3350’) 13.125 g. sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 45.5 g/sachet.

**Dose**

- Faecal impaction, ADULT and CHILD over 12 years, 8 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for max. 3 days
- After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

**Movicol®** (Norgine)

**Oral powder**, macrogol ‘3350’ (polyethylene glycol ‘3350’) 13.125 g. sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 45.5 g/sachet.

**Dose**

- Faecal impaction, ADULT and CHILD over 12 years, 1–3 sachets daily in divided doses usually for up to 2 weeks; contents of each sachet dissolved in half a glass (approx. 125 mL) of water, maintenance, 1–2 sachets daily
- Faecal impaction, ADULT and CHILD over 12 years, 8 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for max. 3 days
- After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

**Movicol®-Half** (Norgine)

**Oral powder**, macrogol ‘3350’ (polyethylene glycol ‘3350’) 6.563 g, sodium bicarbonate 89.3 mg, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet, net price 20–sachet pack = £3.56, 30–sachet pack = £5.34. Label: 13

**Note** also available in natural flavour (sugar-free)

**Cautions** patients with cardiovascular impairment should not take more than 2 sachets in any 1 hour

**Movicol®-Half** (Norgine)

**Oral powder**, macrogol ‘3350’ (polyethylene glycol ‘3350’) 13.125 g. sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 45.5 g/sachet.

**Dose**

- Faecal impaction, ADULT and CHILD over 12 years, 8 sachets daily dissolved in 1 litre of water and drunk within 6 hours, usually for max. 3 days
- After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours
SGastro-intestinal system  
Acute gastro-intestinal conditions  
Elderly and debilitated;  
Caution  
Indications  
Rectal use in constipation; bowel evacuation.  
See preparations  
Dose  
Acute gastro-intestinal conditions  
Contra-indications  
Cardiovascular impairment; renal impairment  
Dose  
Chronic constipation and recurrence of faecal impaction, Child 2–6 years 1 sachet daily, 7–11 years 2 sachets daily, adjust accordingly to response, max. 4 sachets daily  
Faecal impaction, Child (taken in divided doses over 12 hours each day until impaction resolves or for max. 7 days) 5–11 years 4 sachets on first day then increased in steps of 2 sachets daily to 12 sachets daily, content of each sachet dissolved in quarter of a glass (approx. 60–65 mL) of water  
After reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours  
Side-effects  
Local irritation; with enema, electrolyte disturbances  
Dose  
See under preparations  
Carbalax® (Forest)  
Suppositories, sodium acid phosphate (anhydrous)  
1.3 g, sodium bicarbonate 1.08 g, net price 12 = £2.01  
Dose  
Constipation, Adult and Child over 12 years, 1 suppository, inserted 30 minutes before evacuation required; moisten with water before use  
Fleet® Ready-to-use Enema (De Witt)  
Enema, sodium acid phosphate 21.4 g, sodium phosphate 9.4 g/118 mL, net price 133 mL pack (delivers 118 mL dose) with standard tube = £57p  
Dose  
Adult and Child (but see section 1.6) over 12 years, 118 mL. Child 3–12 years, on doctor’s advice only (under 3 years not recommended)  
Phosphates Enema BP Formula B  
Enema, sodium dihydrogen phosphate dihydrate 12.8 g, sodium phosphate dodecahydrate 10.24 g, purified water, freshly boiled and cooled, to 128 mL. Net price 128 mL with standard tube = £2.98, with long rectal tube = £3.98  
Dose  
128 mL, Child (but see section 1.6) over 3 years, reduced according to body weight  
Sodium Citrate (Rectal)  
Indications  
Rectal use in constipation  
Cautions  
Elderly and debilitated; see also notes above  
Contra-indications  
Acute gastro-intestinal conditions  
Dose  
See under preparations  
Micolette Micro-enema® (Pinewood)  
Enema, sodium citrate 450 mg, sodium lauryl sulphoacetate 45 mg, glycerol 625 mg, together with potassium sorbate and sorbitol in a viscous solution, in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 31p  
Dose  
Adult and Child over 3 years, 5–10 mL (but see section 1.6)  
Micralax Micro-enema® (UCB Pharma)  
Enema, sodium citrate 450 mg, sodium alkylsulphoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 41p  
Dose  
Adult and Child over 3 years, 5 mL (but see section 1.6)  
Relaxit Micro-enema® (Crawford)  
Enema, sodium citrate 450 mg, sodium lauryl sulphate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 32p  
Dose  
Adult and Child (but see section 1.6) 5 mL (insert only half nozzle length in child under 3 years)  
MAGNESIUM SALTS  
Indications  
See under preparations below  
Cautions  
Renal impairment (Appendix 3; risk of magnesium accumulation); hepatic impairment (see Appendix 2); elderly and debilitated; see also notes above  
Contra-indications  
Acute gastro-intestinal conditions  
Side-effects  
Colic  
Dose  
Magnesium hydroxide  
Magnesium Hydroxide Mixture, BP  
Aqueous suspension containing about 8% hydrated magnesium oxide. Do not store in cold place  
Dose  
Constipation, 30–45 mL with water at bedtime when required, Child 3–12 years, 5–10 mL with water at bedtime when required  
Magnesium hydroxide with liquid paraffin  
Liquid Paraffin and Magnesium Hydroxide Oral Emulsion, BP  
Oral emulsion, 25% liquid paraffin in aqueous suspension containing 6% hydrated magnesium oxide  
Dose  
Constipation, 5–20 mL when required  
Note  
Liquid paraffin and magnesium hydroxide preparations on sale to the public include: Milpar  
Magnesium sulphate  
Magnesium Sulphate  
Label: 13, 23  
Dose  
Rapid bowel evacuation (acts in 2–4 hours) 5–10 g in a glass of water preferably before breakfast  
Note  
Magnesium sulphate is on sale to the public as Epsom Salts  
Bowel cleansing solutions  
Section 1.6.5  
PHOSPHATES (RECTAL)  
Indications  
Rectal use in constipation; bowel evacuation before abdominal radiological procedures, endoscopy, and surgery  
Cautions  
Elderly and debilitated; with enema, electrolyte disturbances, renal impairment, congestive heart failure, ascites, uncontrolled hypertension, maintain adequate hydration  
Contra-indications  
Acute gastro-intestinal conditions (including gastro-intestinal obstruction, inflammatory bowel disease, and conditions associated with increased colonic absorption)  
Side-effects  
Local irritation; with enema, electrolyte disturbances  
Dose  
See under preparations  
Carbalax® (Forest)  
Suppositories, sodium acid phosphate (anhydrous)  
1.3 g, sodium bicarbonate 1.08 g, net price 12 = £2.01  
Dose  
Constipation, Adult and Child over 12 years, 1 suppository, inserted 30 minutes before evacuation required; moisten with water before use  
Fleet® Ready-to-use Enema (De Witt)  
Enema, sodium acid phosphate 21.4 g, sodium phosphate 9.4 g/118 mL, net price 133 mL pack (delivers 118 mL dose) with standard tube = £57p  
Dose  
Adult and Child (but see section 1.6) over 12 years, 118 mL. Child 3–12 years, on doctor’s advice only (under 3 years not recommended)  
Phosphates Enema BP Formula B  
Enema, sodium dihydrogen phosphate dihydrate 12.8 g, sodium phosphate dodecahydrate 10.24 g, purified water, freshly boiled and cooled, to 128 mL. Net price 128 mL with standard tube = £2.98, with long rectal tube = £3.98  
Dose  
128 mL, Child (but see section 1.6) over 3 years, reduced according to body weight  
SODIUM CITRATE (RECTAL)  
Indications  
Rectal use in constipation  
Cautions  
Elderly and debilitated; see also notes above  
Contra-indications  
Acute gastro-intestinal conditions  
Dose  
See under preparations  
Micolette Micro-enema® (Pinewood)  
Enema, sodium citrate 450 mg, sodium lauryl sulphoacetate 45 mg, glycerol 625 mg, together with potassium sorbate and sorbitol in a viscous solution, in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 31p  
Dose  
Adult and Child over 3 years, 5–10 mL (but see section 1.6)  
Micralax Micro-enema® (UCB Pharma)  
Enema, sodium citrate 450 mg, sodium alkylsulphoacetate 45 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 41p  
Dose  
Adult and Child over 3 years, 5 mL (but see section 1.6)  
Relaxit Micro-enema® (Crawford)  
Enema, sodium citrate 450 mg, sodium lauryl sulphate 75 mg, sorbic acid 5 mg, together with glycerol and sorbitol in a viscous solution in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 32p  
Dose  
Adult and Child (but see section 1.6) 5 mL (insert only half nozzle length in child under 3 years)  
Bowel cleansing solutions  
Bowel cleansing solutions are used before colonic surgery, colonoscopy, or radiological examination to ensure the bowel is free of solid contents. They are not treatments for constipation.
Bowel cleansing solutions

CitraFleet

Indications
See under preparations

Cautions
Electrolyte disturbances; maintain adequate hydration; heart disease; ulcerative colitis; diabetes mellitus; reflux oesophagitis; impaired gag reflex; unconscious or semiconscious or possibility of regurgitation or aspiration; renal impairment

Appendix 3; pregnancy

Contra-indications
Gastro-intestinal obstruction, gastro-intestinal ulceration, perforated bowel, congestive cardiac failure; toxic colitis, toxic megacolon or ileus

Side-effects
Nausea, vomiting, abdominal pain

Gastro-intestinal retention, gastro-intestinal ulceration, perforated megacolon or ileus

Dose

See under preparations

CitraFleet® (De Witt)

Oral powder, sugar-free, sodium picosulfate 10 mg/sachet, with magnesium citrate. Contains 86 mmol Mg and 5 mmol K+/sachet. Net price 2-sachet pack (lemon-flavoured) = £3.25. Label: 10, patient information leaflet, 13, counselling, see below

Dose
Bowel evacuation on day before radiological procedure, endoscopy, or surgery. ADULT over 18 years, 1 sachet before 8 a.m. then 1 sachet 6–8 hours later

Acts within 3 hours of first dose

Note
Low residue diet recommended on the day before procedure and copious intake of water or other clear fluids recommended during treatment

Counselling
One sachet should be reconstituted with 150 mL (approx. half a glass) of cold water; patients should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking

Citramag® (Sanochemia)

Oral powder, sugar-free, effervescent, magnesium carbonate 11.57 g, anhydrous citric acid 17.70 g/sachet, net price 10-sachet pack (lemon and lime flavour) = £14.90. Label: 10, patient information leaflet, 13, counselling, see below

Dose
Bowel evacuation for surgery, colonoscopy or radiological examination, on day before procedure, 1 sachet at 8 a.m. and 1 sachet 6–8 hours later

Note
No further oral intake of food or fluids

Counselling
The patient information leaflet advises that hot water (200 mL) is needed to make the solution and provides guidance on the timing and procedure for reconstitution; it also mentions need for high fluid, low residue diet beforehand (according to hospital advice), and explains that only clear fluids can be taken after Citramag until procedure completed

Fleet Phospho-soda® (De Witt)

Oral solution, sugar-free, sodium dihydrogen phosphate dihydrate 24.4 g, disodium phosphate dodecahydrate 10.8 g/45 mL. Contains about 217 mmol Na+ and 45 mL. Net price 2 × 45 mL bottles = £4.79. Label: 10, patient information leaflet, counselling

Dose
ADULT and CHILD over 15 years, 45 mL diluted with half a glass (120 mL) of cold water, followed by one full glass (240 mL) of cold water

Timing of doses is dependent on the time of the procedure

For morning procedure, first dose should be taken at 7 a.m. and second at 7 p.m. on day before the procedure

For afternoon procedure, first dose should be taken at 7 p.m. on day before and second dose at 7 a.m. on day of the procedure

Solid food must not be taken during dosing period; clear liquids or water should be substituted for meals

Acts within half to 6 hours of first dose

Klean-Prep® (Norgine)

Oral powder, sugar-free, macrogol ‘3350’ (polyethylene glycol ‘3350’) 100 g, anhydrous sodium sulphate 7.5 g, sodium chloride 2.691 g, potassium chloride 1.015 g and Sorbitol (containing ascorbic acid 4.7 g, sodium ascorbate 5.9 g), net price 4-sachet pack (2 each of sachet A and B) = £10.27. Label: 10, patient information leaflet, 13, counselling, see below

Counselling
The patient information leaflet advises that heat is generated during reconstitution and that the solution should be kept in a refrigerator and discarded if unused after 24 hours

Note
Allergic reactions reported. 1 sachet when reconstituted with 1 litre of water provides Na 125 mmol, K 10 mmol

Moviprep® (Norgine)

Oral powder, sugar-free, lemon-flavoured, Sachet A (containing macrogol ‘3350’ (polyethylene glycol ‘3350’) 100 g, anhydrous sodium sulphate 7.5 g, sodium chloride 2.691 g, potassium chloride 1.015 g) and Sachet B (containing ascorbic acid 4.7 g, sodium ascorbate 5.9 g), net price 4-sachet pack (2 each of sachet A and B) = £10.27. Label: 10, patient information leaflet, 13, counselling, see below

Counselling
One pair of sachets (A and B) should be reconstituted in 1 litre of water (providing absorbable Na 56.2 mmol, K 14.2 mmol/litre) and taken over 1–2 hours. Solid food should not be taken during treatment. 1 litre of other clear fluid should also be taken during treatment

Picolax® (Ferring)

Oral powder, sugar-free, sodium picosulfate 10 mg/sachet, with magnesium citrate. Contains 87 mmol Mg and 5 mmol K+/sachet. Net price 2-sachet pack = £3.53. Label: 10, patient information leaflet, 13, counselling, see below

Dose
Bowel evacuation on day before radiological procedure, endoscopy, or surgery. ADULT and CHILD over 9 years, 1 sachet before 8 a.m. then 1 sachet 6–8 hours later; CHILD 1–2 years, quarter sachet before 8 a.m. then quarter sachet 6–8 hours later; 2–4 years, half sachet before 8 a.m. then half sachet 6–8 hours later; 4–9 years, 1 sachet before 8 a.m. then half sachet 6–8 hours later

Note
No further oral intake of food or fluids

Counselling
One sachet should be reconstituted with 150 mL of cold water; patients should be warned that heat is generated during reconstitution and that the solution should be kept in a refrigerator and discarded if unused after 24 hours

Note
Allergic reactions reported. 1 sachet when reconstituted with 1 litre of water provides Na 125 mmol, K 10 mmol
1.6.6 Peripheral opioid-receptor antagonists

Methylnaltrexone is a peripherally acting opioid-receptor antagonist that is licensed for the treatment of opioid-induced constipation in patients receiving palliative care, when response to other laxatives is inadequate; it should be used as an adjunct to existing laxative therapy. Methylnaltrexone does not alter the central analgesic effect of opioids. For the prevention of opioid-induced constipation in palliative care, see p. 17.

**METHYLNALTREXONE BROMIDE**

**Indications** opioid-induced constipation in terminally ill patients, when response to other laxatives is inadequate

**Cautions** diverticular disease; faecal impaction; patients with colostomy or peritoneal catheter; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications** gastro-intestinal obstruction; acute surgical abdominal conditions; severe hepatic impairment (Appendix 2)

**Side-effects** abdominal pain, nausea, diarrhoea, flatulence; dizziness; injection site reactions

**Dose**
- By subcutaneous injection, ADULT over 18 years, body-weight under 38 kg, 150 micrograms/kg on alternate days; body-weight 38–62 kg, 8 mg on alternate days; body-weight 62–114 kg, 12 mg on alternate days; body-weight over 114 kg, 150 micrograms/kg on alternate days; may be given less frequently depending on response; 2 consecutive doses may be given 24 hours apart if no response to treatment on the preceding day; rotate sites of injection; max. duration of treatment 4 months

**Note** May act within 30–60 minutes

Relistor® (Wyeth) ▼

**Injection**, methylnaltrexone bromide 20 mg/mL, net price 0.6-mL vial = £21.05, 7-vial pack (with syringes and needles) = £147.35

When necessary topical preparations containing **local anaesthetics** (section 1.7.1) or **corticosteroids** (section 1.7.2) are used provided perianal thrush has been excluded. Perianal thrush is best treated with **nystatin** by mouth and by local application (see section 5.2, section 7.2.2, and section 13.10.2).

For the management of **anal fissures**, see section 1.7.4.

1.7 Local preparations for anal and rectal disorders

1.7.1 Soothing haemorrhoidal preparations

Soothing preparations containing mild astringents such as bismuth subgallate, zinc oxide, and hamamelis may give symptomatic relief in haemorrhoids. Many proprietary preparations also contain lubricants, vasoconstrictors, or mild antiseptics.

**Local anaesthetics** are used to relieve pain associated with haemorrhoids and pruritus ani but good evidence is lacking. Lidocaine (lignocaine) ointment (section 15.2) is used before emptying the bowel to relieve pain associated with **anal fissure**. Alternative local anaesthetics include tetracaine (amethocaine), cinchocaine (dibucaine), and pramocaine (pramoxime), but they are more irritant. Local anaesthetic ointments can be absorbed through the rectal mucosa therefore excessive application should be avoided, particularly in infants and children. Preparations containing local anaesthetics should be used for short periods only (no longer than a few days) since they may cause sensitisation of the anal skin.

1.7.2 Compound haemorrhoidal preparations with corticosteroids

Corticosteroids are often combined with local anaesthetics and soothing agents in preparations for haemorrhoids. They are suitable for occasional short-term use after exclusion of infections, such as herpes simplex; prolonged use can cause atrophy of the anal skin. See section 13.4 for general comments on topical corticosteroids and section 1.7.1 for comment on local anaesthetics.

**Children** Haemorrhoids in children are rare. Treatment is usually symptomatic and the use of a locally applied cream is appropriate for short periods; however, local anaesthetics can cause stinging initially and this may aggravate the child’s fear of defaecation.

Anugesic-HC® (Pfizer) ▼

**Cream**, benzyl benzoate 1.2%, bismuth oxide 0.875%, hydrocortisone acetate 0.5%, Peru balsam 1.85%, pramocaine hydrochloride 1%, zinc oxide 12.35%. Net price 30 g (with rectal nozzle) = £3.71

**Dose** apply night and morning and after a bowel movement; do not use for longer than 7 days; **CHILD** not recommended

**Suppositories**, buff, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 5 mg, Peru balsam 49 mg, pramocaine

Anal and perianal pruritus, soreness, and excoriation are best treated by application of bland ointments and suppositories (section 1.7.1). These conditions occur commonly in patients suffering from haemorrhoids, fistulas, and proctitis. Cleansing with attention to any minor faecal soiling, adjustment of the diet to avoid hard stools, the use of bulk-forming materials such as bran (section 1.6.1) and a high residue diet are helpful. In proctitis these measures may supplement treatment with corticosteroids or sulfasalazine (see section 1.5).
1.7.3 Rectal sclerosants

Oily phenol injection is used to inject haemorrhoids particularly when unprolapsed.

**PHENOL**

**Indications** see notes above

**Side-effects** irritation, tissue necrosis

**Oily Phenol Injection, BP**

- phenol 5% in a suitable fixed oil. Net price 5-mL amp = £5.00
- Dose 2–3 mL into the submucosal layer at the base of the pile; several injections may be given at different sites, max. total injected 10 mL at any one time
- Available from UCB Pharma

**Management of anal fissures**

The management of anal fissures requires stool softening by increasing dietary fibre in the form of bran or by using a bulk-forming laxative. Short-term use of local anaesthetic preparations may help (section 1.7.1). If these measures are inadequate, the patient should be referred for specialist treatment in hospital. The use of a topical nitrate (e.g. glyceryl trinitrate 0.4% ointment) may be considered. Before considering surgery, topical diltiazem 2% may be used twice daily [unlicensed indication] in patients with chronic anal fissures unresponsive to topical nitrates.

The **Scottish Medicines Consortium** (p. 3) has advised (January 2008) that glyceryl trinitrate 0.4% ointment (Rectogesic®) is not recommended for use within NHS Scotland for the relief of pain associated with chronic anal fissure.

**Suppositories**, cinchocaine (dibucaine) hydrochloride 1 mg, fluocortolone caproate 630 micrograms, fluocortolone pivalate 610 micrograms, net price 12 = £2.15
- Dose insert 1 suppository daily after a bowel movement, for 5–7 days (in severe cases initially 2–3 times daily) then 1 suppository every other day for 1 week

**Uniriod-HC**  (Chemidex)  

- Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, hydrocortisone 0.5%. Net price 30 g (with applicator) = £4.23
- Dose ADULT and CHILD over 12 years, apply twice daily and after a bowel movement, externally or by rectum; do not use for longer than 7 days; CHILD under 12 years on medical advice only

**Suppositories**, cinchocaine (dibucaine) hydrochloride 5 mg, hydrocortisone 5 mg. Net price 12 = £1.91
- Dose ADULT and CHILD over 12 years, insert 1 suppository twice daily and after a bowel movement; do not use for longer than 7 days

**Xyloproct** (AstraZeneca)  

- Ointment (water-miscible), aluminium acetate 3.5%, hydrocortisone acetate 0.275%, lidocaine 5%, zinc oxide 18%, net price 20 g (with applicator) = £2.26
- Dose apply several times daily; short-term use only

**Ultraproct**  (Meadow)  

- Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, fluocortolone caproate 0.095%, fluocortolone pivalate 0.092%, net price 30 g (with rectal nozzle) = £4.57
- Dose apply twice daily for 5–7 days (3–4 times daily on 1st day if necessary), then once daily for a few days after symptoms have cleared

**Scheriproct**  (Valeant)  

- Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, prednisolone hexanoate 0.19%. Net price 30 g = £3.00
- Dose apply twice daily for 5–7 days (3–4 times daily on 1st day if necessary), then once daily for a few days after symptoms have cleared

**Suppositories**, cinchocaine (dibucaine) hydrochloride 1 mg, prednisolone hexanoate 1.3 mg. Net price 12 = £1.41
- Dose insert 1 suppository daily after a bowel movement, for 5–7 days (in severe cases initially 2–3 times daily)

**Proctofoam HC**  (Meda)  

- Foam in aerosol pack, hydrocortisone acetate 1%, pramocaine hydrochloride 1%. Net price 21.2-g pack = £6.39
- Dose ADULT and CHILD over 14 years, spray once over the affected area up to 3 times daily; do not use for longer than 7 days without medical advice; CHILD under 14 years on medical advice only

**Anusol-HC**  (McNeil)  

- Ointment, benzylo benzate 1.25%, bismuth oxide 0.875%, bismuth subgallate 2.25%, hydrocortisone acetate 0.25%, Peru balsam 1.875%, zinc oxide 10.75%. Net price 30 g (with rectal nozzle) = £3.50
- Dose apply night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

**Note** A proprietary brand (Anusol Plus HC ointment) is on sale to the public

**Suppositories**, benzylo benzate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 10 mg, Peru balsam 49 mg, zinc oxide 296 mg. Net price 12 = £2.46
- Dose insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

**Note** A proprietary brand (Anusol Plus HC suppositories) is on sale to the public

**Perinal**  (Dermal)  

- Spray application, hydrocortisone 0.2%, lidocaine hydrochloride 1%. Net price 30-mL pack = £6.99
- Dose ADULT and CHILD over 12 years, apply twice daily and after a bowel movement, externally or by rectum; do not use for longer than 7 days; CHILD not recommended

**Proctosediyl**  (Aventis Pharma)  

- Ointment, cinchocaine (dibucaine) hydrochloride 0.5%, hydrocortisone 0.5%. Net price 30 g = £9.40
- Dose haemorrhoids and proctitis, 1 applicatorful (4–6 mg hydrocortisone acetate, 4–6 mg pramocaine hydrochloride) by rectum 2–3 times daily and after each bowel movement (max. 4 times daily), do not use for longer than 7 days; CHILD not recommended

hydrochloride 27 mg, zinc oxide 296 mg, net price 12 = £2.69
- Dose insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days; CHILD not recommended

**Note** A proprietary brand (Xyloproct Ointment) is on sale to the public

**Ointment**  (AstraZeneca)  

- Dose ADULT and CHILD over 12 years, insert 1 suppository twice daily and after a bowel movement; do not use for longer than 7 days
1.8 Stoma care

Prescribing for patients with stoma calls for special care. The following is a brief account of some of the main points to be borne in mind.

Enteric-coated and modified-release preparations are unsuitable, particularly in patients with an ileostomy, as there may not be sufficient release of the active ingredient.

Laxatives. Enemas and washouts should not be prescribed for patients with an ileostomy as they may cause rapid and severe loss of water and electrolytes. Colostomy patients may suffer from constipation and whenever possible should be treated by increasing fluid intake or dietary fibre. Bulk-forming drugs (section 1.6.1) should be tried. If they are insufficient, as small a dose as possible of senna (section 1.6.2) should be used.

Antidiarrhoeals. Drugs such as loperamide, codeine phosphate, or co-phenotrope (diphenoxylate with atropine) are effective. Bulk-forming drugs (section 1.6.1) may be tried but it is often difficult to adjust the dose appropriately.

Antibacterials should not be given for an episode of acute diarrhoea.

Antacids. The tendency to diarrhoea from magnesium salts or constipation from aluminium salts may be increased in these patients.

Diuretics should be used with caution in patients with an ileostomy as they may become excessively dehydrated and potassium depletion may easily occur. It is usually advisable to use a potassium-sparing diuretic (see section 2.2.3).

Digoxin. Patients with a stoma are particularly susceptible to hypokalaemia if on digoxin therapy and potassium supplements or a potassium-sparing diuretic may be advisable (for comment see section 9.1.1.2) should be used. Modified-release preparations should be avoided for the reasons given above.

Patients are usually given advice about the use of cleansing agents, protective creams, lotions, deodorants, or sealants whilst in hospital, either by the surgeon or by stoma care nurses. Voluntary organisations offer help and support to patients with stoma.

Iron preparations may cause loose stools and sore skin in these patients. If this is troublesome and if iron is definitely indicated an intramuscular iron preparation (see section 9.1.1.2) should be used. Modified-release preparations should be avoided for the reasons given above.

1.9 Drugs affecting intestinal secretions

1.9.1 Drugs affecting biliary composition and flow

The use of laparoscopic cholecystectomy and of endoscopic biliary techniques has limited the place of the bile acid ursodeoxycholic acid in gallstone disease. Ursodeoxycholic acid is suitable for patients with unimpaired gall bladder function, small or medium-sized radiolucent stones, and whose mild symptoms are not amenable to other treatment; it should be used cautiously in those with liver disease (but see below). Patients should be given dietary advice (including avoidance of excessive cholesterol and calories) and they require radiological monitoring. Long-term prophylaxis may be needed after complete dissolution of the gallstones has been confirmed because they may recur in up to 25% of patients within one year of stopping treatment.

Ursodeoxycholic acid is also used in primary biliary cirrhosis; liver tests improve in most patients but the effect on overall survival is uncertain. Ursodeoxycholic acid has also been tried in primary sclerosing cholangitis [unlicensed indication].

1.9.2 Bile acid sequestrants
1.9.3 Aprotinin
1.9.4 Pancreatin

1.10 Ursodeoxycholic acid

Indications see under Dose and under preparations.

Cautions see notes above; Interactions: Appendix 1 (ursodeoxycholic acid)

Contra-indications: radio-opaque stones, pregnancy (Appendix 4), non-functioning gall bladder, inflammatory diseases and other conditions of the small intestine, colon and liver which interfere with entero-hepatic circulation of bile salts.

Side-effects: nausea, vomiting, diarrhoea; gallstone calcification; pruritus.

Dose

- Dissolution of gallstones, 8–12 mg/kg daily as a single dose at bedtime or in two divided doses, for up to 2 years; treatment is continued for 3–4 months after stones dissolve
- Primary biliary cirrhosis, see under Ursodiol®

GLYCERYL TRINITRATE

Indications anal fissure; angina, left ventricular failure (section 2.6.1); extravasation (section 10.3)

Cautions see section 2.6.1

Contra-indications see section 2.6.1

Side-effects see section 2.6.1; also diarrhoea, burning, itching, and rectal bleeding.

Dose

- See preparations

Rectogesic® (Strakan) ▼ (POM)

Rectal ointment, glyceryl trinitrate 0.4%, net price 30 g = £32.80

Excipients include lanolin, propylene glycol

Dose ADULT over 18 years, apply 2.5 cm of ointment to anal canal every 12 hours until pain stops; max. duration of use 8 weeks

Note 2.5 cm of ointment contains glyceryl trinitrate 1.5 mg; discard tube 8 weeks after first opening.

Notes

GLYCERYL TRINITRATE

Indications anal fissure; angina, left ventricular failure (section 2.6.1); extravasation (section 10.3)

Cautions see section 2.6.1

Contra-indications see section 2.6.1

Side-effects see section 2.6.1; also diarrhoea, burning, itching, and rectal bleeding.

Dose

- See preparations

Rectogesic® (Strakan) ▼ (POM)

Rectal ointment, glyceryl trinitrate 0.4%, net price 30 g = £32.80

Excipients include lanolin, propylene glycol

Dose ADULT over 18 years, apply 2.5 cm of ointment to anal canal every 12 hours until pain stops; max. duration of use 8 weeks

Note 2.5 cm of ointment contains glyceryl trinitrate 1.5 mg; discard tube 8 weeks after first opening.

Notes
Colestyramine (cholestyramine) is an anion-exchange resin that is not absorbed from the gastro-intestinal tract. It relieves diarrhoea and pruritus by forming an insoluble complex with bile acids in the intestine. Colestyramine can interfere with the absorption of a number of drugs. Colestyramine is also used in hypercholesterolaemia (section 2.12).

### COLESTYRAMINE

**(Cholestyramine)**

**Indications** pruritus associated with partial biliary obstruction and primary biliary cirrhosis; diarrhoea associated with Crohn’s disease, ileal resection, vagotomy, diabetic vagal neuropathy, and radiation; hypercholesterolaemia (section 2.12)

**Cautions** see section 2.12

**Contra-indications** see section 2.12

**Side-effects** see section 2.12

**Dose**

- Pruritus, 4–8 g daily in a suitable liquid; **CHILD** 6–12 years, consult product literature
- Diarrhoea, initially 4 g daily increased by 4 g at weekly intervals to 12–24 g daily in a suitable liquid in 1–4 divided doses, then adjusted as required; max. 36 g daily; **CHILD** 6–12 years, consult product literature

**Counselling** Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption

**Note** The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content

#### Preparations

**Section 2.12**

### 1.9.3 Aprotinin

Aprotinin is no longer used for the treatment of acute pancreatitis.

### 1.9.4 Pancreatin

Supplements of pancreatin are given by mouth to compensate for reduced or absent exocrine secretion in cystic fibrosis, and following pancreatectomy, gastrectomy, or chronic pancreatitis. They assist the digestion of starch, fat, and protein. Pancreatin may also be necessary if a tumour (e.g. pancreatic cancer) obstructs outflow from the pancreas.

Pancreatin is inactivated by gastric acid therefore pancreatin preparations are best taken with food (or immediately before or after food). Gastric acid secretion may be reduced by giving cimetidine or ranitidine an hour beforehand (section 1.3). Concurrent use of antacids also reduces gastric acidity. Enteric-coated preparations deliver a higher enzyme concentration in the duodenum (provided the capsule contents are swallowed whole without chewing). Higher-strength preparations are also available (important: see CSM advice below).

Since pancreatin is also inactivated by heat, excessive heat should be avoided if preparations are mixed with liquids or food; the resulting mixtures should not be kept for more than one hour.

Dosage is adjusted according to size, number, and consistency of stools, so that the patient thrives; extra allowance may be needed if snacks are taken between meals.

Pancreatin can irritate the peroral skin and buccal mucosa if retained in the mouth, and excessive doses can cause perianal irritation. The most frequent side-effects are gastro-intestinal, including nausea, vomiting, and abdominal discomfort; hyperuricaemia and hyperuricosuria have been associated with very high doses. Hypersensitivity reactions occur occasionally and may affect those handling the powder.

### Preparations

**Section 2.12**

#### 1.9.2 Bile acid sequestrants

Colestyramine is also used in hypercholesterolaemia (section 2.12).
Creon® 10 000 (Solvay)  
**Capsules**, brown/clear, enclosing buff-coloured e/c granules of pancreatin (pork), providing: protease 600 units, lipase 10 000 units, amylase 8000 units. Net price 100-cap pack = £16.66. Counselling, see dose  
**Dose**  
ADULT and CHILD initially 1–2 capsules with each meal either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing)

Nutrizym 10® (Merck)  
**Capsules**, red/yellow, enclosing e/c minitablets of pancreatin (pork), providing minimum of: protease 300 units, lipase 10 000 units, amylase 9000 units. Net price 100–200 units = £20.39. Label: 25, counselling, see dose  
**Dose**  
ADULT and CHILD initially 1–2 capsules with each meal either taken whole or contents mixed with water or sprinkled on soft food (then swallowed immediately without chewing); higher doses may be required according to response

Pancrease® (Paines & Byrne)  
**Granules**, pancreatin (pork), providing minimum of: protease 300 units, lipase 5000 units, amylase 4000 units/g. Net price 300 g = £20.39. Label: 25, counselling, see dose  
**Dose**  
ADULT and CHILD 5–10 g just before meals washed down or mixed with a little milk or water

Pancrease® (Paines & Byrne)  
**Capsules**, pancreatin (pork), providing minimum of: protease 430 units, lipase 8000 units, amylase 9000 units. Net price 300-cap pack = £15.80. Counselling, see dose  
**Dose**  
ADULT and CHILD over 1 year 2–6 capsules with each meal, swallowed whole or sprinkled on food, INFANT up to 1 year contents of 1–2 capsules mixed with feeds

Nutrizym 22® (Merck)  
**Capsules**, red/yellow, enclosing e/c minitablets of pancreatin (pork), providing minimum of: protease 1100 units, lipase 25 000 units, amylase 1700 units. Net price 300-tab pack = £4.51. Label: 5, 25, counselling, see dose  
**Dose**  
ADULT and CHILD 5–15 tablets before each meal

Nutrizym 22® (Merck)  
**Tablets** forte, e/c, pancreatin (pork), providing minimum of: protease 330 units, lipase 5600 units, amylase 5000 units. Net price 300-tab pack = £13.74. Label: 5, 25, counselling, see dose  
**Dose**  
ADULT and CHILD 6–10 tablets before each meal

Nutrizym 22® (Merck)  
**Powder**, pancreatin (pork), providing minimum of: protease 1400 units, lipase 25 000 units, amylase 30 000 units/g. Net price 300 g = £24.28. Counselling, see dose  
**Dose**  
ADULT and CHILD over 1 month, 0.5–2.5 g before each meal, washed down or mixed with liquid, NEONATE 250–500 mg with each feed

Higher-strength preparations  
The CSM has advised of data associating the high-strength pancreatin preparations Nutrizym 22® and Pancrease HL® with the development of large bowel strictures (fibrosing colonopathy) in children with cystic fibrosis aged between 2 and 13 years. No association was found with Creon® 25 000. The following was recommended:

- Pancrease HL®, Nutrizym 22®, Panzytrat® 25 000 [now discontinued] should not be used in children aged 15 years or less with cystic fibrosis;
- the total dose of pancreatic enzyme supplements used in patients with cystic fibrosis should not usually exceed 10 000 units of lipase per kg body-weight daily;
- if a patient on any pancreatin preparation develops new abdominal symptoms (or any change in existing abdominal symptoms) the patient should be reviewed to exclude the possibility of colonic damage.

Possible risk factors are gender (boys at greater risk than girls), more severe cystic fibrosis, and concomitant use of laxatives. The peak age for developing fibrosing colonopathy is between 2 and 8 years.

Counselling  
It is important to ensure adequate hydration at all times in patients receiving higher-strength pancreatin preparations.

Creon® 25 000 (Solvay)  
**Capsules**, orange/clear, enclosing brown-coloured e/c pellets of pancreatin (pork), providing: protease (total) 1000 units, lipase 25 000 units, amylase 18 000 units, net price 100-cap pack = £30.03. Counselling, see above and under dose  
**Dose**  
ADULT and CHILD initially 1 capsule with meals either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing)

Creon® 40 000 (Solvay)  
**Capsules**, brown/clear, enclosing brown-coloured e/c granules of pancreatin (pork), providing: protease (total) 1600 units, lipase 40 000 units, amylase 25 000 units, net price 100-cap pack = £60.00. Counselling, see above and under dose  
**Dose**  
ADULT and CHILD initially 1–2 capsules with meals either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing)

Nutrizym 22® (Merck)  
**Capsules**, red/yellow, enclosing e/c minitablets of pancreatin (pork), providing minimum of: protease 1100 units, lipase 22 000 units, amylase 19 800 units. Net price 100–200 units = £33.33. Counselling, see above and under dose  
**Dose**  
ADULT and CHILD over 15 years, 1–2 capsules with meals and 1 capsule with snacks, swallowed whole or contents taken with water or sprinkled on soft food (then swallowed immediately without chewing)

Pancrease HL® (Janssen-Cilag)  
**Capsules**, enclosing light brown e/c minitablets of pancreatin (pork), providing minimum of: protease 1250 units, lipase 25 000 units, amylase 22 500 units. Net price 100 = £33.65. Counselling, see above and under dose  
**Dose**  
ADULT and CHILD over 15 years, 1–2 capsules during each meal and 1 capsule with snacks swallowed whole or contents sprinkled on slightly acidic liquid or soft food (then swallowed immediately without chewing)
2.1 Positive inotropic drugs

2.1.1 Cardiac glycosides
Cardiac glycosides increase the force of myocardial contraction and reduce conductivity within the atrio-ventricular (AV) node. Digoxin is the most commonly used cardiac glycoside. Cardiac glycosides are most useful in the treatment of supraventricular tachycardias, especially for controlling ventricular response in persistent atrial fibrillation (section 2.3.1). For reference to the role of digoxin in heart failure, see section 2.5.5.

2.1.2 Phosphodiesterase inhibitors
Positive inotropic drugs increase the force of contraction of the myocardium; for sympathomimetics with inotropic activity see section 2.7.1.
by the ventricular rate at rest, which should not be allowed to fall below 60 beats per minute except in special circumstances, e.g. with the concomitant administration of a beta-blocker.

Digoxin is now rarely used for rapid control of heart rate (see section 2.3 for the management of supraventricular arrhythmias). Even with intravenous administration, response may take many hours; persistence of tachycardia is therefore not an indication for exceeding the recommended dose. The intramuscular route is not recommended.

In patients with heart failure who are in sinus rhythm a loading dose is not required, and a satisfactory plasma-digoxin concentration can be achieved over a period of about a week.

Digoxin has a long half-life and maintenance doses need to be given only once daily (although higher doses may be divided to avoid nausea). Digitoxin also has a long half-life and maintenance doses need to be given only once daily or on alternate days. Renal function is the most important determinant of digoxin dosage, whereas elimination of digitoxin depends on metabolism by the liver.

Unwanted effects depend both on the concentration of the cardiac glycoside in the plasma and on the sensitivity of the conducting system or of the myocardium, which is often increased in heart disease. It can sometimes be difficult to distinguish between toxic effects and clinical deterioration because symptoms of both are similar. Also, the plasma concentration alone cannot indicate toxicity reliably but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/litre for digoxin. Cardiac glycosides should be used with special care in the elderly who may be particularly susceptible to digitalis toxicity.

Regular monitoring of plasma-digoxin concentration during maintenance treatment is not necessary unless problems are suspected. Hypokalaemia predisposes the patient to digitalis toxicity; it is managed by giving a potassium sparing diuretic or, if necessary, potassium supplementation.

Toxicity can often be managed by discontinuing digoxin; serious manifestations require urgent specialist management. Digoxin-specific antibody fragments are available for reversal of life-threatening overdosage (see below).

### DIGOXIN

**Indications** heart failure (see also section 2.5.5), supraventricular arrhythmias (particularly atrial fibrillation and atrial flutter; see also section 2.3.2)

**Cautions** recent myocardial infarction; sick sinus syndrome; thyroid disease; reduce dose in the elderly; severe respiratory disease; hypokalaemia, hypomagnesaemia, hypercalcaemia, and hypoxia (risk of digitalis toxicity); monitor serum electrolytes and renal function; avoid rapid intravenous administration (risk of hypertension and reduced coronary flow); renal impairment (Appendix 3); pregnancy (Appendix 4); **interactions**: Appendix 1 (cardiac glycosides)

**Contra-indications** intermittent complete heart block, second degree AV block; supraventricular arrhythmias associated with accessory conducting pathways e.g. Wolff-Parkinson-White syndrome; ventricular tachycardia or fibrillation; hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—but use with caution); myocarditis; constrictive pericarditis (unless to control atrial fibrillation or improve systolic dysfunction—but use with caution);

**Side-effects** see notes above; also nausea, vomiting, diarrhoea; arrhythmias, conduction disturbances; dizziness; blurred or yellow vision; rash, eosinophilia; *less commonly* depression; *very rarely* anorexia, intestinal ischaemia and necrosis, psychosis, apathy, confusion, headache, fatigue, weakness, gynaecomastia on long-term use, and thrombocytopenia

**Dose**

- Rapid digitalisation, for atrial fibrillation or flutter, by mouth, 0.75–1.5 mg over 24 hours in divided doses
- Maintenance, for atrial fibrillation or flutter, by mouth, according to renal function and initial loading dose; usual range 125–250 micrograms daily
- Heart failure (for patients in sinus rhythm), by mouth, 62.5–125 micrograms once daily
- Emergency loading dose, for atrial fibrillation or flutter, by intravenous infusion (but rarely necessary), 0.75–1 mg over at least 2 hours (see also Cautions) then maintenance dose by mouth on the following day

**Note** The above doses may need to be reduced if digoxin (or another cardiac glycoside) has been given in the preceding 2 weeks. Digoxin doses in the BNF may differ from those in product literature. For plasma concentration monitoring, blood should ideally be taken at least 6 hours after a dose

**Digoxin (Non-proprietary)**

- **Tablets**, digoxin 62.5 micrograms, net price 28 = £1.66; 125 micrograms, 28 = £1.34; 250 micrograms, 28 = £1.37
- **Injection**, digoxin 250 micrograms/mL, net price 2-ML amp = 70p

**Available from Antigen**

**Paediatric injection**, digoxin 100 micrograms/mL

**Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939**

**Lanoxin® (GSK)**

- **Tablets**, digoxin 125 micrograms, net price 20 = 32p; 250 micrograms (scored), 20 = 32p
- **Injection**, digoxin 250 micrograms/mL, net price 2-ML amp = 66p

**Lanoxin-PG® (GSK)**

- **Tablets**, blue, digoxin 62.5 micrograms, net price 20 = 32p
- **Elixir**, yellow, digoxin 50 micrograms/mL. Do not dilute, measure with pipette. Net price 60 mL = £5.35. Counselling, use of pipette

### DIGITOXIN

**Indications** heart failure, supraventricular arrhythmias (particularly atrial fibrillation)

**Cautions** see under Digoxin

**Contra-indications** see under Digoxin

**Side-effects** see under Digoxin

**Dose**

- Maintenance, 100 micrograms daily or on alternate days; may be increased to 200 micrograms daily if necessary

**Digoxin (Non-proprietary)**

- **Tablets**, digoxin 100 micrograms, net price 28 = £4.11
Digoxin-specific antibody

Digoxin-specific antibody fragments are indicated for the treatment of known or strongly suspected digoxin or digitoxin overdose, in situations where measures beyond the withdrawal of the cardiac glycoside and correction of any electrolyte abnormalities are felt to be necessary (see also notes above).

Digibind® (GSK) Injection, powder for preparation of infusion, digoxin-specific antibody fragments (F(ab)) 38 mg, net price per vial = £93.97 (hosp. and poisons centres only)

Dose consult product literature

2.1.2 Phosphodiesterase inhibitors

Enoximone and milrinone are selective phosphodiesterase inhibitors which exert most of their effect on the myocardium. Sustained haemodynamic benefit has been observed after administration, but there is no evidence of any beneficial effect on survival.

2.2 Diuretics

2.2.1 Thiazides and related diuretics

2.2.2 Loop diuretics

2.2.3 Potassium-sparing diuretics and aldosterone antagonists

2.2.4 Potassium-sparing diuretics with other diuretics

2.2.5 Osmotic diuretics

2.2.6 Mercurial diuretics

2.2.7 Carbonic anhydrase inhibitors

2.2.8 Diuretics with potassium

Thiazides (section 2.2.1) are used to relieve oedema due to chronic heart failure (section 2.5.5) and, in lower doses, to reduce blood pressure.

Loop diuretics (section 2.2.2) are used in pulmonary oedema due to left ventricular failure and in patients with chronic heart failure (section 2.5.5).

Combination diuretic therapy may be effective in patients with oedema resistant to treatment with one diuretic. Vigorous diuresis, particularly with loop diuretics, may induce acute hypotension; rapid reduction of plasma volume should be avoided.

Elderly Lower initial doses of diuretics should be used in the elderly because they are particularly susceptible to the side-effects. The dose should then be adjusted according to renal function. Diuretics should not be used continuously on a long-term basis to treat simple gravitational oedema (which will usually respond to increased movement, raising the legs, and support stockings).

Potassium loss Hypokalaemia may occur with both thiazide and loop diuretics. The risk of hypokalaemia depends on the duration of action as well as the potency and is thus greater with thiazides than with an equipotent dose of a loop diuretic.
Thiazides and related diuretics are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. They act within 1 to 2 hours of oral administration and most have a duration of action of 12 to 24 hours; they are usually administered early in the day so that the diuresis does not interfere with sleep.

In the management of hypertension a low dose of a thiazide, e.g. bendroflumethiazide (bendrofluazide) 2.5 mg daily, produces a maximal or near-maximal blood pressure lowering effect, with very little biochemical disturbance. Higher doses cause more marked changes in plasma potassium, sodium, uric acid, glucose, and lipids, with little advantage in blood pressure control. For reference to the use of thiazides in chronic heart failure see section 2.5.5.

Bendroflumethiazide (bendrofluazide) is widely used for mild or moderate heart failure and for hypertension—alone in the treatment of mild hypertension or with other drugs in more severe hypertension.

Chlortalidone (chlorthalidone), a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days to control oedema. It is also useful if acute retention is liable to be precipitated by a more rapid diuresis or if patients dislike a domestic diuresis; it is administered early in the day so that the diuresis does not interfere with sleep.

Metolazone is particularly effective when combined with a loop diuretic (even in renal failure); profound diuresis can occur and the patient should therefore be monitored carefully.

Xipamide and indapamide are chemically related to chlortalidone. Indapamide is claimed to lower blood pressure with less metabolic disturbance, particularly less aggravation of diabetes mellitus.

Contra-indications

Thiazides and related diuretics should be avoided in refractory hypokalaemia, hyponatraemia and hypercalcaemia, symptomatic hyperuricaemia, and Addison's disease.

Side-effects

Side-effects of thiazides and related diuretics include mild gastro-intestinal disturbances, postural hypotension, altered plasma lipid concentrations, metabolic and electrolyte disturbances including hypokalaemia (see also notes above), hypernatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hyperchloremic alkalosis, hyperuricaemia, and gout. Less common side-effects include blood disorders such as agranulocytosis, leucopenia, and thrombocytopenia, and impotence. Pancreatitis, intrahepatic cholestasis, cardiac arrhythmias, headache, dizziness, paraesthesia, visual disturbances, and hypersensitivity reactions (including pneumonitis, pulmonary oedema, photosensitivity, and severe skin reactions) have also been reported.

BENEDROFLUMETHIAZIDE

(Bendrofluazide)

Indications

Oedema, hypertension (see also notes above)

Cautions

see notes above

Contra-indications

see notes above

Side-effects

see notes above

Dose

- Oedema, initially 5–10 mg daily in the morning or on alternate days; maintenance 5–10 mg 1–3 times weekly
- Hypertension, 2.5 mg daily in the morning; higher doses rarely necessary (see notes above)

Bendroflumethiazide (Non-proprietary)

Tablets, bendroflumethiazide 2.5 mg. net price 28 = 83p; 5 mg, 28 = 86p

Brands include Aprinox, Neo-NaClex

CHLORTALIDONE

(Chlorthalidone)

Indications

ascites due to cirrhosis in stable patients (under close supervision), oedema due to nephrotic syndrome, hypertension (see also notes above), mild to moderate chronic heart failure; diabetes insipidus (see section 6.5.2)

Cautions

see notes above

Contra-indications

see notes above

Side-effects

see notes above; also rarely jaundice and allergic interstitial nephritis

Dose

- Oedema, up to 50 mg daily
- Hypertension, 25 mg daily in the morning, increased to 50 mg daily if necessary (but see notes above)
- Heart failure, 25–50 mg daily in the morning, increased if necessary to 100–200 mg daily (reduce to lowest effective dose for maintenance)
**Cyclophantiazide**

**Indications**
Oedema, hypertension (see also notes above); heart failure

**Cautions**
see notes above

**Side-effects**
see notes above; also rarely depression

**Dose**
- Heart failure, 250–500 micrograms daily in the morning increased if necessary to 1 mg daily (reduce to lowest effective dose for maintenance)
- Hypertension, initially 250 micrograms daily in the morning, increased if necessary to 500 micrograms daily (but see notes above)
- Oedema, up to 500 micrograms daily for a short period

**Navidrex**

- Tablets, yellow, scored, chlortalidone 50 micrograms, net price 28-tab pack = £1.27
- Excipients include gluten

**Indapamide**

**Indications**
essential hypertension

**Cautions**
see notes above; also acute porphyria (section 9.8.2)

**Contra-indications**
see notes above

**Side-effects**
see notes above; also palpitation, diuresis with doses above 2.5 mg daily

**Dose**
- 2.5 mg daily in the morning

**Indapamide (Non-proprietary)**

- Tablets, s/c, indapamide 2.5 mg, net price 28-tab pack = £1.36, 56-tab pack = £2.24

**Natrilix**

- Tablets, f/c, indapamide 2.5 mg, Net price 30-tab pack = £4.50, 60-tab pack = £9.00

**Modified release**

**Ethibide XL**

- Tablets, m/r, indapamide 1.5 mg, net price 30-tab pack = £4.05. Label: 25
- Dose: hypertension, 1 tablet daily, preferably in the morning

**Natrilix SR**

- Tablets, m/r, indapamide 1.5 mg, net price 30-tab pack = £4.50. Label: 25
- Dose: hypertension, 1 tablet daily, preferably in the morning

**Metenix 5**

- Tablets, blue, metolazone 5 mg, net price 100-tab pack = £18.94

**Xipamide**

**Indications**
Oedema, hypertension (see also notes above)

**Cautions**
see notes above; also acute porphyria (section 9.8.2)

**Contra-indications**
see notes above

**Side-effects**
see notes above

**Dose**
- Oedema, initially 40 mg daily in the morning, increased to 80 mg in resistant cases; maintenance 20 mg in the morning
- Hypertension, 20 mg daily in the morning

**Diurexan**

- Tablets, scored, xipamide 20 mg, net price 140-tab pack = £19.46

---

**Loop diuretics**

Loop diuretics are used in pulmonary oedema due to left ventricular failure; intravenous administration produces relief of breathlessness and reduces pre-load sooner than would be expected from the time of onset of diuresis. Loop diuretics are also used in patients with chronic heart failure. Diuretic-resistant oedema (except lymphoedema and oedema due to peripheral venous stasis or calcium-channel blockers) can be treated with a loop diuretic combined with a thiazide or related diuretic (e.g., bendroflumethiazide 5–10 mg daily or metolazone 5–20 mg daily).

If necessary, a loop diuretic can be added to antihypertensive treatment to achieve better control of blood pressure in those with resistant hypertension, or in patients with impaired renal function or heart failure. Loop diuretics inhibit reabsorption from the ascending limb of the loop of Henle in the renal tubule and are powerful diuretics. Hypokalaemia may develop, and care is needed to avoid hypotension. If there is an enlarged prostate, urinary retention may occur; this is less likely if small doses and less potent diuretics are used initially.

**Furosemide** (frusemide) and **bumetanide** are similar in activity; both act within 1 hour of oral administration and diuresis is complete within 6 hours so that, if necessary, they can be given twice in one day without interfering with sleep. Following intravenous administration they have a peak effect within 30 minutes. The diuresis associated with these drugs is dose related. In patients with impaired renal function very large doses may occasionally be needed; in such doses both drugs may cause deafness and bumetanide can cause myalgia.

**Torasemide** has properties similar to those of furosemide and bumetanide, and is indicated for oedema and for hypertension.

---

**Hygroton**

- Tablets, yellow, scored, chlortalidone 50 mg, net price 28-tab pack = £1.64

**Ethibide XL**

- Tablets, m/r, metolazone 5 mg, net price 30-tab pack = £19.46

**Alliance**

- Tablets, blue, metolazone 5 mg, 60-tab pack = £6.00, 120-tab pack = £12.00

**Genus**

- Tablets, blue, xipamide 20 mg, net price 140-tab pack = £19.46
Furosemide (frusemide)

**Indications** oedema (see notes above); resistant hypertension (see notes above)

**Cautions** section 2.2; also monitor electrolytes; hypotension; prostatic enlargement; impaired micturition; gout; diabetes; intravenous administration rate should not usually exceed 4 mg/minute, however single doses of up to 80 mg may be administered more rapidly; a lower infusion rate may be considered in those with renal impairment; hepatorenal syndrome; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications** see under Furosemide

**Side-effects** mild gastro-intestinal disturbances; hypotension; hyperglycaemia (less common than with thiazides); hyperuricaemia and gout; electrolyte disturbances including hypernatraemia, hypokalaemia (see also section 2.2), hypocalcaemia, and hypomagnesaemia, metabolic alkalosis; rarely paraesthesia, blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia), bone marrow depression (withdrawal treatment), tinnitus and deafness (usually with large parenteral doses and rapid administration, in renal impairment, or in hypoproteinaemia), and hypersensitivity reactions (including rashes, photosensitivity, eosinophilia, exfoliative dermatitis, purpura, and anaphylaxis), pancreatitis, intrabpetic cholesterol; temporary increase in plasma cholesterol and triglyceride concentration also reported

**Dose**

- **By mouth**, oedema, initially 40 mg in the morning; maintenance 20–40 mg daily; CHILD 1–3 mg/kg daily, max. 40 mg daily
- **By intramuscular injection** or slow intravenous injection (rate of administration, see Cautions above), initially 20–50 mg, increased if necessary in steps of 20 mg not less than every 2 hours; doses greater than 50 mg by intravenous infusion only; max. 1.5 g daily; CHILD 0.5–1.5 mg/kg daily, max. 20 mg daily

**Furosemide** (Non-proprietary) Tablets, furosemide 20 mg, net price 28 = £1.22; 5 mg, 28-tab pack = £2.53

**Oral solution**, sugar-free, furosemide, net price 20 mg/5 mL, 150 mL = £12.68; 40 mg/5 mL, 150 mL = £16.31; 50 mg/5 mL, 150 mL = £17.68

**Injection**, furosemide 10 mg/mL, net price 2-mL amp = 55p, 5-mL amp = 66p, 25-mL amp = £2.50

**Lasix** (Sanofi-Aventis) Injection, furosemide 10 mg/mL, net price 2-mL amp = 78p

**Note** Large-volume furosemide injections also available; brands include Minijet

---

Bumetanide

**Indications** oedema (see notes above)

**Cautions** see under Furosemide; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications** see under Furosemide

**Side-effects** see under Furosemide; also headache, dizziness, fatigue, gynaecomastia, myalgia

**Dose**

- **By mouth**, 1 mg in the morning, repeated after 6–8 hours if necessary; severe cases, 5 mg daily increased by 5 mg every 12–24 hours according to response; ELDERLY, 500 micrograms daily may be sufficient
- **By intravenous injection**, 1–2 mg, repeated after 20 minutes if necessary; ELDERLY, 500 micrograms daily may be sufficient
- **By intravenous infusion**, 2–5 mg over 30–60 minutes; ELDERLY, 500 micrograms daily may be sufficient
- **By intramuscular injection**, 1 mg initially then adjusted according to response; ELDERLY, 500 micrograms daily may be sufficient

**Bumetanide** (Non-proprietary) Tablets, bumetanide 1 mg, net price 28-tab pack = £1.22; 5 mg, 28-tab pack = £2.53

**Oral solution**, bumetanide 1 mg/5 mL, net price 150 mL = £128.00

**Injection**, bumetanide 500 micrograms/mL, net price 4-mL amp = £1.79

**Burinex** (LEO) Tablets, scored, bumetanide 1 mg, net price 28-tab pack = £1.52; 5 mg, 28 = £9.67

---

Torasemide

**Indications** oedema (see notes above), hypertension

**Cautions** see under Furosemide; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4)

**Contra-indications** see under Furosemide

**Side-effects** see under Furosemide; also dry mouth; rarely limb paraesthesia

**Dose**

- **Oedema**, 5 mg once daily, preferably in the morning, increased if required to 20 mg once daily; usual max. 40 mg daily
- **Hypertension**, 2.5 mg daily, increased if necessary to 5 mg once daily

**Torasemide** (Non-proprietary) Tablets, torasemide 5 mg, net price 28-tab pack = £5.62; 10 mg, 28-tab pack = £8.09

**Torem** (Roche) Tablets, torasemide 2.5 mg, net price 28-tab pack = £3.78; 5 mg (scored), 28-tab pack = £5.53; 10 mg (scored), 28-tab pack = £8.14
2.2.3 Potassium-sparing diuretics and aldosterone antagonists

Amiloride and triamterene on their own are weak diuretics. They cause retention of potassium and are therefore given with thiazide or loop diuretics as a more effective alternative to potassium supplements. See section 2.2.4 for compound preparations with thiazides or loop diuretics.

Potassium supplements must not be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

Potassium supplements must be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a patient receiving an ACE inhibitor or an angiotensin-II receptor antagonist can also cause severe hyperkalaemia.

AMILORIDE HYDROCHLORIDE

**Indications**  oedema; potassium conservation when used as an adjunct to thiazide or loop diuretics for hypertension, congestive heart failure, or hepatic cirrhosis with ascites

**Cautions**  monitor electrolytes; diabetes mellitus; elderly; renal impairment (manufacturers advise avoid if severe; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions:** Appendix 1 (diuretics)

**Contra-indications**  hyperkalaemia; anuria; Addison’s disease

**Side-effects**  include gastro-intestinal disturbances, dry mouth, rashes, confusion, postural hypotension, hyperkalaemia, hyponatraemia

**Dose**
- Used alone, initially 10 mg daily or 5 mg twice daily, adjusted according to response; max. 20 mg daily
- With other diuretics, congestive heart failure and hypertension, initially 5–10 mg daily; cirrhosis with ascites, initially 5 mg daily

**Amiloride** (Non-proprietary)

**Tablets**, amiloride hydrochloride 5 mg, net price 28-tab pack = £1.03

**Oral solution**, sugar-free, amiloride hydrochloride 5 mg/5 mL, net price 150 mL = £39.73

**Brands include Amilamont** (Excipients include propylene glycol, see Excipients, p. 2)

**Diuretics and aldosterone antagonists**

**Indications**  oedema, potassium conservation with thiazide and loop diuretics

**Cautions**  see under Amiloride Hydrochloride; may cause blue fluorescence of urine

**Contra-indications**  see under Amiloride Hydrochloride

**Side-effects**  include gastro-intestinal disturbances, dry mouth, rashes; slight decrease in blood pressure, hyperkalaemia, hyponatraemia; photosensitivity and blood disorders also reported; triamterene found in kidney stones

**Disease**  include gastro-intestinal disturbances, dry mouth, rashes; slight decrease in blood pressure, hyperkalaemia, hyponatraemia

**Dose**
- Initially 150–250 mg daily, reducing to alternate days after 1 week; taken in divided doses after breakfast and lunch; lower initial dose when given with other diuretics

**Counselling**  Urine may look slightly blue in some lights

**Dyta(®) (Goldshield)**

**Capsules**, maroon, triamterene 50 mg, net price 30-cap pack = £17.35 Label: 14, (see above), 21

**Compound preparations with thiazides or loop diuretics**

Section 2.2.4

**Aldosterone antagonists**

Spironolactone potentiates thiazide or loop diuretics by antagonising aldosterone; it is a potassium-sparing diuretic. Spironolactone is of value in the treatment of oedema and ascites caused by cirrhosis of the liver; furosemide (section 2.2.2) can be used as an adjunct. Low doses of spironolactone are beneficial in severe heart failure, see section 2.5.5.

Spironolactone is also used in primary hyperaldosteronism (Conn’s syndrome). It is given before surgery or if surgery is not appropriate, in the lowest effective dose for maintenance.

**Eplerenone** is licensed for use as an adjunct in left ventricular dysfunction with evidence of heart failure after a myocardial infarction (see also section 2.5.5 and section 2.10.1).

Potassium supplements must not be given with aldosterone antagonists.

**Eplerenone**

**Indications**  adjunct in stable patients with left ventricular dysfunction with evidence of heart failure, following myocardial infarction (start therapy within 3–14 days of event)

**Cautions**  measure plasma-potassium concentration before treatment, during initiation, and when dose changed; elderly; hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 50 mL/minute; Appendix 3); pregnancy; breast-feeding (Appendix 5); **interactions:** Appendix 1 (diuretics)

**Contra-indications**  hyperkalaemia; concomitant use of potassium-sparing diuretics or potassium supplements

**Side-effects**  diarrhoea, nausea; hypotension; dizziness; hyperkalaemia; rash; less commonly flatulence, vomiting, atrial fibrillation, postural hypotension, arterial thrombosis, dyslipidaemia, pharyngitis, headache, insomnia, gynaeacomastia, pycnephritis, hyponatraemia, dehydration, eosinophilia, asthenia, malaise, back pain, leg cramps, impaired renal function, azotaemia, sweating and pruritus

**Dose**
- Initially 25 mg once daily, increased within 4 weeks to 50 mg once daily; **CHILD** not recommended

**Inspra(®) (Pfizer)**

**Tablets**, yellow, 1/2, eplerenone 25 mg, net price 28-tab pack = £42.72; 50 mg, 28-tab pack = £42.72
SIRONOLACTONE

Indications  oedema and ascites in cirrhosis of the liver, malignant ascites, nephrotic syndrome, congestive heart failure (section 2.5.5); primary hyperaldosteronism

Cautions  potential metabolic products carcinogenic in rodents; elderly; monitor electrolytes (discontinue if hyperkalaemia); acute porphyria (section 9.2.2); hepatic impairment; renal impairment (manufacturers advise avoid if severe; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (diuretics)

Contra-indications  hyperkalaemia, hyponatraemia; Addison’s disease

Side-effects  gastro-intestinal disturbances; impotence, gynaecomastia; menstrual irregularities; lethargy, headache, confusion; rash; hyperkalaemia (discontinue); hyponatraemia; hepatotoxicity, osteomalacia, and blood disorders reported

Dose  • 100–200 mg daily, increased to 400 mg if required; CHILD initially 3 mg/kg daily in divided doses

• Heart failure, see section 2.5.5

Spironolactone (Non-proprietary) [H]

Tablets, spironolactone 25 mg, net price 28 = £1.76; 50 mg, 28 = £2.53; 100 mg, 28 = £3.55. Label: 21

Oral suspensions, spironolactone 5 mg/5 mL, 10 mg/5 mL, 25 mg/5 mL, 50 mg/5 mL, and 100 mg/5 mL. Label: 21

Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

Aldactone® (Pharmacia) [H]

Tablets, f/c, spironolactone 25 mg (buff), net price 100-tab pack = £8.89; 50 mg (off-white), 100-tab pack = £17.78; 100 mg (buff), 28-tab pack = £9.96. Label: 21

With thiazides or loop diuretics  Section 2.2.4

2.2.4 Potassium-sparing diuretics with other diuretics

Although it is preferable to prescribe thiazides (section 2.2.1) and potassium-sparing diuretics (section 2.2.3) separately, the use of fixed combinations may be justified if compliance is a problem. Potassium-sparing diuretics are not usually necessary in the routine treatment of hypertension, unless hypokalaemia develops. For interactions, see Appendix 1 (diuretics).

Amiloride with thiazides

Co-amilozide (Non-proprietary) [H]

Tablets, co-amilozide 2.5/25 (amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-tab pack = £2.57

Brands include Moduretic 25

Dose  hypertension, initially 1 tablet daily, increased if necessary to max. 2 tablets daily

Congestive heart failure, initially 1 tablet daily, increased if necessary to max. 4 tablets daily

Oedema and ascites in cirrhosis of the liver, initially 2 tablets daily, increased if necessary to max. 4 tablets daily; reduce for maintenance if possible

Amiloride with loop diuretics

Co-amilofruse (Non-proprietary) [H]

Tablets, co-amilofruse 2.5/20 (amiloride hydrochloride 2.5 mg, furosemide 20 mg), net price 28-tab pack = £1.19, 56-tab pack = £1.63

Brands include Frumil LS

Dose  oedema, 1 tablet in the morning

Tablets, co-amilofruse 5/40 (amiloride hydrochloride 5 mg, furosemide 40 mg), net price 28-tab pack = £1.24, 56-tab pack = £1.61

Brands include Frumil-C O, Frumil

Dose  oedema, 1–2 tablets in the morning

Tablets, co-amilofruse 10/80 (amiloride hydrochloride 10 mg, furosemide 80 mg), net price 28-tab pack = £9.33, 56-tab pack = £14.86

Brands include Andi

Dose  oedema, 1 tablet in the morning

Burinex A® (Chemidex) [H]

Tablets, ivory, scored, amiloride hydrochloride 5 mg, bumetanide 1 mg, net price 28-tab pack = £2.63

Dose  oedema, 1–2 tablets daily

Triameterene with thiazides

Counselling  Urine may look slightly blue in some lights

Co-triamterzide (Non-proprietary) [H]

Tablets, co-triamterzide 50/25 (triameterene 50 mg, hydrochlorothiazide 25 mg), net price 30-tab pack = 95p. Label: 14, (see above), 21

Dose  hypertension, 1 tablet daily after breakfast, increased if necessary, max. 4 daily

Oedema, 2 tablets daily (1 after breakfast and 1 after midday meal) increased to 3 daily if necessary (2 after breakfast and 1 after midday meal), usual maintenance in oedema, 1 daily or 2 on alternate days; max. 4 daily

Brands include Triam-Co

Dyazide® (Goldshield) [H]

Tablets, peach, scored, co-triamteride 50/25 (triameterene 50 mg, hydrochlorothiazide 25 mg), net price 30-tab pack = 95p. Label: 14, (see above), 21

Dose  hypertension, 1 tablet daily after breakfast, increased if necessary, max. 4 daily

Oedema, 2 tablets daily (1 after breakfast and 1 after midday meal) increased to 3 daily if necessary (2 after breakfast and 1 after midday meal), usual maintenance in oedema, 1 daily or 2 on alternate days; max. 4 daily

Brands include Triam-Co

Dytide® (Goldshield) [H]

Capsules, clear/maroon, triameterene 50 mg, benz-thiazide 25 mg, net price 30-cap pack = £17.35.

Label: 14, (see above), 21

Dose  oedema, initially 3 capsules daily (2 after breakfast and 1 after midday meal) for 1 week then 1 or 2 on alternate days
2.2.5 Osmotic diuretics

Mannitol is an osmotic diuretic that can be used to treat cerebral oedema and raised intra-ocular pressure.

MANNITOL

Indications  see notes above; glaucoma (section 11.6)

Cautions  extravasation causes inflammation and thrombophlebitis

Contra-indications  congestive cardiac failure, pulmonary oedema

Side-effects  chills, fever

Dose

- Cerebral oedema and raised intra-ocular pressure, by intravenous infusion over 30–60 minutes, 0.25–2 g/kg repeated if necessary 1–2 times after 4–8 hours

Mannitol (Baxter)  [UK]

Intravenous infusion, mannnitol 10% and 20%

2.2.6 Mercurial diuretics

Mercurial diuretics are effective but are now almost never used because of their nephrotoxicity.

2.2.7 Carbonic anhydrase inhibitors

The carbonic anhydrase inhibitor acetazolamide is a weak diuretic and is little used for its diuretic effect. It is used for prophylaxis against mountain sickness [unlicensed indication] but is not a substitute for acclimatisation. Acetazolamide and eye drops of dorzolamide and brinzolamide inhibit the formation of aqueous humour and are used in glaucoma (section 11.6).

2.2.8 Diuretics with potassium

Many patients on diuretics do not need potassium supplements (section 9.2.1.1). For many of those who do, the amount of potassium in combined preparations may not be enough, and for this reason their use is to be discouraged.

Diuretics with potassium and potassium-sparing diuretics should not usually be given together.

Counselling  Modified-release potassium tablets should be swallowed whole with plenty of fluid during meals while sitting or standing

Centyl K® (LEO)  [UK]

Tablets, green, f/c, bendroflumethiazide 2.5 mg, potassium 7.7 mmol for modified release, net price 56-tab pack = £7.50. Label: 25, 27, counselling, see above

Diuride-K Continus® (Teofarma)  [UK]

Tablets, white/orange, f/c, furosemide 40 mg, potassium 8 mmol for modified release, net price 30-tab pack = £3.00. Label: 25, 27, counselling, see above

Neo-NaClex-K® (Goldshield)  [UK]

Tablets, pink/white, f/c, bendroflumethiazide 2.5 mg, potassium 8.4 mmol for modified release, net price 100 tab-pack = £8.99. Label: 25, 27, counselling, see above

2.3 Anti-arrhythmic drugs

2.3.1 Management of arrhythmias

2.3.2 Drugs for arrhythmias
Atrial fibrillation  Atrial fibrillation can be managed by either controlling the ventricular rate or by attempting to restore and maintain sinus rhythm. All patients with atrial fibrillation should be assessed for their risk of stroke and thromboembolism, and thromboprophylaxis given if necessary (see below).

Ventricular rate can be controlled with a beta-blocker (section 2.4), or diltiazem [unlicensed indication], or verapamil. If rate control is inadequate during normal activities, digoxin can be added; in those who require additional rate control during exercise, a combination of diltiazem or verapamil with digoxin should be used, but care is required if ventricular function is diminished. Digoxin is usually only effective for controlling ventricular rate at rest, therefore digoxin monotherapy should only be used in predominantly sedentary patients; digoxin is also used if atrial fibrillation is accompanied by congestive heart failure.

Sinus rhythm can be restored by electrical cardioversion, or pharmacological cardioversion with an intravenous anti-arrhythmic drug e.g. flecainide or amiodarone. If necessary, sotalol or amiodarone can be started 4 weeks before electrical cardioversion to increase success of the procedure. If drug treatment is required to maintain sinus rhythm, a beta-blocker is used. If a standard beta-blocker is not appropriate or is ineffective, an oral anti-arrhythmic drug such as sotalol (section 2.4), flecainide, propafenone, or amiodarone, is required.

In symptomatic paroxysmal atrial fibrillation, ventricular rhythm is controlled with a beta-blocker. Alternatively, if symptoms persist or a beta-blocker is not appropriate, an oral anti-arrhythmic drug such as sotalol, flecainide, propafenone, or amiodarone can be given (see also Paroxysmal Supraventricular Tachycardia below, and Supraventricular Arrhythmias).

All haemodynamically unstable patients with acute-onset atrial fibrillation should undergo electrical cardioversion. Intravenous amiodarone, or alternatively flecainide, can be used in non-life-threatening cases where electrical cardioversion is delayed. If urgent ventricular rate control is required, a beta-blocker, verapamil, or amiodarone can be given intravenously.

All patients with atrial fibrillation should be assessed for their risk of stroke and the need for thromboprophylaxis. Anticoagulants (section 2.8) are indicated for those with a history of ischaemic stroke, transient ischaemic attacks, or thromboembolic events, and those with valve disease, heart failure, or impaired left ventricular function; anticoagulants should be considered for those with cardiovascular disease, diabetes, hypertension, or thyrotoxicosis, and in the elderly. Anticoagulants are also indicated during cardioversion procedures. Aspirin (section 2.9) is less effective than warfarin at preventing emboli, but may be appropriate if there are no other risk factors for stroke, or if warfarin is contra-indicated.

Paroxysmal supraventricular tachycardia  In most patients this remits spontaneously or can be returned to sinus rhythm by reflex vagal stimulation with respiratory manoeuvres, prompt squatting, or pressure over one carotid sinus (important: pressure over carotid sinus should be restricted to monitored patients—it can be dangerous in recent ischaemia, digitalis toxicity, or the elderly).

If vagal stimulation fails, intravenous administration of adenosine is usually the treatment of choice. Intravenous administration of verapamil is useful for patients without myocardial or valvular disease (important: never in patients recently treated with beta-blockers, see p. 118). For arrhythmias that are poorly tolerated, synchronised d.c. shock usually provides rapid relief.

In cases of paroxysmal supraventricular tachycardia with block, digitalis toxicity should be suspected. In addition to stopping administration of the cardiac glycoside and giving potassium supplements, intravenous administration of a beta-blocker may be useful. Specific digoxin antibody is available if the toxicity is considered life-threatening (section 2.1.1).

Arrhythmias after myocardial infarction  In patients with a paroxysmal tachycardia or rapid irregularity of the pulse it is best not to administer an anti-arrhythmic until an ECG record has been obtained. Bradycardia, particularly if complicated by hypotension, should be treated with 500 micrograms of atropine sulphate given intravenously; the dose may be repeated every 3–5 minutes if necessary up to a maximum total dose of 3 mg. If there is a risk of asystole, or if the patient is unstable and has failed to respond to atropine, adrenaline should be given by intravenous infusion in a dose of 2–10 micrograms/minute, adjusted according to response.

For further advice, refer to the most recent recommendations of the Resuscitation Council (UK) available at www.resus.org.uk.

Ventricular tachycardia  Drug treatment is used both for the treatment of ventricular tachycardia and for prophylaxis of recurrent attacks that merit suppression. Ventricular tachycardia requires treatment most commonly in the acute stage of myocardial infarction, but the likelihood of this and other life-threatening arrhythmias diminishes sharply over the first 24 hours after the attack, especially in patients without heart failure or shock. Lidocaine (lignocaine) is the preferred drug for emergency use. Other drugs are best administered under specialist supervision. Very rapid ventricular tachycardia causes profound circulatory collapse and should be treated urgently with d.c. shock.

Torsade de pointes is a form of ventricular tachycardia associated with a long QT syndrome (usually drug-induced, but other factors including hypokalaemia, severe bradycardia, and genetic predisposition are also implicated). Episodes are usually self-limiting, but are frequently recurrent and can cause impairment or loss of consciousness. If not controlled, the arrhythmia can progress to ventricular fibrillation and sometimes death. Intravenous infusion of magnesium sulphate (section 9.5.1.3) is usually effective. A beta-blocker (but not sotalol) and atrial (or ventricular) pacing can be considered. Anti-arrhythmics can further prolong the QT interval, thus worsening the condition.
2.3.2 Drugs for arrhythmias

Anti-arrhythmic drugs can be classified clinically into those that act on supraventricular arrhythmias (e.g. verapamil), those that act on both supraventricular and ventricular arrhythmias (e.g. disopyramide), and those that act on ventricular arrhythmias (e.g. lidocaine (lignocaine)).

They can also be classified according to their effects on the electrical behaviour of myocardial cells during activity:

- Class I: membrane stabilising drugs (e.g. lidocaine, flecaïnine)
- Class II: beta-blockers
- Class III: amiodarone and sotalol (also Class II)
- Class IV: calcium-channel blockers (includes verapamil but not dihydroprydines)

This latter classification (the Vaughan Williams classification) is of less clinical significance.

Cautions The negative inotropic effects of anti-arrhythmic drugs tend to be additive. Therefore special care should be taken if two or more are used, especially if myocardial function is impaired. Most or all drugs that are effective in countering arrhythmias can also provoke them in some circumstances; moreover, hypokalaemia enhances the arrhythmogenic (pro-arrhythmic) effect of many drugs.

Supraventricular arrhythmias

Adenosine is usually the treatment of choice for terminating paroxysmal supraventricular tachycardia. As it has a very short duration of action (half-life only about 8 to 10 seconds, but prolonged in those taking dipyridamole), most side-effects are short lived. Unlike verapamil, adenosine can be used after a beta-blocker. Verapamil may be preferable to adenosine in asthma.

Oral administration of a cardiac glycoside (such as digoxin, section 2.1.1) slows the ventricular response in cases of atrial fibrillation and atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate. Cardiac glycosides are contra-indicated in supraventricular arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome).

Verapamil (section 2.6.2) is usually effective for supraventricular tachycardias. An initial intravenous dose (important: serious beta-blocker interaction hazard, see p. 118) may be followed by oral treatment; hypotension may occur with large doses. It should not be used for tachyarrhythmias where the QRS complex is wide (i.e. broad complex) unless a supraventricular origin has been established beyond reasonable doubt. It is also contra-indicated in atrial fibrillation with pre-excitation (e.g. Wolff-Parkinson-White syndrome). It should not be used in children with arrhythmias without specialist advice; some supraventricular arrhythmias in childhood can be accelerated by verapamil with dangerous consequences.

Intravenous administration of a beta-blocker (section 2.4) such as esmolol or propranolol, can achieve rapid control of the ventricular rate.

Drugs for both supraventricular and ventricular arrhythmias include amiodarone, beta-blockers (see p. 86), disopyramide, flecaïnine, procainamide (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939), and propafenone, see below under Supraventricular and Ventricular Arrhythmias.

Adenosine

Indications rapid reversion to sinus rhythm of paroxysmal supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome); aid to diagnosis of broad or narrow complex supraventricular tachycardias

Cautions atrial fibrillation or flutter with accessory pathway (conduction down anomalous pathway may increase); heart transplant (see below); interactions: Appendix 1 (adenosine)

Contra-indications second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted); asthma

Side-effects include transient facial flush, chest pain, dyspnoea, bronchospasm, choking sensation, nausea, light-headedness; severe bradycardia reported (requiring temporary pacing); ECG may show transient rhythm disturbances

Dose

- By rapid intravenous injection into central or large peripheral vein, 6 mg over 2 seconds with cardiac monitoring; if necessary followed by 12 mg after 1–2 minutes, and then by 12 mg after a further 1–2 minutes; increments should not be given if high level AV block develops at any particular dose

Important Patients with a heart transplant are very sensitive to effects of adenosine and should receive initial dose of 3 mg over 2 seconds, followed if necessary by 6 mg after 1–2 minutes, and then by 12 mg after a further 1–2 minutes. Also, if essential to give with dipyridamole reduce initial dose to 0.5–1 mg

Note Adenosine doses in the BNF may differ from those in product literature

Adenocor® (Sanofi-Synthelabo) [oral]

Injection, Adenosine 3 mg/mL in physiological saline, net price 2-mL vial = £4.45 (hosp. only)

Note Intravenous infusion of adenosine (Adenocan, Sanofi Winthrop) may be used in conjunction with radionuclide myocardial perfusion imaging in patients who cannot exercise adequately or for whom exercise is inappropriate—consult product literature

Supraventricular and ventricular arrhythmias

Amiodarone is used in the treatment of arrhythmias particularly when other drugs are ineffective or contra-indicated. It may be used for paroxysmal supraventricular, nodal and ventricular tachycardias, atrial fibrillation and flutter, and ventricular fibrillation. It may also be used for tachyarrhythmias associated with Wolff-Parkinson-White syndrome. It should be initiated only under hospital or specialist supervision. Amiodarone may be given by intravenous infusion as well as by mouth, and has the advantage of causing little or no myocardial depression. Unlike oral amiodarone, intravenous amiodarone may act relatively rapidly.

Intravenous injection of amiodarone may be used in cardiopulmonary resuscitation for ventricular fibrilla-
tion or pulseless tachycardia unresponsive to other interventions (section 2.7.3).

Amiodarone has a very long half-life (extending to several weeks) and only needs to be given once daily (but high doses may cause nausea unless divided). Many weeks or months may be required to achieve steady-state plasma-amiodarone concentration; this is particularly important when drug interactions are likely (see also Appendix 1).

Most patients taking amiodarone develop corneal microdeposits (reversible on withdrawal of treatment); these rarely interfere with vision, but drivers may be dazzled by headlights at night. However, if vision is impaired or if optic neuritis or optic neuropathy occur, amiodarone must be stopped to prevent blindness and expert advice sought. Because of the possibility of phototoxic reactions, patients should be advised to shield the skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen (section 13.8.1) to protect against both long-wave ultraviolet and visible light should be used.

Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism may occur. Clinical assessment alone is unreliable, and laboratory tests should be performed before treatment and every 6 months. Thyroxine (T4) may be raised in the absence of hyperthyroidism; therefore tri-iodothyronine (T3), T4, and thyroid-stimulating hormone (thyrotrophin, TSH) should all be measured. A raised T3 and T4 with a very low or undetectable TSH concentration suggests the development of thyrotoxicosis. The thyrotoxicosis may be very refractory, and amiodarone should usually be withdrawn at least temporarily to help achieve control; treatment with carbimazole may be required. Hypothyroidism can be treated with replacement therapy without withdrawing amiodarone if it is essential; careful supervision is required. Pneumonitis should always be suspected if new or worsening respiratory symptoms occur (but high doses may cause nausea unless divided). Many weeks or months may be required to achieve steady-state plasma-amiodarone concentration; this is particularly important when drug interactions are likely (see also Appendix 1).

Propafenone is used for the prophylaxis and treatment of ventricular arrhythmias and also for some supraventricular arrhythmias. It has complex mechanisms of action, including weak beta-blocking activity (therefore caution is needed in obstructive airways disease—contra-indicated if severe).

Drugs for supraventricular arrhythmias include adenosine, cardiac glycosides, and verapamil; see above under Supraventricular Arrhythmias. Drugs for ventricular arrhythmias include lidocaine; see under Ventricular Arrhythmias, p. 84.

Mexiletine and procainamide are both available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939. Mexiletine can be used for life-threatening ventricular arrhythmias; procainamide is given by intravenous injection to control ventricular arrhythmias.

**AMIODARONE HYDROCHLORIDE**

**Indications** see notes above (should be initiated in hospital or under specialist supervision)

**Cautions** liver-function and thyroid-function tests required before treatment and then every 6 months (see notes above for tests of thyroid function); hypokalaemia (measure serum-potassium concentration before treatment); chest x-ray required before treatment; heart failure; elderly; severe bradycardia and conduction disturbances in excessive dosage; intravenous use may cause moderate and transient fall in blood pressure (circulatory collapse precipitated by rapid administration or overdosage) or severe hepatocellular toxicity (monitor transaminases closely); give by central venous catheter only; infusion via peripheral veins may cause pain and inflammation; ECG monitoring and resuscitation facilities must be available during intravenous use; acute porphyria (section 9.8.2); interactions: Appendix 1 (amiodarone)

**Contra-indications** (except in cardiac arrest) sinus bradycardia, sino-atrial heart block; unless pacemaker fitted avoid in severe conduction disturbances or sinus node disease; thyroid dysfunction; iodine sensitivity; avoid intravenous use in severe respiratory failure, circulatory collapse, or severe arterial hypotension; avoid bolus injection in congestive heart failure or cardiomyopathy; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, taste disturbances, raised serum transaminases (may require dose reduction or withdrawal if accompanied by acute liver disorders); jaundice; bradycardia (see Cautions); pulmonary toxicity (including pneumonitis and fibrosis); tremor, sleep disorders; hypothyroïdism, hyperthyroïdism; reversible corneal microdeposits (sometimes with night glare); phototoxicity, persistent slate-grey skin discolouration (see also notes above), injection-site reactions; less commonly onset or worsening of arrhythmia, conduction disturbances (see Cautions), peripheral neuropathy and myopathy (usually reversible on withdrawal); very rarely chronic liver disease including cirrhosis, sinus arrest, bronchospasm (in patients with severe respiratory failure), ataxia, benign intracranial hypertension, headache, vertigo, epididymo-orchitis, impotence, haemolytic or aplastic anaemia, thrombocytopenia, rash (including exfoliative dermatitis), hypersensitivity including vasculitis, alopecia, impaired vision due to optic...
neuritis or optic neuropathy (including blindness), anaphylaxis on rapid injection, also hypotension, respiratory distress syndrome, sweating, and hot flushes

**Dose**

- **By mouth**, 200 mg 3 times daily for 1 week reduced to 200 mg twice daily for a further week; maintenance, usually 200 mg daily or the minimum required to control the arrhythmia
- **By intravenous infusion** via central venous catheter, initially 5 mg/kg over 20–120 minutes with ECG monitoring; subsequent infusion given if necessary according to response up to max. 1.2 g in 24 hours
- Ventricular fibrillation or pulseless ventricular tachycardia refractory to defibrillation, section 2.7.3

**Amiodarone (Non-proprietary)** *(Amynex)*

**Tablets**, amiodarone hydrochloride 100 mg, net price 28-tab pack = £1.39; 200 mg, 28-tab pack = £1.42.

**Injection**, amiodarone hydrochloride 30 mg/mL, net price 10-mL prefilled syringe = £10.25

**Excipients** may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

**Sterile concentrate**, amiodarone hydrochloride 50 mg/mL, net price 3-mL amp = £1.33, 6-mL amp = £2.86. For dilution and use as an infusion

**Excipients** may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

**Cordarone X** *(Sanofi-Aventis)* *(Amyben)*

**Tablets**, scored, amiodarone hydrochloride 100 mg, net price 28-tab pack = £4.45; 200 mg, 28-tab pack = £7.27.

**Label**: 11

**Stere concentrate**, amiodarone hydrochloride 50 mg/mL, net price 3-mL amp = £1.33. For dilution and use as an infusion

**Excipients** include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

### DISOPYRAMIDE

**Indications** ventricular arrhythmias, especially after myocardial infarction; supraventricular arrhythmias

**Cautions** monitor for hypotension, hypoglycaemia, ventricular tachycardia, ventricular fibrillation or torsade de points (discontinue if occur); atrial flutter or atrial tachycardia with partial block, bundle branch block, heart failure (avoid if severe); prostatic enlargement; susceptibility to angle-closure glaucoma; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (disopyramide)

**Contra-indications** second- and third-degree heart block and sinus node dysfunction (unless pacemaker fitted); cardiogenic shock; severe uncompensated heart failure

**Side-effects** ventricular tachycardia, ventricular fibrillation or torsade de points (usually associated with prolongation of QRS complex or QT interval—see Cautions above), myocardial depression, hypotension, AV block; antimuscarnic effects include dry mouth, blurred vision, urinary retention, and very rarely angle-closure glaucoma; gastro-intestinal irritation; psychosis, cholestatic jaundice, hypoglycaemia also reported (see Cautions above)

**Dose**

- **By mouth**, 300–800 mg daily in divided doses
- **By slow intravenous injection**, 2 mg/kg over at least 5 minutes to a max. of 150 mg, with ECG monitoring, followed immediately either by 200 mg **by mouth**, then 200 mg every 8 hours for 24 hours or 400 micrograms/kg/hour **by intravenous infusion**; max. 300 mg in first hour and 800 mg daily

**Disopyramide (Non-proprietary)** *(Amyben)*

**Capsules**, disopyramide (as phosphate) 100 mg, net price 84 = £21.37; 150 mg, 84 = £26.72

**Injection**, disopyramide (as phosphate) 10 mg/mL, net price 5-mL amp = £2.72

### FLECAINIDE ACETATE

**Indications** Capsules, tablets, and injection: AV nodal reciprocating tachycardia, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), disabling symptoms of paroxysmal atrial fibrillation in patients without left ventricular dysfunction (arrhythmias of recent onset will respond more readily)

**Immediate-release tablets only**: symptomatic sustained ventricular tachycardia, disabling symptoms of premature ventricular contractions or non-sustained ventricular tachycardia in patients resistant to or intolerant of other therapy

**Injection only**: ventricular tachyarrhythmias resistant to other treatment

**Cautions** patients with pacemakers (especially those who may be pacemaker dependent because stimulation threshold may rise appreciably); atrial fibrillation following heart surgery; elderly (accumulation may occur); ECG monitoring and resuscitation facilities must be available during intravenous use; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (flecainide)

**Contra-indications** heart failure; abnormal left ventricular function; history of myocardial infarction and either asymptomatic ventricular ectopics or asymptomatic non-sustained ventricular tachycardia; long-standing atrial fibrillation where conversion to sinus rhythm not attempted: haemodynamically significant valvular heart disease; avoid in sinus node dysfunction, atrial conduction defects, second-degree or greater AV block, bundle branch block or distal block unless pacing rescue available

**Side-effects** oedema, pro-arrhythmic effects; dyspnoea, dizziness, asthenia, fatigue, fever, visual disturbances; rarely pneumonitis, hallucinations, depression, confusion, anaemia, dyskinesia, convulsions, peripheral neuropathy; also reported gastro-intestinal disturbances, anorexia, hepatic dysfunction, flushing, syncope, drowsiness, tremor, vertigo, headache, anxiety, insomnia, ataxia, paraesthesia, anaemia, leucopenia, thrombocytopenia, corneal deposits, tis-
2 Cardiovascular system

2.3.2 Drugs for arrhythmias

Tambocor

Flecainide (Non-proprietary)

By mouth.

Dose

- By mouth (initiated under direction of hospital consultant), ventricular arrhythmias, initially 100 mg twice daily (max. 400 mg daily usually reserved for rapid control or in heavily built patients), reduced after 3–5 days to the lowest dose which controls arrhythmia

Supraventricular arrhythmias, 50 mg twice daily, increased if required to max. 300 mg daily

- By slow intravenous injection (in hospital), 2 mg/kg over 10–30 minutes, max. 150 mg, with ECG monitoring; followed if required by infusion at a rate of 1.5 mg/kg/hour for 1 hour, subsequently reduced to 100–250 micrograms/kg/hour for up to 24 hours; max. cumulative dose in first 24 hours, 600 mg; transfer to oral treatment, as above

Flecainide acetate 50 mg, net price 60-tab pack = £9.81; 100 mg, 60-tab pack = £15.04

Tambocor® (3M)

Tablets, flecainide acetate 50 mg, net price 60-tab pack = £14.46; 100 mg (scored), 60-tab pack = £20.66

Injection, flecainide acetate 10 mg/mL, net price 15-mL amp = £4.40

Modified release

Tambocor® XL (Meda)

Capsules, m/r, grey/pink, flecainide acetate 200 mg, net price 30-cap pack = £14.77. Label: 25

Dose

- supraventricular arrhythmias, 200 mg once daily

- supraventricular atrial dysrhythmias, 100 mg twice daily and, if necessary, to max. 300 mg 3 times daily after food under direct hospital supervision with ECG monitoring and blood pressure control (if QRS interval prolonged by more than 20%, reduce dose or discontinue if necessary). Max. 1000 mg daily

Dose

- Body-weight 70 kg and over, initially 150 mg 3 times daily after food under direct hospital supervision with ECG monitoring and blood pressure control (if QRS interval prolonged by more than 20%, reduce dose or discontinue until ECG returns to normal limits); may be increased at intervals of at least 3 days to 300 mg twice daily and, if necessary, to max. 300 mg 3 times daily; body-weight under 70 kg, reduce dose; ELDERLY may respond to lower doses

Verapamil® (Abbott) Tablets, 12.5 mg, propafenone hydrochloride 150 mg, net price 90-tab pack = £7.37; 300 mg, 60-tab pack = £9.34. Label: 21, 25

Ventricular arrhythmias

Lidocaine (lidocaine) is relatively safe when used by slow intravenous injection and should be considered first for emergency use. Though effective in suppressing ventricular tachycardia and reducing the risk of ventricular fibrillation following myocardial infarction, it has not been shown to reduce mortality when used prophylactically in this condition. In patients with cardiac or hepatic failure doses may need to be reduced to avoid convulsions, depression of the central nervous system, or depression of the cardiovascular system.

Moracizine (Ethmazine®, Shire) is available from ‘special-order’ manufacturers or specialist-importing companies (see p. 939) for the prophylaxis and treatment of serious and life-threatening ventricular arrhythmias for patients already stabilised on moracizine.

Drugs for both supraventricular and ventricular arrhythmias include amiodarone, beta-blockers, disopyramide, flecainide, procarinamide (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939), and propafenone, see above under Supraventricular and Ventricular Arrhythmias.

Mexiletine is available from ‘special-order’ manufacturers or specialist-importing companies (see p. 939) for treatment of life-threatening ventricular arrhythmias.

Lidocaine hydrochloride

Indications ventricular arrhythmias, especially after myocardial infarction

Cautions lower doses in congestive cardiac failure and following cardiac surgery; monitor ECG and have resuscitation facilities available; elderly; hepatic impairment (Appendix 2); renal impairment (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (lidocaine)

Contra-indications sino-atrial disorders, all grades of atrioventricular block, severe myocardial depression; acute porphyria (section 9.8.2)

Side-effects dizziness, paraesthesia, or drowsiness (particularly if injection too rapid); other CNS effects include confusion, respiratory depression and convulsions; hypotension and bradycardia (may lead to cardiac arrest); rarely hypersensitivity reactions including anaphylaxis
2.4 Beta-adrenoceptor blocking drugs

Beta-adrenoceptor blocking drugs (beta-blockers) block the beta-adrenoceptors in the heart, peripheral vasculature, bronchi, pancreas, and liver. Many beta-blockers are now available and in general they are all equally effective. There are, however, differences between them which may affect choice in treating particular diseases or individual patients. Intrinsic sympathomimetic activity (ISA, partial agonist activity) represents the capacity of beta-blockers to stimulate as well as to block adrenergic receptors.

Oxprenolol, pindolol, acebutolol, and celiprolol have intrinsic sympathomimetic activity; they tend to cause less bradycardia than the other beta-blockers and may also cause less coldness of the extremities. Some beta-blockers are lipid soluble and some are water soluble. Atenolol, celiprolol, nadolol, and sotalol are the most water-soluble; they are less likely to enter the brain, and may therefore cause less sleep disturbance and nightmares. Water-soluble beta-blockers are excreted by the kidneys and dosage reduction is often necessary in renal impairment.

Beta-blockers with a relatively short duration of action have to be given two or three times daily. Many of these are, however, available in modified-release formulations so that administration once daily is adequate for hypertension. For angina twice-daily treatment may sometimes be needed even with a modified-release formulation. Some beta-blockers such as atenolol, bisoprolol, carvedilol, celiprolol, and nadolol have an intrinsically longer duration of action and need to be given only once daily.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in patients with second- or third-degree heart block. Beta-blockers should also be avoided in patients with worsening unstable heart failure; care is required when initiating a beta-blocker in those with stable heart failure (see also section 2.5.5). Sotalol may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias (important: particular care is required to avoid hypokalaemia in patients taking sotalol).

Labetalol, celiprolol, carvedilol, and nebivolol are beta-blockers that have, in addition, an arteriolar vasodilating action, by diverse mechanisms, and thus lower peripheral resistance. There is no evidence that these drugs have important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers can precipitate asthma and this effect can be dangerous. Beta-blockers should be avoided in patients with a history of asthma or bronchospasm; if there is no alternative, a cardioselective beta-blocker can be used with extreme caution under specialist supervision. Atenolol, bisoprolol, metoprolol, nebivolol, and (to a lesser extent) acebutolol, have less effect on the beta (bronchial) receptors and are, therefore, relatively cardioselective, but they are not cardiospecific. They have a lesser effect on airways resistance but are not free of this side-effect.

Beta-blockers are also associated with fatigue, coldness of the extremities (may be less common with those with ISA, see above), and sleep disturbances with nightmares (may be less common with the water-soluble beta-blockers, see above).

Beta-blockers are not contra-indicated in diabetes; however, they can lead to a small deterioration of glucose tolerance and interfere with metabolic and autonomic responses to hypoglycaemia. Cardioselective beta-blockers (see above) may be preferable and beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia. Beta blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes.

Hypertension The mode of action of beta-blockers in hypertension is not understood, but they reduce cardiac output, alter baroceptor reflex sensitivity, and block peripheral adrenoceptors. Some beta-blockers depress plasma renin secretion. It is possible that a central effect may also partly explain their mode of action.

Beta-blockers are effective for reducing blood pressure but other antihypertensives (section 2.5) are usually more effective for reducing the incidence of stroke, myocardial infarction, and cardiovascular mortality, especially in the elderly. Other antihypertensives are therefore preferred for routine initial treatment of uncomplicated hypertension.

In general, the dose of a beta-blocker does not have to be high; for example, atenolol is given in a dose of 25–50 mg daily and it is rarely necessary to increase the dose to 100 mg.

Beta-blockers can be used to control the pulse rate in patients with phaeochromocytoma (section 2.5.4). However, they should never be used alone as beta-blockade without concurrent alpha-blockade may lead to a hypertensive crisis. For this reason phenoxybenzamine should always be used together with the beta-blocker.
Angina  By reducing cardiac work beta-blockers improve exercise tolerance and relieve symptoms in patients with angina (for further details on the management of stable and unstable angina see section 2.6). As with hypertension there is no good evidence of the superiority of any one drug, although occasionally a patient will respond better to one beta-blocker than to another. There is some evidence that sudden withdrawal may cause an exacerbation of angina and therefore gradual reduction of dose is preferable when beta-blockers are to be stopped. There is a risk of precipitating heart failure when beta-blockers and verapamil are used together in established ischaemic heart disease (important: see p. 118).

Myocardial infarction  For advice on the management of ST-segment-elevation myocardial infarction see section 2.10.1; for advice on the management of non-ST-segment-elevation myocardial infarction see section 2.6. Several studies have shown that some beta-blockers can reduce the recurrence rate of myocardial infarction. However, uncontrolled heart failure, hypotension, bradycardias, and obstructive airways disease render beta-blockers unsuitable in some patients following a myocardial infarction. Atenolol and metoprolol may reduce early mortality after intravenous and subsequent oral administration in the acute phase, while acebutolol, metoprolol, propranolol, and timolol have protective value when started in the early convalescent phase. The evidence relating to other beta-blockers is less convincing; some have not been tested in trials of secondary prevention. Sudden cessation of a beta-blocker can cause a rebound worsening of myocardial ischaemia.

Arrhythmias  Beta-blockers act as antiarrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used in conjunction with digoxin to control the ventricular response in atrial fibrillation, especially in patients with thyrotoxicosis. Beta-blockers are also useful in the management of supraventricular tachycardias, and are used to control those following myocardial infarction (see above).

Esmolol is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias, sinus tachycardia, or hypertension, particularly in the peri-operative period. It may also be used in other situations, such as acute myocardial infarction, where sustained beta blockade might be hazardous.

Sotalol, a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity, is used for prophylaxis in paroxysmal supraventricular arrhythmias. It also suppresses ventricular ectopic beats and non-sustained ventricular tachycardia. It has been shown to be more effective than lidocaine (lignocaine) in the termination of spontaneous sustained ventricular tachycardia due to coronary disease or cardiomyopathy. However, it may induce torsade de pointes in susceptible patients.

Heart failure  Beta-blockers may produce benefit in heart failure by blocking sympathetic activity. Bisoprolol and carvedilol reduce mortality in any grade of stable heart failure; nebivolol is licensed for stable mild to moderate heart failure in patients over 70 years. Treatment should be initiated by those experienced in the management of heart failure (section 2.5.5).

Thyrotoxicosis  Beta-blockers are used in pre-operative preparation for thyroidectomy. Administration of propranolol can reverse clinical symptoms of thyrotoxicosis within 4 days. Routine tests of increased thyroid function remain unaltered. The thyroid gland is rendered less vascular thus making surgery easier (section 6.2.2).

Other uses  Beta-blockers have been used to alleviate some symptoms of anxiety; probably patients with palpitation, tremor, and tachycardia respond best (see also section 4.1.2 and section 4.9.3). Beta-blockers are also used in the prophylaxis of migraine (section 4.7.4.2). Betaxolol, carteolol, levobunolol, metipranolol and timolol are used topically in glaucoma (section 11.6).

**PROPRANOLOL HYDROCHLORIDE**

**Indications** see under Dose

**Cautions** see notes above; also avoid abrupt withdrawal especially in ischaemic heart disease; first-degree AV block; portal hypertension (risk of deterioration in liver function); diabetes; history of obstructive airways disease (introduce cautiously and monitor lung function—see also Bronchospasm below); myasthenia gravis; symptoms of hypoglycaemia and thyrotoxicosis may be masked (also see notes above); psoriasis; history of hypersensitivity—may increase sensitivity to allergens and result in more serious hypersensitivity response, also may reduce response to adrenaline (epinephrine) (see also section 3.4.3); reduce dose of oral propranolol in hepatic impairment; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (beta-blockers), important: verapamil interaction, see also p. 118

**Contra-indications** asthma (important: see Bronchospasm below), uncontrolled heart failure, Prinzmetal’s angina, marked bradycardia, hypotension, sick sinus syndrome, second- or third-degree AV block, cardiogenic shock, metabolic acidosis, severe peripheral arterial disease; phaeochromocytoma (apart from specific use with alpha-blockers, see also notes above)

**Bronchospasm** The CSM has advised that beta-blockers, including those considered to be cardioselective, should not be given to patients with a history of asthma or bronchospasm. However, in rare situations where there is no alternative a cardioselective beta-blocker is given to these patients with extreme caution and under specialist supervision.

**Side-effects** see notes above; also gastro-intestinal disturbances; bradycardia, heart failure, hypotension, conduction disorders, peripheral vasoconstriction (including exacerbation of intermittent claudication and Raynaud’s phenomenon); bronchospasm (see above); dyspnoea; headache, fatigue, sleep disturbances, paraesthesia, dizziness, vertigo, psychoses; sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; rarely rashes and dry eyes (reversible on withdrawal); **overdose**: see Emergency Treatment of Poisoning, p. 32

**Dose**

- **By mouth**, hypertension, initially 80 mg twice daily, increased at weekly intervals as required; maintenance 160–320 mg daily
- Prophylaxis of variceal bleeding in portal hypertension, initially 40 mg twice daily, increased to 80 mg twice daily according to heart rate; max. 160 mg twice daily
Phaeochromocytoma (only with an alpha-blocker),
60 mg daily for 3 days before surgery or 30 mg daily in patients unsuitable for surgery
Angina, initially 40 mg 2–3 times daily; maintenance 120–240 mg daily
Arrhythmias, hypertrophic cardiomyopathy, anxiety tachycardia, and thyrotoxicosis (adjunct), 10–40 mg 3–4 times daily
Anxiety with symptoms such as palpitation, sweating, tremor, 40 mg once daily, increased to 40 mg 3 times daily if necessary
Prophylaxis after myocardial infarction, 40 mg 4 times daily for 2–3 days, then 80 mg twice daily, beginning 5 to 21 days after infarction
Migraine prophylaxis and essential tremor, initially 40 mg 2–3 times daily; maintenance 80–160 mg daily

- **By intravenous injection**, arrhythmias and thyrotoxic crisis, 1 mg over 1 minute; if necessary repeat at 2-minute intervals; max. total dose 10 mg (5 mg in anaesthesia)
  
  **Note** Excessive bradycardia can be countered with **intravenous injection** of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for **overdosage** see Emergency Treatment of Poisoning, p. 32

**Propranolol** (Non-proprietary) (**A**)

- **Tablets**, propranolol hydrochloride 10 mg, net price 28 = 91p; 40 mg, 28 = 97p; 80 mg, 56 = £1.68; 160 mg, 56 = £3.29. Label: 8  
  **Brands include** Angiol

- **Oral solution**, propranolol hydrochloride 5 mg/5 mL, net price 150 mL = £12.50; 10 mg/5 mL, 150 mL = £16.45; 50 mg/5 mL, 150 mL = £19.98. Label: 8  
  **Brands include** Syprol

**Inderal** (**A**)

- **Injection**, propranolol hydrochloride 1 mg/mL, net price 1-mL amp = 21p

**Modified release**

**Note** Modified-release preparations can be used for once daily administration

**Half-Inderal LA** (**A**)

- **Capsules**, m/r, lavender/pink, propranolol hydrochloride 80 mg, net price 28-cap pack = £5.40. Label: 8, 25  
  **Note** Modified-release capsules containing propranolol hydrochloride 80 mg also available; brands include Bedranol SR, Half Beta Prograne

**Inderal-LA** (**A**)

- **Capsules**, m/r, lavender/pink, propranolol hydrochloride 160 mg, net price 28-cap pack = £6.67. Label: 8, 25  
  **Note** Modified-release capsules containing propranolol hydrochloride 160 mg also available; brands include Bedranol SR, Beta Prograne, Slo-Pro

**ACEBUTOLOL**

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride; renal impairment (Appendix 3)

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** see under Propranolol Hydrochloride

**Dose**

- Hypertension, initially 400 mg once daily or 200 mg twice daily, increased after 2 weeks to 400 mg twice daily if necessary
- Angina, initially 400 mg once daily or 200 mg twice daily; 300 mg 3 times daily in severe angina; up to 1.2 g daily has been used
- Arrhythmias, 0.4–1.2 g daily in 2–3 divided doses

**Sectral** (**Sanofi-Aventis**) (**FM**)

- **Capsules**, acebutolol (as hydrochloride) 100 mg (buff/white), net price 84-cap pack = £14.97; 200 mg (buff/pink), 56-cap pack = £19.18. Label: 8  
  **Tablets**, f/c, acebutolol 400 mg (as hydrochloride), net price 28-tab pack = £18.62. Label: 8

**ATENOLOL**

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride; renal impairment (Appendix 3)

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** see under Propranolol Hydrochloride

**Dose**

- **By mouth**, hypertension, 25–50 mg daily (higher doses rarely necessary)
- Angina, 100 mg daily in 1 or 2 doses
- Arrhythmias, 50–100 mg daily

- **By intravenous injection**, arrhythmias, 2.5 mg at a rate of 1 mg/minute, repeated at 5-minute intervals to a max. of 10 mg

  **Note** Excessive bradycardia can be countered with **intravenous injection** of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for **overdosage** see Emergency Treatment of Poisoning, p. 32

- **By intravenous infusion**, arrhythmias, 150 micrograms/kg over 20 minutes, repeated every 12 hours if required

  Early intervention within 12 hours of myocardial infarction (section 2.10.1), by **intravenous injection** over 5 minutes, 5 mg, then by mouth, 50 mg after 15 minutes, 50 mg after 12 hours, then 100 mg daily

**Atenolol** (Non-proprietary) (**FM**)

- **Tablets**, atenolol 25 mg, net price 28-tab pack = 81p; 50 mg, 28-tab pack = 85p; 100 mg, 28-tab pack = 86p. Label: 8  
  **Brands include** Atenex

**Tenormin** (**AstraZeneca**) (**FM**)

- **‘25’ tablets**, f/c, atenolol 25 mg, net price 28-tab pack = £4.41. Label: 8  
  **LS tablets**, orange, f/c, scored, atenolol 50 mg, net price 28-tab pack = £5.11. Label: 8  
  **Tablets**, orange, f/c, scored, atenolol 100 mg, net price 28-tab pack = £6.50. Label: 8  
  **Syrup**, sugar-free, atenolol 25 mg/5mL, net price 500 mL = £8.55. Label: 8  
  **Injection**, atenolol 500 micrograms/mL, net price 10-mL amp = 96p (hosp. only)

**With diuretic**

**Co-tenidone** (Non-proprietary) (**FM**)

- **Tablets**, co-tenidone 50/12.5 (atenolol 50 mg, chlortalidone 12.5 mg), net price 28-tab pack = £1.15; co-
Bisoprolol Fumarate

**Adjunct in stable moderate to severe heart failure**
Hypertension and angina, usually 10 mg once daily.

**Dose**
- Hypertension, 1 tablet daily (but see also under Dose above).

**Kalten** *(BPC 100)*
Capsules, red/ivory, atenolol 50 mg, co-amiloizide 2.5/25 (anhydrous amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-cap pack = £10.01. Label: 8
- Hypertension, 1 capsule daily

**Tenoret 50** *(AstraZeneca)*
Tablets, brown, f/c, co-tenidone 50/12.5 (atenolol 50 mg, chlortalidone 12.5 mg), net price 28-tab pack = £5.70. Label: 8
- Hypertension, 1 tablet daily

**Tenoretic** *(AstraZeneca)*
Tablets, brown, f/c, co-tenidone 100/25 (atenolol 100 mg, chlortalidone 25 mg), net price 28-tab pack = £8.12. Label: 8
- Hypertension, 1 tablet daily (but see also under Dose above)

**With calcium-channel blocker**

**Betad-Adalat** *(Bayer)*
Capsules, reddish-brown, atenolol 50 mg, nifedipine 20 mg (m/r), net price 28-cap pack = £10.41. Label: 8, 25
- Hypertension, 1 capsule daily, increased if necessary to twice daily; elderly, 1 daily
- Angina, 1 capsule twice daily

**Tenif** *(AstraZeneca)*
Capsules, reddish-brown, atenolol 50 mg, nifedipine 20 mg (m/r), net price 28-cap pack = £10.63. Label: 8, 25
- Hypertension, 1 capsule daily, increased if necessary to twice daily; elderly, 1 daily
- Angina, 1 capsule twice daily

**BISOPROLOL FUMARATE**

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride; ensure heart failure not worsening before increasing dose; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** see under Propranolol Hydrochloride; severe chronic heart failure; acute or decompensated heart failure requiring intravenous inotropes; hepatic impairment

**Side-effects** postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia; occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, eye irritation or disturbed vision, impotence, disturbances of micturition, influenza-like symptoms; rarely angina, AV block, exacerbation of intermittent claudication or Raynaud's phenomenon; allergic skin reactions, exacerbation of psoriasis, nasal stuffiness, wheezing, depressed mood, sleep disturbances, paraesthesia, heart failure, changes in liver enzymes, thrombocytopenia, leucopenia also reported

**Dose**
- Hypertension, initially 12.5 mg once daily, increased after 2 days to usual dose of 25 mg once daily; if necessary may be further increased at intervals of at least 2 weeks to max. 50 mg daily in single or divided doses; ELDERS initial dose of 12.5 mg daily may provide satisfactory control
- Angina, initially 12.5 mg twice daily, increased after 2 days to 25 mg twice daily
- Adjunct in heart failure (section 2.5.5) initially 3.125 mg twice daily (with food), dose increased at intervals of at least 2 weeks to 6.25 mg twice daily, then to 12.5 mg twice daily, then to 25 mg twice daily; increase to highest dose tolerated, max. 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg and 50 mg twice daily in patients over 85 kg

**Carvedilol** *(Non-proprietary)*
Tablets, carvedilol 3.125 mg, net price 28-tab pack = £5.73; 6.25 mg, 28-tab pack = £6.09; 12.5 mg, 28-tab pack = £6.14; 25 mg, 28-tab pack = £7.24. Label: 8

**Eucardic** *(Roche)*
Tablets, scored, carvedilol 3.125 mg (pink), net price 28-tab pack = £7.60; 6.25 mg (yellow), 28-tab pack = £7.84; 12.5 mg (peach), 28-tab pack = £9.35; 25 mg, 28-tab pack = £11.68. Label: 8

**CARDIOVASCULAR SYSTEM**

**Bisoprolol Fumarate**

**Indications** hypertension, 1 tablet daily (but see also under Dose above).

**Kalten** *(BPC 100)*
Capsules, red/ivory, atenolol 50 mg, co-amiloizide 2.5/25 (anhydrous amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-cap pack = £10.01. Label: 8
- Hypertension, 1 capsule daily

**Tenoret 50** *(AstraZeneca)*
Tablets, brown, f/c, co-tenidone 50/12.5 (atenolol 50 mg, chlortalidone 12.5 mg), net price 28-tab pack = £5.70. Label: 8
- Hypertension, 1 tablet daily

**Tenoretic** *(AstraZeneca)*
Tablets, brown, f/c, co-tenidone 100/25 (atenolol 100 mg, chlortalidone 25 mg), net price 28-tab pack = £8.12. Label: 8
- Hypertension, 1 tablet daily (but see also under Dose above)

**With calcium-channel blocker**

**Betad-Adalat** *(Bayer)*
Capsules, reddish-brown, atenolol 50 mg, nifedipine 20 mg (m/r), net price 28-cap pack = £10.41. Label: 8, 25
- Hypertension, 1 capsule daily, increased if necessary to twice daily; elderly, 1 daily
- Angina, 1 capsule twice daily

**Tenif** *(AstraZeneca)*
Capsules, reddish-brown, atenolol 50 mg, nifedipine 20 mg (m/r), net price 28-cap pack = £10.63. Label: 8, 25
- Hypertension, 1 capsule daily, increased if necessary to twice daily; elderly, 1 daily
- Angina, 1 capsule twice daily

**BISOPROLOL FUMARATE**

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride; ensure heart failure not worsening before increasing dose; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** see under Propranolol Hydrochloride; severe chronic heart failure; acute or decompensated heart failure requiring intravenous inotropes; hepatic impairment

**Side-effects** postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia; occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, eye irritation or disturbed vision, impotence, disturbances of micturition, influenza-like symptoms; rarely angina, AV block, exacerbation of intermittent claudication or Raynaud's phenomenon; allergic skin reactions, exacerbation of psoriasis, nasal stuffiness, wheezing, depressed mood, sleep disturbances, paraesthesia, heart failure, changes in liver enzymes, thrombocytopenia, leucopenia also reported

**Dose**
- Hypertension, initially 12.5 mg once daily, increased after 2 days to usual dose of 25 mg once daily; if necessary may be further increased at intervals of at least 2 weeks to max. 50 mg daily in single or divided doses; ELDERS initial dose of 12.5 mg daily may provide satisfactory control
- Angina, initially 12.5 mg twice daily, increased after 2 days to 25 mg twice daily
- Adjunct in heart failure (section 2.5.5) initially 3.125 mg twice daily (with food), dose increased at intervals of at least 2 weeks to 6.25 mg twice daily, then to 12.5 mg twice daily, then to 25 mg twice daily; increase to highest dose tolerated, max. 25 mg twice daily in patients with severe heart failure or body-weight less than 85 kg and 50 mg twice daily in patients over 85 kg

**Carvedilol** *(Non-proprietary)*
Tablets, carvedilol 3.125 mg, net price 28-tab pack = £5.73; 6.25 mg, 28-tab pack = £6.09; 12.5 mg, 28-tab pack = £6.14; 25 mg, 28-tab pack = £7.24. Label: 8

**Eucardic** *(Roche)*
Tablets, scored, carvedilol 3.125 mg (pink), net price 28-tab pack = £7.60; 6.25 mg (yellow), 28-tab pack = £7.84; 12.5 mg (peach), 28-tab pack = £9.35; 25 mg, 28-tab pack = £11.68. Label: 8
**CELPROLOL HYDROCHLORIDE**

**Indications** mild to moderate hypertension

**Cautions** see under Propranolol Hydrochloride; renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3)

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** headache, dizziness, fatigue, nausea and somnolence; also bradycardia, bronchospasm; depression and pneumonitis reported rarely

**Dose**
- 200 mg once daily in the morning, increased to 400 mg once daily if necessary

**Celprolol (Non-proprietary)**

**Tablets**, celprolol hydrochloride 200 mg, net price 28-tab pack = £6.41; 400 mg, 28-tab pack = £37.89. Label: 8, 22

**Celectol®** (Winthrop)

**Tablets**, f/c, scored, celprolol hydrochloride 200 mg (yellow), net price 28-tab pack = £20.63; 400 mg, 28-tab pack = £41.26. Label: 8, 22

**ESMOLOL HYDROCHLORIDE**

**Indications** short-term treatment of supraventricular arrhythmias (including atrial fibrillation, atrial flutter, sinus tachycardia); tachycardia and hypertension in peri-operative period

**Cautions** see under Propranolol Hydrochloride; renal impairment

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** see under Propranolol Hydrochloride; also on infusion venous irritation and thrombophlebitis

**Dose**
- By iv inf, usually within range 50–200 micrograms/kg/minute (consult product literature for details of dose titration and doses during peri-operative period)

**Brevibloc®** (Baxter)

**Injection**, esmolol hydrochloride 10 mg/mL, net price 10-mL vial = £7.79, 250-mL infusion bag = £89.69

**METOPROLOL TARTRATE**

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride; hepatic impairment (Appendix 2)

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** see under Propranolol Hydrochloride

**Dose**
- By mouth, initially 100 mg (50 mg in elderly) twice daily with food, increased at intervals of 14 days to usual dose of 200 mg twice daily; up to 800 mg daily in 2 divided doses (3–4 divided doses if higher); max. 2.4 g daily

**Note** Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for overdosage see Emergency Treatment of Poisoning, p. 32

**By intravenous injection**, 50 mg over at least 1 minute, repeated after 5 minutes if necessary; max. total dose 200 mg

Hypertension of pregnancy, 20 mg/hour, doubled every 30 minutes; usual max. 160 mg/hour

Hypertension following myocardial infarction, 15 mg/hour, gradually increased to max. 120 mg/hour

**Labetalol Hydrochloride** (Non-proprietary)

**Tablets**, f/c, labetalol hydrochloride 100 mg, net price, 56 = £7.80; 200 mg, 56 = £11.83; 400 mg, 56 = £17.73. Label: 8, 21

**Trandate®** (UCB Pharma)

**Tablets**, all orange, f/c, labetalol hydrochloride 50 mg, net price 56-tab pack = £3.79; 100 mg, 56-tab pack = £4.17; 200 mg, 56-tab pack = £6.77; 400 mg, 56-tab pack = £9.42. Label: 8, 21

**Injection**, labetalol hydrochloride 5 mg/mL, net price 20-mL amp = £2.12

**LABETALOL HYDROCHLORIDE**

**Indications** hypertension (including hypertension in pregnancy, hypertension with angina, and hypertension following acute myocardial infarction); hypertensive crisis (but see section 2.5); controlled hypotension in anaesthesia

**Cautions** see under Propranolol Hydrochloride; interferes with laboratory tests for catecholamines; liver damage (see below); renal impairment (Appendix 3)

**Liver damage** Severe hepato cellular damage reported after both short-term and long-term treatment. Appropriate laboratory testing needed at first symptom of liver dysfunction and if laboratory evidence of damage (or if jaundice) labetalol should be stopped and not restarted

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** postural hypotension (avoid upright position during and for 3 hours after intravenous administration), tiredness, weakness, headache, rashes, scalp tingling, difficulty in micturition, episodic gastric pain, nausea, vomiting; liver damage (see above); rarely lichenoid rash

**Dose**
- By mouth, initially 100 mg (50 mg in elderly) twice daily with food, increased at intervals of 14 days to usual dose of 200 mg twice daily; up to 800 mg daily in 2 divided doses (3–4 divided doses if higher); max. 2.4 g daily

**By intravenous injection**, 50 mg over at least 1 minute, repeated after 5 minutes if necessary; max. total dose 200 mg

**Note** Excessive bradycardia can be countered with intravenous injection of atropine sulphate 0.6–2.4 mg in divided doses of 600 micrograms; for overdosage see Emergency Treatment of Poisoning, p. 32

In surgery, by slow intravenous injection 2–4 mg at induction or to control arrhythmias developing during anaesthesia; 2-mg doses may be repeated to a max. of 10 mg
Early intervention within 12 hours of infarction, **by intravenous injection** 5 mg every 2 minutes to a max. of 15 mg, followed after 15 minutes by 50 mg **by mouth** every 6 hours for 48 hours; maintenance 200 mg daily in divided doses

Metoprolol Tartrate (Non-proprietary) *(BNF)*

**Tablets**, metoprolol tartrate 50 mg, net price 28 = £1.39, 56 = £1.54; 100 mg, 28 = £1.88, 56 = £2.24. Label: 8

**Betaloc** *(AstraZeneca) (BNF)*

**Injection**, metoprolol tartrate 1 mg/mL, net price 5-ml amp. = 42p

Lopresor *(Novartis) (BNF)*

**Tablets**, I/c, scored, metoprolol tartrate 50 mg (pink), net price 56-tab pack = £2.57; 100 mg (blue), 56-tab pack = £6.88. Label: 8

**NADOLOL** *(Menarini)* *(BNF)*

**Tablets**, red, s/c, co-prenozide 160/0.25 (oxprenolol chloride 160 mg, cyclopenthiazide 250 micrograms), net price 28-tab pack = £10.66. Label: 8

**OXPRENOLOL HYDROCHLORIDE** *(BNF)*

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride; reduce dose in hepatic impairment

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** see under Propranolol Hydrochloride; oedema, headache, dizziness, depression, visual disturbances, paraesthesia, impotence

**Dose**

- Hypertension, 5 mg daily. **ELDERLY** initially 2.5 mg daily, increased if necessary to 5 mg daily
- Adjunct in heart failure (section 2.5.5), initially 1.25 mg once daily, then if tolerated increased at intervals of 1–2 weeks to 2.5 mg once daily, then to 5 mg once daily, then to max. 10 mg once daily

**Nebilet** *(Menarini)* *(BNF)*

**Tablets**, scored, nebivolol (as hydrochloride) 5 mg, net price 28-tab pack = £9.23. Label: 8

**NEBIVOLOL** *(Menarini)* *(BNF)*

**Tablets**, red, s/c, co-prenozide 160/0.25 (oxprenolol hydrochloride 160 mg, co-prenozide 250 micrograms), net price 28-tab pack = £10.66. Label: 8

**With diuretic**

**Trasidrex** *(Goldshield)* *(BNF)*

**Tablets**, red, s/c, co-prenozide 160/0.25 (oxprenolol hydrochloride 160 mg (m/r), cyclopenthiazide 250 micrograms), net price 28-tab pack = £10.66. Label: 8
**PINDOLOL**

**Indications** see under Dose

**Cautions** see under Propranolol Hydrochloride

**Contra-indications** see under Propranolol Hydrochloride; severe renal impairment (Appendix 3)

**Side-effects** see under Propranolol Hydrochloride

**Dose**
- Hypertension, initially 5 mg 2–3 times daily or 15 mg once daily, increased as required at weekly intervals; usual maintenance 15–30 mg daily; max. 45 mg daily
- Angina, 2.5–5 mg up to 3 times daily

**Pindolol (Non-proprietary)**

**Tablets**, pindolol 5 mg, net price 100-tab pack = £7.81. Label: 8

**Visken®** (Amidpharm)

**Tablets**, scored, pindolol 5 mg, net price 56-tab pack = £5.85; 15 mg, 28-tab pack = £8.79. Label: 8

**With diuretic**

**Viskaldix®** (Amidpharm)

**Tablets**, scored, pindolol 10 mg, clopamide 5 mg, net price 28-tab pack = £6.70. Label: 8

**Dose** hypertension, 1 tablet daily in the morning, increased if necessary to 2 daily; max. 3 daily

---

**SOTALOL HYDROCHLORIDE**

**Indications** Tablets and injection: life-threatening arrhythmias including ventricular tachyarrhythmias, symptomatic non-sustained ventricular tachyarrhythmias

**Tablets only**: prophylaxis of paroxysmal atrial tachycardia or fibrillation, paroxysmal AV re-entrant tachycardias (both nodal and involving accessory pathways), paroxysmal supraventricular tachycardia after cardiac surgery; maintenance of sinus rhythm following cardioversion of atrial fibrillation or flutter

**Injection only**: electrophysiological study of inducible ventricular and supraventricular arrhythmias; temporary substitution for tablets

**CSM advice.** The use of sotalol should be limited to the treatment of ventricular arrhythmias or prophylaxis of supraventricular arrhythmias (see above). It should no longer be used for angina, hypertension, thyrotoxicosis or for secondary prevention after myocardial infarction; when stopping sotalol for these indications, the dose should be reduced gradually

**Cautions** see under Propranolol Hydrochloride; reduce dose in renal impairment (avoid if creatinine clearance less than 10 ml/minute; Appendix 3); correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances; severe or prolonged diarrhoea; interactions: Appendix 1 (beta-blockers), important: verapamil interaction see also p. 118

**Contra-indications** see under Propranolol Hydrochloride; congenital or acquired long QT syndrome; torsade de pointes; renal failure

**Side-effects** see under Propranolol Hydrochloride; arrhythmicogenic (pro-arrhythmic) effect (torsade de pointes—increased risk in women)

**Dose**
- **By mouth** with ECG monitoring and measurement of corrected QT interval, arrhythmias, initially 80 mg daily in 1–2 divided doses increased gradually at intervals of 2–3 days to usual dose of 160–320 mg daily in 2 divided doses; higher doses of 480–640 mg daily for life-threatening ventricular arrhythmias under specialist supervision
- **By intravenous injection** over 10 minutes, acute arrhythmias, 20–120 mg with ECG monitoring, repeated if necessary with 6-hour intervals between injections

**Sotalol (Non-proprietary)**

**Tablets**, sotalol hydrochloride 40 mg, net price 56 = £1.34; 80 mg, 56 = £1.99; 160 mg, 28 = £2.21. Label: 8

**Beta-Cardone®** (UCB Pharma)

**Tablets**, scored, sotalol hydrochloride 40 mg (green), net price 56-tab pack = £1.34; 80 mg (pink), 56-tab pack = £1.99; 200 mg, 28-tab pack = £2.50. Label: 8

**Sotacor®** (Bristol-Myers Squibb)

**Tablets**, scored, sotalol hydrochloride 80 mg, net price 28-tab pack = £3.25; 160 mg, 28-tab pack = £6.41. Label: 8

**Injection**, sotalol hydrochloride 10 mg/mL, net price 4-mL amp = £1.76

---

**TIMOLOL MALEATE**

**Indications** see under Dose: glaucoma (section 11.6)

**Cautions** see under Propranolol Hydrochloride; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** see under Propranolol Hydrochloride

**Side-effects** see under Propranolol Hydrochloride

**Dose**
- Hypertension, initially 10 mg daily in 1–2 divided doses; gradually increased if necessary to max. 60 mg daily, usual maintenance dose 10–30 mg daily (doses above 30 mg daily given in divided doses)
- Angina, initially 5 mg twice daily increased if necessary by 10 mg daily every 3–4 days; max. 30 mg twice daily
- Prophylaxis after myocardial infarction, initially 5 mg twice daily, increased after 2 days to 10 mg twice daily if tolerated
- Migraine prophylaxis, 10–20 mg daily in 1–2 divided doses

**Betim®** (Valeant)

**Tablets**, scored, timolol maleate 10 mg, net price 30-tab pack = £2.08. Label: 8

**With diuretic**

**Prestim®** (Valeant)

**Tablets**, scored, timolol maleate 10 mg, bendroflumethiazide 2.5 mg, net price 30-tab pack = £3.49. Label: 8

**Dose** hypertension, 1–2 tablets daily; max. 4 daily
2 Cardiovascular system

2.5 Hypertension and heart failure

2.5.1 Vasodilator antihypertensive drugs
2.5.2 Centrally acting antihypertensive drugs
2.5.3 Adrenergic neurone blocking drugs
2.5.4 Alpha-adrenoceptor blocking drugs
2.5.5 Drugs affecting the renin-angiotensin system

Lowering raised blood pressure decreases the risk of stroke, coronary events, heart failure, and renal impairment. Advice on antihypertensive therapy in this section takes into account the recommendations of the Joint British Societies (JBS2: British Societies' guidelines on prevention of cardiovascular disease in clinical practice. Heart 2005; 91 (Suppl V): v1–v52).

Possible causes of hypertension (e.g. renal disease, endocrine causes), contributory factors, risk factors, and the presence of any complications of hypertension, such as left ventricular hypertrophy, should be established. Patients should be given advice on lifestyle changes to reduce blood pressure or cardiovascular risk; these include smoking cessation, weight reduction, reduction of excessive intake of alcohol, reduction of dietary salt, reduction of total and saturated fat, increasing exercise, and increasing fruit and vegetable intake.

Thresholds and targets for treatment1 The following thresholds for treatment are recommended:

- Accelerated (malignant) hypertension (with papilloedema or fundal haemorrhages and exudates) or acute cardiovascular complications, admit for immediate treatment;
- Where the initial blood pressure is systolic \( \geq 160 \text{ mmHg} \) or diastolic \( \geq 100 \text{ mmHg} \), treat immediately;
- Where the initial blood pressure is systolic \( 160–219 \text{ mmHg} \) or diastolic \( 110–119 \text{ mmHg} \), confirm over 1–2 weeks then treat if these values are sustained;
- Where the initial blood pressure is systolic \( 160–179 \text{ mmHg} \) or diastolic \( 100–109 \text{ mmHg} \), and the patient has cardiovascular complications, target-organ damage (e.g. left ventricular hypertrophy, renal impairment) or diabetes mellitus (type 1 or 2), confirm over 3–4 weeks then treat if these values are sustained;
- Where the initial blood pressure is systolic \( 160–179 \text{ mmHg} \) or diastolic \( 100–109 \text{ mmHg} \), but the patient has no cardiovascular complications, no target-organ damage, or no diabetes, advise lifestyle changes, reassess weekly initially and treat if these values are sustained on repeat measurements over 4–12 weeks;
- Where the initial blood pressure is systolic \( 140–159 \text{ mmHg} \) or diastolic \( 90–99 \text{ mmHg} \) and the patient has cardiovascular complications, target-

1. Thresholds and targets for treatment based on blood pressure measured in clinic may not apply to ambulatory or home blood-pressure monitoring, which usually give lower values.

A target systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg is suggested. A lower target systolic blood pressure < 130 mmHg and diastolic blood pressure < 80 mmHg should be considered for those with established atherosclerotic cardiovascular disease, diabetes, or chronic renal failure. In some individuals it may not be possible to reduce blood pressure below the suggested targets despite the use of appropriate therapy.

Drug treatment of hypertension Response to drug treatment for hypertension may be affected by the patient’s age and ethnic background. An ACE inhibitor (section 2.5.5.1) or an angiotensin-II receptor antagonist (section 2.5.5.2) may be the most appropriate initial drug in younger Caucasians; however a beta-blocker may be considered if an ACE inhibitor or an angiotensin-II receptor antagonist is not tolerated or is contra-indicated (see also Hypertension in Pregnancy, p. 93). Afro-Caribbean patients and those aged over 55 years respond less well to ACE inhibitors and angiotensin-II receptor antagonists, therefore a thiazide (section 2.2.1) or a calcium-channel blocker (section 2.6.2) may be chosen for initial treatment.

Beta-blockers, especially when combined with a thiazide diuretic, should be avoided for the routine treatment of uncomplicated hypertension in patients with diabetes or in those at high risk of developing diabetes. A single antihypertensive drug is often not adequate and other antihypertensive drugs are usually added in a step-wise manner until control is achieved. Unless it is necessary to lower the blood pressure urgently, an interval of at least 4 weeks should be allowed to determine response.

Where two antihypertensive drugs are needed, an ACE inhibitor or an angiotensin-II receptor antagonist may be combined with either a thiazide or a calcium-channel blocker.

If control is inadequate with 2 drugs, a thiazide and a calcium-channel blocker may be added. The addition of an alpha-blocker (section 2.5.4), spironolactone, another diuretic, or a beta-blocker should be considered in resistant hypertension. In patients with primary hyperaldosteronism, spironolactone (section 2.2.3) is effective.

Other measures to reduce cardiovascular risk Aspirin (section 2.9) in a dose of 75 mg daily reduces the risk of cardiovascular events and myocardial infarction. Unduly high blood pressure must be controlled before aspirin is given. Unless contra-indicated, aspirin is recommended for all patients with established cardiovascular disease or those with a 10-year cardiovascular risk.

2. Cardiovascular disease risk may be determined from the chart issued by the Joint British Societies (Heart 2005; 91 (Suppl V): v1–v52)—see inside back cover. The Joint British Societies’ ‘Cardiac Risk Assessor’ computer programme may also be used to determine cardiovascular disease risk.
Hypertension in the elderly

Benefit from antihypertensive therapy is evident up to at least 80 years of age, but it is probably inappropriate to apply a strict age limit when deciding on drug therapy. Patients who reach 80 years of age while taking antihypertensive drugs should continue treatment, provided that it continues to be of benefit and does not cause significant side-effects. The thresholds for treatment are diastolic pressure averaging \( \geq 90 \text{ mmHg} \) or systolic pressure averaging \( \geq 160 \text{ mmHg} \) over 3 to 6 months’ observation (despite appropriate lifestyle interventions). Treatment with a low dose of a thiazide or a dihydropyridine calcium-channel blocker is effective. An ACE inhibitor (or an angiotensin-II receptor antagonist) (section 2.5.5) can be added if necessary.

Isolated systolic hypertension

Isolated systolic hypertension (systolic pressure \( \geq 160 \text{ mmHg} \), diastolic pressure \(< 90 \text{ mmHg}\)) is associated with an increased cardiovascular disease risk, particularly in those aged over 60 years. Systolic blood pressure averaging 160 mmHg or higher over 3 to 6 months (despite appropriate lifestyle interventions) should be lowered in those over 80 years, even if diastolic hypertension is absent. Treatment with a low dose of a thiazide or a dihydropyridine calcium-channel blocker is effective. An ACE inhibitor (or an angiotensin-II receptor antagonist) (section 2.5.5) can be added if necessary. Patients with severe postural hypotension should not receive blood pressure lowering drugs.

Isolated systolic hypertension in younger patients is uncommon but treatment may be indicated in those with a threshold systolic pressure of 160 mmHg (or less if at increased risk of cardiovascular disease, see above).

Hypertension in diabetes

For patients with diabetes, the aim should be to maintain systolic pressure \(< 130 \text{ mmHg}\) and diastolic pressure \( < 80 \text{ mmHg}\). However, in some individuals, it may not be possible to achieve this level of control despite appropriate therapy. Most patients require a combination of antihypertensive drugs.

Hypertension in renal disease

The threshold for antihypertensive treatment in patients with renal impairment or persistent proteinuria is a systolic blood pressure \( \geq 140 \text{ mmHg} \) or a diastolic blood pressure \( \geq 90 \text{ mmHg} \). Optimal blood pressure is a systolic blood pressure \(< 130 \text{ mmHg}\) and a diastolic pressure \( < 80 \text{ mmHg}\), or lower if proteinuria exceeds 1 g in 24 hours. An ACE inhibitor (or an angiotensin-II receptor antagonist) should be considered for patients with proteinuria; however, ACE inhibitors should be used with caution in renal impairment, see section 2.5.5.1. Thiazide diuretics may be ineffective and high doses of loop diuretics may be required. A dihydropyridine calcium channel blocker can be added.

Hypertension in pregnancy

High blood pressure in pregnancy may usually be due to pre-existing essential hypertension or to pre-eclampsia. Methylodopa (section 2.5.2) is safe in pregnancy. Beta-blockers are effective and safe in the third trimester. Modified-release preparations of nifedipine (unlicensed) are also used for hypertension in pregnancy. Intravenous administration of labetalol (section 2.4) can be used to control hypertensive crises; alternatively, hydralazine (section 2.5.1) may be used by the intravenous route. For use of magnesium sulphate in pre-eclampsia and eclampsia, see section 9.5.1.3.

Accelerated or very severe hypertension

Accelerated (or malignant) hypertension or very severe hypertension (e.g. diastolic blood pressure \( > 140 \text{ mmHg}\)) requires urgent treatment in hospital, but it is not an indication for parenteral antihypertensive therapy. Normally treatment should be by mouth with a beta-blocker (atenolol or labetalol) or a long-acting calcium-channel blocker (e.g. amlodipine or modified-release nifedipine). Within the first 24 hours the diastolic blood pressure should be reduced to 100–110 mmHg. Over the next 2 or 3 days blood pressure should be further reduced using a calcium-channel blocker, diuretic, ACE inhibitor, beta-blocker, or vasodilator, alone or in combination. Rapid reduction in blood pressure can reduce organ perfusion leading to cerebral infarction and blindness, deterioration in renal function, and myocardial ischaemia. Sodium nitroprusside (unlicensed) by infusion is the drug of choice on the rare occasions when parenteral treatment is necessary.

For advice on short-term management of hypertensive episodes in pheochromocytoma, see under Phaeochromocytoma, section 2.5.4.

Vasodilator antihypertensive drugs

Vasodilators have a potent hypotensive effect, especially when used in combination with a beta-blocker and a thiazide. Important: for a warning on the hazards of a very rapid fall in blood pressure, see Accelerated or Very Severe Hypertension, above.

Diazoxide has been used by intravenous injection in hypertensive emergencies. Hydralazine is given by mouth as an adjunct to other antihypertensives for the treatment of resistant hypertension but is rarely used; when used alone it causes tachycardia and fluid retention. The incidence of side-effects is lower if the dose is kept below 100 mg daily, but systemic lupus erythematosus should be suspected.
if there is unexplained weight loss, arthritis, or any other unexplained ill health.

**Sodium nitroprusside** [unlicensed] is given by intravenous infusion to control severe hypertensive crises on the rare occasions when parenteral treatment is necessary.

**Minoxidil** should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilation is accompanied by increased cardiac output and tachycardia and the patients develop fluid retention. For this reason the addition of a beta-blocker and a diuretic (usually furosemide, in high dosage) are mandatory. Hypertrichosis is troublesome and renders this drug unsuitable for women.

Prazosin, doxazosin, and terazosin (section 2.5.4) have alpha-blocking and vasodilator properties.

**Ambrisentan, bosentan, epoprostenol (section 2.8.1), iloprost, sildenafil, and sitaxentan** are licensed for the treatment of some types of pulmonary hypertension and should be used under specialist supervision. Bosentan is also licensed to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The **Scottish Medicines Consortium** (p. 3) has advised (November 2005) that iloprost (Ventavis®) is accepted for restricted use within NHS Scotland in patients in whom bosentan is ineffective or not tolerated.

The **Scottish Medicines Consortium** (p. 3) has advised (May 2008) that bosentan (Tracleer®) is not recommended for use within NHS Scotland to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

The **Scottish Medicines Consortium** (p. 3) has advised (October 2008) that ambrisentan (Volibris®) should be prescribed only by specialists in the Scottish Pulmonary Vascular Unit or other similar specialists.

## AMBRISENTAN

**Indications** pulmonary arterial hypertension

**Cautions** not to be initiated in significant anaemia; monitor haemoglobin or haematocrit concentration after 1 month and 3 months of starting treatment, and periodically thereafter (reduce dose or discontinue treatment if significant decrease in haemoglobin or haematocrit concentration observed); monitor liver function before treatment, and monthly thereafter—discontinue if liver enzymes raised significantly or if symptoms of liver impairment develop; hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3)

**Contra-indications** pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** abdominal pain, constipation; palpitation, flushing, peripheral oedema; upper respiratory-tract disorders; headache; anaemia; *less commonly* hypersensitivity reactions (including angioedema and rash)

**Dose**
- **ADULT** over 18 years, 5 mg once daily, increased if necessary to 10 mg once daily

**Volibris®** (GSK) Tablets, 1, c, orange, ambrisentan 5 mg (pale pink), net price 30-tab pack = £1651.07; 10 mg (dark pink), 30-tab pack = £1651.07

## BOSENTAN

**Indications** pulmonary arterial hypertension; systemic sclerosis with ongoing digital ulcer disease (to reduce number of new digital ulcers)

**Cautions** not to be initiated if systemic systolic blood pressure is below 85 mmHg; monitor haemoglobin before and during treatment (monthly for first 4 months, then 3-monthly); avoid abrupt withdrawal; monitor liver function before treatment, at monthly intervals during treatment, and 2 weeks after dose increase (reduce dose or suspend treatment if liver enzymes raised significantly)—discontinue if symptoms of liver impairment; hepatic impairment (Appendix 2); interactions: Appendix 1 (bosentan)

**Contra-indications** acute porphyria (section 9.8.2) pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances, dry mouth, rectal haemorrhage, hepatic impairment (see Cautions, above); flushing; hypotension, palpitation, oedema, chest pain; dyspnoea; headache, dizziness, fatigue; back pain and pain in extremities; anaemia; hypersensitivity reactions (including rash, pruritus, and anaphylaxis)

**Dose**
- Pulmonary arterial hypertension, initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily; max. 250 mg twice daily; **CHILD** under 12 years see **BNF for Children**
- Systemic sclerosis with ongoing digital ulcer disease, initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily

**Tracleer®** (Actelion) Tablets, 1, c, orange, bosentan (as monohydrate) 62.5 mg, net price 56-tab pack = £1541.00; 125 mg, 56-tab pack = £1541.00

## DIAZOXIDE

**Indications** hypertensive emergency including severe hypertension associated with renal disease (but see section 2.5); hypoglycaemia (section 6.1.4)

**Cautions** ischaemic heart disease; renal impairment (Appendix 3); pregnancy and labour (Appendix 4); interactions: Appendix 1 (diazoxide)

**Side-effects** tachycardia, hypotension, hyperglycaemia, sodium and water retention; rarely cardiomegaly, hyperosmolar non-ketotic coma, leucopenia, thrombocytopenia, and hirsuitism

**Dose**
- By rapid intravenous injection (less than 30 seconds), 1–3 mg/kg to max. single dose of 150 mg (see below); may be repeated after 5–15 minutes if required
- **Note** Single doses of 300 mg have been associated with angina and with myocardial and cerebral infarction

**Eudemine®** (Goldshield) **Injection** diazoxide 15 mg/mL, net price 20-mL amp = £30.00

**Tablets**, see section 6.1.4

## HYDRAZINE HYDROCHLORIDE

**Indications** moderate to severe hypertension (adjunct); heart failure (with long-acting nitrate, but see section 2.5.5); hypertensive crisis (including during pregnancy) (but see section 2.5)
Cautions hepatic impairment (Appendix 2); renal impairment (Appendix 3); coronary artery disease (may provoke angina, avoid after myocardial infarction until stabilised), cerebrovascular disease; occasionally blood pressure reduction too rapid even with low parenteral doses; pregnancy (Appendix 4); breastfeeding (Appendix 5); manufacturer advises test for antinuclear factor and for proteinuria every 6 months and check acetylator status before increasing dose above 100 mg daily; but evidence of clinical value unsatisfactory; interactions: Appendix 1 (hydralazine)

Contra-indications idiopathic systemic lupus erythematosus, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, coronary pulmonary, dissecting aortic aneurysm; acute porphyria (section 9.8.2)

Side-effects tachycardia, palpitation, flushing, hypotension, fluid retention, gastro-intestinal disturbances; headache, dizziness; systemic lupus erythematosus-like syndrome after long-term therapy with over 100 mg daily (or less in women and in slow acetylator individuals) (see also notes above); rarely rashes, fever, peripheral neuritis, polyneuritis, paraesthesia, arthralgia, myalgia, increased lacrimation, nasal congestion, dyspnoea, agitation, anxiety, anorexia; blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia), abnormal liver function, jaundice, increased to usual max. 50 mg twice daily (see notes above)

Dose
- By mouth, hypertension, 25 mg twice daily, increased to usual max. 50 mg twice daily (see notes above)
- Heart failure (initiated in hospital) 25 mg 3–4 times daily, increased every 2 days if necessary; usual maintenance dose 50–75 mg 4 times daily
- By slow intravenous injection, hypertension with renal complications and hypertensive crisis, 5–10 mg diluted with 10 ml sodium chloride 0.9%; may be repeated after 20–30 minutes (see Cautions)
- By intravenous infusion, hypertension with renal complications and hypertensive crisis, initially 200–300 micrograms/minute; maintenance usually 50–150 micrograms/minute

Hydralazine (Non-proprietary) Tablets, hydralazine hydrochloride 25 mg, net price 56 = £11.79; 50 mg, 56 = £18.54

Apresoline® (Amdipharm) Tablets, yellow, s/c, hydralazine hydrochloride 25 mg, net price 84-tab pack = £2.82

Injection, powder for reconstitution, hydralazine hydrochloride, net price 20-mg amp = £1.84

Contra-indications unstable angina; within 6 months of myocardial infarction; decompensated cardiac failure (unless under close medical supervision); severe arrhythmias; congenital or acquired heart-valve defects; within 3 months of cerebrovascular events; pulmonary veno-occlusive disease; conditions which increase risk of bleeding; pregnancy (Appendix 4); breastfeeding (Appendix 5)

Side-effects vasodilation, hypotension, syncope, cough, headache, throat or jaw pain; nausea, vomiting, diarrhoea, chest pain, dyspnoea, bronchospasm, and wheezing also reported

Dose
- By inhalation of nebulised solution, initial dose 2.5 micrograms increased to 5 micrograms for second dose, if tolerated maintain at 5 micrograms 6–9 times daily according to response; reduce to 2.5 micrograms 6–9 times daily if higher dose not tolerated; CHILD 8–18 years see BNF for Children

Ventavis® (Schering Health) Nebuliser solution, iloprost (as trentalometal) 10 micrograms/mL, net price 30 × 1-mL (10 microgram) unit-dose vials = £425.00, 168 × 1-mL = £2377.20. For use with Prodose® or Venta-Neb® nebuliser

MINOXIDIL

Indications severe hypertension, in addition to a diuretic and a beta-blocker

Cautions see notes above; angina; after myocardial infarction (until stabilised); lower doses in dialysis patients; acute porphyria (section 9.8.2); pregnancy (Appendix 4); interactions: Appendix 1 (vasodilator antihypertensives)

Contra-indications phaeochromocytoma

Side-effects sodium and water retention; weight gain, peripheral oedema, tachycardia, hypertrichosis; reversible rise in creatinine and blood urea nitrogen; occasionally, gastro-intestinal disturbances, breast tenderness, rashes

Dose
- Initially 5 mg (ELDERLY, 2.5 mg) daily, in 1–2 divided doses, increased in steps of 5–10 mg at intervals of at least 3 days; max. 100 mg daily (seldom necessary to exceed 50 mg daily)

Loniten® (Pharmacon) Tablets, scored, minoxidil 2.5 mg, net price 60-tab pack = £8.88; 5 mg, 60-tab pack = £15.83; 10 mg, 60-tab pack = £30.68

SILDENAFIL

Indications pulmonary arterial hypertension; erectile dysfunction (section 7.4.5)

Cautions hypotension (avoid if systolic blood pressure below 90 mmHg); intravascular volume depletion; left ventricular outflow obstruction; cardiovascular disease; autonomic dysfunction; pulmonary veno-occlusive disease; anatomical deformation of the penis, predisposition to priapism; bleeding disorders or active peptic ulceration; consider gradual withdrawal; hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 ( sildenafil)
### Cardiovascular system

**Contra-indications** recent history of stroke or myocardial infarction, history of non-arteritic anterior ischaemic optic neuropathy; hereditary degenerative retinal disorders; avoid concomitant use of nitrates

**Side-effects** gastro-intestinal disturbances, dry mouth; flushing, oedema; bronchitis, cough; headache, migraine, night sweats, paraesthesia, insomnia, anxiety, tremor, vertigo; fever, influenza-like symptoms; anaemia; back and limb pain, myalgia; visual disturbances, retinal haemorrhage, photophobia, painful red eyes; nasal congestion, epistaxis; cellulitis, alopecia, less commonly nausea, constipation, impotence, Raynaud's phenomenon, acute transient plebitis

**Cautions** hypothyroidism, hyponatraemia, ischaemic hypertensive crisis (but see section 2.5); Thelin ADULT

**Dose**

- 20 mg 3 times daily; CHILD under 18 years see BNF for Children

**Revatio® (Pfizer)**

**Tablets, f/c, sildenafil (as citrate), 20 mg, net price 90-tab pack = £373.50**

**Viagra® (Pfizer)**

**Tablets 20 mg, net price 28-tab pack = £1540.00**

Section 7.4.5 (erectile dysfunction)

### SITAXENTAN SODIUM

**Indications** pulmonary arterial hypertension

**Cautions** test liver function before treatment and monitor monthly during treatment (discontinue treatment if liver enzymes significantly raised); measure haemoglobin concentration before treatment, after 1–3 months, then every 3 months; pregnancy (Appendix 4); interactions. Appendix 1 (sitaxentan)

**Contra-indications** hepatic impairment; breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances; peripheral oedema, flushing; headache, insomnia, fatigue, diziness; decreased haemoglobin, prolonged prothrombin time, increased INR; muscle cramp; nasal congestion, epistaxis

**Dose**

- ADULT over 18 years 100 mg once daily

**Thelin® (Encysive)**

**Tablets, f/c, yellow-orange, sitaxentan sodium 100 mg, net price 28-tab pack = £1540.00**

### SODIUM NITROPRUSSIDE

**Indications** hypertensive crisis (but see section 2.5); controlled hypotension in anaesthesia; acute or chronic heart failure

**Cautions** hypothyroidism, hyponatraemia, ischaemic heart disease, impaired cerebral circulation, elderly; hypothermia; monitor blood pressure and blood-cyanide concentration and if treatment exceeds 3 days, also blood-thiocyanate concentration; avoid sudden withdrawal—terminate infusion over 15–30 minutes; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding; interactions: Appendix 1 (sodium nitroprusside)

**Contra-indications** severe vitamin B deficiency; Leber's optic atrophy; compensatory hypertension

**Side-effects** associated with over rapid reduction in blood pressure (reduce infusion rate): headache, dizziness, nausea, retching, abdominal pain, perspiration, palpitation, anxiety, retrosternal discomfort; occasionally reduced platelet count, acute transient plebitis

**Cyanide** Side-effects caused by excessive plasma concentration of the cyanide metabolite include tachycardia, sweating, hyperventilation, arrhythmias, marked metabolic acidosis (discontinue and give antidote, see p. 34)

**Dose**

- Hypertensive crisis, by intravenous infusion, initially 0.5–1.5 micrograms/kg/minute, then increased in steps of 500 nanograms/kg/minute every 5 minutes within range 0.5–8 micrograms/kg/minute (lower doses if already receiving other anti-hypertensives); stop if response unsatisfactory with max. dose in 10 minutes

**Note** Lower initial dose of 300 nanograms/kg/minute has been used

- Maintenance of blood pressure at 30–40% lower than pretreatment diastolic blood pressure, 20–400 micrograms/minute (lower doses for patients being treated with other anti-hypertensives)

- Controlled hypotension in surgery, by intravenous infusion, max. 1.5 micrograms/kg/minute

- Heart failure, by intravenous infusion, initially 10–15 micrograms/minute, increased every 5–10 minutes as necessary; usual range 10–200 micrograms/minute normally for max. 3 days

**Sodium Nitroprusside (Non-proprietary)** Intravenous infusion, powder for reconstitution, sodium nitroprusside 10 mg/mL Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

2.5.2 Centrally acting antihypertensive drugs

Methyldopa is a centrally acting antihypertensive; it may be used for the management of hypertension in pregnancy. Side-effects are minimised if the daily dose is kept below 1 g.

Clonidine has the disadvantage that sudden withdrawal may cause a hypertensive crisis.

Moxonidine, a centrally acting drug, is licensed for mild to moderate essential hypertension. It may have a role when thiazides, calcium-channel blockers, ACE inhibitors, and beta-blockers are not appropriate or have failed to control blood pressure.

### CLONIDINE HYDROCHLORIDE

**Indications** hypertension; migraine (section 4.7.4.2); menopausal flushing (section 6.4.1.1)

**Cautions** must be withdrawn gradually to avoid hypertensive crisis; Raynaud's syndrome or other occlusive peripheral vascular disease; history of depression; avoid in acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (clonidine)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

**Side-effects** dry mouth, sedation, depression, fluid retention, bradycardia, Raynaud's phenomenon, headache, dizziness, euphoria, nocturnal unrest, rash, nausea, constipation, rarely impotence
Dose
- **By mouth**, 50–100 micrograms 3 times daily, increased every second or third day; usual max. dose 1.2 mg daily
- By slow intravenous injection, 150–300 micrograms; max. 750 micrograms in 24 hours

Catapres® (Boehringer Ingelheim) Tablets, scored, clonidine hydrochloride 100 micrograms, net price 100-tab pack = £5.60; 300 micrograms, 100-tab pack = £13.04. Label: 3, 8

Injection, clonidine hydrochloride 150 micrograms/mL, net price 1-mL amp = 29p

**Dixarit®**

Section 4.7.4.2

---

**METHYLDOPA**

**Indications** hypertension

**Cautions** monitor blood counts and liver-function before treatment and at intervals during first 6–12 weeks or if unexplained fever occurs; history of depression; positive direct Coombs’ test in up to 20% of patients (may affect blood cross-matching); interference with laboratory tests; hepatic impairment (avoid in active liver disease; Appendix 2); renal impairment (Appendix 3); **interactions**: Appendix 1 (methyl dopa)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

**Contra-indications** depression, active liver disease, phaeochromocytoma, acute porphyria (section 9.8.2)

**Side-effects** gastro-intestinal disturbances, dry mouth, stomatitis, sialadenitis; bradycardia, exacerbation of angina, postural hypotension, oedema; sedation, headache, dizziness, asthenia, myalgia, arthralgia, paraesthesia, nightmares, mild psychosis, depression, impaired mental acuity, parkinsonism, Bell’s palsy; abnormal liver function tests, hepatitis, jaundice; pancreatitis; haemolytic anaemia; bone marrow depression, leucopenia, thrombocytopenia, eosinophilia; hypersensitivity reactions including lupus erythematosus-like syndrome, drug fever, myocarditis, pericarditis; rashes (including toxic epidermal necrolysis); nasal congestion, failure of ejaculation, impotence, decreased libido, gynaecomastia, hyperprolactinaemia, amenorrhoea

**Dose**
- Initially 250 mg 2–3 times daily, increased gradually at intervals of at least 2 days, max. 3 g daily; **ELDERLY** initially 125 mg twice daily, increased gradually, max. 2 g daily

**Methyl dopa** (Non-proprietary) Tablets, coated, methyl dopa (anhydrous) 125 mg, net price 56-tab pack = £13.60; 250 mg, 56-tab pack = £8.36; 300 mg, 56-tab pack = £12.78. Label: 3, 8

**Aldomet®** (MSD) Tablets, all yellow, f/c, methyl dopa (anhydrous) 250 mg, net price 60 = £1.88; 500 mg, 30 = £1.90. Label: 3, 8

---

**MOXONIDINE**

**Indications** mild to moderate essential hypertension

**Cautions** avoid abrupt withdrawal (if concomitant treatment with beta-blocker has to be stopped, discontinue beta-blocker first, then moxonidine after a few days); susceptibility to angle-closure glaucoma; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); **interactions**: see Appendix 1 (moxonidine)

**Contra-indications** history of angioedema; conduction disorders (sick sinus syndrome, sino-atrial block, second- or third-degree AV block); bradycardia; life-threatening arrhythmia; severe heart failure; severe coronary artery disease, unstable angina; severe liver disease; also on theoretical grounds: Raynaud’s syndrome, intermittent claudication, epilepsy, depression, Parkinson’s disease; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** dry mouth; headache, fatigue, dizziness, nausea, sleep disturbance (rarely sedation), asthenia, vasodilatation; rarely skin reactions; very rarely angle-closure glaucoma

**Dose**
- 200 micrograms once daily in the morning, increased if necessary after 3 weeks to 400 micrograms daily in 1–2 divided doses; max. 600 micrograms daily in 2 divided doses (max. single dose 400 micrograms)

**Moxonidine** (Non-proprietary) Tablets, f/c, moxonidine 200 micrograms, net price 28-tab pack = £5.50; 300 micrograms, net price 28-tab pack = £8.10; 400 micrograms, net price 28-tab pack = £6.25. Label: 3

**Physiosters®** (Solvay) Tablets, f/c, moxonidine 200 micrograms (pink), net price 28-tab pack = £9.72; 300 micrograms (red), 28-tab pack = £11.49; 400 micrograms (red), 28-tab pack = £13.26. Label: 3

---

**2.5.3 Adrenergic neurone blocking drugs**

Adrenergic neurone blocking drugs prevent the release of noradrenaline from postganglionic adrenergic neurones. These drugs do not control supine blood pressure and may cause postural hypotension. For this reason they have largely fallen from use, but may be necessary with other therapy in resistant hypertension.

**Guamethidine**, which also depletes the nerve endings of noradrenaline, is licensed for rapid control of blood pressure.

---

**GUANETHIDINE MONOSULPHATE**

**Indications** hypertensive crisis (but see section 2.5)

**Cautions** coronary or cerebral arteriosclerosis, asthma, history of peptic ulceration; renal impairment (avoid if creatinine clearance less than 40 mL/minute; Appendix 3); pregnancy (Appendix 4); **interactions**: Appendix 1 (adrenergic neurone blockers)

**Contra-indications** phaeochromocytoma, heart failure

**Side-effects** postural hypotension, failure of ejaculation, fluid retention, nasal congestion, headache, diarrhoea, drowsiness

**Dose**
- By intramuscular injection, 10–20 mg, repeated after 3 hours if required

---
2.5.4 Alpha-adrenoceptor blocking drugs

Prazosin has post-synaptic alpha-blocking and vasodilator properties and rarely causes tachycardia. It may, however, reduce blood pressure rapidly after the first dose and should be introduced with caution. **Doxazosin**, **indoramin**, and **terazosin** have properties similar to those of prazosin.

Alpha-blockers can be used with other antihypertensive drugs in the treatment of resistant hypertension (section 2.5).

### Prostatic hyperplasia

Alfuzosin, doxazosin, indoramin, prazosin, tamsulosin, and terazosin are indicated for benign prostatic hyperplasia (section 7.4.1).

---

### DOXAZOSIN

#### Indications

Hypertension (see notes above); benign prostatic hyperplasia (section 7.4.1).

#### Caution

Care with initial dose (postural hypotension); cataract surgery (risk of intra-operative floppy iris syndrome); susceptibility to heart failure; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (alpha-blockers).

#### Side-effects

Gastro-intestinal disturbances; oedema, hypotension, postural hypotension; dyspnoea, rhinitis, coughing; asthenia, fatigue, vertigo, dizziness, headache, paraesthesia, sleep disturbance, anxiety, depression; respiratory-tract infection, urinary-tract infection, influenza-like symptoms; back pain, myalgia; less commonly weight changes, flushing, syncope, tremor, agitation, micturition disturbance, impotence, epistaxis, arthralgia, tinnitus, hypersensitivity reactions (including pruritus, purpura, rash); alopecia; very rarely cholestatics, hepatits, jaundice, bronchospasms, gynaecomastia, priapism, abnormal ejaculation, leucopenia, thrombocytopenia, blurred vision.

#### Dose

- Hypertension, 1 mg daily, increased after 1–2 weeks to 2 mg once daily, and thereafter to 4 mg once daily if necessary; max. 16 mg daily.

**Doxazosin** (Non-proprietary) Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = £9.39; 2 mg, 28-tab pack = £9.47; 4 mg, 28-tab pack = £14.42. Counselling, driving.

**Cardura** (Pfizer) Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = £10.56; 2 mg, 28-tab pack = £14.08. Counselling, driving.

---

### INDORAMIN

#### Indications

Hypertension (see notes above); benign prostatic hyperplasia (section 7.4.1).

#### Caution

Avoid alcohol (enhances rate and extent of absorption); control incipient heart failure before initiating indoramin; elderly; Parkinson's disease; epilepsy (convulsions in animal studies); history of depression; cataract surgery (risk of floppy iris syndrome); hepatic impairment; renal impairment; interactions: Appendix 1 (alpha-blockers).

#### Driving

Drowsiness may affect performance of skilled tasks e.g. driving; effects of alcohol may be enhanced.

#### Contra-indications

Established heart failure.

#### Side-effects

See section 7.4.1; drowsiness, sedation; less commonly dry mouth, hypotension, syncope, nasal congestion, dizziness, depression, fatigue, headache, weight gain, failure of ejaculation; rarely hypersensitivity reactions (including rash and puritus); diarrhoea, nausea, palpitation, urinary frequency and incontinence, and priapism also reported.

#### Dose

- Hypertension, initially 25 mg twice daily, increased by 25–50 mg daily at intervals of 2 weeks; max. daily dose 200 mg in 2–3 divided doses.

**Baratol** (Amdipharm) Tablets, blue, f/c, indoramin (as hydrochloride) 25 mg, net price 84-tab pack = £9.00. Label: 2

**Doralese** (Pfizer) Tablets, indoramin (as mesilate) 25, counselling, driving.

#### Section 7.4.1 (prostatic hyperplasia)

---

### PRAZOSIN

#### Indications

Hypertension (see notes above); congestive heart failure (but see section 2.5.5); Raynald's syndrome (see also section 2.6.4); benign prostatic hyperplasia (section 7.4.1).

#### Caution

First dose may cause collapse due to hypotension (therefore should be taken on retiring to bed); elderly; cataract surgery (risk of intra-operative floppy iris syndrome); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (alpha-blockers).

#### Contra-indications

Not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis).

#### Side-effects

See section 7.4.1; also gastro-intestinal disturbances; postural hypotension, oedema, palpitation; dyspnoea, nasal congestion; drowsiness, headache, depression, nervousness, vertigo; urinary frequency; weakness; blurred vision; less commonly tachycardia, insomnia, paraesthesia, sweating, impo-
tence, arthralgia, eye disorders, tinnitus, epistaxis, allergic reactions including rash, pruritus, and urticaria; rarely pancreatitis, flushing, vasculitis, bradycardia, hallucinations, worsening of narcolepsy, gynaecomastia, priapism, urinary incontinence, and alopecia.

**Dose**

- Hypertension (see notes above), 500 micrograms 2–3 times daily for 3–7 days, the initial dose on retiring to bed at night (to avoid collapse, see Cautions); increased to 1 mg 2–3 times daily for a further 3–7 days; further increased if necessary to max. 20 mg daily in divided doses.
- Congestive heart failure (but see section 2.5.5), 500 micrograms 2–4 times daily (initial dose at bedtime, see above), increasing to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses (but rarely used).
- Raynaud’s syndrome (but efficacy not established, see section 2.6.4), initially 500 micrograms twice daily (initial dose at bedtime, see above) increased, if necessary, after 3–7 days to usual maintenance 1–2 mg twice daily.

**Prazosin**

**Indications**

- Mild to moderate hypertension (see notes above);
- Benign prostatic hyperplasia (section 7.4.1).

**Cautions**

- First dose may cause collapse due to hypotension (within 30–90 minutes, therefore should be taken on retiring to bed) (may also occur with rapid dose increase); pregnancy (Appendix 4).

**Side-effects**

- See section 7.4.1; also drowsiness, dizziness, lack of energy, peripheral oedema; urinary frequency and priapism reported.

**Dose**

- Hypertension, 1 mg at bedtime (compliance with bedtime dose important, see Cautions); dose doubled after 7 days if necessary; usual maintenance dose 2–10 mg once daily; more than 20 mg daily rarely improves efficacy.

**Phaeochromocytoma**

Long-term management of phaeochromocytoma involves surgery. Alpha-blockers are used in the short-term management of hypertensive episodes in phaeochromocytoma. Once alpha blockade is established, tachycardia can be controlled by the cautious addition of a beta-blocker (section 2.4); a cardioselective beta-blocker is preferred.

**Phenoxybenzamine**, a powerful alpha-blocker, is effective in the management of phaeochromocytoma but it has many side-effects. *Phentolamine* is a short-acting alpha-blocker used mainly during surgery of phaeochromocytoma; its use for the diagnosis of phaeochromocytoma has been superseded by measurement of catecholamines in blood and urine.

**Metirosine** (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) inhibits the enzyme tyrosine hydroxylase, and hence the synthesis of catecholamines. It is rarely used in the pre-operative management of phaeochromocytoma, and long term in patients unsuitable for surgery; an alpha-adrenoceptor blocking drug may also be required. Metirosine should not be used to treat essential hypertension.

**PHENOXYBENZAMINE HYDROCHLORIDE**

**Indications**

- Hypertensive episodes in phaeochromocytoma.

**Cautions**

- Elderly; congestive heart failure; severe heart disease (see also Contra-indications); cerebrovascular disease (avoid if history of cerebrovascular accident); renal impairment; carcinogenic in animals; avoid in acute porphyria (section 9.8.2); avoid infusion in hypovolaemia; avoid extravasation (irritant to tissues); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications**

- History of cerebrovascular accident; during recovery period after myocardial infarction (usually 3–4 weeks).

**Side-effects**

- Postural hypotension with dizziness and marked compensatory tachycardia, lassitude, nasal congestion, miosis, inhibition of ejaculation; rarely gastrointestinal disturbances; decreased sweating and dry mouth after intravenous infusion; idiosyncratic profound hypotension within few minutes of starting infusion.

**Dose**

- See under preparations.

**Phenoxybenzamine**

**Indication**

- Hypertensive episodes in phaeochromocytoma.

**Dose**

- Oral route: 2 mg 2–4 times daily for 3–7 days, then increased, if necessary, to max. 20 mg daily in divided doses.

**Phenoxybenzamine hydrochloride**

**Indications**

- Hypertensive episodes in phaeochromocytoma.

**Cautions**

- Elderly; congestive heart failure; severe heart disease (see also Contra-indications); cerebrovascular disease (avoid if history of cerebrovascular accident); renal impairment; carcinogenic in animals; avoid in acute porphyria (section 9.8.2); avoid infusion in hypovolaemia; avoid extravasation (irritant to tissues); pregnancy (Appendix 4); breast-feeding (Appendix 5).

**Contra-indications**

- History of cerebrovascular accident; during recovery period after myocardial infarction (usually 3–4 weeks).

**Side-effects**

- Postural hypotension with dizziness and marked compensatory tachycardia, lassitude, nasal congestion, miosis, inhibition of ejaculation; rarely gastrointestinal disturbances; decreased sweating and dry mouth after intravenous infusion; idiosyncratic profound hypotension within few minutes of starting infusion.

**Dose**

- See under preparations.

**Phenoxybenzamine**

**Dose**

- Oral route: 2 mg 2–4 times daily for 3–7 days, then increased, if necessary, to max. 20 mg daily in divided doses.

**Phenoxybenzamine hydrochloride**

**Indication**

- Hypertensive episodes in phaeochromocytoma.

**Dose**

- Oral route: 2 mg 2–4 times daily for 3–7 days, then increased, if necessary, to max. 20 mg daily in divided doses.
2 Cardiovascular system

2.5.5 Drugs affecting the renin-angiotensin system

2.5.5.1 Angiotensin-converting enzyme inhibitors

2.5.5.2 Angiotensin-II receptor antagonists

2.5.5.3 Renin inhibitors

Heart failure

Drug treatment of heart failure due to left ventricular systolic dysfunction is covered below; optimal management of heart failure with preserved left ventricular function is not established.

The treatment of chronic heart failure aims to relieve symptoms, improve exercise tolerance, reduce the incidence of acute exacerbations, and reduce mortality. An ACE inhibitor, titrated to a 'target dose' (or the maximum tolerated dose if lower), and a beta-blocker is recommended to achieve these aims. A diuretic is also necessary in most patients to reduce symptoms of fluid overload.

An ACE inhibitor (section 2.5.5.1) is generally advised for patients with asymptomatic left ventricular dysfunction or symptomatic heart failure. An angiotensin-II receptor antagonist (section 2.5.5.2) may be a useful alternative for patients who, because of side-effects such as cough, cannot tolerate ACE inhibitors; a relatively high dose of the angiotensin-II receptor antagonist may be required to produce benefit.

The beta-blockers bisoprolol and carvedilol (section 2.4) are of value in any grade of stable heart failure and left-ventricular systolic dysfunction; nebivolol (section 2.4) is licensed for stable mild to moderate heart failure in patients over 70 years. Beta-blocker treatment should be started by those experienced in the management of heart failure, at a very low dose and titrated very slowly over a period of weeks or months. Symptoms may deteriorate initially, calling for adjustment of concomitant therapy.

Patients with fluid overload should also receive either a loop or a thiazide diuretic (with salt or fluid restriction where appropriate). A thiazide diuretic (section 2.2.1) may be of benefit in patients with mild heart failure and good renal function; however, thiazide diuretics are ineffective in patients with poor renal function (estimated creatinine clearance less than 30 mL/minute, see Appendix 3) and a loop diuretic (section 2.2.2) is preferred. If diuresis with a single diuretic is insufficient, a combination of a loop diuretic and a thiazide diuretic may be tried; addition of metolazone (section 2.2.1) may also be considered but the resulting diuresis may be profound and care is needed to avoid potentially dangerous electrolyte disturbances.

The aldosterone antagonist spironolactone (section 2.2.3) can be considered for patients with moderate to severe heart failure who are already taking an ACE inhibitor and a beta-blocker; low doses of spironolactone (usually 25 mg daily) reduce symptoms and mortality in these patients. If spironolactone cannot be used, eplerenone (section 2.2.3) may be considered for the management of heart failure after an acute myocardial infarction with evidence of left ventricular dysfunction. Close monitoring of serum creatinine and potassium is necessary with any change in treatment or in the patient's condition.

Digoxin (section 2.1.1) improves symptoms of heart failure and exercise tolerance and reduces hospitalisation due to acute exacerbations but it does not reduce mortality. Digoxin is reserved for patients with atrial fibrillation and also for selected patients in sinus rhythm who remain symptomatic despite treatment with an ACE inhibitor, a beta-blocker, and a diuretic.

Patients who cannot tolerate an ACE inhibitor or an angiotensin-II receptor antagonist, or in whom they are contra-indicated, may be given isosorbide dinitrate (section 2.6.1) with hydralazine (section 2.5.1), but this combination may be poorly tolerated. In African-American patients, the combination of isosorbide dinitrate and hydralazine may be considered in addition to standard therapy if necessary.

Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. They have many uses and are generally well tolerated. The main indications of ACE inhibitors are shown below.

Heart failure

ACE inhibitors are used in all grades of heart failure, usually combined with a beta-blocker (section 2.5.5). Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. However, a low dose of spironolactone may be beneficial in severe heart failure (section 2.5.5) and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Profound first-dose hypo-
tension may occur when ACE inhibitors are introduced to patients with heart failure who are already taking a high dose of a loop diuretic (e.g. furosemide 80 mg daily or more). Temporary withdrawal of the loop diuretic reduces the risk, but may cause severe rebound pulmonary oedema. Therefore, for patients on high doses of loop diuretics, the ACE inhibitor may need to be initiated under specialist supervision, see below. An ACE inhibitor can be initiated in the community in patients who are receiving a low dose of a diuretic or who are not otherwise at risk of serious hypotension; nevertheless, care is required and a very low dose of the ACE inhibitor is given initially.

**Hypertension** An ACE inhibitor may be the most appropriate initial drug for hypertension in younger Caucasian patients; Afro-Caribbean patients, those aged over 55 years, and those with primary aldosteronism respond less well (see section 2.5). ACE inhibitors are particularly indicated for hypertension in patients with type 1 diabetics with nephropathy (see also section 6.1.5). They may reduce blood pressure very rapidly in some patients particularly in those receiving diuretic therapy (see Cautions, below); the first dose should preferably be given at bedtime.

**Diabetic nephropathy** For comment on the role of ACE inhibitors in the management of diabetic nephropathy, see section 6.1.5.

**Prophylaxis of cardiovascular events** ACE inhibitors are used in the early and long-term management of patients who have had a myocardial infarction, see section 2.10.1. ACE inhibitors may also have a role in preventing cardiovascular events.

**Initiation under specialist supervision** ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in those with severe heart failure or in those:
- receiving multiple or high-dose diuretic therapy (e.g. more than 80 mg of furosemide daily or its equivalent);
- with hypovolaemia;
- with hyponaatraemia (plasma-sodium concentration below 130 mmol/litre);
- with hypotension (systolic blood pressure below 90 mmHg);
- with unstable heart failure;
- receiving high-dose vasodilator therapy;
- known renovascular disease.

**Renal effects** Renal function and electrolytes should be checked before starting ACE inhibitors (or increasing the dose) and monitored during treatment (more frequently if features mentioned below present); hyperkalaemia and other side-effects of ACE inhibitors are more common in those with impaired renal function and the dose may need to be reduced (Appendix 3). Although ACE inhibitors now have a specialised role in some forms of renal disease, including chronic kidney disease, they also occasionally cause impairment of renal function which may progress and become severe in other circumstances (at particular risk are the elderly). A specialist should be involved if renal function is significantly reduced as a result of treatment with an ACE inhibitor.

Concomitant treatment with NSAIDs increases the risk of renal damage, and potassium-sparing diuretics (or potassium-containing salt substitutes) increase the risk of hyperkalaemia.

In patients with severe bilateral renal artery stenosis (or severe stenosis of the artery supplying a single functioning kidney), ACE inhibitors reduce or abolish glomerular filtration and are likely to cause severe and progressive renal failure. They are therefore not recommended in patients known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in patients with severe unilateral renal artery stenosis and a normal contralateral kidney, but glomerular filtration is likely to be reduced (or even abolished) in the affected kidney and the long-term consequences are unknown.

ACE inhibitors are therefore best avoided in patients with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If ACE inhibitors are used, they should be initiated only under specialist supervision and renal function should be monitored regularly.

ACE inhibitors should also be used with particular caution in patients who may have undiagnosed and clinically silent renovascular disease. This includes patients with peripheral vascular disease or those with severe generalised atherosclerosis.

**Cautions** ACE inhibitors need to be initiated with care in patients receiving diuretics (important: see Concomitant diuretics, below); first doses can cause hypotension especially in patients taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated or with heart failure (see above). They should also be used with caution in peripheral vascular disease or generalised atherosclerosis owing to risk of clinically silent renovascular disease; for use in known renovascular disease, see Renal Effects above. The risk of agranulocytosis is possibly increased in collagen vascular disease (blood counts recommended). ACE inhibitors should be used with care in patients with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy. They should also be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema. ACE inhibitors should be used with caution in breast-feeding (Appendix 5). Interactions: Appendix 1 (ACE inhibitors).

**Anaphylactoid reactions** To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polycrylonitrile membranes and during low-density lipoprotein apheresis with dextran sulphate; they should also be withheld before desensitisation with wasp or bee venom.

**Concomitant diuretics** ACE inhibitors can cause a very rapid fall in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. If the dose of diuretic is greater than 80 mg furosemide or equivalent, the ACE inhibitor should be initiated under close supervision and in some patients the diuretic dose may need to be reduced or the diuretic discontinued at least 24 hours beforehand (may not be possible in heart failure—risk of pulmonary oedema). If high-dose diuretic therapy cannot be stopped, close observation is recommended after administration of the first dose of ACE inhibitor, for at least 2 hours or until the blood pressure has stabilised.
Contra-indications  ACE inhibitors are contra-indicated in patients with hypersensitivity to ACE inhibitors (including angioedema). ACE inhibitors should not be used in pregnancy (Appendix 4).

Side-effects  ACE inhibitors can cause profound hypotension (see Cautions) and renal impairment (see Renal effects above), and a persistent dry cough. They can also cause angioedema (onset may be delayed; higher incidence reported in Afro-Caribbean patients), rash (which may be associated with pruritus and urticaria), pancreatitis, and upper respiratory-tract symptoms such as sinusitis, rhinitis, and sore throat. Gastro-intestinal effects reported with ACE inhibitors include nausea, vomiting, dyspepsia, diarrhoea, constipation, and abdominal pain. Altered liver function tests, cholestasis jaundice, and hepatitis have been reported. Hyperkalaemia, hypoglycaemia, and blood disorders including thrombocytopenia, leucopenia, neutropenia, and haemolytic anaemia have also been reported. Other reported side-effects include headache, dizziness, fatigue, malaise, taste disturbance, paraesthesia, bronchospasm, fever, soroitis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis, and photosensitivity.

Combination products  Products incorporating an ACE inhibitor with a thiazide diuretic or a calcium-channel blocker are available for the management of hypertension. Use of these combination products should be reserved for patients whose blood pressure has not responded adequately to a single antihypertensive drug and who have been stabilised on the individual components of the combination in the same proportions.

CAPTOPRIL

Indications  mild to moderate essential hypertension alone or with thiazide therapy and severe hypertension resistant to other treatment; congestive heart failure with left ventricular dysfunction (adjunct—see section 2.5.5); following myocardial infarction, see dose; diabetic nephropathy (microalbuminuria greater than 30 mg/day) in type 1 diabetes

Cautions  see notes above

Contra-indications  see notes above

Side-effects  see notes above; tachycardia, serum sickness, weight loss, stomatitis, maculopapular rash, photosensitivity, flushing and acidosis

Dose  • Hypertension, used alone, initially 12.5 mg twice daily; if used in addition to diuretic (see notes above), or in elderly, initially 6.25 mg twice daily (first dose at bedtime); usual maintenance dose 25 mg twice daily; max. 50 mg twice daily (rarely 3 times daily in severe hypertension)

• Heart failure (adjunct), initially 6.25–12.5 mg 2–3 times daily under close medical supervision (see notes above), increased gradually at intervals of at least 2 weeks up to max. 150 mg daily in divided doses if tolerated

• Prophylaxis after infarction in clinically stable patients with asymptomatic or symptomatic left ventricular dysfunction (radionuclide ventriculography or echocardiography undertaken before initiation), initially 6.25 mg, starting as early as 3 days after infarction, then increased over several weeks to 150 mg daily (if tolerated) in divided doses

• Diabetic nephropathy, 75–100 mg daily in divided doses; if further blood pressure reduction required, other antihypertensives may be used in conjunction with captopril; in severe renal impairment, initially 12.5 mg twice daily (if concomitant diuretic therapy required, loop diuretic rather than thiazide should be chosen)

Captopril (Non-proprietary)  £14.10

Tablets, captopril 12.5 mg, net price 56-tab pack = £1.59; 25 mg, 56-tab pack = £1.70; 50 mg, 56-tab pack = £2.22

Brands include Ecopace, Kaplon, Tenospril

Capoten® (Squibb)  £14.00

Tablets, captopril 12.5 mg (scored), net price 56-tab pack = £9.82; 25 mg, 56-tab pack = £11.19; 50 mg (scored), 56-tab pack = £19.07 (also available as Acepr®)

With diuretic  Note  For mild to moderate hypertension in patients stabilised on the individual components in the same proportions. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1

Co-zidocapt (Non-proprietary)  £14.00

Tablets, co-zidocapt 12.5/25 (hydrochlorothiazide 12.5 mg, captopril 25 mg), net price 28-tab pack = £14.10

Brands include Capto-co

Tablets, co-zidocapt 25/50 (hydrochlorothiazide 25 mg, captopril 50 mg), net price 28-tab pack = £14.00

Brands include Capto-co

Capozide® (Squibb)  £7.45 (also available as Acezide®)

Indications  essential hypertension; congestive heart failure (adjunct—see section 2.5.5)

Cautions  see notes above; severe hepatic impairment (Appendix 2)

Contra-indications  see notes above; ascites

Side-effects  see notes above; dyspnoea and bronchitis

Dose  • Hypertension, initially 1 mg once daily (reduced to 500 micrograms daily if used in addition to diuretic (see notes above), in the elderly, and in renal impairment), then adjusted according to response; usual maintenance dose 2.5–5 mg once daily; max. 5 mg daily

• Heart failure (adjunct), initially 500 micrograms once daily under close medical supervision (see notes above), increased gradually to 1–2.5 mg once daily if tolerated; max. 5 mg once daily

Vascace® (Roche)  £7.65

Tablets, f/c, cilazapril 500 micrograms (white), net price 28-tab pack = £3.65; 1 mg (yellow), 28-tab pack = £6.01; 2.5 mg (pink), 28-tab pack = £7.64; 5 mg (brown), 28-tab pack = £13.28
ENALAPRIL MALEATE

**Indications** hypertension; symptomatic heart failure (adjunct—see section 2.5.5); prevention of symptomatic heart failure in patients with asymptomatic left ventricular dysfunction

**Cautions** see notes above; hepatic impairment

**Side-effects** see notes above; also dyspnoea; depression, asthenia; blurred vision; less commonly dry mouth, peptic ulcer, anorexia, ileus; arrhythmias, palpitation, flushing; confusion, nervousness, drowsiness, insomnia, vertigo; impotence; muscle cramps; tinnitus; alopecia, sweating; hyponatraemia; rarely stomatitis, glossitis, hepatic failure, Raynaud’s syndrome, pulmonary infiltrates, allergic alveolitis, dream abnormalities, gynaecomastia, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus; very rarely gastro-intestinal angiooedema

**Dose**
- Hypertension, used alone, initially 5 mg once daily; if used in addition to diuretic (see notes above), or in renal impairment, lower initial doses may be required; usual maintenance dose 20 mg once daily; max. 40 mg once daily
- Heart failure (adjunct), asymptomatic left ventricular dysfunction, initially 2.5 mg once daily under close medical supervision (see notes above), increased gradually over 2–4 weeks to 10–20 mg twice daily if tolerated

Enalapril Maleate (Non-proprietary) Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £1.12; 10 mg, 28-tab pack = £1.22

Brands include Edney

Innovace® (MSD) Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £5.35; 5 mg (scored), 28-tab pack = £7.51; 10 mg (red), 28-tab pack = £10.53; 20 mg (peach), 28-tab pack = £12.51

With diuretic

**Note** For mild to moderate hypertension in patients stabilised on the individual components in the same proportions. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1

Imidapril hydrochloride

**Indications** essential hypertension

**Cautions** see notes above; hepatic impairment

**Side-effects** see notes above; dry mouth, glossitis, ileus; bronchitis, dyspnoea; sleep disturbances, depression, confusion, blurred vision, tinnitus, impotence

**Dose**
- Initially 5 mg daily before food; if used in addition to diuretic (see notes above), in elderly, in patients with heart failure, angina or cerebrovascular disease, or in renal or hepatic impairment, initially 2.5 mg daily; if necessary increase dose at intervals of at least 3 weeks; usual maintenance dose 10 mg once daily; max. 20 mg daily (elderly, 10 mg daily)

Tanatril® (Trinity) Tablets, scored, imidapril hydrochloride 5 mg, net price 28-tab pack = £6.78; 10 mg, 28-tab pack = £7.66; 20 mg, 28-tab pack = £9.20

**Lisinopril**

**Indications** hypertension (but see notes above); symptomatic heart failure (adjunct—see section 2.5.5); short-term treatment following myocardial infarction in haemodynamically stable patients; renal complications of diabetes mellitus

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; also less commonly tachycardia, palpitation, cerebrovascular accident, myocardial infarction, Raynaud’s syndrome, confusion, mood changes, vertigo, sleep disturbances, asthenia, impotence; rarely dry mouth, gynaecomastia, alopecia, psoriasis; very rarely allergic alveolitis, pulmonary infiltrates, profuse sweating, pemphigus, Stevens-Johnson syndrome, and toxic epidermal necrolysis

**Dose**
- Hypertension, initially 10 mg once daily; if used in addition to diuretic (see notes above) or in cardiac decompensation or in volume depletion, initially 2.5–5 mg once daily; usual maintenance dose 20 mg once daily; max. 80 mg once daily
- Heart failure (adjunct), initially 2.5 mg once daily under close medical supervision (see notes above); increased in steps no greater than 10 mg at intervals of at least 2 weeks up to max. 35 mg once daily if tolerated
- Prophylaxis after myocardial infarction, systolic blood pressure over 120 mmHg, 5 mg within 24 hours, fol-
lowed by further 5 mg 24 hours later, then 10 mg after a further 24 hours, and continuing with 10 mg once daily for 6 weeks (or continued if heart failure); systolic blood pressure 100–120 mmHg, initially 2.5 mg once daily, increased to maintenance dose of 5 mg once daily

Note Should not be started after myocardial infarction if systolic blood pressure less than 100 mmHg; temporarily reduce maintenance dose to 5 mg and if necessary 2.5 mg daily if systolic blood pressure 100 mmHg or less during treatment; withdraw if prolonged hypotension occurs (systolic blood pressure less than 90 mmHg for more than 1 hour)

- Renal complications of diabetes mellitus, initially 2.5–5 mg once daily adjusted according to response; usual dose range 10–20 mg once daily

Lisinopril (Non-proprietary) (HM)

Tablets, lisinopril (as dihydrate) 2.5 mg, net price 28-tab pack = £1.02; 10 mg, 28-tab pack = £1.10; 20 mg, 28-tab pack = £1.37

Carace® (Bristol-Myers Squibb) (HM)

Tablets, scored, lisinopril 5 mg, net price 28-tab pack = £8.51; 10 mg (yellow), 28-tab pack = £10.51; 20 mg (orange), 28-tab pack = £11.89

Zestril® (AstraZeneca) (HM)

Tablets, lisinopril (as dihydrate) 2.5 mg, net price 28-tab pack = £6.26; 5 mg (pink), 28-tab pack = £7.86; 10 mg (pink), 28-tab pack = £9.70; 20 mg (pink), 28-tab pack = £10.97

With diuretic

Note For mild to moderate hypertension in patients stabilised on the individual components in the same proportions. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1

Carace Plus® (Bristol-Myers Squibb) (HM)

Carace 10 Plus tablets, blue, lisinopril 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £11.88

Carace 20 Plus tablets, yellow, scored, lisinopril 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £13.44

Lisicostad® (Genus) (HM)

Lisicostad 10/12.5 mg tablets, scored, lisinopril (as dihydrate) 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £10.99

Lisicostad 20/12.5 mg tablets, scored, lisinopril (as dihydrate) 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £11.99

Zestoretic® (AstraZeneca) (HM)

Zestoretic 10 tablets, peach, lisinopril (as dihydrate) 10 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £13.01

Zestoretic 20 tablets, lisinopril (as dihydrate) 20 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £14.72

MOEXIPRIL HYDROCHLORIDE

Indications essential hypertension

Cautions see notes above; hepatic impairment (Appendix 2)

Contra-indications see notes above

Side-effects see notes above; arrhythmias, angina, chest pain, syncope, cerebrovascular accident, myocardial infarction; appetite and weight changes; dry mouth, photosensitivity, flushing, nervousness, mood changes, anxiety, drowsiness, sleep disturbance, tinnitus, influenza-like syndrome, sweating and dyspnoea

Dose

- Used alone, initially 7.5 mg once daily; if used in addition to diuretic (see notes above), with nifedipine, in elderly, in renal or hepatic impairment, initially 3.75 mg once daily; usual range 15–30 mg once daily; doses above 30 mg daily not shown to increase efficacy

Perdix® (UBC Pharma) (HM)

Tablets, f/c, pink, scored, moexipril hydrochloride 7.5 mg, net price 28-tab pack = £7.55; 15 mg, 28-tab pack = £8.70

PERINDOPRIL ERBUMINE

Indications hypertension (but see notes above); symptomatic heart failure (adjunct—see section 2.5.5); prophylaxis of cardiac events following myocardial infarction or revascularisation in stable coronary artery disease

Cautions see notes above; hepatic impairment (Appendix 2)

Contra-indications see notes above

Side-effects see notes above; asthenia, mood and sleep disturbances

Dose

- Hypertension, initially 4 mg once daily in the morning for 1 month, subsequently adjusted according to response; if used in addition to diuretic (see notes above), in elderly, in renal impairment, in cardiac decompensation, or in volume depletion, initially 2 mg once daily; max. 8 mg daily

- Heart failure (adjunct), initially 2 mg once daily in the morning under close medical supervision (see notes above), increased after at least 2 weeks to max. 4 mg once daily if tolerated

- Following myocardial infarction or revascularisation, initially 4 mg once daily in the morning increased after 2 weeks to 8 mg once daily if tolerated; ELDERLY 2 mg once daily for 1 week, then 4 mg once daily for 1 week, thereafter increased to 8 mg once daily if tolerated

Perindopril (Non-proprietary) (HM)

Tablets, perindopril erbumine (= tert-butylamine) 2 mg, net price 30-tab pack = £4.45; 4 mg, 30-tab pack = £4.21; 8 mg, 30-tab pack = £4.60. Label: 22

Perindopril arginine

Coverys® Arginine (Servier) (HM)

Tablets, f/c, perindopril arginine 2.5 mg (white), net price 30-tab pack = £11.36; 5 mg (light green, scored), 30-tab pack = £11.36; 10 mg (green), 30-tab pack = £11.36. Label: 22

Dose Hypertension, initially 5 mg once daily in the morning for 1 month, subsequently adjusted according to response; if used in addition to diuretic (see notes above), in elderly, in renal impairment, in cardiac decompensation, or in volume depletion, initially 2.5 mg once daily; max. 10 mg daily

Heart failure (adjunct), initially 2.5 mg once daily in the morning under close medical supervision (see notes above), increased after 2 weeks to max. 5 mg once daily if tolerated

Following myocardial infarction or revascularisation, initially 5 mg once daily in the morning increased after 2 weeks to 10 mg once daily if tolerated; ELDERLY 2.5 mg once daily for 1 week, then 5 mg once daily for 1 week, thereafter increased to 10 mg once daily if tolerated
indapamide, see section 2.2.1

Coversyl® Arginine Plus (Servier) (W)
Tablets, f/c, perindopril arginine 5 mg, indapamide 1.25 mg, net price 30-tab pack = £14.49. Label: 22

INDICATIONS
- Essential hypertension; congestive heart failure (adjunct—see section 2.5.5)

CAUTIONS
- See notes above; hepatic impairment (Appendix 2)

CONTRA-INDICATIONS
- See notes above

SIDE-EFFECTS
- See notes above; asthenia, chest pain, oedema, flatulence, nervousness, depression, insomnia, blurred vision, impotence, and back pain

DOSE
- Hypertension, initially 10 mg once daily; with a diuretic (see notes above), in elderly, or in renal impairment initially 2.5 mg daily; usual maintenance dose 20–40 mg daily in single or 2 divided doses; up to 80 mg daily has been given
- Heart failure (adjunct), initial dose 2.5 mg daily under close medical supervision (see notes above), increased gradually to 10–20 mg daily in 1–2 divided doses if tolerated; max. 40 mg daily

Quinapril

Tablets, quinapril (as hydrochloride) 5 mg, net price 28-tab pack = £17.8; 10 mg, 28-tab pack = £2.16; 20 mg, 28-tab pack = £2.56; 40 mg, 28-tab pack = £3.26. Brands include Quinil

With diuretic

Note: For hypertension in patients stabilised on the individual components in the same proportions. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1

Accuretic® (Pfizer) (W)
Tablets, f/c, quinapril (as hydrochloride) 5 mg (brown), net price 28-tab pack = £8.60; 10 mg (brown), 28-tab pack = £8.80; 20 mg (brown), 28-tab pack = £18.79; 40 mg (red-brown), 28-tab pack = £9.75

RAMIPRIL

INDICATIONS
- Mild to moderate hypertension; congestive heart failure (adjunct—see section 2.5.5); following myocardial infarction in patients with clinical evidence of heart failure; susceptible patients over 55 years, prevention of myocardial infarction, stroke, cardiovascular death or need of revascularisation procedures (consult product literature)

CAUTIONS
- See notes above; hepatic impairment (Appendix 2)

CONTRA-INDICATIONS
- See notes above

SIDE-EFFECTS
- See notes above; arrhythmias, angina, chest pain, syncope, cerebrovascular accident, myocardial infarction, loss of appetite, stomatitis, dry mouth, skin reactions including erythema multiforme and pemphigoid exanthema; precipitation or exacerbation of Raynaud’s syndrome; conjunctivitis, onyx-cholyasis, confusion, nervousness, depression, anxiety, impotence, decreased libido, alopecia, bronchitis and muscle cramps

DOSE
- Hypertension, initially 1.25 mg once daily, increased at intervals of 1–2 weeks; usual range 2.5–5 mg once daily; max. 10 mg once daily; if used in addition to diuretic see notes above
- Heart failure (adjunct), initially 1.25 mg once daily under close medical supervision (see notes above), increased gradually at intervals of 1–2 weeks to max. 10 mg daily if tolerated (daily doses of 2.5 mg or more may be taken in 1–2 divided doses)
- Prophylaxis after myocardial infarction (started in hospital 3 to 10 days after infarction), initially 2.5 mg twice daily, increased after 2 days to 5 mg twice daily; maintenance 2.5–5 mg twice daily

Note
- If initial 2.5-mg dose not tolerated, give 1.25 mg twice daily for 2 days before increasing to 2.5 mg twice daily, then 5 mg twice daily
- Prophylaxis of cardiovascular events or stroke, initially 2.5 mg once daily, increased after 1 week to 5 mg once daily, then increased after a further 3 weeks to 10 mg once daily

Ramipril (Non-proprietary) (W)
Capsules, ramipril 1.25 mg, net price 28-cap pack = £1.07; 2.5 mg, 28-cap pack = £1.15; 5 mg, 28-cap pack = £1.29; 10 mg, 28-cap pack = £1.54. Brands include Lopace

Tablets, ramipril 1.25 mg, net price 28-tab pack = £1.42; 2.5 mg, 28-tab pack = £1.58; 5 mg, 28-tab pack = £1.93; 10 mg, 28-tab pack = £2.44

Triatrace (Aventis Pharma) (W)
Tablets, scored, ramipril 1.25 mg (white), net price 28-tab pack = £5.30; 2.5 mg (yellow), 28-tab pack = £7.51; 5 mg (red), 28-tab pack = £10.46; 10 mg (white), 28-tab pack = £14.24

Tiratrace pack, tablets, 35-day starter pack of ramipril 7 × 2.5 mg with 21 × 5 mg and 7 × 10 mg, net price = £13.00

With calcium-channel blocker

Note
- For hypertension in patients stabilised on the individual components in the same proportions. For cautions, contra-indications, and side-effects of felodipine, see section 2.6.2

Triapin® (Aventis Pharma) (W)
Triapin tablets, f/c, brown, ramipril 5 mg, felodipine 5 mg (m/r), net price 28-tab pack = £26.25. Label: 25

Triapin mite® tablets, f/c, orange, ramipril 2.5 mg, felodipine 2.5 mg (m/r), net price 28-tab pack = £28.55. Label: 25

TRANDOLAPRIL

INDICATIONS
- Mild to moderate hypertension; following myocardial infarction in patients with left ventricular dysfunction

CAUTIONS
- See notes above; hepatic impairment (Appendix 2)

CONTRA-INDICATIONS
- See notes above

SIDE-EFFECTS
- See notes above; also ileus, dry mouth; tachycardia, palpitation, arrhythmias, angina, transient ischaemic attacks, cerebral haemorrhage, myocardial infarction, syncope; dyspnoea, bronchitis; asthenia, nervousness, sleep disturbances; hot flushes; alopecia, sweating, skin reactions including
2 Cardiovascular system

2.5.5 Drugs affecting the renin-angiotensin system

Stevens-Johnson syndrome, toxic epidermal necrolysis, and psoriasis-like efflorescence

Dose

- Hypertension, initially 500 micrograms once daily, increased at intervals of 2–4 weeks; usual range 1–2 mg once daily; max. 4 mg daily; if used in addition to diuretic see notes above
- Prophylaxis after myocardial infarction (starting as early as 3 days after infarction), initially 500 micrograms once daily, gradually increased to max. 4 mg once daily
- Note If symptomatic hypotension develops during titration, do not increase dose further; if possible, reduce dose of any adjunctive treatment and if this is not effective or feasible, reduce dose of trandolapril

Trandolapril (Non-proprietary) 

Capsules, trandolapril 500 micrograms, net price 14-cap pack = £1.41; 1 mg, 28-cap pack = £6.86; 2 mg, 28-cap pack = £6.86; 4 mg, 28-cap pack = £11.61

Gopten (Abbott) 

Capsules, trandolapril 500 micrograms (red/yellow), net price 14-cap pack = £1.40; 1 mg (red/orange), 28-cap pack = £12.28; 2 mg (red/red), 28-cap pack = £6.86; 4 mg (red/maroon), 28-cap pack = £11.64

With calcium-channel blocker

Note For hypertension in patients stabilised on the individual components in the same proportions. For cautions, contra-indications, and side-effects of verapamil, see section 2.6.2

Tarka (Abbott) 

Capsules, pink, trandolapril 2 mg, verapamil hydrochloride 180 mg (m/r), net price 28 cap-pack = £17.85. Label: 25

2.5.5.2 Angiotensin-II receptor antagonists

Candesartan, eprosartan, irbesartan, losartan, olmesartan, telmisartan, and valsartan are angiotensin-II receptor antagonists with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, they do not inhibit the breakdown of bradykinin and other kinins, and thus are unlikely to cause the persistent dry cough which commonly complicates ACE inhibitor therapy. They are therefore a useful alternative for patients who have to discontinue an ACE inhibitor because of persistent cough.

An angiotensin-II receptor antagonist may be used as an alternative to an ACE inhibitor in the management of heart failure (section 2.5.5) or diabetic nephropathy (section 6.1.5).

Cautions Angiotensin-II receptor antagonists should be used with caution in renal artery stenosis (see also Renal Effects under ACE Inhibitors, section 2.5.5.1). Monitoring of plasma-potassium concentration is advised, particularly in the elderly and in patients with renal impairment; lower initial doses may be appropriate in these patients. Angiotensin-II receptor antagonists should be used with caution in aortic or mitral valve stenosis and in hypertrophic cardiomyopathy. Those with primary aldosteronism, and Afro-Caribbean patients (particularly those with left ventricular hypertrophy), may not benefit from an angiotensin-II receptor antagonist. Interactions: Appendix 1 (angiotensin-II receptor antagonists).

Contra-indications Angiotensin-II receptor antagonists, like the ACE inhibitors, should also be avoided in pregnancy (Appendix 4) and breast-feeding (Appendix 5).

Side-effects Side-effects are usually mild. Symptomatic hypotension including dizziness may occur, particularly in patients with intravascular volume depletion (e.g. those taking high-dose diuretics). Hyperkalaemia occurs occasionally; angioedema has also been reported with some angiotensin-II receptor antagonists.

Candesartan Cilexetil

Indications hypertension; heart failure with impaired left ventricular systolic function in conjunction with an ACE inhibitor, or when ACE inhibitors are not tolerated (see also section 2.5.5)

Cautions see notes above; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

Contra-indications see notes above; also cholestasis

Side-effects see notes above; also vertigo, headache; very rarely nausea, hepatitis, blood disorders, hypotension, back pain, arthralgia, myalgia, rash, urticaria, pruritus

Dose

- Hypertension, initially 8 mg (hepatic impairment 2 mg, renal impairment or intravascular volume depletion 4 mg) once daily, increased if necessary at intervals of 4 weeks to max. 32 mg once daily; usual maintenance dose 8 mg once daily
- Heart failure, initially 4 mg once daily, increased at intervals of at least 2 weeks to 'target' dose of 32 mg once daily or to max. tolerated dose

Amias (Takeda) 

Tablets, candesartan cilexetil 2 mg (white), net price 7-tab pack = £2.99; 4 mg (white, scored), 7-tab pack = £3.24, 28-tab pack = £8.15; 8 mg (pink, scored), 28-tab pack = £9.89; 16 mg (pink, scored), 28-tab pack = £12.72; 32 mg (pink, scored), 28-tab pack = £16.13

Eprosartan

Indications hypertension (see also notes above)

Cautions see notes above; also hepatic impairment (Appendix 2); renal impairment (Appendix 3)

Contra-indications see notes above

Side-effects see notes above; also flatulence, hypertriglyceridaemia, arthralgia, rhinitis; rarely headache, asthma, anaemia, hypersensitivity reactions (including rash, pruritus, urticaria); very rarely nausea

Dose

- 600 mg once daily (elderly over 75 years, mild to moderate hepatic impairment, renal impairment, initially 300 mg once daily); if necessary increased after 2–3 weeks to 800 mg once daily

Teveten (Solvay) 

Tablets, 1.25 mg, eprosartan (as mesilate) 300 mg (white), net price 28-tab pack = £11.63; 400 mg (pink), 56-tab pack = £15.77; 600 mg (white), 28-tab pack = £14.31. Label: 21
IRBESARTAN

**Indications** hypertension; renal disease in hypertensive type 2 diabetes mellitus (see also notes above)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; also nausea, vomiting; fatigue; musculoskeletal pain; less commonly diarrhoea, dyspepsia, flushing, tachycardia, chest pain, cough, and sexual dysfunction; rarely rash, urticaria; very rarely headache, myalgia, arthralgia, tinnitus, taste disturbance, hepatitis, renal dysfunction, and cutaneous vasculitis

**Dose**

- Hypertension, initially 150 mg once daily, increased if necessary to 300 mg once daily (in haemodialysis or in ELDERLY over 75 years, initial dose of 75 mg once daily may be used); CHILD not recommended
- Renal disease in hypertensive type 2 diabetes mellitus, initially 150 mg once daily, increased to 300 mg once daily if tolerated (in haemodialysis or in ELDERLY over 75 years, consider initial dose of 75 mg once daily); CHILD not recommended

**CoAprovel** (Bristol-Myers Squibb, Sanofi-Synthelabo) (A)

Tablets, f/c, irbesartan 75 mg, net price 28-tab pack = £10.29; 150 mg, 28-tab pack = £12.57; 300 mg, 28-tab pack = £16.91

**With diuretic**

**Note** For hypertension not adequately controlled with irbesartan alone. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1

**OLMESARTAN MEDOXOMIL**

**Indications** hypertension (see also notes above)

**Cautions** see notes above; hepatic impairment (avoid in severe impairment; Appendix 2); renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3)

**Contra-indications** see notes above; biliary obstruction

**Side-effects** see notes above; also gastro-intestinal disturbances; chest pain, peripheral oedema, hypertriglyceridaemia; fatigue; influenza-like symptoms, cough, pharyngitis, rhinitis; urinary-tract infection; haematuria, hyperuricaemia; arthritis, musculoskeletal pain; less commonly angina, vertigo, rash; very rarely headache, thrombocytopenia, myalgia, pruritus, urticaria

**Dose**

- Initially 10 mg once daily; if necessary increased to 20 mg once daily; max. 40 mg daily

**Olmetec** (Sankyo) (A)

Tablets, f/c, olmesartan medoxomil 10 mg, net price 28-tab pack = £10.95; 20 mg, 28-tab pack = £12.95, 40 mg, 28-tab pack = £17.50

**With diuretic**

**Note** For hypertension not adequately controlled with olmesartan alone. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1

**TELMSARTAN**

**Indications** hypertension (see also notes above)

**Cautions** see notes above; hepatic impairment (Appendix 2); avoid in severe impairment; renal impairment (Appendix 3)

**Contra-indications** see notes above; biliary obstruction

**Side-effects** see notes above; also gastro-intestinal disturbances; chest pain; influenza-like symptoms including pharyngitis and sinusitis; urinary-tract infection; arthralgia, myalgia, back pain, leg cramps; eczema; less commonly dry mouth, flatulence, anxiety, vertigo, tendinitis-like symptoms, abnormal vision,
increased sweating; rarely bradycardia, tachycardia, dyspnoea, insomnia, depression, blood disorders, increase in uric acid, eosinophilia, rash, and pruritis; syncope and asthma also reported.

Dose

- Usually 40 mg once daily (but 20 mg may be sufficient), increased if necessary after at least 4 weeks, to max. 80 mg once daily.

Micardis® (Boehringer Ingelheim)  Tablets, telmisartan 20 mg, net price 28-tab pack = £9.25; 40 mg, 28-tab pack = £11.34; 80 mg, 28-tab pack = £14.18.

- For hypertension, usually 80 mg once daily (initially 40 mg once daily; see notes above; With diuretic.

Note For patients with hypertension not adequately controlled by telmisartan alone. For cautions, contra-indications, and side-effects of thiazides, see section 2.2.1.

Co-Diovan® (Novartis) Tablets 80/12.5, orange, f/c, valsartan 80 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £16.44.

- Tablets 160/12.5, red, f/c, valsartan 160 mg, hydrochlorothiazide 12.5 mg, net price 28-tab pack = £21.66.


2.5.5.3 Renin inhibitors

Renin inhibitors inhibit renin directly; renin converts angiotensinogen to angiotensin I. Aliskiren is licensed for the treatment of hypertension, either alone or in combination with other antihypertensives.

The Scottish Medicines Consortium (p. 3) has advised (December 2008) that aliskiren (Rasilez®) is not recommended for use within NHS Scotland for the treatment of essential hypertension.

ALISKIREN

Indications essential hypertension.

Cautions patients taking concomitant diuretics, on a low-sodium diet, or who are dehydrated (first doses may cause hypotension—initiate with care); renal artery stenosis; renal impairment (Appendix 3); monitor plasma-potassium concentration and renal function in renal impairment, diabetes mellitus, and heart failure; interactions: Appendix 1 (aliskiren).

Contra-indications pregnancy (Appendix 4); breastfeeding (Appendix 5).

Side-effects diarrhea; less commonly rash; rarely angioedema; anaemia and hyperkalaemia also reported.

Dose

- ADULT over 18 years, 150 mg once daily, increased if necessary to 300 mg once daily.

Rasilez® (Novartis) Tablets, f/c, aliskiren (as hemifumarate) 150 mg (pink), net price 28-tab pack = £19.80; 300 mg (red), net price 28-tab pack = £23.80. Label: 21.

2.6 Nitrates, calcium-channel blockers, and other antianginal drugs

2.6.1 Nitrates

2.6.2 Calcium-channel blockers

2.6.3 Other antianginal drugs

2.6.4 Peripheral vasodilators and related drugs

Nitrates, calcium-channel blockers, and potassium-channel activators have vasodilating effects. Vaso-
Angina

It is important to distinguish unstable angina from stable angina. Stable angina usually results from atherosclerotic plaques in the coronary arteries and is often precipitated by exertion and relieved by rest. Unstable angina is usually due to plaque rupture and is often characterised by new onset severe angina or sudden worsening of previously stable angina. Treatment of stable and unstable angina involves management of acute anginal pain, and long-term management to prevent angina attacks and to reduce the risk of cardiovascular events.

Stable angina

Acute attacks of stable angina should be managed with sublingual glyceryl trinitrate; sublingual glyceryl trinitrate can also be taken before performing activities that are known to bring on an attack. If attacks occur more than twice a week, regular drug therapy is required and should be introduced in a stepwise manner according to response.

Patients with mild or moderate stable angina should be given a beta-blocker (section 2.4). In those with left-ventricular dysfunction, beta-blocker treatment should be started at a very low dose and titrated very slowly over a period of weeks or months (section 2.5.5).

For those patients in whom beta-blockers are not tolerated or are contra-indicated, a long-acting nitrate (section 2.6.1) or a rate-limiting calcium-channel blocker (diltiazem or verapamil, section 2.6.2) can be used; in patients with left-ventricular dysfunction, diltiazem and verapamil are contra-indicated because heart failure may be precipitated (important: see p. 113); however, a long-acting dihyd rolepine calcium-channel blocker, such as amiodipine or felodipine, is suitable. Nicorandil or ivabradine (section 2.6.3) are alternatives.

When a single drug fails to control symptoms, combination treatment can be used. A calcium-channel blocker can be added to a beta-blocker, although combining verapamil with a beta-blocker should be avoided (see p. 118); combinations including diltiazem and a beta-blocker should be used with caution. Long-acting nitrates can also be used with a beta-blocker or a calcium-channel blocker, if appropriate. Combinations that include nicorandil can also be considered.

Patients should be referred to a specialist if a combination of two drugs fails to control symptoms. Revascularisation procedures may be appropriate.

Unstable angina

Unstable angina and non-ST-segment elevation myocardial infarction are managed similarly. The aims of management are to provide supportive care and pain relief during the acute attack and to prevent further cardiac events and death. For advice on the management of patients with ST-segment elevation acute myocardial infarction, see section 2.10.1.

Initial management Oxygen (section 3.6) should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hyperoxia should be avoided and particular care is required in patients with chronic obstructive Airways disease.

Nitrates (section 2.6.1) are used to relieve ischaemic pain. If sublingual glyceryl trinitrate is not effective, intravenous or buccal glyceryl trinitrate or intravenous isosorbide dinitrate is given. If pain continues, diamorphine (section 4.7.2) can be given by slow intravenous injection; an antiemetic such as metoclopramide should also be given (section 4.6).

Aspirin (chewed or dispersed in water) is given for its antiplatelet effect in a dose of 300 mg (section 2.9). If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel in a dose of 300 mg (section 2.9) and a low molecular weight heparin or fondaparinux (section 2.8.1), should also be given.

Patients without contra-indications should receive beta-blockers (section 2.4) which should be continued indefinitely. In patients without left ventricular dysfunction and in whom beta-blockers are inappropriate, diltiazem or verapamil can be given (section 2.6.2).

The glycoprotein IIb/IIIa inhibitors eptifibatide and tirofiban (section 2.9) are recommended (with aspirin and heparin) for unstable angina or for non-ST-segment elevation myocardial infarction in patients at a high risk of either myocardial infarction or death. Abciximab, eptifibatide, or tirofiban can also be used with aspirin and heparin in patients undergoing percutaneous coronary intervention, to reduce the immediate risk of vascular occlusion.

Revascularisation procedures are often appropriate for patients with unstable angina.

Long-term management

The need for long-term angina treatment or for coronary angiography should be assessed. Most patients will require standard angina treatment (see Stable angina) to prevent recurrence of symptoms.

Prevention of cardiovascular events

Patients with stable and unstable angina should be given advice and treatments to reduce their cardiovascular risk. The importance of life-style changes, especially stopping smoking, should be emphasised. Patients should take aspirin indefinitely in a dose of 75 mg daily. A combination of aspirin and clopidogrel is given for up to 12 months in patients with non-ST-segment elevation acute coronary syndromes (section 2.9). An ACE inhibitor (section 2.5.5.1) and a statin (section 2.12) should also be given.

2.6.1 Nitrates

Nitrates have a useful role in angina (for details on the management of stable angina, see section 2.6). Although they are potent coronary vasodilators, their principal benefit follows from a reduction in venous return which reduces left ventricular work. Unwanted effects such as flushing, headache, and postural hypotension may limit therapy, especially when angina is severe or when patients are unusually sensitive to the effects of nitrates. Sublingual glyceryl trinitrate is one of the most effective drugs for providing rapid symptomatic relief of
angina, but its effect lasts only for 20 to 30 minutes; the 300-microgram tablet is often appropriate when glyceryl trinitrate is first used. The aerosol spray provides an alternative method of rapid relief of symptoms for those who find difficulty in dissolving sublingual preparations. Duration of action may be prolonged by modified-release and transdermal preparations (but tolerance may develop, see below).

Isosorbide dinitrate is active sublingually and is a more stable preparation for those who only require nitrates infrequently. It is also effective by mouth for prophylaxis; although the effect is slower in onset, it may persist for several hours. Duration of action of up to 12 hours is claimed for modified-release preparations. The activity of isosorbide dinitrate may depend on the production of active metabolites, the most important of which is isosorbide mononitrate. Isosorbide mononitrate itself is also licensed for angina prophylaxis; modified-release formulations (for once daily administration) are available. Glyceryl trinitrate or isosorbide dinitrate may be tried by intravenous injection when the sublingual form is ineffective in patients with chest pain due to myocardial infarction or severe ischaemia. Intravenous injections are also useful in the treatment of acute left ventricular failure.

Tolerance Many patients on long-acting or transdermal nitrates rapidly develop tolerance (with reduced therapeutic effects). Reduction of blood-nitrate concentrations to low levels for 4 to 8 hours each day usually maintains effectiveness in such patients. If tolerance is suspected during the use of transdermal patches they should be left off for several consecutive hours in each 24 hours; in the case of modified-release tablets of isosorbide dinitrate (and conventional formulations of isosorbide mononitrate), the second of the two daily doses should be given after about 8 hours rather than after 12 hours. Conventional formulations of isosorbide mononitrate should not usually be given more than twice daily unless small doses are used; modified-release formulations of isosorbide mononitrate should only be given once daily, and used in this way do not produce tolerance.

GLYCERYL TRINITRATE

Indications prophylaxis and treatment of angina; left ventricular failure; anal fissure (section 1.7.4); extra-sascular (section 10.3)

Cautions hypothyroidism, malnutrition, hypothermia; head trauma, cerebral haemorrhage; recent history of myocardial infarction; hypoxaemia or other ventilation and perfusion abnormalities; susceptibility to angle-closure glaucoma; metal-containing transdermal systems should be removed before cardioversion or diathermy; avoid abrupt withdrawal; tolerance (see notes above); severe hepatic impairment; severe renal impairment; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (nitrates)

Contra-indications hypersensitivity to nitrates; hypotensive conditions and hypovolaemia; hypertrophic cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia

Side-effects postural hypotension, tachycardia (but paradoxical bradycardia also reported); throbbing headache, dizziness; less commonly nausea, vomiting, heartburn; flushing; temporary hypoxaemia; rash; application site reactions with transdermal patches; very rarely angle-closure glaucoma

Injection Specific side-effects following injection (particularly if given too rapidly) include severe hypotension, dia phoresis, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, abdominal pain, syncope; prolonged administration has been associated with methaemoglobinemia

Dose • Sublingually, 0.3–1 mg, repeated as required • By intravenous infusion, 10–200 micrograms/minute • By transdermal application, see under preparations

Short-acting tablets and sprays

Glyceryl Trinitrate (Non-proprietary)

Sublingual tablets, glyceryl trinitrate 300 micro- grammes, net price 100 = £2.71; 500 micrograms, 100 = £2.84; 600 micrograms, 100 = £3.13. Label: 16

Note Glyceryl trinitrate tablets should be supplied in glass containers of not more than 100 tablets, closed with a foil-lined cap, and containing no cotton wool wadding; they should be discarded after 8 weeks in use

Aerosol spray, glyceryl trinitrate 400 micrograms/ metered dose, net price 200-dose unit = £3.13

Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Coro-Nitro Pump Spray® (Ayrton Saunders)

Aerosol spray, glyceryl trinitrate 400 micrograms/ metered dose, net price 200-dose unit = £3.13

Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Glytrin Spray® (Sanofi-Synthelabo)

Aerosol spray, glyceryl trinitrate 400 micrograms/ metered dose, net price 200-dose unit = £3.49

Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Cautions flammable

GTN 300 mcg (Martindale)

Sublingual tablets, glyceryl trinitrate 300 micro- grammes, net price 100 = £2.71. Label: 16

Nitrolingual Pumpspray® (Merck)

Aerosol spray, glyceryl trinitrate 400 micrograms/ metered dose, net price 200-dose unit = £3.65

Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Nitromin® (Egis)

Aerosol spray, glyceryl trinitrate 400 micrograms/ metered dose, net price 180-dose unit = £2.63, 200- dose unit = £2.82

Dose treatment or prophylaxis of angina, spray 1–2 doses under tongue and then close mouth

Longer-acting tablets

Suscard® (Forest)

Buccal tablets, m/r, glyceryl trinitrate 2 mg, net price 100-tab pack = £12.70; 3 mg, 100-tab pack = £18.33; 5 mg, 100-tab pack = £24.96. Counselling, see below

Dose treatment of angina, 2 mg as required, increased to 3 mg if necessary; prophylaxis 2–3 mg 3 times daily, 5 mg in severe angina

Unstable angina (adjunct), up to 5 mg with ECG monitoring

Congestive heart failure, 5 mg 3 times daily, increased to 10 mg 3 times daily in severe cases

Acute heart failure, 5 mg repeated until symptoms abate

Counselling Tablets have rapid onset of effect; they are placed between upper lip and gum, and left to dissolve; vary site to reduce risk of dental caries
Parenteral preparations

**Note** Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used.

**Glyceryl Trinitrate** (Non-proprietary) (\(\text{\textregistered}\))

Injection, glyceryl trinitrate 5 mg/mL. To be diluted before use. Net price 5-mL amp = £6.49; 10-mL amp = £12.98

Excipients may include ethanol, propylene glycol (see Excipients, p. 2)

**Nitroine** (UCB Pharma) (\(\text{\textregistered}\))

Injection, glyceryl trinitrate 1 mg/mL. To be diluted before use or given undiluted with syringe pump. Net price 10-mL amp = £7.34; 50-mL bottle = £17.21

Excipients include propylene glycol (see Excipients, p. 2)

**Nitronal** (Merck) (\(\text{\textregistered}\))

Injection, glyceryl trinitrate 5 mg/mL. To be diluted before use or given undiluted with syringe pump. Net price 5-mL vial = £1.92; 50-mL vial = £15.67

Transdermal preparations

**Deponit** (UCB Pharma)

Patches, self-adhesive, transparent, glyceryl trinitrate, ‘5’ patch (releasing approx. 5 mg/24 hours when in contact with skin), net price 28 = £15.96; ‘10’ patch (releasing approx. 10 mg/24 hours), 28 = £17.57

Dose prophylaxis of angina, apply one ‘5’ or one ‘10’ patch to lateral chest wall, upper arm, thigh, abdomen, or shoulder; increase to two ‘10’ patches every 24 hours if necessary; replace every 24 hours, siting replacement patch on different area; see also notes above (Tolerance)

**Minitran** (3M)

Patches, self-adhesive, transparent, glyceryl trinitrate, ‘5’ patch (releasing approx. 5 mg/24 hours when in contact with skin), net price 30 = £11.62; ‘10’ patch (releasing approx. 10 mg/24 hours), 30 = £12.87; ‘15’ patch (releasing approx. 15 mg/24 hours), 30 = £14.19

Dose prophylaxis of angina, apply one ‘5’ patch to chest or upper arm, replace every 24 hours, siting replacement patch on different area; adjust dose according to response; see also notes above (Tolerance)

Maintenance of venous potency (‘5’ patch only), consult product literature

**Nitro-Dur** (Schering-Plough)

Patches, self-adhesive, buff, glyceryl trinitrate, ‘0.2 mg/h’ patch (releasing approx. 5 mg/24 hours when in contact with skin), net price 28 = £11.01; ‘0.4 mg/h’ patch (releasing approx. 10 mg/24 hours), 28 = £12.18; ‘0.6 mg/h’ patch (releasing approx. 15 mg/24 hours), 28 = £13.41

Dose prophylaxis of angina, apply one ‘0.2 mg/h’ patch to chest or outer upper arm, replace every 24 hours, siting replacement patch on different area; adjust dose according to response; see also notes above (Tolerance)

**Carmicin** (Novartis)

Ointment, glyceryl trinitrate 2%, net price 60 g = £9.55. Counselling, see administration below

Excipients include w/o fat

Dose prophylaxis of angina, usual dose 1–2 inches of ointment measured on to Applicule, and applied (usually to chest, arm, or thigh) without rubbing in and secured with surgical tape, every 3–4 hours as required; to determine dose, ½ inch on first day then increased by ½ inch/day until headache occurs, then reduced by ½ inch

Note Approx. 800 micrograms/hour absorbed from 1 inch of ointment

Transderm-Nitro (Novartis)

Patches, self-adhesive, pink, glyceryl trinitrate, ‘5’ patch (releasing approx. 5 mg/24 hours when in contact with skin), net price 28 = £21.31; ‘10’ patch (releasing approx. 10 mg/24 hours), 28 = £23.43

**Trintek** (Goldshield)

Patches, self-adhesive, glyceryl trinitrate, ‘5’ patch (releasing approx. 5 mg/24 hours when in contact with skin), net price 30 = £11.84; ‘10’ patch (releasing approx. 10 mg/24 hours), net price 30 = £13.10; ‘15’ patch (releasing approx. 15 mg/24 hours), net price 30 = £14.42

Dose prophylaxis of angina, apply one ‘5’ patch to lateral chest wall; replace every 24 hours, siting replacement patch on different area; adjust dose according to response, max one ‘15’ patch daily; see also notes above (Tolerance)

ISOSORBIDE DINITRATE

**Indications** prophylaxis and treatment of angina; left ventricular failure

**Cautions** see under Glyceryl Trinitrate

**Contra-indications** see under Glyceryl Trinitrate

**Side-effects** see under Glyceryl Trinitrate

**Dose**

- **By mouth**, daily in divided doses, angina 30–120 mg, left ventricular failure 40–160 mg, up to 240 mg if required
- **By intravenous infusion**, 2–10 mg/hour; higher doses up to 20 mg/hour may be required

**Short-acting tablets and sprays**

**Isosorbide Dinitrate** (Non-proprietary)

Tablets, isosorbide dinitrate 10 mg, net price 56-tab pack = £9.30; 20 mg, net price 56-tab pack = £11.49

**Angitak** (LPC)

Aerosol spray, isosorbide dinitrate 1.25 mg/metered dose, net price 200-dose unit = £3.95

**Dose** treatment or prophylaxis of angina, spray 1–3 doses under tongue whilst holding breath; allow 30 second interval between each dose

**Modified-release preparations**

**Cedocard Retard** (Pharmacia)

Retard-20 tablets, m/r, yellow, scored, isosorbide dinitrate 20 mg, net price 60-tab pack = £6.85. Label: 25

Dose prophylaxis of angina, 1 tablet every 12 hours

**Retard-40 tablets, m/r, scored, isosorbide dinitrate 40 mg, net price 60-tab pack = £13.31. Label: 25

Dose prophylaxis of angina, 1–2 tablets every 12 hours

**Isoket Retard** (UCB Pharma)

Retard-20 tablets, m/r, scored, isosorbide dinitrate 20 mg, net price 56-tab pack = £3.23. Label: 25

Dose prophylaxis of angina, 30–120 mg daily

**Retard-40 tablets, m/r, scored, isosorbide dinitrate 40 mg, net price 56-tab pack = £7.95. Label: 25

Dose prophylaxis of angina, 40 mg daily in 1–2 divided doses, increased if necessary to 60–80 mg daily in 2–3 divided doses

**Parenteral preparations**

**Isoket** (UCB Pharma) (\(\text{\textregistered}\))

Injection 0.05%, isosorbide dinitrate 500 micrograms/mL. To be diluted before use or given undi-
luted with syringe pump. Net price 50-mL bottle = £8.94

Injection 0.1%, isosorbide dinitrate 1 mg/mL. To be diluted before use. Net price 10-mL amp = £3.37; 50-mL bottle = £16.70; 100-mL bottle = £25.98

Note Glass or polyethylene infusion apparatus is preferable. Loss of potency if PVC used

ISOSORBIDE MONONITRATE

Indications prophylaxis of angina; adjunct in congestive heart failure

Cautions see under Glyceryl Trinitrate

Contra-indications see under Glyceryl Trinitrate

Side-effects see under Glyceryl Trinitrate

Dose

• Initially 20 mg 2–3 times daily or 40 mg twice daily (10 mg twice daily in those who have not previously received nitrates); up to 120 mg daily in divided doses if required

Isosorbide Mononitrate (Non-proprietary)

Tablets, isosorbide mononitrate 10 mg, net price = £1.02; 20 mg, 56 = £1.05; 40 mg, 56 = £1.51. Label: 25

Brands include Angeze

Elantan® (UCB Pharma)

Elantan 10 tablets, scored, isosorbide mononitrate 10 mg, net price 56-tab pack = £3.31; 84-tab pack = £4.97. Label: 25

Elantan 20 tablets, scored, isosorbide mononitrate 20 mg, net price 56-tab pack = £4.32; 84-tab pack = £6.13. Label: 25

Elantan 40 tablets, scored, isosorbide mononitrate 40 mg, net price 56-tab pack = £7.03; 84-tab pack = £10.56. Label: 25

Ismo® (Riemser)

Ismo 10 tablets, isosorbide mononitrate 10 mg, net price 60-tab pack = £3.31. Label: 25

Ismo 20 tablets, scored, isosorbide mononitrate 20 mg, net price 60-tab pack = £4.85. Label: 25

Chemydur® 60XL (Sovereign)

Tablets, m/r, scored, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £5.99. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet for 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets

Elantan LA® (UCB Pharma)

Elantan LA 25 capsules, m/r, brown/white, enclosing white micropellets, isosorbide mononitrate 25 mg, net price 28-cap pack = £6.59. Label: 25

Dose prophylaxis of angina, 1 capsule in the morning, increased if necessary to 2 capsules

Elantan LA 50 capsules, m/r, brown/pink, enclosing white micropellets, isosorbide mononitrate 50 mg, net price 28-cap pack = £10.54. Label: 25

Dose prophylaxis of angina, 1 capsule daily in the morning, increased if necessary to 2 capsules

Imdur® (AstraZeneca)

Duana® (= tablets m/r), yellow, f/c, scored, isosorbide mononitrate 60 mg, net price 28-tab pack = £11.14. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet if headache occurs), increased to 2 tablets in the morning if required

Isib 60XL® (Ranbaxy)

Tablets, m/r, scored, yellow, isosorbide mononitrate 60 mg, net price 28-tab pack = £8.15. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet for 2–4 days if headache occurs), increased if necessary to 2 tablets

Ismo Retard® (Riemser)

Tablets, m/r, s/c, isosorbide mononitrate 40 mg, net price 30-tab pack = £10.71. Label: 25

Dose prophylaxis of angina, 1 tablet daily in morning

Isodur® (Galen)

Isodur 25XL capsules, m/r, brown/white, isosorbide mononitrate 25 mg, net price 28-cap pack = £5.63. Label: 25

Isodur 50XL capsules, m/r, brown/pink, isosorbide mononitrate 50 mg, net price 28-cap pack = £9.07. Label: 25

Dose prophylaxis of angina, 25–50 mg daily in the morning, increased if necessary to 50–100 mg once daily

Isodur® (ProStrakan)

Isodur 25XL tablets, m/r, ivory, isosorbide mononitrate 25 mg, net price 28-tab pack = £6.95. Label: 25

Isodur 40XL tablets, m/r, ivory, isosorbide mononitrate 40 mg, net price 28-tab pack = £6.78. Label: 25

Isodur 50XL tablets, m/r, ivory, isosorbide mononitrate 50 mg, net price 28-tab pack = £6.78. Label: 25

Isodur 60XL tablets, m/r, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £6.78. Label: 25

Dose prophylaxis of angina, 25–60 mg daily in the morning (if headache occurs with 60-mg tablet, half a 60-mg tablet may be given for 2–4 days), increased if necessary to 50–120 mg daily

Modisal LA® (UCB Pharma)

Modisal LA25 capsules, m/r, brown/white, isosorbide mononitrate 25 mg, net price 28-cap pack = £6.22. Label: 25

Modisal LA50 capsules, m/r, brown/peach, isosorbide mononitrate 50 mg, net price 28-cap pack = £10.03. Label: 25

Dose prophylaxis of angina, 25–50 mg daily in the morning, increased if necessary to 100 mg once daily

Modisal XL® (Sanofi)

Tablets, m/r, ivory, isosorbide mononitrate 60 mg, net price 28-tab pack = £10.36. Label: 25

Dose prophylaxis of angina, 1 tablet daily in the morning (half a tablet for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets once daily

Monomax® (Trinity-Chiesi)

Monomax® SR, capsules, m/r, isosorbide mononitrate 40 mg, net price 28-cap pack = £8.31; 60 mg, 28-cap pack = £9.03. Label: 25

Dose prophylaxis of angina, 40–60 mg daily in the morning, increased if necessary to 120 mg daily

Note Also available as Angeze SR

Monomax® XL tablets, m/r, isosorbide mononitrate 60 mg, net price 28-tab pack = £6.75. Label: 25

Dose prophylaxis of angina, 1 tablet in the morning (half a tablet for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets

Monomil XL® (IVAX)

Tablets, m/r, isosorbide mononitrate 60 mg, net price 28-tab pack = £4.50. Label: 25

Dose prophylaxis of angina, 1 tablet daily in the morning (half a tablet daily for first 2–4 days to minimise possibility of headache), increased if necessary to 2 tablets once daily
Monogen XL 60 © (Neolab)  
Zemon 60XL tablets, m/r, t/c, isosorbide mononitrate 60 mg, net price 28-tab pack = £11.14. Label: 25
Zemon 40XL tablets, m/r, t/c, isosorbide mononitrate 40 mg, net price 28-tab pack = £14.25. Label: 25

2.6.2 Calcium-channel blockers

Calcium-channel blockers (less correctly called ‘calcium-antagonists’) interfere with the inward displacement of calcium ions through the slow channels of active cell membranes. They influence the myocardial cells, the cells within the specialised conducting system of the heart, and the cells of vascular smooth muscle. Thus, myocardial contractility may be reduced, the formation and propagation of electrical impulses within the heart may be depressed, and coronary or systemic vascular tone may be diminished.

Calcium-channel blockers differ in their predilection for the various possible sites of action and, therefore, their therapeutic effects are disparate, with much greater variation than those of beta-blockers. There are important differences between verapamil, diltiazem, and the dihydropyridine calcium-channel blockers (amlodipine, felodipine, isradipine, lacidipine, nicardipine, nifedipine, and nimodipine). Verapamil and diltiazem should usually be avoided in heart failure because they may further depress cardiac function and cause clinically significant deterioration.

Verapamil is used for the treatment of angina (section 2.6), hypertension (section 2.5), and arrhythmias (section 2.3.2). It is a highly negatively inotropic calcium channel-blocker and it reduces cardiac output, slows the heart rate, and may impair atrioventricular conduction. It may precipitate heart failure, exacerbate conduction disorders, and cause hypotension at high doses and should not be used with beta-blockers (see p. 118). Constipation is the most common side-effect.

Nifedipine relaxes vascular smooth muscle and dilates coronary and peripheral arteries. It has more influence on vessels and less on the myocardium than does verapamil, and unlike verapamil has no anti-arrhythmic activity. It rarely precipitates heart failure because any negative inotropic effect is offset by a reduction in left ventricular work. Short-acting formulations of nifedipine are not recommended for angina or long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia. Nicardipine has similar effects to those of nifedipine and may produce less reduction of myocardial contractility. Amlodipine and felodipine also resemble nifedipine and nicardipine in their effects and do not reduce myocardial contractility and they do not produce clinical deterioration in heart failure. They have a longer duration of action and can be given once daily. Nifedipine, nicardipine, amlodipine, and felodipine are used for the treatment of angina (section 2.6) or hypertension. All are valuable in forms of angina associated with coronary vasospasm. Side-effects associated with vasodilatation such as flushing and headache (which become less obtrusive after a few days), and ankle swelling (which may respond only partially to diuretics) are common.

Isradipine, lacidipine, and lercanidipine have similar effects to those of nifedipine and nicardipidine; they are indicated for hypertension only.

Nimodipine is related to nifedipine but the smooth muscle relaxant effect preferentially acts on cerebral arteries. Its use is confined to prevention and treatment of vascular spasm following aneurysmal subarachnoid haemorrhage.

Diltiazem is effective in most forms of angina (section 2.6); the longer-acting formulation is also used for hypertension. It may be used in patients for whom beta-blockers are contra-indicated or ineffective. It has a less negative inotropic effect than verapamil and significant myocardial depression occurs rarely. Nevertheless because of the risk of bradycardia it should be used with caution in association with beta-blockers.

Unstable angina Calcium-channel blockers do not reduce the risk of myocardial infarction in unstable angina. The use of diltiazem or verapamil should be reserved for patients resistant to treatment with beta-blockers.

Withdrawal There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of angina.

AMLODIPINE

Indications hypertension, prophylaxis of angina
Cautions hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (calcium-channel blockers)

Contra-indications cardiogenic shock, unstable angina, significant aortic stenosis: acute porphyria (section 9.8.2); breast-feeding (Appendix 5)

Side-effects abdominal pain, nausea; palpitation, flushing, oedema; headache, dizziness, sleep disturbances, fatigue; less commonly gastrointestinal disturbances, dry mouth, taste disturbances, hypotension, syncope, chest pain, dyspnoea, rhinitis, mood changes, asthenia, tremor, paraesthesia, urinary disturbances, impotence, gynaecomastia, weight changes, myalgia, muscle cramps, back pain, arthralgia, visual disturbances, tinnitus, purpura, and skin discoloration; very rarely gastritis, pancreatitis, hepatitis, jaundice, cholestasis, gingival hyperplasia, myocardial infarction, arrhythmias, tachycardia, vasculitis, coughing, peripheral neuropathy, hyperglycaemia, thrombocytopenia, angioedema, and urticaria
Diltiazem hydrochloride

**Indications**
Prophylaxis and treatment of angina; hypertension

**Cautions**
Reduce dose in hepatic and renal impairment; heart failure or significantly impaired left ventricular function, bradycardia (avoid if severe), first degree AV block, or prolonged PR interval, interactions: Appendix 1 (calcium-channel blockers)

**Contra-indications**
Severe bradycardia, left ventricular failure with pulmonary congestion, third-degree AV block (unless pacemaker fitted), sick sinus syndrome; acute porphyria (but see section 9.8.2); pregnancy; breast-feeding (Appendix 5)

**Side-effects**
Bradycardia, sino-atrial block, AV block, palpitation, dizziness, hypotension, malaise, asthenia, headache, hot flushes, gastro-intestinal disturbances, oedema (notably of ankles); rarely rashes (including erythema multiforme and exfoliative dermatitis), photosensitivity; hepatitis, gynaecomastia, gum hyperplasia, extrapyramidal symptoms, depression reported

**Dose**
- Angina, 60 mg 3 times daily (elderly initially twice daily); increased if necessary to 360 mg daily
- Longer-acting formulations, see under preparations below

**Standard formulations**
- Tablets, m/r (see note above), diltiazem hydrochloride 60 mg, net price 84 = £3.34. Label: 25
- Brains include: Optil

**Diltiazem**

**Indications**
- Angina, initially 90 mg twice daily (elderly, dose form not appropriate for initial dose titration); increased to 120 mg or 180 mg twice daily (dose form not appropriate for initial dose titration), increased if necessary to 300 mg once daily in elderly and in hepatic or renal impairment, initially 120 mg daily
- Angina, initially 90 mg twice daily; increased if necessary to 240 mg once daily
- Angina, initially 90 mg twice daily (elderly, dose form not appropriate for initial dose titration), increased if necessary to 180 mg twice daily if required

**Longer-acting formulations**
- Note Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of diltiazem, prescribers should specify the brand to be dispensed

**Adizem®**

**Capsules**
- Capsules, m/r, diltiazem hydrochloride 90 mg (white), net price 56-cap pack = £7.86; 120 mg (brown), 56-cap pack = £8.73; 180 mg (brown), 56-cap pack = £9.66. Label: 25

**Calcicard®**

**Tablets**
- Tablets, m/r, diltiazem hydrochloride 90 mg, net price 56-tab pack = £6.33; 120 mg, 56-tab pack = £7.04. Label: 25

**Dicardia®**

**Capsules**
- Capsules, m/r, diltiazem hydrochloride 60 mg (pink/white), net price 56-cap pack = £8.31; 90 mg (pink/yellow), 56-cap pack = £10.33; 120 mg (pink/orange), 56-cap pack = £11.49. Label: 25

**Diltiazem SR®**

**Capsules**
- Capsules, m/r, diltiazem hydrochloride 120 mg (pink/blue), net price 28-cap pack = £9.66; 180 mg (dark pink/blue), 28-cap pack = £10.96; 200 mg (brown), 28-cap pack = £6.66; 240 mg (red/blue), 28-cap pack = £12.17; 300 mg (maroon/blue), 28-cap pack = £9.66. Label: 25
Dilzem SR® (Cephalon) *(NH)*  
**Capsules**, m/r, all beige, diltiazem hydrochloride 60 mg, net price 56-cap pack = £6.40; 90 mg, 56-cap pack = £9.59; 120 mg, 56-cap pack = £10.95. Label: 25  
**Dose** angina and mild to moderate hypertension, initially 90 mg twice daily (elderly 60 mg twice daily); up to 180 mg twice daily may be required

Dilzem XL® (Cephalon) *(NH)*  
**Capsules**, m/r, diltiazem hydrochloride 120 mg, net price 28-cap pack = £6.61; 180 mg, 28-cap pack = £9.81; 240 mg, 28-cap pack = £11.70. Label: 25  
**Dose** angina and mild to moderate hypertension, initially 180 mg once daily (elderly and in hepatic and renal impairment, 120 mg once daily); if necessary may be increased to 360 mg once daily

Sllozem® (Merck) *(NH)*  
**Capsules**, m/r, diltiazem hydrochloride 120 mg (pink/clear), net price 28-cap pack = £7.00; 180 mg (pink/clear), 28-cap pack = £7.80; 240 mg (red/clear), 28-cap pack = £8.20; 300 mg (red/white), 28-cap pack = £8.50. Label: 25  
**Dose** angina and mild to moderate hypertension, initially 240 mg once daily (elderly and in hepatic and renal impairment, 120 mg once daily); if necessary may be increased to 360 mg once daily

Tildiem LA® (Sanofi-Synthelabo) *(NH)*  
**Capsules**, m/r, diltiazem hydrochloride 200 mg (pink/grey, containing white pellets), net price 28-cap pack = £6.66; 300 mg (white/yellow, containing white pellets), 28-cap pack = £7.51. Label: 25  
**Dose** angina and mild to moderate hypertension, initially 200 mg once daily before or with food, increased if necessary to 300–400 mg daily, max. 500 mg daily; **ELDERLY** and in hepatic or renal impairment, initially 200 mg daily, increased if necessary to 300 mg daily

Tildiem Retard® (Sanofi-Synthelabo) *(NH)*  
**Tablets**, m/r, diltiazem hydrochloride 90 mg, net price 56-tab pack = £8.55; 120 mg, 56-tab pack = £9.53. Label: 25  
**Counselling** Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy  
**Dose** mild to moderate hypertension, initially 90 mg or 120 mg twice daily; increased if necessary to 360 mg daily in divided doses; **ELDERLY** in hepatic or renal impairment, initially 120 mg once daily; increased if necessary to 10 mg once daily

Viazem XL® (Genus) *(NH)*  
**Capsules**, m/r, diltiazem hydrochloride 120 mg (lavender), net price 28-cap pack = £6.60; 180 mg (white/blue-green), 28-cap pack = £7.36; 240 mg (blue-green/lavender), 28-cap pack = £7.74; 300 mg (white/lavender), 28-cap pack = £8.03; 360 mg (blue-green), 28-cap pack = £14.70. Label: 25  
**Dose** angina and mild to moderate hypertension, initially 180 mg once daily; adjusted according to response to 240 mg once daily; max. 360 mg once daily; **ELDERLY** in hepatic or renal impairment, initially 120 mg once daily, adjusted according to response

Zemtard® (Galen) *(NH)*  
**Zemtard 300XL capsules**, m/r, white/blue, diltiazem hydrochloride 300 mg, net price 28-cap pack = £7.45. Label: 25  
**Dose** angina and mild to moderate hypertension, 180–300 mg once daily, increased if necessary to 360 mg once daily in hypertension and to 480 mg once daily in angina; **ELDERLY** and in hepatic or renal impairment, initially 120 mg once daily

### FELODIPINE

**Indications** hypertension, prophylaxis of angina  
**Cautions** withdraw if ischaemic pain occurs or existing pain worsens shortly after initiating treatment or if cardiogenic shock develops; severe left ventricular dysfunction; avoid grapefruit juice (may affect metabolism); reduce dose in hepatic impairment; breast-feeding (Appendix 5); **interactions**: Appendix 1 (calcium-channel blockers)  
**Contra-indications** unstable angina, uncontrolled heart failure; significant aortic stenosis; within 1 month of myocardial infarction; acute porphyria (section 9.8.2); pregnancy (Appendix 4)  
**Side-effects** flushing, headache, palpitation, dizziness, fatigue, gravitational oedema; rarely rash, pruritus, cutaneous vasculitis, gum hyperplasia, urinary frequency, impotence, fever  
**Dose**  
- Hypertension, initially 5 mg (elderly 2.5 mg) daily in the morning; usual maintenance 5–10 mg once daily; doses above 20 mg daily rarely needed  
- Angina, initially 5 mg daily in the morning, increased if necessary to 10 mg once daily

**Felodipine** (Non-proprietary) *(NH)*  
**Tablets**, m/r, felodipine 2.5 mg, net price 28-tab pack = £6.70; 5 mg, 28-tab pack = £8.93; 10 mg, 28-tab pack = £12.01, 30-tab pack = £12.87. Label: 25  
**Brands include** Cardioplén XL, Feloten XL, Keloc SR, Neofel XL, Parmid XL, Vasalupa  
**Plendil®** (AstraZeneca) *(NH)*  
**Tablets**, m/r, f/c, felodipine 2.5 mg (yellow), net price 28-tab pack = £6.70; 5 mg (pink), 28-tab pack = £4.47; 10 mg (brown), 28-tab pack = £6.01. Label: 25

### ISRADIPINE

**Indications** hypertension  
**Cautions** sick sinus syndrome (if pacemaker not fitted); avoid grapefruit juice (may affect metabolism); poor cardiac reserve; reduce dose in hepatic or renal impairment; pregnancy (Appendix 4); **interactions**: Appendix 1 (calcium-channel blockers)  
**Contra-indications** cardiogenic shock; symptoms of or mild left ventricular dysfunction; avoid grapefruit juice (may affect metabolism); reduce dose in hepatic impairment; breast-feeding (Appendix 5)  
**Side-effects** abdominal discomfort; tachycardia, palpitation, flushing, peripheral oedema; dyspnoea; headache, fatigue, dizziness; polyuria; rash; less commonly, hypotension, weight gain; very rarely vomiting, nausea, gum hyperplasia, anorexia, drowsiness, arthralgia, bradycardia, heart failure, cough, depression, paraesthesia, anxiety, erectile dysfunction, blood disorders (such as thrombocytopenia, leucopenia, anaemia), arthralgia, visual disturbance, hypersensitivity reactions; hepatitis and gynaecomastia also reported
Dose
- 2.5 mg twice daily, increased if necessary after 3–4 weeks to 5 mg twice daily (exceptionally up to 10 mg twice daily); **ELDERLY** (or in hepatic or renal impairment) 1.25 mg twice daily, increased if necessary after 3–4 weeks according to response, maintenance dose of 2.5 mg or 5 mg once daily may be sufficient

Prescal® (Novartis) [FAM]  
Tablets, yellow, scored, isradipine 2.5 mg, net price 56-tab pack = £16.54

**LACIDIPINE**

**Indications**  hypertension

**Cautions**  cardiac conduction abnormalities; poor cardiac reserve; avoid grapefruit juice (may affect metabolism); hepatic impairment (Appendix 2); **interactions:** Appendix 1 (calcium-channel blockers)

**Contra-indications**  cardiacogenic shock, unstable angina, aortic stenosis; avoid within 1 month of myocardial infarction; acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**  flushing, palpitation, oedema; headache, dizziness; rarely gastro-intestinal disturbances, gum hyperplasia, aggravation of angina, mood disturbances, asthenia, polyuria, muscle cramps, skin rash (including pruritus and erythema)

**Dose**  
- Initially 2 mg as a single daily dose, preferably in the morning; increased after 3–4 weeks to 4 mg daily, then if necessary to 6 mg daily

Motens® (Boehringer Ingelheim) [FAM]  
Tablets, both f/c, lacidipine 2 mg, net price 28-tab pack = £9.92; 4 mg (scored), 28-tab pack = £13.48

**LERCANIDIPINE HYDROCHLORIDE**

**Indications**  mild to moderate hypertension

**Cautions**  left ventricular dysfunction; sick sinus syndrome (if pacemaker not fitted); avoid grapefruit juice (may affect metabolism); hepatic impairment (Appendix 2); **interactions:** Appendix 1 (calcium-channel blockers)

**Contra-indications**  aortic stenosis; unstable angina, uncontrolled heart failure; within 1 month of myocardial infarction; renal impairment; acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**  flushing, peripheral oedema, palpitation, tachycardia, headache, dizziness, asthenia, also gastro-intestinal disturbances, hypotension, drowsiness, myalgia, polyuria, rash

**Dose**  
- Initially 10 mg once daily; increased, if necessary, after at least 2 weeks to 20 mg daily

Zanidip® (Recordati) [FAM]  
Tablets, f/c, lercanidipine hydrochloride 10 mg (yellow), net price 28-tab pack = £5.80; 20 mg (pink), 28-tab pack = £11.00. Label: 22

**NICARDIPINE HYDROCHLORIDE**

**Indications**  prophylaxis of angina; mild to moderate hypertension

**Cautions**  withdraw if ischaemic pain occurs or existing pain worsens within 30 minutes of initiating treatment or increasing dose; congestive heart failure or significantly impaired left ventricular function; elderly; avoid grapefruit juice (may affect metabolism); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); **interactions:** Appendix 1 (calcium-channel blockers)

**Contra-indications**  cardiogenic shock; advanced aortic stenosis; unstable or acute attacks of angina; avoid within 1 month of myocardial infarction; acute porphyria (section 9.8.2); breast-feeding (Appendix 5)

**Side-effects**  dizziness, headache, peripheral oedema, flushing, palpitation, nausea; also gastro-intestinal disturbances, drowsiness, insomnia, tinnitus, hypertension, rash, dyspnoea, paraesthesia, frequency of micturition; thrombocytopenia, depression and impotence reported

**Dose**  
- Initially 20 mg 3 times daily, increased, after at least three days, to 30 mg 3 times daily (usual range 60–120 mg daily)

Nicardipine (Non-proprietary) [FAM]  
Capsules, nicardipine hydrochloride 20 mg, net price 56-cap pack = £3.09; 30 mg, 56-cap pack = £4.93

Cardene® (Astellas) [FAM]  
Capsules, nicardipine hydrochloride 20 mg (blue/white), net price 56-cap pack = £8.57; 30 mg (blue/pale blue), 56-cap pack = £9.95

**Modified release**

Cardene SR® (Astellas) [FAM]  
Capsules, m/r, nicardipine hydrochloride 30 mg, net price 56-cap pack = £10.21; 45 mg (blue), 56-cap pack = £14.86. Label: 25  
**Dose**  mild to moderate hypertension, initially 30 mg twice daily; usual effective dose 45 mg twice daily (range 30–60 mg twice daily)

**NIFEDIPINE**

**Indications**  prophylaxis of angina; hypertension; Raynaud’s phenomenon

**Cautions**  see notes above; also withdraw if ischaemic pain occurs or existing pain worsens shortly after initiating treatment; poor cardiac reserve; heart failure or significantly impaired left ventricular function (heart failure deterioration observed); severe hypotension; elderly; diabetes mellitus; hepatic impairment (Appendix 2); may inhibit labour; pregnancy (Appendix 4); breast-feeding (Appendix 5); avoid grapefruit juice (may affect metabolism); **interactions:** Appendix 1 (calcium-channel blockers)

**Contra-indications**  cardiogenic shock; advanced aortic stenosis; within 1 month of myocardial infarction; unstable or acute attacks of angina; acute porphyria (section 9.8.2)

**Side-effects**  gastro-intestinal disturbance; hypotension, oedema, vasodilatation, palpitation; headache, dizziness, lethargy, asthenia; rare anorexia, gum hyperplasia, mood disturbances, hyperglycaemia, male infertility, purpura, and photosensitivity reactions; also reported

**Dose**  
- Initially 30 mg twice daily; increased to 60 mg, then further increased if necessary

Cardene SR® (Astellas) [FAM]  
Capsules, nicardipine hydrochloride 30 mg, net price 56-cap pack = £3.09; 30 mg, 56-cap pack = £4.93
dysphagia, intestinal obstruction, intestinal ulcer, bezoar formation (with some modified-release preparations), gynaecomastia, agranulocytosis, and anaphylaxis

**Dose**

- See preparations below

**Nifedipine** (Non-proprietary)  
**Capsules**, nifedipine 5 mg, net price 84-cap pack = £2.84; 10 mg, 84-cap pack = £3.94  
**Dose** angina prophylaxis (but not recommended, see notes above) and Raynaud's phenomenon, initially 5 mg 3 times daily, adjusted according to response to 20 mg 3 times daily  
**Hypertension**, not recommended therefore no dose stated

**Adalat** (Bayer)  
**Capsules**, orange, nifedipine 5 mg, net price 90-cap pack = £6.08; 10 mg, 90-cap pack = £7.74  
**Dose** angina prophylaxis (but not recommended, see notes above) and Raynaud's phenomenon, initially 5 mg 3 times daily, adjusted according to response to max. 20 mg 3 times daily  
**Hypertension**, not recommended therefore no dose stated

**Modified release**

**Note** Different versions of modified-release preparations may not have the same clinical effect. To avoid confusion between these different formulations of nifedipine, prescribers should specify the brand to be dispensed. Modified-release formulations may not be suitable for dose titration in hepatic disease

**Adalat Retard** (Bayer)  
**LA 20 tablets**, m/r, t/c, pink, nifedipine 20 mg, net price 28-tab pack = £5.27. Label: 25  
**LA 30 tablets**, m/r, t/c, pink, nifedipine 30 mg, net price 28-tab pack = £7.59. Label: 25  
**LA 60 tablets**, m/r, t/c, pink, nifedipine 60 mg, net price 28-tab pack = £9.69. Label: 25  
**Counselling** Tablet membrane may pass through gastro-intestinal tract unchanged, but being porous has no effect on efficacy  
**Dose** hypertension, 20–30 mg once daily, increased if necessary to max. 90 mg once daily  
**Angina** prophylaxis, 30 mg once daily, increased if necessary to max. 90 mg once daily  
**Cautions** dose form not appropriate for use in hepatic impairment or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease (including Crohn’s disease)

**Adalat Retard 10 tablets**  
**Retard 20 tablets**, m/r, t/c, pink-grey, nifedipine 20 mg, net price 56-tab pack = £8.50. Label: 25  
**Dose** hypertension and angina prophylaxis, 10 mg twice daily, adjusted according to response to 40 mg twice daily

**Adipine MR** (Trinity-Chiesi)  
**Tablets**, m/r, nifedipine 10 mg (apricot), net price 56-tab pack = £5.96; 20 mg (pink), 56-tab pack = £7.43. Label: 21, 25  
**Dose** hypertension and angina prophylaxis, 10 mg twice daily, after food (initial titration 10 mg twice daily), max. 40 mg twice daily

**Adipine XL** (Trinity-Chiesi)  
**Tablets**, m/r, red, nifedipine 30 mg, net price 28-tab pack = £5.89; 60 mg, 28-tab pack = £8.84. Label: 25  
**Dose** hypertension and angina prophylaxis, 30 mg once daily, increased if necessary, max. 90 mg once daily

**Coracten SR** (UCB Pharma)  
**Capsules**, m/r, nifedipine 10 mg (grey/pink, enclosing yellow pellets), net price 60-cap pack = £4.70;  
20 mg (pink/brown, enclosing yellow pellets), 60-cap pack = £6.52. Label: 25  
**Dose** hypertension and angina prophylaxis, initially 10 mg twice daily, increased if necessary to max. 40 mg twice daily

**Coracten XL** (UCB Pharma)  
**Capsules**, m/r, nifedipine 30 mg (brown), net price 28-cap pack = £5.89; 60 mg (orange), 28-cap pack = £8.84. Label: 25  
**Dose** hypertension and angina prophylaxis, 30 mg once daily, increased if necessary; max. 90 mg once daily

**Fortipine LA 40** (Goldshield)  
**Tablets**, m/r, red, nifedipine 40 mg, net price 30-tab pack = £9.60. Label: 21, 25  
**Dose** hypertension and angina prophylaxis, 40 mg once daily, increased if necessary to 80 mg daily in 1–2 divided doses

**Hypolar Retard 20** (Sandoz)  
**Tablets**, m/r, red, t/c, nifedipine 20 mg, net price 56-tab pack = £5.75. Label: 25  
**Dose** hypertension and angina prophylaxis, 20 mg twice daily, increased if necessary to 40 mg twice daily

**Nifedipress MR** (Dexcel)  
**Tablets**, m/r, pink, nifedipine 10 mg, net price 56-tab pack = £9.23; 20 mg, 56-tab pack = £10.06. Label: 25  
**Dose** hypertension and angina prophylaxis, initially 10 mg twice daily, adjusted according to response to 40 mg twice daily

**Tensipine MR** (Genus)  
**Tablets**, m/r, pink-grey, nifedipine 10 mg, net price 56-tab pack = £4.30; 20 mg, 56-tab pack = £5.49. Label: 21, 25  
**Dose** hypertension and angina prophylaxis, initially 10 mg twice daily, adjusted according to response to 40 mg twice daily

**Valni XL** (Winthrop)  
**Tablets**, m/r, red, nifedipine 30 mg, net price 28-tab pack = £9.89; 60 mg, 28-tab pack = £14.71. Label: 25  
**Dose** severe hypertension and prophylaxis of angina, 30 mg once daily, increased if necessary to max. 90 mg once daily  
**Cautions** dose form not appropriate for use in hepatic impairment, or where there is a history of oesophageal or gastro-intestinal obstruction, decreased lumen diameter of the gastro-intestinal tract, or inflammatory bowel disease, or ileostomy after proctocolectomy

**With atenolol**  
Section 2.4

**NIMODIPINE**

**Indications** prevention and treatment of ischaemic neurological deficits following aneurysmal subarachnoid haemorrhage

**Cautions** cerebral oedema or severely raised intracranial pressure; hypotension; avoid concomitant administration of nimodipine tablets and infusion, other calcium-channel blockers, or beta-blockers; concomitant nephrotoxic drugs; avoid grapefruit juice (may affect metabolism); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (calcium-channel blockers, alcohol (infusion only))

**Contra-indications** within 1 month of myocardial infarction; unstable angina; acute porphyria (section 9.8.2)

**Side-effects** hypotension, variation in heart-rate, flushing, headache, gastro-intestinal disorders, nausea, sweating and feeling of warmth; thrombocyto-penia and ileus reported
Dose

- Prevention, by mouth, 60 mg every 4 hours, starting within 4 days of aneurysmal subarachnoid haemorrhage and continued for 21 days
- Treatment, by intravenous infusion via central catheter, initially 1 mg/hour (up to 500 micrograms/hour if body-weight less than 70 kg or if blood pressure unstable), increased after 2 hours to 2 mg/hour if no severe fall in blood pressure; continue for at least 5 days (max. 14 days); if surgical intervention during treatment, continue for at least 5 days after surgery; max. total duration of nimodipine use 21 days

Nimotop® (Bayer) Tablets, yellow, f/c, nimodipine 30 mg, net price 100-tab pack = £38.85
Intravenous injection, nimodipine 200 micrograms/mL; also contains ethanol 20% and macrogol ‘400’ 17%, net price 50-mL vial (with polyethylene infusion catheter) = £13.24
Note Polyethylene, propylene, or glass apparatus should be used. PVC should be avoided

VERAPAMIL HYDROCHLORIDE

Indications see under Dose and preparations

Cautions first-degree AV block; acute phase of myocardial infarction (avoid if bradycardia, hypertension, left ventricular failure); patients taking beta-blockers (important: see below); hepatic impairment (Appendix 2); children, specialist advice only (section 3.2.2); pregnancy (Appendix 4) and breast-feeding (Appendix 5); avoid grapefruit juice (may affect metabolism); interactions: Appendix 1 (calcium-channel blockers)

Verapamil and beta-blockers Verapamil injection should not be given to patients recently treated with beta-blockers because of the risk of hypotension and asystole. The suggestion that when verapamil injection has been given first, an interval of 30 minutes before giving a beta-blocker is sufficient has not been confirmed.

It may also be hazardous to give verapamil and a beta-blocker together by mouth (should only be contemplated if myocardial function well preserved).

Contra-indications hypotension, bradycardia, second- and third-degree AV block, sick sinus syndrome, cardiogenic shock, sino-atrial block; history of heart failure or significantly impaired left ventricular function, even if controlled by therapy; atrial flutter or fibrillation complicating syndromes associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome); acute porphyria (section 9.8.2)

Side-effects constipation; less commonly nausea, vomiting, flushing, headache, dizziness, fatigue, ankle oedema; rarely allergic reactions (erythema, pruritus, urticaria, angioedema, Stevens-Johnson syndrome); malagia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; rarely gynaecomastia and gingival hyperplasia after long-term treatment; after intravenous administration or high doses, hypotension, heart failure, bradycardia, heart block, and asystole

Dose

- By mouth, supraventricular arrhythmias (but see also Contra-indications), 40–120 mg 3 times daily
- By slow intravenous injection over 2 minutes (3 minutes in elderly), supraventricular arrhythmias (but see also Contra-indications), 5–10 mg (preferably with ECG monitoring); in paroxysmal tachyarrhythmias a further 5 mg after 5–10 minutes if required

Verapamil (Non-proprietary) Tablets, coated, verapamil hydrochloride 40 mg, net price 84-tab pack = £1.54; 80 mg, 84-tab pack = £1.68; 120 mg, 28-tab pack = £1.41; 160 mg, 56-tab pack = £20.23
Oral solution, verapamil hydrochloride 40 mg/5 mL, net price 150 mL = £36.90
Brands include Zolivera

Cordilox® (Dexcel) Tablets, yellow, f/c, verapamil hydrochloride 40 mg, net price 84-tab pack = £1.50; 80 mg, 84-tab pack = £2.05; 120 mg, 28-tab pack = £1.15; 160 mg, 56-tab pack = £2.80
Injection, verapamil hydrochloride 2.5 mg/mL, net price 2-mL amp = £1.11

Securon® (Abbott) Injection, verapamil hydrochloride 2.5 mg/mL, net price 2-mL amp = £1.08

Modified release

Half Securon MR® (Abbott) Tablets, m/r, f/c, verapamil hydrochloride 120 mg, net price 28-tab pack = £7.50. Label: 25
Dose see Securon SR

Securon SR® (Abbott) Tablets, m/r, pale green, f/c, scored, verapamil hydrochloride 240 mg, net price 28-tab pack = £6.29. Label: 25
Dose hypertension, 240 mg daily (new patients initially 120 mg), increased if necessary to max. 480 mg daily (doses above 240 mg daily as 2 divided doses)
Angina, 240 mg twice daily (may sometimes be reduced to once daily)
Prophyaxis after myocardial infarction where beta-blockers not appropriate (started at least 1 week after infarction), 360 mg daily in divided doses, given as 240 mg in the morning and 120 mg in the evening or 120 mg 3 times daily

Univer® (Cephalon) Capsules, m/r, verapamil hydrochloride 120 mg (yellow/dark blue), net price 28-cap pack = £7.51; 180 mg (yellow), 56-cap pack = £18.15; 240 mg (yellow/dark blue), 28-cap pack = £12.24. Label: 25
Dose hypertension, 240 mg daily, max. 480 mg daily (new patients, initial dose 120 mg), angina, 360 mg daily, max. 480 mg daily

Verapress MR® (Dexcel) Tablets, m/r, pale green, f/c, verapamil hydrochloride 240 mg, net price 28-tab pack = £9.90. Label: 25
Dose hypertension, 1 tablet daily, increased to twice daily if necessary; angina, 1 tablet twice daily (may sometimes be reduced to once daily)
Note Also available as Cordilox® MR

Vertab® SR 240 (Trinity-Chiesi) Tablets, m/r, pale green, f/c, scored, verapamil hydrochloride 240 mg, net price 28-tab pack = £8.63. Label: 25
Dose mild to moderate hypertension, 240 mg daily, increased to twice daily if necessary, angina, 240 mg twice daily (may sometimes be reduced to once daily)
### 2.6.3 Other antianginal drugs

**Nicorandil**, a potassium-channel activator with a nitrate component, has both arterial and venous vasodilating properties and is licensed for the prevention and long-term treatment of angina (section 2.6). Nicorandil has similar efficacy to other antianginal drugs in controlling symptoms; it may produce additional symptomatic benefit in combination with other antianginal drugs [unlicensed indication].

Ivabradine lowers the heart rate by its action on the sinus node. It is licensed for the treatment of angina in patients in normal sinus rhythm when beta-blockers are contra-indicated or not tolerated.

### IVABRADINE

**Indications** treatment of angina in patients in normal sinus rhythm (see notes above)

**Cautions** mild heart failure including asymptomatic left ventricular dysfunction; monitor for atrial fibrillation or other arrhythmias (treatment ineffective); hypotension (avoid if severe); retinitis pigmentosa; elderly; hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (ivabradine)

**Contra-indications** severe bradycardia (not to be initiated if heart rate below 60 beats per minute); cardiogenic shock; acute myocardial infarction; immediately after cerebrovascular accident; sick-sinus syndrome; sino-atrial block; moderate to severe left ventricular dysfunction; monitor for atrial fibrillation (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** bradycardia, first-degree heart block, ventricular extrasystoles; headache, dizziness; visual disturbances includingophthalmis and blurred vision; less commonly nausea, constipation, diarrhoea, palpitations, supraventricular extrasystoles, dyspnoea, vertigo, muscle cramps, eosinophilia, hyperuricaemia, and raised plasma-creatinine concentration

**Dose**
- Initially 5 mg twice daily, increased if necessary after 3–4 weeks to 7.5 mg twice daily (if not tolerated reduce dose to 2.5–5 mg twice daily); **ELDERLY** initially 2.5 mg twice daily
- Note Ventricular rate at rest should not be allowed to fall below 50 beats per minute

**Procoralan®** (Servier) Tablets, pink, 1/2, 1, 2 mg, ivabradine (as hydrochloride) 5 mg (scored), net price 56-tab pack = £39.00; 7.5 mg, 56-tab pack = £39.00

### NICORANDIL

**Indications** prophylaxis and treatment of angina

**Cautions** hypovolaemia; low systolic blood pressure; acute pulmonary oedema; acute myocardial infarction with acute left ventricular failure and low filling pressures; pregnancy (Appendix 4); interactions: Appendix 1 (nicorandil)

**Driving** Patients should be warned not to drive or operate machinery until it is established that their performance is unimpaired

**Contra-indications** cardiogenic shock; left ventricular failure with low filling pressures; hypotension; breast-feeding

**Side-effects** headache (especially on initiation, usually transitory); cutaneous vasodilatation with flushing; nausea, vomiting, dizziness, weakness also reported; rarely oral ulceration, myalgia, and rash; at high dosage, reduction in blood pressure and/or increase in heart rate; angioedema, hepatic dysfunction, and anal ulceration also reported

**Dose**
- Initially 10 mg twice daily (if susceptible to headache 5 mg twice daily); usual dose 10–20 mg twice daily; up to 30 mg twice daily may be used

**Ikorel®** (Rhône-Poulenc Rorer) Tablets, scored, nicorandil 10 mg, net price 60-tab pack = £8.18; 20 mg, 60-tab pack = £15.54

### 2.6.4 Peripheral vasodilators and related drugs

Peripheral vascular disease can be either occlusive (e.g. intermittent claudication) where occlusion of the peripheral arteries is caused by atherosclerosis, or vasospastic (e.g. Raynaud’s syndrome).

Peripheral arterial occlusive disease is associated with an increased risk of cardiovascular events; this risk is reduced by measures such as smoking cessation (section 4.10), effective control of blood pressure (section 2.5), regulating blood lipids (section 2.12), optimising glycaemic control in diabetes (section 6.1), taking aspirin in a dose of 75 mg daily (section 2.9), and possibly weight reduction in obesity (section 4.5). Exercise training, treatment with cilostazol or naftidrofuryl (see below), and possibly statin therapy can improve symptoms of intermittent claudication.

Cilostazol is licensed for use in intermittent claudication to improve walking distance in patients without peripheral tissue necrosis who do not have pain at rest. Patients receiving cilostazol should be assessed for improvement after 3 months. The **Scottish Medicines Consortium** has advised (October 2005) that cilostazol is not recommended for the treatment of intermittent claudication.

Naftidrofuryl can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking naftidrofuryl should be assessed for improvement after 3–6 months.

Inositol nicotinate, pentoxifylline (oxpentifylline), and cinnarizine are not established as being effective for the treatment of intermittent claudication.

**Naftidrofuryl** can alleviate symptoms of intermittent claudication and improve pain-free walking distance in moderate disease. Patients taking naftidrofuryl should be assessed for improvement after 3–6 months.

Inositol nicotinate, pentoxifylline (oxpentifylline), and cinnarizine are not established as being effective for the treatment of intermittent claudication.

**Management of Raynaud’s syndrome** includes avoidance of exposure to cold and stopping smoking. More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud’s syndrome.

Nifedipine (section 2.6.2) is useful for reducing the frequency and severity of vasospastic attacks. Alternatively, naftidrofuryl may produce symptomatic improvement; inositol nicotinate (a nicotinic acid derivative) may also be considered. Cinnarizine, pentoxifylline, prazosin, and moxisylyte (thymoxamine) are not established as being effective for the treatment of Raynaud’s syndrome.

Vasodilator therapy is not established as being effective for chilblains (section 13.13).
## Cardiovascular system

### CILOSTAZOL

**Indications** intermittent claudication in patients without rest pain and no peripheral tissue necrosis

**Cautions** atrial or ventricular ectopy, atrial fibrillation, atrial flutter, diabetes mellitus (higher risk of intravascular bleeding); concomitant drugs that increase risk of bleeding; hepatic impairment (Appendix 2); **interactions**: Appendix 1 (cilostazol)

**Contra-indications** predisposition to bleeding (e.g. active peptic ulcer, haemorrhagic stroke in previous 6 months, surgery in previous 3 months, proliferative diabetic retinopathy, poorly controlled hypertension); history of ventricular tachycardia, of ventricular fibrillation and of multifocal ventricular ectopics, prolongation of QT interval, congestive heart failure; renal impairment (avoid if creatinine clearance less than 25 mL/minute); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances; tachycardia, palpitation, angina, arrhythmia, chest pain, oedema; rhinitis; dizziness; headache; rash, pruritus, ecchymosis; less commonly gastro-intestinal disturbances. Effects include headache, flushing, rashes, mild gastro-intestinal disturbances, dizziness, headache, pruritus, ecchymosis; side-effects include rash, pruritus, flushing, rashes, mild gastrointestinal disturbances.

**Dose**
- 100 mg twice daily (30 minutes before or 2 hours after food)

**Pletal** (Otsuka) Tablets, cilostazol 50 mg, net price 56-tab pack = £35.31; 100 mg, 56-tab pack = £35.31

### INOSITOL NICOTINATE

**Indications** peripheral vascular disease; hyperlipidemia (section 2.12)

**Cautions** cerebrovascular insufficiency, unstable angina

**Contra-indications** recent myocardial infarction, acute phase of a cerebrovascular accident; pregnancy (Appendix 4)

**Side-effects** nausea, vomiting, hypotension, flushing, syncpe, oedema, headache, dizziness, paraesthesia, rash

**Dose**
- 3 g daily in 2–3 divided doses; max. 4 g daily

**Hexoplal** (Genus) Tablets, scored, inositol nicotinate 500 mg, net price 20 = £4.10

**Tablets forte** scored, inositol nicotinate 750 mg, net price 112-tab pack = £34.02

### MOXISYLYTE

(Thymoxamine)

**Indications** primary Raynaud’s syndrome (short-term treatment)

**Cautions** diabetes mellitus

**Contra-indications** active liver disease; pregnancy (Appendix 4)

**Side-effects** nausea, diarrhoea, flushing, headache, dizziness; hepatic reactions including cholestatic jaundice and hepatitis reported to CSM

**Dose**
- Initially 40 mg 4 times daily, increased to 80 mg 4 times daily if poor initial response; discontinue after 2 weeks if no response

**Opilon** (Concord) Tablets, yellow, t/c, moxisylyte 40 mg (as hydrochloride), net price 112-tab pack = £79.98. Label: 21

### NAFTIDROFURYL OXALATE

**Indications** see under Dose

**Side-effects** nausea, epigastric pain, rash, hepatitis, hepatic failure

**Dose**
- Peripheral vascular disease (see notes above), 100–200 mg 3 times daily
- Cerebral vascular disease, 100 mg 3 times daily

**Naftidrofuryl** (Non-proprietary)

**Capsules** naftidrofuryl oxalate 100 mg, net price 84-cap pack = £5.57. Label: 25, 27

**Praxilene** (Merck) Capsules, pink, naftidrofuryl oxalate 100 mg, net price 84-cap pack = £8.60. Label: 25, 27

### PENTOXIFYLLINE

(Oxpentifylline)

**Indications** peripheral vascular disease; venous leg ulcers [unlicensed indication] (Appendix A8.2.5)

**Cautions** hypotension, coronary artery disease; renal impairment (Appendix 3), severe hepatic impairment; avoid in acute porphyria (section 9.8.2); **interactions**: Appendix 1 (pentoxifylline)

**Contra-indications** cerebral haemorrhage, extensive retinal haemorrhage, acute myocardial infarction; pregnancy and breast-feeding

**Side-effects** gastro-intestinal disturbances, dizziness, agitation, sleep disturbances, headache; rarely flushing, tachycardia, angina, hypotension, thrombocytopenia, intrahepatic cholestasis, hypersensitivity reactions including rash, pruritus and bronchospasm

**Dose**
- 400 mg 2–3 times daily

**Trental** (Aventis Pharma) Tablets, m/r, pink, s/c, pentoxifylline 400 mg, net price 90-tab pack = £20.48. Label: 21, 25

### Other preparations used in peripheral vascular disease

Rutosides (oxerutins, Paroven®) are not vasodilators and are not generally regarded as effective preparations as capillary sealants or for the treatment of cramps; side-effects include headache, flushing, rashes, mild gastrointestinal disturbances.
Shock

Shock is a medical emergency associated with a profound hypotension of shock must be corrected. The underlying causes of shock such as haemorrhage, sepsis, or myocardial insufficiency should be corrected. The profound hypotension of shock must be treated promptly to prevent tissue hypoxia and organ failure. Volume replacement is essential to correct the hypovolaemia associated with haemorrhage and sepsis but may be detrimental in cardiogenic shock. Depending on haemodynamic status, cardiac output may be improved by the use of sympathomimetic inotropes such as adrenaline (epinephrine), dobutamine or dopamine (see notes above). In septic shock, when fluid replacement and inotropic support fail to maintain blood pressure, the vasoconstrictor noradrenaline (norepinephrine) (section 2.7.2) may be considered. In cardiogenic shock peripheral resistance is frequently high and to raise it further may worsen myocardial performance and exacerbate tissue ischaemia.

The use of sympathomimetic inotropes and vasoconstrictors should preferably be confined to the intensive care setting and undertaken with invasive haemodynamic monitoring.

For advice on the management of anaphylactic shock, see section 3.4.3.

2.7 Sympathomimetics

2.7.1 Inotropic sympathomimetics

The cardiac stimulants dobutamine and dopamine act on beta receptors in cardiac muscle, and increase contractility with little effect on rate.

Dopamine (epinephrine) (section 2.7.1) acts on both alpha and beta receptors and increases both heart rate and contractility (beta effects); it can cause peripheral vasodilation (a beta effect) or vasoconstriction (an alpha effect).

Dopexamine (non-proprietary) (Novartis Consumer Health) Strong sterile solution, dopamine hydrochloride 12.5 mg/mL. For dilution and use as an intravenous infusion. Net price 20-mL amp = £5.20

Indications cardionic shock in infarction or cardiac surgery

Cautions correct hypovolaemia; low dose in shock due to acute myocardial infarction—see notes above; hyperthyroidism; pregnancy (Appendix 4); interactions: Appendix 1 (sympathomimetics)

Contra-indications tachyarrhythmia, phaeochromocytoma

Side-effects nausea and vomiting, peripheral vasoconstriction, hypotension, hypertension, tachycardia

Dose

- By intravenous infusion, 2.5–10 micrograms/kg/minute, adjusted according to response

Dobutamine (non-proprietary) (Novartis Consumer Health) Strong sterile solution, dobutamine (as hydrochloride) 12.5 mg/mL. For dilution and use as an intravenous infusion. Net price 20-mL amp = £5.20

Indications inotropic support in infarction, cardiac surgery, cardiomyopathies, septic shock, and cardiogenic shock

Cautions pregnancy; interactions: Appendix 1 (sympathomimetics)

Side-effects tachycardia and marked increase in systolic blood pressure indicate overdosage; phlebitis; rarely thrombocytopenia

Dose

- By intravenous infusion, 2.5–10 micrograms/kg/minute, adjusted according to response

Dopamine hydrochloride

Indications cardionic shock in infarction or cardiac surgery

Cautions correct hypovolaemia; low dose in shock due to acute myocardial infarction—see notes above; hyperthyroidism; pregnancy (Appendix 4); interactions: Appendix 1 (sympathomimetics)

Contra-indications tachyarrhythmia, phaeochromocytoma

Side-effects nausea and vomiting, peripheral vasoconstriction, hypotension, hypertension, tachycardia

Dose

- By intravenous infusion, 2–5 micrograms/kg/minute initially (see notes above)

Dopamine (non-proprietary) (Novartis Consumer Health) Strong sterile solution, dopamine hydrochloride 40 mg/mL. Net price 5-mL amp = £3.88; 160 mg/mL, 5-mL amp = £14.75. For dilution and use as an intravenous infusion

Intravenous infusion, dopamine hydrochloride 1.6 mg/mL in glucose 5% intravenous infusion, net price 250-mL container (400 mg) = £11.69; 3.2 mg/mL, 250-mL container (800 mg) = £22.93 (both hosp. only)

Select-A-Jet® Dopamine (UCB Pharma) Strong sterile solution, dopamine hydrochloride 40 mg/mL. Net price 5-mL vial = £5.01; 10-mL vial = £8.05. For dilution and use as an intravenous infusion

Dopamine hydrochloride

Indications inotropic support and vasodilator in exacerbations of chronic heart failure and in heart failure associated with cardiac surgery

Cautions myocardial infarction, recent angina, hypokalaemia, hyperglycaemia; correct hypovolaemia before starting and during treatment, monitor blood pressure, pulse, plasma potassium, and blood glucose; avoid abrupt withdrawal; pregnancy; interactions: Appendix 1 (sympathomimetics)

Contra-indications left ventricular outlet obstruction such as hypertrophic cardiomyopathy or aortic stenosis; phaeochromocytoma, thrombocytopenia

Side-effects nausea, vomiting; tachycardia, bradycardia, arrhythmias, angina, myocardial infarction; tremor, headache; dyspnoea; reversible thrombocytopenia; sweating
2.7.2 Vasoconstrictor sympathomimetics

Vasoconstrictor sympathomimetics raise blood pressure transiently by acting on alpha-adrenergic receptors to constrict peripheral vessels. They are sometimes used as an emergency method of elevating blood pressure where other measures have failed (see also section 2.7.1).

The danger of vasoconstrictors is that although they raise blood pressure they also reduce perfusion of vital organs such as the kidney. Spinal and epidural anaesthesia may result in sympathetic block with resultant hypotension. Management may include intravenous fluids (which are usually given prophylactically), oxygen (section 3.6), elevation of the legs, and injection of a pressor drug such as ephedrine. As well as constricting peripheral vessels ephedrine also accelerates the heart rate (by acting on beta receptors). Use is made of this dual action of ephedrine to manage associated bradycardia (although intravenous injection of atropine sulphate 400 to 600 micrograms may also be required if bradycardia persists).

### Ephedrine Hydrochloride

**Indications** see under Dose

**Cautions** hyperthyroidism, diabetes mellitus, ischaemic heart disease, hypertension, susceptibility to angle-closure glaucoma, elderly, pregnancy (Appendix 4); may cause acute urine retention in Laennec’s cirrhosis

**Contra-indications** hypertensive response

**Dose**
- By intravenous infusion, 15–100 mg, adjusted according to response
- In emergency, by intravenous injection, 0.5–5 mg then by intravenous infusion, 15–100 mg, adjusted according to response

**Note** Contact with metal in infusion apparatus should be minimised

**Metaraminol**

**Indications** acute hypotension (see notes above); priapism (section 7.4.5) [unlicensed indication]

**Cautions** see under Noradrenaline Acid Tartrate; longer duration of action than noradrenaline (norepinephrine), see below; cirrhosis; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Hypertensive response** Metaraminol has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

**Contra-indications** see under Noradrenaline Acid Tartrate

**Side-effects** see under Noradrenaline Acid Tartrate; tachycardia; fatal ventricular arrhythmia reported in Laennec’s cirrhosis

**Dose**
- By intravenous infusion, 1–100 mg, adjusted according to response
- In emergency, by intravenous injection, 0.5–5 mg then by intravenous infusion, 12–120 mg, adjusted according to response

**Note** Strong sterile solution

**Contact with metal in infusion apparatus should be minimised

**Norepinephrine Bitartrate**

**Indications** see under dose

**Cautions** coronary, mesenteric, or peripheral vascular thrombosis; following myocardial infarction, Prinzmetal’s variant angina, hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypervolaemia; elderly; extravasation at injection site may cause necrosis; interactions: Appendix 1 (sympathomimetics)

**Contra-indications** hypertension (monitor blood pressure and rate of flow frequently); pregnancy (Appendix 4)

**Side-effects** hypertension, headache, bradycardia, arrhythmias, peripheral ischaemia

**Dose**
- Acute hypotension, by intravenous infusion, via central venous catheter, of a solution containing noradrenaline acid tartrate 80 micrograms/mL (equivalent to noradrenaline base 40 micrograms/mL) at an initial rate of 0.16–0.33 mL/minute, adjusted according to response
- Cardiac arrest, by rapid intravenous or intracardiac injection, 0.5–0.75 mL of a solution containing noradrenaline acid tartrate 200 micrograms/mL (equivalent to noradrenaline base 100 micrograms/mL)

**Noradrenaline/Norepinephrine**

**Indications** see under dose

**Cautions** coronary, mesenteric, or peripheral vascular thrombosis; following myocardial infarction, Prinzmetal’s variant angina, hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypervolaemia; elderly; extravasation at injection site may cause necrosis; interactions: Appendix 1 (sympathomimetics)

**Contra-indications** hypertension (monitor blood pressure and rate of flow frequently); pregnancy (Appendix 4)

**Side-effects** hypertension, headache, bradycardia, arrhythmias, peripheral ischaemia

**Dose**
- Acute hypotension, by intravenous infusion, via central venous catheter, of a solution containing noradrenaline acid tartrate 80 micrograms/mL (equivalent to noradrenaline base 40 micrograms/mL) at an initial rate of 0.16–0.33 mL/minute, adjusted according to response
- Cardiac arrest, by rapid intravenous or intracardiac injection, 0.5–0.75 mL of a solution containing noradrenaline acid tartrate 200 micrograms/mL (equivalent to noradrenaline base 100 micrograms/mL)

**Noradrenaline/Norepinephrine**

**Indications** see under dose

**Cautions** coronary, mesenteric, or peripheral vascular thrombosis; following myocardial infarction, Prinzmetal’s variant angina, hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypervolaemia; elderly; extravasation at injection site may cause necrosis; interactions: Appendix 1 (sympathomimetics)

**Contra-indications** hypertension (monitor blood pressure and rate of flow frequently); pregnancy (Appendix 4)

**Side-effects** hypertension, headache, bradycardia, arrhythmias, peripheral ischaemia

**Dose**
- Acute hypotension, by intravenous infusion, via central venous catheter, of a solution containing noradrenaline acid tartrate 80 micrograms/mL (equivalent to noradrenaline base 40 micrograms/mL) at an initial rate of 0.16–0.33 mL/minute, adjusted according to response
- Cardiac arrest, by rapid intravenous or intracardiac injection, 0.5–0.75 mL of a solution containing noradrenaline acid tartrate 200 micrograms/mL (equivalent to noradrenaline base 100 micrograms/mL)
**Phenylephrine Hydrochloride**

**Indications** acute hypotension (see notes above); priapism (section 7.4.5) [unlicensed indication]

**Cautions** see under Noradrenaline Acid Tartrate; longer duration of action than noradrenaline (norepinephrine), see below; coronary disease

**Side-effects** see under Noradrenaline Acid Tartrate; tachycardia or reflex bradycardia

**Dose**
- By subcutaneous or intramuscular injection, 2–5 mg, followed if necessary by further doses of 1–10 mg
- By slow intravenous injection of a 1 mg/mL solution, 100–500 micrograms repeated as necessary after at least 15 minutes
- By intravenous infusion, initial rate up to 180 micrograms/minute reduced to 30–60 micrograms/minute according to response

**Phenylephrine** (Sovereign) Injection, phenylephrine hydrochloride 10 mg/mL (1%), net price 1-mL amp = £5.50

---

**Cardiopulmonary resuscitation**

The algorithm for cardiopulmonary resuscitation (see inside back cover) reflects the most recent recommendations of the Resuscitation Council (UK). These guidelines are available at www.resus.org.uk. Cardiac arrest can be associated with ventricular fibrillation, pulseless ventricular tachycardia, asystole, and electromechanical dissociation (pulseless electrical activity). **Adrenaline** (epinephrine) in 10 000 (100 micrograms/mL) is recommended in a dose of 1 mg (10 mL) by intravenous injection repeated every 3–5 minutes if necessary. Administration through a central line is preferred, however if adrenaline is injected through a peripheral line, it must be flushed with at least 20 mL Sodium Chloride 0.9% injection to aid entry into the central circulation. Intravenous injection of amiodarone 300 mg or 5 mg/kg (from a prefilled syringe or diluted in 20 mL Glucose 5%) should be considered after adrenaline to treat ventricular fibrillation or pulseless ventricular tachycardia in cardiac arrest refractory to defibrillation. An additional dose of amiodarone 150 mg (or 2.5 mg/kg) can be given by intravenous injection if necessary, followed by an intravenous infusion of amiodarone 900 mg over 24 hours.

**Lidocaine**, in a dose of 1 mg/kg, is an alternative if amiodarone is not available; a total dose of 3 mg/kg should not be exceeded during the first hour. **Atropine** 3 mg by intravenous injection (section 15.1.3) as a single dose is also used in non-shockable cardiopulmonary resuscitation to block vagal activity. During cardiopulmonary arrest if intravenous access cannot be obtained, the intraosseous route can be considered; if circulatory access cannot be obtained at all, the endotracheal route can be considered for some drugs.

**Heparin** initiates anticoagulation rapidly but has a short duration of action. It is often referred to as ‘standard’ or ‘unfractionated heparin’ to distinguish it from the low molecular weight heparins (see p. 125), which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, heparin can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.

---

**Adrenaline/Epinephrine** 1 in 10 000, Dilute (Non-proprietary) Injection, adrenaline (as acid tartrate) 100 micrograms/mL. 10-mL amp. Brands include Minijet Adrenaline

---

**2.8 Anticoagulants and protamine**

**2.8.1 Parenteral anticoagulants**

**2.8.2 Oral anticoagulants**

**2.8.3 Protamine sulphate**

The main use of anticoagulants is to prevent thrombus formation or extension of an existing thrombus in the slower-moving venous side of the circulation, where the thrombus consists of a fibrin web enmeshed with platelets and red cells. They are therefore widely used in the prevention and treatment of deep-vein thrombosis in the legs.

Anticoagulants are of less use in preventing thrombus formation in arteries, for in faster-flowing vessels thrombi are composed mainly of platelets with little fibrin. They are used to prevent thrombi forming on prosthetic heart valves.

---

**Heparin**

Heparin initiates anticoagulation rapidly but has a short duration of action. It is often referred to as ‘standard’ or ‘unfractionated heparin’ to distinguish it from the low molecular weight heparins (see p. 125), which have a longer duration of action. Although a low molecular weight heparin is generally preferred for routine use, heparin can be used in those at high risk of bleeding because its effect can be terminated rapidly by stopping the infusion.
Treatment
For the initial treatment of deep-vein thrombosis and pulmonary embolism a low molecular weight heparin is used; alternatively, heparin is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection. Intermittent intravenous injection of heparin is no longer recommended. An oral anticoagulant (usually warfarin, section 2.8.2) is started at the same time as the heparin (the heparin needs to be continued for at least 5 days and until the INR has been in the therapeutic range for 2 consecutive days). Laboratory monitoring, preferably on a daily basis, is essential; determination of the activated partial thromboplastin time (APTT) is the most widely used measure. A low molecular weight heparin or, in some circumstances, heparin is also used in regimens for the management of myocardial infarction (section 2.10.1) and unstable angina (section 2.6).

Thrombosis and pulmonary embolism
Thrombosis and pulmonary embolism (section 2.6.2) is the most widely used measure. A low molecular weight heparin or, in some circumstances, heparin is also used in regimens for the management of myocardial infarction (section 2.10.1) and unstable angina (section 2.6).

Prophylaxis
In patients undergoing general surgery, a low molecular weight heparin is effective for the prevention of postoperative deep-vein thrombosis and pulmonary embolism in 'high-risk' patients (i.e. those with obesity, malignant disease, history of deep-vein thrombosis or pulmonary embolism, patients over 40 years, or those with an established thrombophilic disorder or who are undergoing major or complicated surgery). Subcutaneous injection of low-dose heparin is an alternative; this regimen does not require laboratory monitoring.

To combat the increased risk in major orthopaedic surgery an adjusted dose regimen of heparin (with monitoring), low molecular weight heparin (p. 125) or fondaparinux (p. 128) can be used—a low molecular weight heparin is probably more effective.

Pregnancy
Heparins are used for the management of venous thromboembolism in pregnancy because they do not cross the placenta. Low molecular weight heparins are preferred because they have a lower risk of osteoporosis and of heparin-induced thrombocytopenia. Low molecular weight heparins are eliminated more rapidly in pregnancy, requiring alteration of the dosage regimen for drugs such as dalteparin, enoxaparin, and tinzaparin. Treatment should be stopped at the onset of labour and advice sought from a specialist on continuing therapy after birth.

Extracorporeal circuits
Heparin is also used in the maintenance of extracorporeal circuits in cardiopulmonary bypass and haemodialysis.

Haemorrhage
If haemorrhage occurs it is usually sufficient to withdraw heparin, but if rapid reversal of the effects of heparin is required, protamine sulphate (section 2.8.3) is a specific antidote (but only partially reverses the effects of low molecular weight heparins).

HEPARIN
Indications see under Dose
Cautions see notes above; also elderly; concomitant use of drugs that increase risk of bleeding; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); Interactions: Appendix 1 (heparin).

Heparin-induced thrombocytopenia
Clinically important heparin-induced thrombocytopenia is immune-mediated and does not usually develop until after 5–10 days; it can be complicated by thrombosis. Platelet counts should be measured just before treatment with heparin or low molecular weight heparins, and regular monitoring of platelet counts is recommended if given for longer than 4 days. Signs of heparin-induced thrombocytopenia include a 50% reduction of platelet count, thrombosis, or skin allergy. If heparin-induced thrombocytopenia is strongly suspected or confirmed, heparin should be stopped and an alternative anticoagulant, such as lepirudin or danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin.

Contra-indications
Haemorrhagic disorders, thrombocytopenia (including history of heparin-induced thrombocytopenia), recent cerebral haemorrhage, severe hypertension; severe liver disease (including oesophageal varices), peptic ulcer; after major trauma or recent surgery to eye or nervous system; acute bacterial endocarditis; spinal or epidural anaesthesia with treatment doses of heparin; hypersensitivity to heparin or to low molecular weight heparins.

Side-effects
Haemorrhage (see notes above), thrombocytopenia (see Cautions), rarely rebound hyperlipidaemia following heparin withdrawal, priapism, hyperkalaemia (see Cautions), osteoporosis (risk lower with low molecular weight heparins), alopecia on prolonged use, injection-site reactions, skin necrosis, and hypersensitivity reactions (including urticaria, angioedema, and anaphylaxis).

Dose
- Treatment of deep-vein thrombosis, pulmonary embolism, unstable angina, and acute peripheral arterial occlusion, by intravenous injection, loading dose 5000–10 000 units, followed by 10 000 units in severe pulmonary embolism), followed by continuous intravenous infusion of 18 units/kg/hour or treatment of deep-vein thrombosis, by subcutaneous injection of 15 000 units every 12 hours (laboratory monitoring essential—preferably on a daily basis, and dose adjusted accordingly): CHILD under 18 years see BNF for Children.
- Prophylaxis in orthopaedic surgery, see notes above.
- Prophylaxis in general and gynaecological surgery (see notes above), by subcutaneous injection, 5000 units 2 hours before surgery, then every 8–12 hours for 7–10 days or until patient is ambulant (monitoring not needed); during pregnancy (with monitoring), 5000–10 000 units every 12 hours (important: prevention of prosthetic heart-valve thrombosis in pregnancy calls for specialist management).
- Haemodialysis by intravenous injection initially 1000–5000 units, followed by continuous intravenous infusion of 250–1000 units/hour.
- Myocardial infarction, see notes above.
- Prevention of clotting in extracorporeal circuits, consult product literature.

Doses above reflect the guidelines of the British Society for Haematology, for doses of the low molecular weight heparins, see p. 125.
**Heparin** (Non-proprietary) *(Ph)*

**Injection**, heparin sodium 1000 units/mL, net price 1-mL amp = £37p, 5-mL amp = £93p, 5-mL vial = £92p, 10-mL amp = £1.60, 20-mL amp = £2.63; 5000 units/mL, 1-mL amp = £72p, 5-mL amp = £1.87, 5-mL vial = £2.09; 25 000 units/mL, 1-mL amp = £1.90, 5-mL vial = £3.68

**Monoparin** *(CP) (Ph)*

**Injection**, heparin sodium (mucous) 1000 units/mL, net price 1-mL amp = £28p; 5-mL amp = £52p; 10-mL amp = £69p; 20-mL amp = £1124; 5000 units/mL, 1-mL amp = £54p; 5-mL amp = £74p; 25 000 units/mL, 0.2-mL amp = £46p, 1-mL amp = £1.52

**Monoparin Calcium** *(CP) (Ph)*

**Injection**, heparin calcium 25 000 units/mL, net price 0.2-mL amp = 73p

**Multiparin** *(CP) (Ph)*

**Injection**, heparin sodium (mucous) 1000 units/mL, net price 5-mL vial = 70p; 5000 units/mL, 5-mL vial = £1.57; 25 000 units/mL, 5-mL vial = £5.93

*Excipients* include benzyl alcohol (avoid in neonates, see *Excipients*, p 2)

---

**Low molecular weight heparins**

Low molecular weight heparins (bemiparin, dalteparin, enoxaparin, and tinzaparin) are usually preferred over unfractionated heparin in the *prevention* of venous thromboembolism because they are as effective and they have a lower risk of heparin-induced thrombocytopenia. Also, the standard prophylactic regimen does not require monitoring. In orthopaedic practice low molecular weight heparins are probably more effective than unfractionated heparin; fondaparinux (p. 128) can also be used. The duration of action of low molecular weight heparins is longer than that of unfractionated heparin; *once-daily subcutaneous* dosage means that they are convenient to use.

Low molecular weight heparins are also used in the *treatment* of deep-vein thrombosis, pulmonary embolism, myocardial infarction (section 2.10.1), unstable coronary artery disease (section 2.6) and for the prevention of clotting in extracorporeal circuits.

Routine monitoring of anti-Factor Xa activity is not usually required during treatment with low molecular weight heparins, but may be necessary in patients at increased risk of bleeding (e.g. in renal impairment and those who are underweight or overweight).

**Haemorrhage** See under Heparin.

**Pregnancy** See under Heparin.

**BEMIPARIN SODIUM**

**Indications** see notes above and under preparations

**Cautions** see under Heparin and notes above

**Contra-indications** see under Heparin; breast-feeding (Appendix 5)

**Side-effects** see under Heparin

**Dose**

- See under preparations below

**Zibor** *(Amdipharm)* ▼ *(Ph)*

**Injection**, bemiparin sodium 12 500 units/mL, net price 2500-unit (0.2-mL) prefilled syringe = £1.86; 17 500 units/mL, 3500-unit (0.2-mL) prefilled syringe = £2.75

**Dose** prophylaxis of deep-vein thrombosis, *by subcutaneous injection*, moderate risk, 2500 units 2 hours before or 6 hours after surgery then 2500 units every 24 hours for 7–10 days; high risk, 3500 units 2 hours before or 6 hours after surgery then 3500 units every 24 hours for 7–10 days

Prevention of clotting in extracorporeal circuits, consult product literature

**Injection**, bemiparin sodium 25 000 units/mL, net price 0.2-mL (5000-unit) prefilled syringe = £4.22, 0.3-mL (7500-unit) prefilled syringe = £5.34, 0.4-mL (10 000-unit) prefilled syringe = £8.44

**Dose** treatment of deep-vein thrombosis (with or without pulmonary embolism), *by subcutaneous injection*, 115 units/kg every 24 hours for 5–9 days (and until adequate oral anti-coagulation established)

**DALTEPARIN SODIUM**

**Indications** see notes above and under preparations

**Cautions** see under Heparin and notes above

**Contra-indications** see under Heparin

**Side-effects** see under Heparin

**Dose**

- See under preparations below

**Fragmin** *(Pharmacia)* *(Ph)*

**Injection** *(single-dose syringe)*, dalteparin sodium 12 500 units/mL, net price 2500-unit (0.2-mL) syringe = £1.86; 25 000 units/mL, 5000-unit (0.2-mL) syringe = £2.82, 7500-unit (0.3-mL) syringe = £4.23, 10 000-unit (0.4-mL) syringe = £5.65, 12 500-unit (0.5-mL) syringe = £7.06, 15 000-unit (0.6-mL) syringe = £8.47, 18 000-unit (0.72-mL) syringe = £10.16

**Dose** prophylaxis of deep-vein thrombosis, in surgical patients, *by subcutaneous injection*, moderate risk, 2500 units 1–2 hours before surgery then 2500 units every 24 hours for 5–7 days or longer; high risk, 2500 units 1–2 hours before surgery, then 2500 units 8–12 hours later (or 5000 units on the evening before surgery, then 5000 units on the following evening), then 5000 units every 24 hours for 5–7 days or longer (3 weeks in hip replacement)

**Dose** prophylaxis of deep-vein thrombosis in medical patients, *by subcutaneous injection*, 5000 units every 24 hours

**Dose** Treatment of deep-vein thrombosis and of pulmonary embolism, *by subcutaneous injection*, as a single daily dose, ADULT body-weight under 46 kg, 7500 units daily; body-weight 46–56 kg, 10000 units daily; body-weight 57–68 kg, 12 500 units daily; body-weight 69–82 kg, 15 000 units daily; body-weight 83 kg and over, 18 000 units daily, with oral anticoagulant treatment until prothrombin complex concentration in therapeutic range (usually for at least 5 days); monitoring of anti-Factor Xa not usually required; for patients at increased risk of haemorrhage, see below

**Dose** Treatment of venous thromboembolism in pregnancy [unlicensed indication], *by subcutaneous injection*, early pregnancy body-weight under 50 kg, 5000 units twice daily; body-weight 50–70 kg, 6000 units twice daily; body-weight 70–90 kg, 8000 units twice daily; body-weight over 90 kg, 10 000 units twice daily

**Injection**, dalteparin sodium 2500 units/mL *(for subcutaneous or intravenous use)*, net price 4-mL *(10 000-unit)* amp = £5.12; 10 000 units/mL *(for subcutaneous or intravenous use)*, 1-mL *(10 000-unit)* amp = £5.12; 25 000 units/mL *(for subcutaneous use only)*, 4-mL *(100 000-unit)* vial = £48.66

**Dose** treatment of deep-vein thrombosis and of pulmonary embolism, *by subcutaneous injection*, 200 units/kg (max. 18 000 units) as a single daily dose (or 100 units/kg twice daily if increased risk of haemorrhage) with oral anticoagulant treatment until prothrombin complex concentration in therapeutic range (usually for at least 5 days)

**Note** For monitoring, blood should be taken 3–4 hours after a dose (recommended plasma concentration of anti-Factor Xa 0.5–
ENOXAPARIN SODIUM

Indications see notes above and under preparations

Caution see under Heparin and notes above; low body-weight (increased risk of bleeding)

Contra-indications see under Heparin; breast-feeding

(Appendix 5)

Side-effects see under Heparin

Dose

See under preparation below

Clexane® (Rhoˆne-Poulenc Rorer) [R]

Injection, enoxaparin sodium 100 mg/mL, net price 20-mg (0.2-mL, 2000-units) syringe = £3.15, 40-mg (0.4-mL, 4000-units) syringe = £4.20, 60-mg (0.6-mL, 6000-units) syringe = £4.75, 80-mg (0.8-mL, 8000-units) syringe = £5.40, 100-mg (1-mL, 10 000-units) syringe = £6.69; 300 mg (3-mL, 30 000-units) vial (Clexane® Multidose) = £22.20; 150 mg/mL (Clexane® Forte), 120-mg (0.8-mL, 12 000-units) syringe = £9.77, 150-mg (1-mL, 15 000-units) syringe = £11.10

Dose prophylaxis of deep-vein thrombosis especially in surgical patients, by subcutaneous injection, moderate risk, 20 mg (2000 units) approx 2 hours before surgery then 20 mg (2000 units) every 24 hours for 7–10 days, high risk (e.g. orthopaedic surgery), 40 mg (4000 units) 12 hours before surgery then 40 mg (4000 units) every 24 hours for 7–10 days

Prophylaxis of deep-vein thrombosis in medical patients, by subcutaneous injection, 40 mg (4000 units) every 24 hours for at least 6 days and continued until patient ambulant (max. 14 days)

Treatment of deep-vein thrombosis or pulmonary embolism, by subcutaneous injection, 1.5 mg/kg (150 units/kg) every 24 hours, usually for at least 5 days (and until adequate oral anticoagulation established)

Unstable angina and non-ST-segment-elevation myocardial infarction, by subcutaneous injection, 1 mg/kg (100 units/kg) every 12 hours usually for 2–8 days (minimum 2 days)

Prevention of clotting in extracorporeal circuits, consult product literature

Treatment of venous thromboembolism in pregnancy (unlicensed indication), by subcutaneous injection, early pregnancy body-weight under 30 kg, 40 mg (4000 units) twice daily; body-weight 50–70 kg, 60 mg (6000 units) twice daily; body-weight 70–90 kg, 80 mg (8000 units) twice daily; body-weight over 90 kg, 100 mg (10 000 units) twice daily

Heparinoids

Danaparoid is a heparinoid used for prophylaxis of deep-vein thrombosis in patients undergoing general or orthopaedic surgery. Providing there is no evidence of cross-reactivity, it also has a role in patients who develop thrombocytopenia in association with heparin.

DANAPAROID SODIUM

Indications prevention of deep-vein thrombosis in general or orthopaedic surgery; thromboembolic disease in patients with history of heparin-induced thrombocytopenia

Caution recent bleeding or risk of bleeding; concomitant use of drugs that increase risk of bleeding; antibodies to heparins (risk of antibody-induced thrombocytopenia); body-weight over 90 kg (monitor anti factor Xa activity); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Contra-indications haemophilia and other haemorrhagic disorders, thrombocytopenia (unless patient has heparin-induced thrombocytopenia), recent cerebral haemorrhage, severe hypertension, active peptic ulcer (unless this is the reason for operation), diabetic retinopathy, acute bacterial endocarditis, spinal or epidural anaesthesia with treatment doses of danaparoid

Side-effects bleeding; hypersensitivity reactions (including rash)

Dose

See under preparations below

Innohep® (LEO) [R]

Injection, tinzaparin sodium 10 000 units/mL, net price 2500-unit (0.25-mL) syringe = £1.98, 3500-unit (0.35-mL) syringe = £2.77, 4500-unit (0.45-mL) syringe = £3.56, 20 000-unit (2-mL) vial = £10.56

Dose prophylaxis of deep-vein thrombosis, by subcutaneous injection, general surgery, 3500 units 2 hours before surgery, then 3500 units every 24 hours for 7–10 days; orthopaedic surgery, 50 units/kg 2 hours before surgery, then 50 units/kg every 24 hours for 7–10 days or 4500 units 12 hours before surgery, then 4500 units every 24 hours for 7–10 days

Prevention of clotting in extracorporeal circuits, consult product literature

Injection, tinzaparin sodium 20 000 units/mL, net price 0.5-mL (10 000-unit) syringe = £8.98, 0.7-mL (14 000-unit) syringe = £12.57, 0.9-mL (18 000-unit) syringe = £16.16, 2-mL (40 000-unit) vial = £34.20

Dose treatment of deep-vein thrombosis and of pulmonary embolism, by subcutaneous injection, 175 units/kg once daily for at least 6 days (and until adequate oral anticoagulation established)

Treatment of venous thromboembolism in pregnancy (unlicensed indication), by subcutaneous injection, 175 units/kg once daily

Note Treatment regimens do not require anticoagulation monitoring

Asthma Presence of sulphites in formulation may (especially in patients with asthma) lead to hypersensitivity (with broncho-spasm and shock)
injection, 2500 units (1250 units if body-weight under 55 kg, 3750 units if over 90 kg), followed by intravenous infusion of 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days

Orgaran® (Organon) \[\text{INN}\]
Injection, danaparoid sodium 1250 units/mL, net price 0.6-mL amp (750 units) = £29.80

Hirudins

Lepirudin, a recombinant hirudin, is licensed for anticoagulation in patients with Type II (immune) heparin-induced thrombocytopenia who require parenteral anti-thrombotic treatment. The dose of lepirudin is adjusted according to activated partial thromboplastin time (APTT). Bivalirudin, a hirudin analogue, is a thrombin inhibitor which is licensed as an anticoagulant for patients undergoing percutaneous coronary intervention. The Scottish Medicines Consortium has advised (November 2008) that bivalirudin is accepted for restricted use for patients with acute coronary syndromes planned for urgent or early intervention who would have been considered for treatment with unfractionated heparin combined with a glycoprotein IIb/IIIa inhibitor; it should not be used alone.

BIVALIRUDIN

Indications anticoagulation for patients undergoing percutaneous coronary intervention

Cautions exposure to lepirudin (theoretical risk from lepirudin antibodies); brachytherapy procedures; concomitant use of drugs that increase risk of bleeding; renal impairment (avoid if creatinine clearance less than 30 mL/minute); Appendix 3); pregnancy and breast-feeding (Appendix 5)

Contra-indications severe hypertension; subacute thrombocytopenia, anaemia, back and chest pain, and injection-site reactions; very rarely thrombosis

Side-effects bleeding (discontinue); less commonly nausea, vomiting, tachycardia, bradycardia, hypotension, angina, dyspnoea, allergic reactions (including isolated reports of anaphylaxis), headache, thrombocytopenia, anaemia, back and chest pain, and injection-site reactions; very rarely thrombosis

Dose
- Initially by slow intravenous injection, 750 micrograms/kg body-weight or with heparin; haemorrhagic diathesis; dose titration for pulmonary hypertension should be increased by at least once daily thereafter

Contra-indications pregnancy and breast-feeding

Side-effects bleeding; reduced haemoglobin concentration without obvious source of bleeding; fever; hypersensitivity reactions (including rash); injection-site reactions

Heparin flushes

The use of heparin flushes should be kept to a minimum. For maintaining patency of peripheral venous catheters, sodium chloride injection 0.9% is as effective as heparin flushes. The role of heparin flushes in maintaining patency of arterial and central venous catheters is unclear.

Heparin Sodium (Non-proprietary) \[\text{INN}\]
Solution, heparin sodium 10 units/mL, net price 5-mL amp = 25p; 100 units/mL, 2-mL amp = 28p

Dose to maintain patency of catheters, cannulas, etc. 10–200 units flushed through every 4–8 hours. Not for therapeutic use

Excipients may include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Canusal® (CP) \[\text{INN}\]
Solution, heparin sodium 100 units/mL. Net price 2-mL amp = 57p

Dose to maintain patency of catheters, cannulas, etc., 200 units flushed through every 4 hours or as required. Not for therapeutic use

Hepsal® (CP) \[\text{INN}\]
Solution, heparin sodium 10 units/mL. Net price 5-mL amp = 54p

Dose to maintain patency of catheters, cannulas, etc., 50 units flushed through every 4 hours or as required. Not for therapeutic use

Epoprostenol

Epoprostenol (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis either alone or with heparin. It is also licensed for the treatment of primary pulmonary hypertension resistant to other treatment, usually with oral anticoagulation. Since its half-life is only about 3 minutes it must be given by continuous intravenous infusion. It is a potent vasodilator and therefore its side-effects include flushing, headache, and hypotension.

LEPIRUDIN

Indications thromboembolic disease requiring parenteral anticoagulation in patients with heparin-induced thrombocytopenia type II

Caution hepatic impairment (Appendix 2); renal impairment (Appendix 3); recent bleeding or risk of bleeding including recent puncture of large vessels, organ biopsy, recent major surgery, stroke, bleeding disorders, severe hypertension, bacterial endocarditis; concomitant use of drugs that increase risk of bleeding; determine activated partial thromboplastin time 4 hours after start of treatment (or after infusion rate altered) and at least once daily thereafter

Side-effects bleeding; reduced haemoglobin concentration without obvious source of bleeding; fever; hypersensitivity reactions (including rash); injection-site reactions

Dose
- Initially by slow intravenous injection (of 5 mg/mL solution), 400 micrograms/kg followed by continuous intravenous infusion of 150 micrograms/kg/hour (max. 16.5 mg/hour), adjusted according to activated partial thromboplastin time, for 2–10 days (longer if necessary)

Refudan® (Cellgene) \[\text{INN}\]
Injection, powder for reconstitution, lepirudin, net price 50-mg vial = £57.00

EPROPROSTENOL

Indications see notes above

Cautions anticoagulant monitoring required when given with heparin; haemorrhagic diathesis; dose titration for pulmonary hypertension should be in hospital (risk of pulmonary oedema); concomitant use of drugs that increase risk of bleeding; pregnancy (Appendix 4)
Contra-indications severe left ventricular dysfunction
Side-effects see notes above; also bradycardia, tachycardia, pallor, sweating with higher doses; gastrointestinal disturbances; lassitude, anxiety, agitation; dry mouth, jaw pain, chest pain; also reported, hyperglycaemia and injection-site reactions

Dose
• See product literature

Fionaparin
Fondaparinux sodium is a synthetic pentasaccharide that inhibits activated factor X.

FONDAPARINUX SODIUM

Indications prophylaxis of venous thromboembolism in medical patients immobilised because of acute illness, and patients undergoing major orthopaedic surgery of the legs or abdominal surgery; treatment of deep-vein thrombosis and of pulmonary embolism; treatment of unstable angina or non-ST-segment elevation myocardial infarction; treatment of ST-segment elevation myocardial infarction

Cautions bleeding disorders, active gastrointestinal ulcer disease; recent intracranial haemorrhage; brain, spinal, or ophthalmic surgery; spinal or epidural anaesthesia (risk of spinal haematoma—avoid if using treatment doses); risk of catheter thrombus during percutaneous coronary intervention; low body weight; elderly patients; concomitant use of drugs that increase risk of bleeding; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Contra-indications active bleeding; bacterial endocarditis

Side-effects bleeding, purpura, anaemia; less commonly gastro-intestinal disturbances, oedema, hepatic impairment, chest pain, dyspnoea, thrombocytopenia, thrombocytopenia, rash, pruritus; rarely hypotension, flushing, cough, vertigo, dizziness, anxiety, drowsiness, confusion, headache, hypokalaemia, hyperbilirubinaemia, injection-site reactions; also reported atrial fibrillation, tachycardia, and pyrexia

Dose
• See under preparation below

Arixtra® (GSK) ↓ FM
Injection, fondaparinux sodium 5 mg/mL, net price 0.3-mL (1.5-mg) prefilled syringe = £6.67
Dose prophylaxis of venous thromboembolism after surgery, by subcutaneous injection, 2.5 mg once daily after surgery then 2.5 mg once daily for 5–9 days (longer after hip surgery), CHILD under 17 years not recommended
Prophylaxis of venous thromboembolism in medical patients, by subcutaneous injection, 2.5 mg once daily for 8 days (or until hospital discharge if sooner), CHILD under 17 years not recommended
ST-segment elevation myocardial infarction, initially by intravenous injection or infusion, 2.5 mg for first day, thereafter by subcutaneous injection 2.5 mg once daily for up to 8 days (or until hospital discharge if sooner), CHILD under 17 years not recommended
Injection, fondaparinux sodium 12.5 mg/mL, net price 0.4-mL (5-mg) prefilled syringe = £12.37, 0.6-mL (7.5-mg) prefilled syringe = £12.37, 0.8-mL (10-mg) prefilled syringe = £12.37
Dose treatment of deep-vein thrombosis and of pulmonary embolism, by subcutaneous injection, ADULT body-weight under 50 kg, 5 mg every 24 hours; body-weight 50–100 kg, 7.5 mg every 24 hours; body-weight over 100 kg, 10 mg every 24 hours; usually for at least 5 days (and until adequate oral anticoagulation established), CHILD under 17 years not recommended

2.8.2 Oral anticoagulants

Coumarins and phenindione

The oral anticoagulants, warfarin, acenocoumarol (nicoumalone) and phenindione, antagonise the effects of vitamin K, and take at least 48 to 72 hours for the anticoagulant effect to develop fully; if an immediate effect is required, heparin must be given concomitantly.

Uses The main indication for these oral anticoagulants is deep-vein thrombosis. Patients with pulmonary embolism should also be treated, as should those with atrial fibrillation who are at risk of embolisation (see also section 2.3.1), and those with mechanical prosthetic heart valves (to prevent emboli developing on the valves); an anti-platelet drug may also be useful in these patients but this combination increases the risk of bleeding.

Warfarin is the drug of choice; acenocoumarol (nicoumalone) and phenindione are seldom required.

These oral anticoagulants should not be used in cerebral artery thrombosis or peripheral artery occlusion as first-line therapy; aspirin (section 2.9) is more appropriate for reduction of risk in transient ischaemic attacks. Heparin or a low molecular weight heparin (section 2.8.1) is usually preferred for the prophylaxis of venous thromboembolism in patients undergoing surgery; alternatively, warfarin can be continued in selected patients currently taking long-term warfarin and who are at high risk of thromboembolism (seek expert advice).

Dose Whenever possible, the base-line prothrombin time should be determined but the initial dose should not be delayed whilst awaiting the result.

For patients who require rapid anticoagulation the usual adult induction dose of warfarin is 10 mg1 on the first day; subsequent doses depend upon the prothrombin time, reported as INR (international normalised ratio).

1. First dose reduced if base-line prothrombin time prolonged, if liver-function tests abnormal, or if patient in cardiac failure, on parenteral feeding, less than average body weight, elderly, or receiving other drugs known to potentiate oral anticoagulants.
For patients who do not require rapid anticoagulation, a lower loading dose can be used over 3–4 weeks. The daily maintenance dose of warfarin is usually 3–9 mg (taken at the same time each day). The following indications and target INRs\(^1\) take into account recommendations of the British Society for Haematology\(^2\):

- **INR 2.5** for treatment of deep-vein thrombosis and pulmonary embolism (including those associated with antiphospholipid syndrome or for recurrence in patients no longer receiving warfarin), for atrial fibrillation, cardioversion (higher target values, such as an INR of 3, can be used for up to 4 weeks before the procedure to avoid cancellations due to low INR), dilated cardiomyopathy, mural thrombus, symptomatic inherited thrombophilia, coronary artery thrombosis (if anticoagulated), and paroxysmal nocturnal haemoglobinuria;

- **INR 3.5** for recurrent deep-vein thrombosis and pulmonary embolism (in patients currently receiving warfarin with INR above 3);

- For mechanical prosthetic heart valves, the recommended target INR depends on the type and location of the valve. Generally, a target INR of 3 is recommended for mechanical aortic valves, and 3.5 for mechanical mitral valves.

**Monitoring** It is essential that the INR be determined daily or on alternate days in early days of treatment, then at longer intervals (depending on response\(^3\)) then up to every 12 weeks.

**Haemorrhage** The main adverse effect of all oral anticoagulants is haemorrhage. Checking the INR and omitting doses when appropriate is essential; if the anticoagulant is stopped but not reversed, the INR should be measured 2–3 days later to ensure that it is falling. The following recommendations (which take into account the recommendations of the British Society for Haematology\(^2\)) are based on the result of the INR and whether there is major or minor bleeding; the recommendations apply to patients taking warfarin:

- Major bleeding—stop warfarin; give phytonadione (vitamin K) 5–10 mg by slow intravenous injection; give dried prothrombin complex (factors II, VII, IX, and X—section 2.11), 30–50 units/kg or fresh frozen plasma 15 mL/kg (if dried prothrombin complex not available);

- **INR > 8.0**, no bleeding or minor bleeding—stop warfarin, restart when INR < 5.0; if there are other risk factors for bleeding give phytonadione (vitamin K) 500 micrograms by slow intravenous injection or 5 mg by mouth (for partial reversal of anticoagulation give smaller oral doses of phytonadione e.g. 0.5–2.5 mg using the intravenous preparation orally); repeat dose of phytonadione if INR still too high after 24 hours

**Unexplained bleeding at therapeutic levels**—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology.

**Pregnancy** Warfarin, acenocoumarol, and phenindione are teratogenic and should not be given in the first trimester of pregnancy. Women of child-bearing age should be warned of this danger since stopping warfarin before the sixth week of gestation may largely avoid the risk of fetal abnormality. These oral anticoagulants cross the placenta with risk of placental or fetal haemorrhage, especially during the last few weeks of pregnancy and at delivery. Therefore, if at all possible, they should be avoided in pregnancy, especially in the first and third trimesters. Difficult decisions may have to be made, particularly in women with prosthetic heart valves, atrial fibrillation, or with a history of recurrent venous thrombosis or pulmonary embolism.

**Treatment booklets** Anticoagulant treatment booklets should be issued to patients, and are available for distribution to local healthcare professionals from Health Authorities and from:

3M Security Printing and Systems Limited
Gorse Street
Chadderton
Oldham
OL9 9QH
0845 610 1112
nhsforms@spsl.uk.com

These booklets include advice for patients on anticoagulant treatment, an alert card to be carried by the patient at all times, and a section for recording of INR results and dosage information. Electronic copies and further advice are also available at www.npsa.nhs.uk/health/alerts.

**WARFARIN SODIUM**

### Indications

- prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks

### Cautions

- see notes above; also recent surgery; concomitant use of drugs that increase risk of bleeding; bacterial endocarditis (increased risk of bleeding; use only if warfarin otherwise indicated); hepatic impairment (Appendix 2); breast-feeding (Appendix 5); avoid cranberry juice; **interactions**: Appendix 1 (coumarins)

### Contra-indications

- peptic ulcer, severe hypertension; renal impairment (avoid if creatinine clearance less than 10 mL/minute); pregnancy (see notes above and Appendix 4)

### Side-effects

- haemorrhage—see notes above; other side-effects reported include hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haemocrit, ‘purple toes’, skin necrosis, jaundice, hepatic dysfunction; also nausea, vomiting, and pancreatitis

---

1. An INR which is within 0.5 units of the target value is generally satisfactory; larger deviations require dosage adjustment. Target values (rather than ranges) are now recommended.
3. Change in patient’s clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. See also **interactions**, Appendix 1 (warfarin). Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect warfarin control.
2 Cardiovascular system

Dose

- See notes above

Warfarin (Non-proprietary)

Tablets, warfarin sodium 500 micrograms (white), net price 28-tab pack = £93p; 1 mg (brown), 28 = £1.03; 3 mg (blue), 28 = £1.14; 5 mg (pink), 28 = £1.24. Label: 10, anticoagulant card

Acenocoumarol

(Nicoumalone)

Indications see under Warfarin Sodium

Cautions see under Warfarin Sodium

Contra-indications see under Warfarin Sodium

Side-effects see under Warfarin Sodium

Dose

- 4 mg on first day; 4–8 mg on second day; maintenance dose usually 1–8 mg daily adjusted according to response

Sinthrome® (Alliance)

Tablets, acenocoumarol 1 mg, net price 20 = 92p. Label: 10, anticoagulant card

Phenindione

Indications prophylaxis of embolisation in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism

Cautions see under Warfarin Sodium; interactions: Appendix 1 (phenindione)

Contra-indications see under Warfarin Sodium; breast-feeding (Appendix 5)

Side-effects see under Warfarin Sodium; also hyper-sensitivity reactions including rashes, exfoliative dermatitis, exanthema, fever, leucopenia, agranulocytosis, eosinophilia, diarrhoea, renal and hepatic damage; urine coloured pink or orange

Dose

- 200 mg on day 1; 100 mg on day 2; maintenance dose usually 50–150 mg daily

Phenindione (Non-proprietary)

Tablets, phenindione 10 mg, net price 28-tab pack = £11.93; 25 mg, 28-tab pack = £15.61; 50 mg, 28-tab pack = £18.45. Label: 10, anticoagulant card

Dabigatran etexilate

Dabigatran etexilate, a direct thrombin inhibitor, is given orally for prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery. Dabigatran etexilate has a rapid onset of action and does not require therapeutic monitoring. The most common side-effect is haemorrhage and patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

NICE guidance

Dabigatran etexilate for the prevention of venous thromboembolism after hip or knee replacement surgery in adults (September 2008)

Dabigatran etexilate is an option for the prophylaxis of venous thromboembolism in adults after total hip replacement or total knee replacement surgery.

Rivaroxaban

Rivaroxaban, a direct inhibitor of activated factor X, is given orally for prophylaxis of venous thromboembolism in adults after hip or knee replacement surgery. Rivaroxaban does not require therapeutic monitoring. The common side-effects are nausea and haemorrhage and patients should be monitored for signs of bleeding or anaemia; treatment should be stopped if severe bleeding occurs.

Pradaxa® (Boehringer Ingelheim)

Capsules, blue/ivory, dabigatran etexilate (as mesilate) 75 mg, net price 10-cap pack = £21.00, 60-cap pack = £126.00; 110 mg 10-cap pack = £21.00, 60-cap pack = £126.00 (all hosp. only). Label: 25

Rivaroxaban

Indications see notes above

Cautions see notes above; also bleeding disorders; concomitant use of drugs that increase risk of bleeding; severe hypertension; active or recent gastrointestinal ulceration; vascular retinopathy; anaesthesia with postoperative indwelling epidural catheter (risk of paralysis—monitor neurological signs and
wait at least 18 hours after rivaroxaban dose before removing catheter and do not give next dose until at least 6 hours after catheter removal; recent surgery; hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3); interactions: (Appendix 1)

Contra-indications active bleeding; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects nausea; haemorrhage (see notes above); less common constipation, diarrhoea, dyspepsia, dry mouth, vomiting, hypotension, oedema, tachycardia, thrombocytopenia, syncope, dizziness, headache, renal impairment, pain in extremities, pruritus, and rash; jaundice also reported

Dose

- Prophylaxis of venous thromboembolism following knee replacement surgery, ADULT over 18 years, 10 mg once daily for 2 weeks starting 6–10 hours after surgery
- Prophylaxis of venous thromboembolism following hip replacement surgery, ADULT over 18 years, 10 mg once daily for 5 weeks starting 6–10 hours after surgery

Xarelto® (Bayer) Tablets, red, f/c, rivaroxaban 10 mg, net price 10-tab pack = £45.00, 30-tab pack = £135.00, 100-tab pack = £450.00

2.8.3 Protamine sulphate

Protamine sulphate is used to treat overdosage of heparin, and low molecular weight heparins. The long half-life of low molecular weight heparins should be taken into consideration when determining the dose of protamine sulphate; the effects of low molecular weight heparins can persist for up to 24 hours after administration. Excessive doses of protamine sulphate can have an anticoagulant effect.

PROTAMINE SULPHATE (Protamine Sulfate)

Indications see above
Caution see above; also monitor activated partial thromboplastin time or other appropriate blood clotting parameters; increased risk of allergic reaction to protamine (including previous treatment with protamine or protamine insulin, allergy to fish, men who are infertile or who have had a vasectomy)

Side-effects nausea, vomiting, lassitude, flushing, hypotension, hypertension, Bradycardia, dyspnoea, rebound bleeding, back pain; hypersensitivity reactions (including angioedema, anaphylaxis) and pulmonary oedema reported

Dose

- Overdosage with subcutaneous injection of heparin, by intravenous injection (rate not exceeding 5 mg/minute), 1 mg neutralises 100 units heparin; give 25–50 mg by intravenous injection (rate not exceeding 5 mg/minute) then any remaining dose given by intravenous infusion over 8–16 hours; max. total dose 50 mg
- Overdosage with subcutaneous injection of low molecular weight heparin, by intermittent intravenous injection (rate not exceeding 5 mg/minute) or by continuous intravenous infusion, 1 mg neutralises approx. 100 units low molecular weight heparin (consult product literature of low molecular weight heparin for details); max. 50 mg

Protamine Sulphate (Non-proprietary)

Injection, protamine sulphate 10 mg /mL, net price 5-mL amp = £1.14, 10-mL amp = £4.15

Prosul® (CP)

Injection, protamine sulphate 10 mg/mL, net price 5-mL amp = 96p (glass), £1.20 (polypropylene)

2.9 Antiplatelet drugs

Antiplatelet drugs decrease platelet aggregation and may inhibit thrombus formation in the arterial circulation, where anticoagulants have little effect.

A single dose of aspirin 300 mg is given as soon as possible after an ischaemic event, preferably dispersed in water or chewed. The initial dose is followed by long-term treatment of aspirin 75 mg daily in order to prevent further cardiovascular disease events.

Long-term use of aspirin, in a dose of 75 mg daily, is also of benefit for all patients with established cardiovascular disease, for patients with a 10-year cardiovascular disease risk of 20% or more and aged over 50 years, for patients with diabetes aged over 50 years or who have had diabetes for more than 10 years, and for patients with diabetes who are receiving antihyperglycaemic treatment. Unduly high blood pressure must be controlled before aspirin is given.

Aspirin in a dose of 75 mg daily is also given following coronary bypass surgery. For details on the use of aspirin in atrial fibrillation see section 2.3.1, for stable angina see section 2.6 and for intermittent claudication see section 2.6.4.

If the patient is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor (section 1.3.5) can be added.

Clopidogrel is licensed for the prevention of ischaemic events in patients with a history of symptomatic ischaemic disease. Clopidogrel, in combination with low-dose aspirin, is also licensed for acute coronary syndrome without ST-segment elevation (section 2.6); in these circumstances the combination is usually given for 12 months (there is no evidence of benefit beyond 12 months). Clopidogrel, in combination with low-dose aspirin, is also licensed for acute myocardial infarction with ST-segment elevation (section 2.10.1); the combi-

---

1. Cardiovascular disease risk may be determined from the chart issued by the Joint British Societies (Heart 2005; 91 (Suppl V): v1–v52)—see inside back cover. The Joint British Societies’ ‘Cardiac Risk Assessor’ computer programme may also be used to determine cardiovascular disease risk.
nation should be continued for at least 4 weeks. Use of clopidogrel with aspirin increases the risk of bleeding. Clopidogrel monotherapy is an alternative when aspirin is contra-indicated, for example in those with aspirin hypersensitivity, or when aspirin is not tolerated despite the addition of a proton pump inhibitor.

The Scottish Medicines Consortium has advised (February 2004) that clopidogrel be accepted for restricted use for the treatment of confirmed acute coronary syndrome (without ST-segment elevation), in combination with aspirin. The Scottish Medicines Consortium has also advised (July 2007) that clopidogrel be accepted for restricted use for patients with ST-segment elevation acute myocardial infarction in combination with aspirin; treatment with clopidogrel is restricted to 4 weeks only. Clopidogrel should be initiated in hospital inpatients only.

**NICE guidance**

**Clopidogrel in the treatment of non-ST-segment elevation acute coronary syndrome** (July 2004)

Clopidogrel in combination with low-dose aspirin is recommended for the management of non-ST-segment elevation acute coronary syndrome in those at moderate to high risk of myocardial infarction or of death. Clopidogrel in combination with low-dose aspirin may be used for up to 12 months after the last event of non-ST-segment elevation acute coronary syndrome.

Dipyridamole is used by mouth as an adjunct to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves. Modified-release preparations are licensed for secondary prevention of ischaemic stroke and transient ischaemic attacks.

A combination of modified-release dipyridamole and low-dose aspirin is used after an ischaemic stroke or transient ischaemic attack, and may reduce the risk of recurrent stroke and other cardiovascular events compared to aspirin alone (see also NICE guidance below).

**NICE guidance**

**Clopidogrel and modified-release dipyridamole in the prevention of occlusive vascular events** (May 2005)

The combination of modified-release dipyridamole and aspirin is recommended to prevent occlusive vascular events in those who have had a transient ischaemic attack or an ischaemic stroke; this combination should be used for 2 years after the last event. Long-term treatment with low-dose aspirin is continued after this period. Clopidogrel monotherapy may be used for those who cannot tolerate low-dose aspirin and have had an occlusive vascular event or have symptomatic peripheral arterial disease.

**Glycoprotein IIb/IIIa inhibitors**

Glycoprotein IIb/IIIa inhibitors prevent platelet aggregation by blocking the binding of fibrinogen to receptors on platelets. Abciximab is a monoclonal antibody which binds to glycoprotein IIb/IIIa receptors and to other related sites; it is licensed as an adjunct to heparin and aspirin for the prevention of ischaemic complications in high-risk patients undergoing percutaneous transluminal coronary intervention. Abciximab should be used once only (to avoid additional risk of thrombocytopenia). Eptifibatide and tirofiban also inhibit glycoprotein IIb/IIIa receptors; they are licensed for use with heparin and aspirin to prevent early myocardial infarction in patients with unstable angina (section 2.6) or non-ST-segment-elevation myocardial infarction. Abciximab, eptifibatide and tirofiban should be used by specialists only.

For use of epoprostenol, see section 2.8.1.

**ABCIXIMAB**

**Indications** prevention of ischaemic cardiac complications in patients undergoing percutaneous coronary intervention; short-term prevention of myocardial infarction in patients with unstable angina not responding to conventional treatment and who are scheduled for percutaneous coronary intervention (use under specialist supervision)

**Cautions** measure baseline prothrombin time, activated clotting time, activated partial thromboplastin time, platelet count, haemoglobin and haematocrit; monitor haemoglobin and haematocrit 12 hours and 24 hours after start of treatment and platelet count 2–4 hours and 24 hours after start of treatment; concomitant use of drugs that increase risk of bleeding; discontinue if uncontrollable serious bleeding occurs or emergency cardiac surgery needed; consult product literature for details of procedures to minimise bleeding; elderly; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4)

**Contra-indications** active internal bleeding; major surgery, intracranial or intraspinal surgery or trauma within last 2 months; stroke within last 2 years; intracranial neoplasm, arteriovenous malformation or aneurysm, severe hypertension, haemorrhagic diathesis, thrombocytopenia, vasculitis, hypertensive retinopathy; breast-feeding (Appendix 5)

**Side-effects** bleeding manifestations; nausea, vomiting, hypotension, bradycardia, chest pain, back pain, headache, fever, puncture site pain, thrombocytopenia.
1. Aspirin tablets 75 mg may be sold to the public in packs of up to 100 tablets; for details relating to other strengths see section 4.7.1 and Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available).

### Dose

- **ADULT** initially by intravenous injection over 1 minute, 250 micrograms/kg, then by intravenous infusion, 125 nanograms/kg/minute (max. 10 micrograms/minute); for prevention of ischaemic complications start 10–60 minutes before percutaneous coronary intervention and continue infusion for 12 hours; for unstable angina start up to 24 hours before possible percutaneous coronary intervention and continue infusion for 12 hours after intervention.

**ReoPro** (Lilly) injection, abciximab 2 mg/mL, net price 5-mL vial = £260.40

### ASPIRIN (antiplatelet)

**Acetylsalicylic Acid**

**Indications** prophylaxis of cerebrovascular disease or myocardial infarction (see section 2.10.1 and notes above)

**Cautions** asthma; uncontrolled hypertension; previous peptic ulceration (but manufacturers may advise avoidance of low-dose aspirin in history of peptic ulceration); concomitant use of drugs that increase risk of bleeding; G6PD deficiency (section 9.1.5); hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); pregnancy (Appendix 4); **interactions**: Appendix 1 (aspirin)

**Contra-indications** use other than as an antiplatelet in asthma; angioedema, urticaria, or rhinitis have been precipitated by aspirin or any other NSAID

**Side-effects** bronchospasm; gastro-intestinal haemorrhage (occasionally major), also other haemorrhage (e.g. subconjunctival)

**Dose**

- See notes above

1. **Aspirin** (Non-proprietary) Dispersible tablets, aspirin 75 mg, net price 28 = 83p; 300 mg, see section 4.7.1. Label: 13, 21, 32

2. **Tablets**, e/c, aspirin 75 mg, net price 28-tab pack = 95p; 56-tab pack = £1.08; 300 mg, see section 4.7.1. Label: 5, 25, 32

**Brands include** Micropirin

3. **Angettes 75** (Bristol-Myers Squibb) Tablets, aspirin 75 mg, net price 28-tab pack = 94p. Label: 32

4. **Caprin** (Pinewood) Tablets, e/c, pink, aspirin 75 mg, net price 28-tab pack = £1.55, 56-tab pack = £3.08, 100-tab pack = £5.24; 300 mg, see section 4.7.1. Label: 5, 25, 32

### Nu-Seals® Aspirin (Alliance) Tablets, e/c, aspirin 75 mg, net price 56-tab pack = £2.60; 300 mg, see section 4.7.1. Label: 5, 25, 32

**Note** Tablets may be chewed at diagnosis for rapid absorption

### CLOPIDOGREL

**Indications** prevention of atherosclerotic events in peripheral arterial disease, or within 35 days of myocardial infarction, or within 6 months of ischaemic stroke; prevention of atherosclerotic events in acute coronary syndrome without ST-segment elevation (given with aspirin—see notes above) and in acute myocardial infarction with ST-segment elevation (given with aspirin—see notes above)

**Cautions** patients at risk of increased bleeding from trauma, surgery or other pathological conditions; concomitant use of drugs that increase risk of bleeding; discontinue 7 days before elective surgery if antiplatelet effect not desirable; liver impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); **interactions**: Appendix 1 (clopidogrel)

**Contra-indications** active bleeding, breast-feeding (Appendix 5)

**Side-effects** dyspepsia, abdominal pain, diarrhoea; bleeding disorders (including gastro-intestinal and intracranial); less commonly nausea, vomiting, gastritis, flatulence, constipation, gastric and duodenal ulcers, headache, dizziness, paraesthesias, leucopenia, decreased platelets (very rarely severe thrombocytopenia), eosinophilia, rash, and pruritus; rarely vertigo; very rarely colitis, pancreatitis, hepatitis, acute liver failure, vasculitis, confusion, hallucinations, taste disturbance, stomatitis, bronchospasm, interstitial pneumonitis, blood disorders (including thrombocytopenic purpura, agranulocytosis and pancytopenia), and hypersensitivity-like reactions (including fever, glomerulonephritis, arthralgia, Stevens-Johnson syndrome, toxic epidermal necrolysis, lichen planus)

**Dose**

- Prevention of atherosclerotic events in peripheral arterial disease or after myocardial infarction or ischaemic stroke, 75 mg once daily

- Acute coronary syndrome (without ST-segment elevation), initially 300 mg then 75 mg daily (with aspirin—see notes above)

- Acute myocardial infarction (with ST-segment elevation), initially 300 mg then 75 mg daily (with aspirin—see notes above); initial dose omitted if patient over 75 years

5. **Plavix** (Bristol-Myers Squibb, Sanofi-Synthelabo) Tablets, pink, 1/6 clopidogrel (as hydrogen sulphate) 75 mg, net price 30-tab pack = £37.83; 300 mg, 30-tab pack = £151.32

### DIPYRIDAMOLE

**Indications** see notes above and under **Dose**

**Cautions** rapidly worsening angina, aortic stenosis, recent myocardial infarction, left ventricular outflow obstruction, heart failure; may exacerbate migraine; hypotension; myasthenia gravis (risk of exacerbation); coagulation disorders; concomitant use of drugs that increase risk of bleeding; breast-feeding (Appendix 5); **interactions**: Appendix 1 (dipyridamole)
Side-effects  gastro-intestinal effects, dizziness, myalgia, throbbing headache, hypotension, hot flushes and tachycardia; worsening symptoms of coronary heart disease; hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioedema; increased bleeding during or after surgery; thrombocytopenia reported

Dose
- By mouth, 300–600 mg daily in 3–4 divided doses. Modified-release preparations, see under preparation below.
- By intravenous injection, diagnostic only, consult product literature.

Dipyridamole (Non-proprietary)
- Tablets, coated, dipyridamole 25 mg, net price 84 = £4.28; 100 mg, 84 = £3.19. Label: 22
- Oral suspension, dipyridamole 50 mg/5 mL, net price 150 mL = £37.00
- Persantin® (Boehringer Ingelheim) Tablets, s/c, dipyridamole 25 mg (orange), net price 84-tab pack = £1.57; 100 mg, 84-tab pack = £4.38. Label: 22
- Injection, dipyridamole 5 mg/mL, net price 2-mL amp = 11p

Modified release
- Persantin® Retard (Boehringer Ingelheim) Capsules, m/r, red/orange containing yellow pellets, dipyridamole 200 mg, net price 60-cap pack = £8.38. Label: 21, 25
- Dose secondary prevention of ischaemic stroke and transient ischaemic attacks (used alone or with aspirin), adjacent to oral anticoagulation for prophylaxis of thromboembolism associated with prosthetic heart valves, 200 mg twice daily preferably with food.
- Note Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening.

With aspirin
- For cautious, contra-indications and side-effects of aspirin, see under Aspirin, above.

Asasantin® Retard (Boehringer Ingelheim)
- Capsules, red/ivory, aspirin 25 mg, dipyridamole 200 mg (m/r), net price 60-cap pack = £8.20. Label: 21, 25
- Dose secondary prevention of ischaemic stroke and transient ischaemic attacks, 1 capsule twice daily.
- Note Dispense in original container (pack contains a desiccant) and discard any capsules remaining 6 weeks after opening.

Eptifibatide

Indications prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 12 hours (use under specialist supervision)

Cautions risk of bleeding, concomitant drugs that increase risk of bleeding—discontinue immediately if uncontrolled serious bleeding; measure baseline prothrombin time, activated partial thromboplastin time, platelet count, haemoglobin, haematocrit and serum creatinine; monitor haemoglobin, haematocrit and platelets within 6 hours after start of treatment then at least once daily; discontinue if thrombolytic therapy, intra-aortic balloon pump or emergency cardiac surgery necessary; hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Contra-indications abnormal bleeding within 30 days, major surgery or severe trauma within 6 weeks, stroke within last 30 days or any history of haemorrhagic stroke, intracranial disease (aneurysm, neoplasm or arteriovenous malformation), severe hypertension, haemorrhagic diathesis, increased prothrombin time or INR, thrombocytopenia, significant hepatic impairment; breast-feeding.

Side-effects bleeding manifestations; very rarely anaphylaxis and rash

Dose
- Initially by intravenous infusion, 180 micrograms/kg, then by intravenous infusion, 2 micrograms/kg/minute for up to 72 hours (up to 96 hours if percutaneous coronary intervention during treatment).

Integrilin® (GSK) Injection, eptifibatide 2 mg/mL, net price 10-mL (20-mg) vial = £14.45
- Infusion, eptifibatide 750 micrograms/mL, net price 100-mL (75-mg) vial = £45.42

TIROFIBAN

Indications prevention of early myocardial infarction in patients with unstable angina or non-ST-segment-elevation myocardial infarction and with last episode of chest pain within 12 hours (use under specialist supervision)

Cautions major surgery or severe trauma within 3 months (avoid if within 6 weeks); traumatic or protracted cardiopulmonary resuscitation, organ biopsy or lithotripsy within last 2 weeks; risk of bleeding including active peptic ulcer within 3 months; acute pericarditis, aortic dissection, haemorrhagic retinopathy, vasculitis, haematuria, faecal occult blood; severe heart failure, cardiogenic shock, anaemia; puncture of non-compressible vessel within 24 hours; concomitant drugs that increase risk of bleeding (including within 48 hours of thrombolytic administration); monitor platelet count, haemoglobin and haematocrit before treatment, 2–6 hours after start of treatment and then at least once daily; discontinue if thrombolytic therapy, intra-aortic balloon pump or emergency cardiac surgery necessary; discontinue immediately if serious bleeding uncontrolled by pressure occurs; hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (tirofiban)

Contra-indications abnormal bleeding within 30 days, stroke within 30 days or any history of haemorrhagic stroke, intracranial disease (aneurysm, neoplasm or arteriovenous malformation), severe hypertension, haemorrhagic diathesis, increased prothrombin time or INR, thrombocytopenia; breast-feeding (Appendix 5)

Side-effects bleeding manifestations; reversible thrombocytopenia

Dose
- By intravenous infusion, initially 400 nanograms/kg/minute for 30 minutes, then 100 nanograms/kg/minute for at least 48 hours (continue during and for 12–24 hours after percutaneous coronary intervention); max. duration of treatment 108 hours.
Myocardial infarction is part of the spectrum of acute coronary syndromes which includes unstable angina, and myocardial infarction with or without ST-segment elevation.

These notes give an overview of the initial and long-term management of myocardial infarction with ST-segment elevation. For advice on the management of non-ST-segment elevation myocardial infarction and unstable angina, see section 2.6. The aims of management of ST-segment elevation myocardial infarction are to provide supportive care and pain relief, to promote reperfusion and to reduce mortality. Oxygen, diamorphine and nitrates can provide initial support and pain relief; aspirin and percutaneous coronary intervention or thrombolytics promote reperfusion; long-term use of aspirin, beta-blockers, ACE inhibitors, and statins help to reduce mortality further.

Initial management Oxygen (section 3.6) should be administered if there is evidence of hypoxia, pulmonary oedema, or continuing myocardial ischaemia; hypoxia should be avoided and particular care is required in patients with chronic obstructive airways disease. The pain (and anxiety) of myocardial infarction is managed with slow intravenous injection of diamorphine (section 4.7.2); an antiemetic such as metoclopramide (or, if left ventricular function is not compromised, cyclizine) by intravenous injection should also be given (section 4.6).

Aspirin (chewed or dispersed in water) is given for its antiplatelet effect (section 2.9); a dose of 300 mg is suitable. If aspirin is given before arrival at hospital, a note saying that it has been given should be sent with the patient. Clopidogrel, in a dose of 300 mg, should also be given (section 2.9).

Patency of the occluded artery can be restored by percutaneous coronary intervention or by giving a thrombolytic drug (section 2.10.2), unless contra-indicated. Percutaneous coronary intervention is the preferred method and patients should receive a glycopro-
used, an angiotensin-II receptor antagonist may be used for patients with heart failure. A relatively high dose of either the ACE inhibitor or angiotensin-II receptor antagonist may be required to produce benefit.

Nitrates (section 2.6.1) are used for patients with angina.

Eplerenone (section 2.2.3) is licensed for use following a myocardial infarction in those with left ventricular dysfunction and evidence of heart failure. For the role of statins in preventing recurrent cardiovascular events, see section 2.12.

2.10.2 Fibrinolytic drugs

Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

The value of thrombolytic drugs for the treatment of myocardial infarction has been established (section 2.10.1). Streptokinase and alteplase have been shown to reduce mortality. Reteplase and tenecteplase are also licensed for acute myocardial infarction. Thrombolytic drugs are indicated for any patient with acute myocardial infarction for whom the benefit is likely to outweigh the risk of treatment. Trials have shown that the benefit is greatest in those with ECG changes that include ST segment elevation (especially in those with anterior infarction) and in patients with bundle branch block. Patients should not be denied thrombolytic treatment on account of age alone because mortality in the elderly is high and the reduction in mortality is the same as in younger patients.

Alteplase, reteplase and streptokinase need to be given within 12 hours of symptom onset, ideally within 1 hour; use after 12 hours requires specialist advice. Tenecteplase should be given as early as possible and usually within 6 hours of symptom onset.

Alteplase, streptokinase, and urokinase can be used for other thromboembolic disorders such as deep-vein thrombosis and pulmonary embolism. Alteplase is also used for acute ischaemic stroke. Treatment must be started promptly.

Urokinase is also licensed to restore the patency of occluded intravenous catheters and cannulas blocked with fibrin clots.

Contra-indications Thrombolytic drugs are contra-indicated in recent haemorrhage, trauma, or surgery (including dental extraction), coagulation defects, bleeding diatheses, aortic dissection, aneurysm, coma, history of cerebrovascular disease especially recent events or with any residual disability, recent symptoms of possible peptic ulceration, heavy vaginal bleeding, severe hypertension, active pulmonary disease with cavitation, acute pancreatitis, pericarditis, bacterial endocarditis, severe liver disease, and oesophageal varices; also in the case of streptokinase, previous allergic reactions to either streptokinase or anistreplase (no longer available).

Prolonged persistence of antibodies to streptokinase and anistreplase (no longer available) can reduce the effectiveness of subsequent treatment; therefore, streptokinase should not be used again beyond 4 days of first administration of either streptokinase or anistreplase.

Side-effects Side-effects of thrombolytics are mainly nausea and vomiting and bleeding. When thrombolytics are used in myocardial infarction, reperfusion arrhythmias and recurrent ischaemia and angina may occur. Reperfusion may also cause cerebral and pulmonary oedema. Hypotension can also occur and can usually be controlled by elevating the patient’s legs, or by reducing the rate of infusion or stopping it temporarily. Back pain, fever, and convulsions have been reported. Bleeding is usually limited to the site of injection, but intracerebral haemorrhage or bleeding from other sites can occur. Serious bleeding calls for discontinuation of the thrombolytic and may require administration of coagulation factors and antifibrinolytic drugs (e.g. tranexamic acid).

Rarely further embolism may occur (either due to clots that break away from the original thrombus or to cholesterol crystal emboli). Thrombolytics can cause allergic reactions (including rash, swelling and uveitis) and anaphylaxis has been reported (for details of management see Allergic Emergencies, section 3.4.3). Guillain-Barré syndrome has been reported rarely after streptokinase treatment.

NICE guidance Alteplase for the treatment of acute ischaemic stroke (June 2007)

Alteplase, used in accordance with the licence for Actilyse®, is recommended for the treatment of acute ischaemic stroke.

Cautions Thrombolytic drugs should be used with caution if there is a risk of bleeding including that from venepuncture or invasive procedures. They should also be used with caution in external chest compression, pregnancy (Appendix 4), elderly, hypertension, conditions in which thrombolysis might give rise to embolic complications such as enlarged left atrium with atrial fibrillation (risk of dissolution of clot and subsequent embolisation), and recent or concurrent use of drugs that increase the risk of bleeding.

Side-effects see notes above; also risk of cerebral bleeding increased in acute stroke

Dose

- Myocardial infarction, accelerated regimen (initiated within 6 hours of symptom onset), 15 mg by intravenous injection, followed by intravenous infusion of 50 mg over 30 minutes, then 35 mg over 60 minutes (total dose 100 mg over 90 minutes); in patients less than 65 kg, 15 mg by intravenous injection, followed by intravenous infusion of...
0.75 mg/kg over 30 minutes, then 0.5 mg/kg over 60 minutes (max. total dose 100 mg over 90 minutes)

- Myocardial infarction, initiated within 6–12 hours of symptom onset, 10 mg by intravenous injection, followed by intravenous infusion of 50 mg over 60 minutes, then 4 infusions each of 10 mg over 30 minutes (total dose 100 mg over 3 hours; max. 1.5 mg/kg in patients less than 65 kg)

- Pulmonary embolism, 10 mg by intravenous injection over 1–2 minutes, followed by intravenous infusion of 90 mg over 2 hours; max. 1.5 mg/kg in patients less than 65 kg

- Acute stroke (treatment must begin within 3 hours of symptom onset), by intravenous administration over 60 minutes, 900 micrograms/kg (max. 90 mg); initial 10% of dose by intravenous injection, remainder by intravenous infusion; ELDERLY over 80 years not recommended

**Actilyse**® (Boehringer Ingelheim) *(INN)*

**Injection** powder for reconstitution, alteplase 10 mg (5.8 million units)/vial, net price per vial (with diluent) = £135.00; 20 mg (11.6 million units)/vial (with diluent and transfer device) = £180.00; 50 mg (29 million units)/vial (with diluent, transfer device, and infusion bag) = £300.00

<table>
<thead>
<tr>
<th><strong>STREPTOKINASE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>acute myocardial infarction (see notes above and section 2.10.1); deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism, and central retinal venous or arterial thrombosis</td>
</tr>
<tr>
<td><strong>Contra-indications</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Myocardial infarction (initiated within 12 hours of symptom onset), by intravenous infusion, 1.5 million units over 60 minutes</td>
</tr>
<tr>
<td>Deep-vein thrombosis, pulmonary embolism, acute arterial thromboembolism, central retinal venous or arterial thrombosis, by intravenous infusion, 250 000 units over 30 minutes, then 100 000 units every hour for up to 12–72 hours according to condition with monitoring of clotting parameters (consult product literature)</td>
<td></td>
</tr>
</tbody>
</table>

**Streptokinase** (Non-proprietary) *(INN)*

**Injection** powder for reconstitution, streptokinase, net price 100 000-unit vial = £10.00; 250 000-unit vial = £14.33; 750 000-unit vial = £38.20; 1.5 million-unit vial = £81.18

<table>
<thead>
<tr>
<th><strong>Streptase®</strong> (CSL Behring) <em>(INN)</em></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection</strong> powder for reconstitution, streptokinase, net price 250 000-unit vial = £15.91; 750 000-unit vial = £41.72; 1.5 million-unit vial = £83.44 (hosp. only)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>TENECTEPLASE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>acute myocardial infarction (see notes above and section 2.10.1)</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>see notes above; breast-feeding (Appendix 5)</td>
</tr>
<tr>
<td><strong>Contra-indications</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>By intravenous injection over 10 seconds (initiated within 6 hours of symptom onset), 30–50 mg according to body-weight—consult product literature; max. 50 mg</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Metalyse®</strong> (Boehringer Ingelheim) <em>(INN)</em></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection</strong> powder for reconstitution, tenecteplase, net price 40-mg (8000-unit) vial = £612.50; 50-mg (10 000-unit) vial = £612.50 (both with prefilled syringe of water for injection)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>UROKINASE</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
<td>thromboembolic occlusive vascular disease including deep-vein thrombosis, pulmonary embolism, and peripheral vascular occlusion; occluded intravenous catheters and cannulas blocked by fibrin clots</td>
</tr>
<tr>
<td><strong>Cautions</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Contra-indications</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td>see notes above</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Deep-vein thrombosis, by intravenous infusion, initially 4400 units/kg in 15 mL sodium chloride 0.9% over 10 minutes, followed by 4400 units/kg/hour for 12–24 hours</td>
</tr>
<tr>
<td>Pulmonary embolism, by intravenous infusion, initially 4400 units/kg in 15mL sodium chloride 0.9% over 10 minutes, followed by 4400 units/kg/hour for 12 hours or by injection into pulmonary artery, initially 15 000 units/kg, subsequent doses adjusted according to response; max. 3 doses in 24 hours</td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular occlusion, consult product literature</td>
<td></td>
</tr>
<tr>
<td>Occluded catheters and cannulas, by injection directly into catheter or cannula, 5000–25 000 units in 2 mL sodium chloride 0.9%; leave for up to 4 hours then aspirate the lysate</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Syner-KINASE®</strong> (Syner-Med) <em>(INN)</em></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injection</strong> powder for reconstitution, urokinase, net price 25 000-unit vial = £45.95; 100 000-unit vial = £112.95</td>
<td></td>
</tr>
</tbody>
</table>

Note 10 000-unit vial, 50 000-unit vial, and 250 000-unit vial also available from 'special-order' manufacturers or specialist-importing companies, see p. 939
2.11 Antifibrinolytic drugs and haemostatics

Fibrin dissolution can be impaired by the administration of tranexamic acid, which inhibits fibrinolysis. It can be used to prevent bleeding or to treat bleeding associated with excessive fibrinolysis (e.g. in prostatectomy, bladder surgery, in dental extraction in patients with haemophilia, in cinisation of the cervix, and in traumatic haemoptysis) and in the management of menorrhagia. Tranexamic acid may also be used in hereditary angioedema, epistaxis, and in thrombotic overdose.

Desmopressin (section 6.5.2) is used in the management of mild to moderate haemophilia and von Willebrand’s disease. It is also used for fibrinolytic response testing.

Etamsylate (ethamsylate) reduces capillary bleeding in testing.

Desmopressin (section 6.5.2) is used in the management of mild to moderate haemophilia and von Willebrand’s disease.

Tranexamic acid may also be used in hereditary angioedema, epistaxis, and in thrombotic overdose.

Blood products

ANTITHROMBIN III CONCENTRATE
Dried antithrombin III is prepared from human plasma

Indications congenital deficiency of antithrombin III

Side-effects nausea, flushing, headache, dizziness; rarely allergic reactions and fever

Available from BPL (Dried Antithrombin III)

Note Preparation of recombinant human antithrombin (antithrombin alfa) available from LEO (ATryn) indicated for the prophylaxis of venous thromboembolism in surgery in patients with congenital antithrombin deficiency

DRIED PROTHROMBIN COMPLEX
(Human Prothrombin Complex)
Dried prothrombin complex is prepared from human plasma by a suitable fractionation technique, and contains factor IX, together with variable amounts of factors II, VII, and X

Indications treatment and peri-operative prophylaxis of prothrombin of haemorrhage in patients with congenital deficiency of factors II, VII, IX, or X if purified specific coagulation factors not available; treatment and perioperative prophylaxis of haemorrhage in patients with acquired deficiency of factors II, VII, IX, or X (e.g. during warfarin treatment—see section 2.8.2)

Cautions risk of thrombosis, disseminated intravascular coagulation; history of myocardial infarction or coronary heart disease; hepatic disease; postoperative use

Contra-indications angina; recent myocardial infarction (except in life-threatening haemorrhage following overdosage of oral anticoagulants, and before induction of fibrinolytic therapy); history of heparin-induced thrombocytopenia

Side-effects thrombotic events (including disseminated intravascular coagulation); very rarely pyrexia, antibody formation, hypersensitivity reactions (including anaphylaxis); nephrotic syndrome also reported

Available from CSL Behring (Beriplex P/N▼)

DROTRECOGIN ALFA (ACTIVATED)
Recombinant activated protein C

Indications adjunctive treatment of severe sepsis with multiple organ failure—start treatment within 24 hours (and no later than 48 hours) after onset of organ failure

TRANEXAMIC ACID

Indications see notes above

Cautions renal impairment (Appendix 3); massive haematuria (avoid if risk of urteric obstruction); not for use in disseminated intravascular coagulation; irregular menstrual bleeding (establish cause before initiating therapy); pregnancy (Appendix 4); regular liver function tests in long-term treatment of hereditary angioedema

Contra-indications thromboembolic disease

Side-effects nausea, vomiting, diarrhoea (reduce dose); rarely disturbances in colour vision (discontinue), thromboembolic events, allergic skin reactions; giddiness and hypotension on rapid intravenous injection

Dose

• By mouth, local fibrinolysis, 1–1.5 g (or 15–25 mg/kg) 2–3 times daily

Menorrhagia (initiated when menstruation has started), 1 g 3 times daily for up to 4 days; max. 4 g daily

Hereditary angioedema, 1–1.5 g 2–3 times daily

Epistaxis, 1 g 3 times daily for 7 days

• By slow intravenous injection, local fibrinolysis, 0.5–1 g 3 times daily

• By continuous intravenous infusion, local fibrinolysis, following initial treatment by intravenous injection, 25–50 mg/kg over 24 hours

Cyklokapron® (Meda) Tablets, f/c, scored, tranexamic acid 500 mg, net price 60-tab pack = £14.30

Cyklokapron® (Pfizer) Injection, tranexamic acid 100 mg/mL, net price 5-ml amp = £1.55

ETAMSYLATE
(Ethamsylate)

Indications blood loss in menorrhagia

Contra-indications acute porphyria (see section 9.8.2)

Side-effects nausea, headache, rashes

Dose

500 mg 4 times daily during menstruation

Dicylene® (Sanofi-Synthelabo) Tablets, scored, etamsylate 500 mg, net price 100–tab pack = £8.78

TRANEXAMIC ACID

(Non-proprietary)

Tablets, tranexamic acid 500 mg 60-tab pack = £7.80

Drotrecogen alfa (activated) Recombinant activated protein C

Indications adjunctive treatment of severe sepsis with multiple organ failure—start treatment within 24 hours (and no later than 48 hours) after onset of organ failure
**FACTOR VIII INHIBITOR BYPASSING FRACTION**

Preparations with factor VIII inhibitor bypassing activity are prepared from human plasma.

**Indications**
treatment and prophylaxis of haemorrhage in patients with congenital factor VIII deficiency (haemophilia A) and factor VIII inhibitors; treatment of haemorrhage in non-haemophilic patients with acquired factor VIII inhibitors

**Contra-indications**
disseminated intravascular coagulation

**Side-effects**
paraeesthesia; pyrexia; allergic reactions including hypotension, flushing, urticaria, rash, and anaphylaxis

Available from Baxter (FEIBA)

**FACTOR IX FRACTION, DRIED**

Dried factor IX fraction is prepared from human plasma by a suitable fractionation technique; it may also contain clotting factors II, VII, and X

**Indications**
treatment and prophylaxis of haemorrhage in congenital factor IX deficiency (haemophilia B)

**Cautions**
risk of thrombosis—principally with former low purity products

**Contra-indications**
disseminated intravascular coagulation

**Side-effects**
gastro-intestinal disturbances; headache, dizziness; allergic reactions, including chills, fever

Available from CSL Behring (NovoSeven)

**FACTOR VIIa (RECOMBINANT)**

**Eptacog alfa (activated)**

**Indications**
treatment and prophylaxis of haemorrhage in patients with haemophilia A or B with inhibitors to factors VIII or IX, acquired haemophilia, factor VII deficiency, or Glanzmann's thrombasthenia

**Cautions**
risk of thrombosis or disseminated intravascular coagulation

**Side-effects**
very rarely, nausea, thrombotic events (including myocardial infarction and cerebrovascular accident), coagulation disorders, fever, pain, and allergic reactions including rash

Available from Novo Nordisk (NovoSeven)

**FACTOR VIII FRACTION, DRIED**

(Human Antihaemophilic Fraction, Dried)

Dried factor VIII fraction is prepared from human plasma by a suitable fractionation technique

**Indications**
treatment and prophylaxis of haemorrhage in patients with haemophilia A or B, acquired factor VIII deficiency, von Willebrand's disease

**Cautions**
monitor for development of factor VIII inhibitors; intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B, or AB—less likely with high potency concentrates

**Side-effects**
gastro-intestinal disturbances, taste disturbances; flushing, palpitation; dyspnoea, coughing; headache, dizziness, paraesthesia, drowsiness; blurred vision; antibody formation; hypersensitivity reactions including hypotension, angioedema, chills, fever, urticaria, and anaphylaxis

Available from Biotest UK (Haemocin ), CSL Behring (Hemate VP), BPL (Optivate , High Purity Factor VIII and von Willebrand factor concentrate; 60%), Grifols (Alphanate , Fanvido ), Octapharma (Octanate )

**Note**
Preparation of recombinant human antihaemophilic factor VIII (octocog alfa) available from CSL Behring (Helixate NexGen), Baxter (Advate ), Bayer (Kogenate-Bayer), Wyeth (ReFacto )

**PROTEIN C CONCENTRATE**

Protein C is prepared from human plasma

**Indications**
congenital protein C deficiency

**Cautions**
hypersensitivity to heparin

**Side-effects**
fever, arrhythmia, bleeding and thrombosis reported; rarely allergic reactions

Available from Baxter (Ceprotin )
2.12 Lipid-regulating drugs

Preventative measures should be taken in individuals with a high risk of developing cardiovascular disease (primary prevention) and to prevent recurrence of events in those with established cardiovascular disease (secondary prevention). Individuals at high risk include those who already have atherosclerotic disease, those with diabetes mellitus aged over 40 years, and those with familial hypercholesterolaemia. The risk also increases with age; those over 75 years are at particularly high risk, especially if they smoke or have hypertension.

Preventative measures are also required for other individuals who may be at high risk of developing atherosclerotic cardiovascular disease; those with a 10-year risk of cardiovascular disease of 20% or more stand to benefit most from drug treatment. The risk is assessed on the basis of lipid concentration as well as smoking status, blood pressure, gender, and age; other risk factors, such as premature menopause, ethnicity, obesity, triglyceride concentration, chronic kidney disease, impaired glucose tolerance, and a family history of premature cardiovascular disease, should also be taken into account when assessing risk in individual patients.

Lowering the concentration of low-density lipoprotein (LDL) cholesterol and raising high-density lipoprotein (HDL) cholesterol slows the progression of atherosclerosis and may even induce regression. All patients at high risk of cardiovascular disease should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation. Lipid-regulating drug treatment must be combined with advice on diet and lifestyle measures, lowering of raised blood pressure (section 2.5), the use of low-dose aspirin (section 2.9), and management of diabetes (section 6.1).

The prescribing of drug therapy in homozygous familial hypercholesterolaemia should be undertaken within a specialist centre. A statin (see below) reduces the risk of cardiovascular disease events, irrespective of serum cholesterol concentration, and is the drug of first choice for primary and secondary prevention of cardiovascular disease. If statins are contra-indicated or not tolerated, a fibrate (p. 144) or a bile acid sequestrant (p. 143) may be considered for primary or secondary prevention, nicotinic acid (p. 146) is also an option for secondary prevention. Fibrates, bile acid sequestrants, or nicotinic acid should not be used in combination with a statin or ezetimibe.

Individuals at high risk include those who already have atherosclerotic disease, those with diabetes mellitus aged over 40 years, and those with familial hypercholesterolaemia. The risk also increases with age; those over 75 years are at particularly high risk, especially if they smoke or have hypertension.

Preventive measures are also required for other individuals who may be at high risk of developing atherosclerotic cardiovascular disease; those with a 10-year risk of cardiovascular disease of 20% or more stand to benefit most from drug treatment. The risk is assessed on the basis of lipid concentration as well as smoking status, blood pressure, gender, and age; other risk factors, such as premature menopause, ethnicity, obesity, triglyceride concentration, chronic kidney disease, impaired glucose tolerance, and a family history of premature cardiovascular disease, should also be taken into account when assessing risk in individual patients.

Lowering the concentration of low-density lipoprotein (LDL) cholesterol and raising high-density lipoprotein (HDL) cholesterol slows the progression of atherosclerosis and may even induce regression. All patients at high risk of cardiovascular disease should be advised to make lifestyle modifications that include beneficial changes to diet, exercise, weight management, alcohol consumption, and smoking cessation. Lipid-regulating drug treatment must be combined with advice on diet and lifestyle measures, lowering of raised blood pressure (section 2.5), the use of low-dose aspirin (section 2.9), and management of diabetes (section 6.1).

The prescribing of drug therapy in homozygous familial hypercholesterolaemia should be undertaken within a specialist centre. A statin (see below) reduces the risk of cardiovascular disease events, irrespective of serum cholesterol concentration, and is the drug of first choice for primary and secondary prevention of cardiovascular disease. If statins are contra-indicated or not tolerated, a fibrate (p. 144) or a bile acid sequestrant (p. 143) may be considered for primary or secondary prevention, nicotinic acid (p. 146) is also an option for secondary prevention. Fibrates, bile acid sequestrants, or nicotinic acid should not be used in combination with a statin or ezetimibe.

The statins (atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin) competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. Statins are more effective than other lipid-regulating drugs at lowering LDL-cholesterol concentration but they are less effective than the fibrates in reducing triglyceride concentration. However, statins reduce cardiovascular disease events and total mortality irrespective of the initial cholesterol concentration.

Statins should be considered for all patients, including the elderly, with symptomatic cardiovascular disease such as those with coronary heart disease (including history of angina or acute myocardial infarction), occlusive arterial disease (including peripheral vascular disease, non-haemorrhagic stroke, or transient ischaemic attacks). In patients with diabetes mellitus, the risk of developing cardiovascular disease depends on the duration and complications of diabetes, age, and concomitant risk factors. Statin therapy should be considered for all patients over 40 years with diabetes mellitus (type 1 and 2). In younger patients with diabetes, treatment with a statin should be considered if there is target-risk of myositis with lipid-regulating drugs.
organ damage, poor glycaemic control (HbA1c greater than 9%), low HDL-cholesterol and raised triglyceride concentration, hypertension, or a family history of premature cardiovascular disease.

Statins are also used for the prevention of cardiovascular disease events in asymptomatic individuals who are at increased risk (see p. 140). Statin treatment should also be considered if the total cholesterol concentration to HDL-cholesterol ratio exceeds 6.

Cautions Statins should be used with caution in those with a history of liver disease or with a high alcohol intake (use should be avoided in active liver disease). Hypothyroidism should be managed adequately before starting treatment with a statin (see p. 140). There is little information available on a rational approach to liver-function monitoring; however, a NICE guideline suggests that liver enzymes should be measured before treatment, and repeated within 3 months and at 12 months of starting treatment, unless indicated at other times by signs or symptoms suggestive of hepatotoxicity. Those with severe transaminases that are raised, but less than 3 times the upper limit of the reference range, should not be routinely excluded from statin therapy. Those with serum transaminases of more than 3 times the upper limit of the reference range should discontinue statin therapy. Statins should be used with caution in those with risk factors for myopathy, such as infections, hypothyroidism, or renal impairment secondary to myoglobinuria. Rhabdomyolysis with acute renal impairment secondary to myoglobinuria has also been reported.

Counselling Advise patient to report promptly unexplained muscle pain, tenderness, or weakness.

ATORVASTATIN

Indications primary hypercholesterolaemia, heterozygous familial hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures; prevention of cardiovascular events in patients with type 2 diabetes and at least one additional risk factor for cardiovascular disease

Cautions see notes above; also haemorrhagic stroke

Side-effects see notes above; also chest pain; back pain; less commonly anorexia, malaise, weight gain, hypoglycaemia, hyperglycaemia, tinnitus; rarely cholesterol jaundice, peripheral oedema; very rarely taste disturbances, gyanaecomastia, hearing loss, Stevens-Johnson Syndrome, and toxic epidermal necrolysis

Dose • Primary hypercholesterolaemia and combined hyperlipidaemia, usually 10 mg once daily; if necessary, may be increased at intervals of at least 4 weeks to max. 80 mg once daily; CHILD 10–17 years usually 10 mg once daily (limited experience with doses above 20 mg daily)
• Familial hypercholesterolaemia, initially 10 mg daily, increased at intervals of at least 4 weeks to 40 mg once daily; if necessary, further increased to max. 80 mg once daily (or 40 mg once daily combined with anion-exchange resin in heterozygous familial hypercholesterolaemia); CHILD 10–17 years initially 10 mg daily, increased if necessary after at least 4 weeks to 20 mg once daily (limited experience with higher doses)
• Prevention of cardiovascular events in type 2 diabetes, 10 mg once daily

Note Max. 10 mg daily with concomitant ciclosporin; max. 20 mg daily (or temporarily discontinue atorvastatin) with concomitant clarithromycin; close monitoring of liver function and, if symptomatic, of creatine kinase is required in patients receiving these drugs. Rhabdomyolysis with acute renal impairment secondary to myoglobinuria has also been reported.

Lipitor® (Pfizer) \[A\] Tablets, all U.K. atorvastatin (as calcium trihydrate) 10 mg, net price 28-tab pack = £18.03; 20 mg, 28-tab pack = £24.64; 40 mg 28-tab pack = £28.21; 80 mg, 28-tab pack = £28.21. Counselling, muscle effects, see notes above

FLUVASTATIN

Note The Scottish Medicines Consortium has advised (February 2004) that fluvastatin is accepted for restricted use for the secondary prevention of coronary events after percutaneous coronary angioplasty; if the patient has previously been receiving another statin, then there is no need to change the statin

Indications adjunct to diet in primary hypercholesterolaemia or combined (mixed) hyperlipidaemia (types IIa and IIb); adjunct to diet to slow
progression of coronary atherosclerosis in primary hypercholesterolaemia and concomitant coronary heart disease; prevention of coronary events after percutaneous coronary intervention

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; also very rarely vasculitis

**Dose**
- Hypercholesterolaemia or combined hyperlipidaemia, initially 20–40 mg daily in the evening, adjusted at intervals of at least 4 weeks; up to 80 mg daily may be required; **CHILD** under 18 years, not recommended
- Prevention of progression of coronary atherosclerosis, 40 mg daily in the evening
- Following percutaneous coronary intervention, 80 mg daily

**Lescol** (Novartis) (Pink)
- **Capsules**, pravastatin (as sodium salt) 20 mg (brown/orange), net price 28-cap pack = £15.26; 40 mg (brown/orange), 28-cap pack = £15.26, 56-cap pack = £30.53. Counselling, muscle effects, see notes above

**Modified release**
- **Lescol® XL** (Novartis) (Pink)
  - **Tablets**, m/r, yellow, pravastatin (as sodium salt) 80 mg, net price 28-tab pack = £19.20. Label: 25, counselling, muscle effects, see notes above
  - **Dose** 80 mg once daily (dose form not appropriate for initial dose titration in hypercholesterolaemia or combined hyperlipidaemia)

### PRAVASTATIN SODIUM

**Indications** adjunct to diet for primary hypercholesterolaemia or combined (mixed) hyperlipidaemias in patients who have not responded adequately to dietary control; adjunct to diet to prevent cardiovascular events in patients with hypercholesterolaemia; prevention of cardiovascular events in patients with previous myocardial infarction or unstable angina; reduction of hyperlipidaemia in patients receiving immunosuppressive therapy following solid-organ transplantation

**Cautions** see notes above; renal impairment (Appendix 3)

**Contra-indications** see notes above

**Side-effects** see notes above; less commonly abnormal urination (including dysuria, nocturia and frequency); very rarely fulminant hepatic necrosis

**Dose**
- Hypercholesterolaemia or combined hyperlipidaemias, 10–40 mg once daily at night, adjusted at intervals of at least 4 weeks
- Familial hypercholesterolaemia, **CHILD** 8–14 years 10–20 mg once daily at night, 14–18 years 10–40 mg once daily at night
- Prevention of cardiovascular events, 40 mg once daily at night
- Post-transplantation hyperlipidaemia, initially 20 mg once daily at night, increased if necessary (under close medical supervision) to max. 40 mg once daily at night

**Pravastatin** (Non-proprietary) (Pink)
- **Tablets**, pravastatin sodium 10 mg, net price 28-tab pack = £1.73; 20 mg, 28-tab pack = £2.22; 40 mg, 28-tab pack = £2.77. Counselling, muscle effects, see notes above

**Lipostat** (Squibb) (Pink)
- **Tablets**, all yellow, pravastatin sodium 10 mg, net price 28-tab pack = £15.05; 20 mg, 28-tab pack = £27.61; 40 mg, 28-tab pack = £27.61. Counselling, muscle effects, see notes above

### ROSUVASTATIN

**Indications** primary hypercholesterolaemia (type IIa including heterozygous familial hypercholesterolaemia), mixed dyslipidaemia (type IIb), or homozygous familial hypercholesterolaemia in patients who have not responded adequately to diet and other appropriate measures

**Cautions** see notes above; patients of Asian origin (see under Dose): max. dose 20 mg in patients with risk factors for myopathy or rhabdomyolysis (including personal or family history of muscular disorders or toxicity); renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3)

**Contra-indications** see notes above

**Side-effects** see notes above; also proteinuria; very rarely haematuria

**Dose**
- Initially 5–10 mg once daily increased if necessary at intervals of at least 4 weeks to 20 mg once daily, increased after further 4 weeks to 40 mg daily only in severe hypercholesterolaemia with high cardiovascular risk and under specialist supervision; **ELDERLY** initially 5 mg once daily; patient of **ASIAN** origin, initially 5 mg once daily increased if necessary to max. 20 mg daily

**Note** Initially 5 mg once daily with concomitant fibrate increased if necessary to max. 20 mg daily

**Crestor** (AstraZeneca) (Pink)
- **Tablets**, 1/c, rosuvastatin (as calcium salt) 5 mg (yellow), net price 28-tab pack = £18.03; 10 mg (pink), 28-tab pack = £18.03; 20 mg (pink), 28-tab pack = £26.02; 40 mg (pink), 28-tab pack = £29.69. Counselling, muscle effects, see notes above

### SIMVASTATIN

**Indications** primary hypercholesterolaemia, homozygous familial hypercholesterolaemia or combined (mixed) hyperlipidaemia in patients who have not responded adequately to diet and other appropriate measures; prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease or diabetes mellitus

**Cautions** see notes above; renal impairment (Appendix 3)

**Contra-indications** see notes above

**Side-effects** see notes above; also rarely anaemia

**Dose**
- Primary hypercholesterolaemia, combined hyperlipidaemia, 10–20 mg daily at night, adjusted at intervals of at least 4 weeks; usual range 10–80 mg once daily at night
- Homozygous familial hypercholesterolaemia, 40 mg daily at night or 80 mg daily in 3 divided doses (with largest dose at night)
Bile acid sequestrants

Colestyramine, colestipol, and colestyramine (cholestyramine) are bile acid sequestrants used in the management of hypercholesterolaemia. They act by binding bile acids, preventing their reabsorption; this promotes hepatic conversion of cholesterol into bile acids; the resultant increased LDL-receptor activity of liver cells increases the clearance of LDL-cholesterol from the plasma. Bile acid sequestrants effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia.

The Scottish Medicines Consortium (p. 3) has advised (January 2008) that colestyramine hydrochloride (Colestyramine) is not recommended for use within NHS Scotland for the treatment of primary hypercholesterolaemia as an adjunct to dietary measures, either alone or with a statin.

Cautions Bile acid sequestrants interfere with the absorption of fat-soluble vitamins; supplements of vitamins A, D, and K may be required when treatment is prolonged. Interactions: Appendix 1 (bile acid sequestrants)

Side-effects As bile acid sequestrants are not absorbed, gastro-intestinal side-effects predominate.

1. Simvastatin 10mg tablets can be sold to the public to reduce risk of first coronary event in individuals at moderate risk of coronary heart disease (approx. 10–15% risk of major event in 10 years), max. daily dose 10 mg and pack size of 28 tablets; treatment should form part of a programme to reduce risk of coronary heart disease; a proprietary brand Zocor Heart-Pro is on sale to the public

Constipation is common, but diarrhoea has occurred, as have nausea, vomiting, and gastro-intestinal discomfort. Hypertriglyceridaemia may be aggravated. An increased bleeding tendency has been reported due to hypoprothrombinaemia associated with vitamin K deficiency.

Counselling Other drugs should be taken at least 1 hour before or 4–6 hours after bile acid sequestrants to reduce possible interference with absorption. Colesevelam and a statin can be taken at the same time.

COLESEVELAM HYDROCHLORIDE

Indications primary hypercholesterolaemia as an adjunct to dietary measures, either alone or with a statin

Cautions see notes above; also gastro-intestinal motility disorders, major gastro-intestinal surgery, inflammatory bowel disease, hepatic impairment; pregnancy (Appendix 4); breastfeeding (Appendix 5)

Contra-indications bowel or biliary obstruction

Side-effects see notes above; also headache; myalgia

Dose

• Monotherapy, 3.75 g daily in 1–2 divided doses; max. 4.375 g daily

• Combination therapy with statin, 2.5–3.75 g daily in 1–2 divided doses

Cholestyramine COLESTYRAMINE (Cholestyramine)

Indications hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures; primary prevention of coronary heart disease in men aged 35–59 years with primary hypercholesterolaemia who have not responded to diet and other appropriate measures; pruritus associated with partial biliary obstruction and primary biliary cirrhosis (section 1.9.2); diarrhoeal disorders (section 1.9.2)

Cautions see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (colestyraralmine)

Contra-indications complete biliary obstruction (not likely to be effective)

Side-effects see notes above; intestinal obstruction reported rarely and hyperchloraemic acidosis reported on prolonged use

Dose

• Lipid reduction, initially 4 g daily increased by 4 g at weekly intervals to 12–24 g daily in 1–4 divided doses, then adjusted as required; max. 56 g daily

• Pruritus, see section 1.9.2

• Diarrhoeal disorders, see section 1.9.2

• CHILD 6–12 years, see BNF for Children

Note The contents of each sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, and pulpy fruits with a high moisture content
Colestyramine (Non-proprietary) (TM)
Powder, sugar-free, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £18.20. Label: 13, counselling, avoid other drugs at same time (see notes above) Excipients include aspartame (section 9.4.1)

Questran® (Bristol-Myers Squibb) (TM)
Powder, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £11.42. Label: 13, counselling, avoid other drugs at same time (see notes above) Excipients include sucrose 3.79g/sachet

Questran Light® (Bristol-Myers Squibb) (TM)
Powder, sugar-free, colestyramine (anhydrous) 4 g/sachet, net price 50-sachet pack = £16.99. Label: 13, counselling, avoid other drugs at same time (see notes above) Excipients include aspartame (section 9.4.1)

Ezetimibe
Indications adjunct to dietary measures and statin treatment in primary hypercholesterolaemia and homozygous familial hypercholesterolaemia (ezetimibe alone in primary hypercholesterolaemia if statin inappropriate or not tolerated); adjunct to dietary measures in homozygous sitosterolaemia
Cautions hepatic impairment (avoid if moderate or severe; Appendix 2); pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (ezetimibe)
Side-effects gastro-intestinal disturbances; headache; fatigue; myalgia; rarely arthralgia, hypersensitivity reactions (including rash, angioedema, and anaphylaxis); hepatitis; very rarely pancreatitis, cholelithiasis, cholecystitis, thrombocytopenia, raised creatine kinase, myopathy, and rhabdomyolysis

Dose • ADULT and CHILD over 10 years, 10 mg once daily
Ezetrol® (MSD, Schering-Plough) ▼ (TM)
Tablets, ezetimibe 10 mg, net price 28-tab pack = £26.31

Ezetimibe 10 mg, net price 28-tab pack = £26.31

COLESTIPOL HYDROCHLORIDE
Indications hyperlipidaemias, particularly type IIa, in patients who have not responded adequately to diet and other appropriate measures
Cautions see notes above; pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (colestipol)
Side-effects see notes above

Dose • Initially 5 g 1–2 times daily in liquid increased if necessary in 5-g increments at intervals of 1 month to max. 30 g daily (in 1–2 divided doses)

Note The contents of each sachet should be mixed with at least 100 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, yoghurt, and pulpy fruits with a high moisture content

Colestid® (Pharmacia) (TM)
Granules, yellow, colestipol hydrochloride 5 g/sachet, net price 30 sachets = £15.05. Label: 13, counselling, avoid other drugs at same time (see notes above)

Colestid Orange, granules, yellow/orange, colestipol hydrochloride 5 g/sachet, with aspartame, net price 30 sachets = £15.05. Label: 13, counselling, avoid other drugs at same time (see notes above)

Ezetimibe
Ezetimibe inhibits the intestinal absorption of cholesterol. It is licensed as an adjunct to dietary manipulation in patients with primary hypercholesterolaemia in combination with a statin or alone (if a statin is inappropriate), in patients with homozygous familial hypercholesterolaemia in combination with a statin, and in patients with homozygous familial sitosterolaemia (phytosterolaemia). If ezetimibe is used in combination with a statin, there is an increased risk of rhabdomyolysis (see also CSM advice on p. 140).

NICE guidance
Ezetimibe for the treatment of primary hypercholesterolaemia (November 2007)
Ezetimibe, used in accordance with the licensed indications for Ezetrol®, is an option for the treatment of adults with primary hypercholesterolaemia.

Ezetimibe
Indications hyperlipidaemias, particularly type IIa, IIb, III, IV, and V in patients who have not responded adequately to diet and other appropriate measures; also see notes above
Cautions correct hypothyroidism before initiating treatment (see p. 140); hepatic impairment (avoid if severe; Appendix 2); renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3; see also under Myotoxicity below); interactions: Appendix 1 (fibrate)
Myotoxicity Special care needed in patients with renal disease, as progressive increases in serum creatinine concentration or failure to follow dosage guidelines may result in myotoxicity (rhabdomyolysis); discontinue if myotoxicity suspected or creatine kinase concentration increases significantly
**Contra-indications** hypoalbuminaemia, primary biliary cirrhosis, gall bladder disease, nephrotic syndrome, pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances, anorexia; less commonly cholestasis, weight gain, dizziness, headache, fatigue, drowsiness, renal impairment, raised serum creatinine (unrelated to renal impairment), erectile dysfunction, myotoxicity (with myasthenia or myalgia)—special risk in renal impairment (see Cautions), urticaria, pruritus, photosensitivity reactions; very rarely gallstones, hypoglycaemia, anaemia, leucopenia, thrombocytopenia, increased platelet count, alopecia, Stevens-Johnson syndrome, and toxic epidermal necrolysis

**Dose**
- See preparations below

**Bezafibrate** (Non-proprietary) Tablets, bezafibrate 200 mg, net price 100-tab pack = £11.23. Label: 21
- Dose 200 mg 3 times daily; CHILD over 10 years, see BNF for Children

**Bezalip** (Roche) Tablets, f/c, bezafibrate 200 mg, net price 100-tab pack = £9.15. Label: 21
- Dose 200 mg 3 times daily; CHILD over 10 years, see BNF for Children

**Modified release** Bezafibrate (Non-proprietary) Tablets, m/r, bezafibrate 400 mg, net price 28-tab pack = £7.68. Label: 21, 25
- Dose 400 mg once daily (dose form not appropriate in patients with renal impairment)
- Brands include Fibrazate XL, Zimbacol XL

**Bezalip® Mono** (Roche) Tablets, m/r, f/c, bezafibrate 400 mg, net price 30-tab pack = £8.09. Label: 21, 25
- Dose 400 mg once daily (dose form not appropriate in patients with renal impairment)

**CIPROFIBRATE**

**Indications** hyperlipidaemias of types IIa, IIb, III, and IV in patients who have not responded adequately to diet; also see notes above

**Cautions** see under Bezafibrate; renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3)

**Contra-indications** see under Bezafibrate

**Side-effects** see under Bezafibrate

**Dose**
- 100 mg daily

**Modalin®** (Winthrop) Tablets, scored, ciprofibrate 100 mg, Net price 28-tab pack = £17.66

**FENOFIBRATE**

**Indications** hyperlipidaemias of types IIa, IIb, III, IV, and V in patients who have not responded adequately to diet and other appropriate measures; also see notes above

**Cautions** see under Bezafibrate; liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised); renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3)

**Contra-indications** gall bladder disease; photosensitivity to ketoprofen; severe hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see under Bezafibrate; also very rarely hepatitis, pancreatitis, and interstitial pneumopathies

**Dose**
- See preparations below

**Fenofibrate** (Non-proprietary) Capsules, fenofibrate (micronised) 200 mg, net price 28-cap pack = £14.23. Label: 21
- Dose 1 capsule daily (dose form not appropriate for children or in renal impairment)

**Lipantil®** (Solvay) Capsules, fenofibrate (micronised) 67 mg, net price 90-cap pack = £23.30. Label: 21
- Dose initially 3 capsules daily in divided doses; usual range 2–4 capsules daily. CHILD 4–15 years 1 capsule/20 kg daily

**Lipantil® Micro** Capsules, orange, fenofibrate (micronised) 200 mg, net price 28-cap pack = £17.95. Label: 21
- Dose initially 1 capsule daily (dose form not appropriate for children or in renal impairment)

**Supralip® 160** (Solvay) Capsules, orange/cream, fenofibrate (micronised) 267 mg, net price 28-cap pack = £21.75. Label: 21
- Dose severe hyperlipidaemia, 1 capsule daily (dose form not appropriate for children or in renal impairment)

**GEMFIBROZIL**

**Indications** hyperlipidaemias of types IIa, IIb, III, IV and V in patients who have not responded adequately to diet and other appropriate measures; primary prevention of cardiovascular disease in men with hyperlipidaemias that have not responded to diet and other appropriate measures; also see notes above

**Cautions** lipid profile, blood counts, and liver-function tests before initiating long-term treatment; preferably avoid use with statins (high risk of rhabdomyolysis); correct hypothyroidism before initiating treatment (see p. 140); elderly; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); interactions: Appendix 1 (fibrates)

**Contra-indications** alcoholism, biliary-tract disease including gallstones; photosensitivity to fibrates; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances; headache, fatigue, vertigo; eczema, rash; less commonly atrial fibrillation; rarely pancreatitis, appendicitis, disturbances in liver function including hepatitis and cholestatic jaundice, dizziness, paraesthesia, sexual dysfunction, thrombocytopenia, anaemia, leucopenia, eosinophilia, bone-marrow suppression, myalgia, myopathy, myasthenia, myositis accompanied by increase in creatine kinase (discontinue if raised sig-
2 Cardiovascular system

2.12 Lipid-regulating drugs

BNF 57

nificantly), blurred vision, exfoliative dermatitis, alopecia, and photosensitivity)

**Dose**
- 1.2 g daily, usually in 2 divided doses; range 0.9–1.2 g daily; **CHILD** not recommended

**Gemfibrozil** (Non-proprietary) \(\text{Gemfibrozil} \) 300 mg, net price 112-cap pack = £46.70. Label: 22

**Capsules**, gemfibrozil 300 mg, net price 30-tab pack = £10.94. Label: 22

**Tablets**, gemfibrozil 600 mg, net price 30-tab pack = £33.30. Label: 22

**Lolid** (Pfizer) \(\text{Gemfibrozil} \) \(\text{Pfizer} \)

‘300’ capsules, white/maroon, gemfibrozil 300 mg, net price 112-cap pack = £35.57. Label: 22

‘600’ tablets, f/c, gemfibrozil 600 mg, net price 56-tab pack = £35.57. Label: 22

**Nicotinic acid group**

The value of **nicotinic acid** is limited by its side-effects, especially vasodilatation. In doses of 1.5 to 3 g daily it lowers both cholesterol and triglyceride concentrations by inhibiting synthesis; it also increases HDL-cholesterol. Nicotinic acid is licensed for use with a statin if the statin alone cannot adequately control dyslipidaemia (raised LDL-cholesterol, triglyceridaemia, and low HDL-cholesterol); it can be used alone if the patient is intolerant of statins (for advice on treatment of dyslipidaemia, including use of combination treatment, see p. 140). The Scottish Medicines Consortium has advised (January 2006) that **Niaspan** is not recommended for the treatment of dyslipidaemia.

**Acipimox** seems to have fewer side-effects than nicotinic acid but may be less effective in its lipid-modulating capabilities.

**ACIPIMOX**

**Indications** hyperlipidaemias of types IIb and IV in patients who have not responded adequately to diet and other appropriate measures

**Cautions** renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3)

**Contra-indications** peptic ulcer; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** vasodilatation, flushing, itching, rashes, urticaria, erythema; heartburn, epigastric pain, nausea, diarrhoea, headache, malaise, dry eyes; rarely angioedema, bronchospasm, anaphylaxis

**Dose**
- Usually 500–750 mg daily in divided doses

**Olibetam** (Pharmacia) \(\text{Olibetam} \) \(\text{Pharmacia} \)

**Capsules**, brown/pink, acipimox 250 mg, net price 90-cap pack = £46.33. Label: 21

**NICOTINIC ACID**

**Indications** adjunct to statin in dyslipidaemia or used alone if statin not tolerated (see also p. 140)

**Cautions** unstable angina, acute myocardial infarction, diabetes mellitus, gout, history of peptic ulceration; hepatic impairment (Appendix 2); renal impairment; pregnancy (Appendix 4); **interactions**: Appendix 1 (nicotinic acid)

**Contra-indications** arterial bleeding; active peptic ulcer disease; breast-feeding

**Side-effects** diarrhoea, nausea, vomiting, abdominal pain, dyspepsia; flushing; pruritus, rash; **less commonly** tachycardia, palpitation, shortness of breath, peripheral oedema, headache, dizziness, increase in uric acid, hypophosphataemia, prolonged prothrombin time, and reduced platelet count; **rarely** hypotension, syncope, rhinitis, insomnia, reduced glucose tolerance, myalgia, myopathy, and myasthenia; **very rarely** anorexia, rhabdomyolysis

**Note** Prostaglandin-mediated symptoms (such as flushing) can be reduced by low initial doses taken with meals or, if patient taking aspirin, aspirin dose should be taken 30 minutes before nicotinic acid

**Dose**
- See under preparation

**Modified release**

**Niaspan** (Abbott) \(\text{Niaspan} \) \(\text{Abbott} \)

**Tablets**, m/r, nicotinic acid 500 mg, net price 56-tab pack = £17.25. 750 mg, 56-tab pack = £26.25. 1 g, 56-tab pack = £34.75. 21-day starter pack of 7 × 375-mg tab with 7 × 500-mg tab and 7 × 750-mg tab = £14.00. Label: 21, 25

**Dose**
- 375 mg once daily at night (after a low-fat snack) for 1 week, then 500 mg once daily at night for 1 week, then 750 mg once daily at night for 1 week, then 1 g once daily at night for 4 weeks. Increased if necessary in steps of 500 mg at intervals of at least 4 weeks to max. 2 g daily; usual maintenance dose 1–2 g once daily at night

**Omega-3 fatty acid compounds**

The omega-3 fatty acid compounds comprise omega-3-acid ethyl esters (**Omacor**) and omega-3-marine triglycerides (**Maxepa**). Omega-3 fatty acid compounds may be used to reduce triglycerides, as an alternative to a fibrate and in addition to a statin, in patients with combined (mixed) hyperlipidaemia not adequately controlled with a statin alone. A triglyceride concentration exceeding 10 mmol/litre is associated with acute pancreatitis and lowering the concentration reduces this risk. The fat content of omega-3 fatty acid compounds (including excipients in the preparations) should be taken into consideration when treating hypertriglyceridaemia. There is little clinical trial evidence that the triglyceride lowering effect decreases the risk of cardiovascular disease.

The Scottish Medicines Consortium (p. 3) has advised (November 2002) that **omega-3-acid ethyl esters** (**Omacor**) is not recommended for use within NHS Scotland for the treatment of hypertriglyceridaemia.

**OMEGA-3-ACID ETHYL ESTERS**

**Indications** adjunct to diet and statin in type IIb or III hypertriglyceridaemia; adjunct to diet in type IV hypertriglyceridaemia; adjunct in secondary prevention in those who have had a myocardial infarction in the preceding 3 months

**Cautions** haemorrhagic disorders, anticoagulant treatment (bleeding time increased); hepatic impairment (Appendix 2); pregnancy (Appendix 4)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances; **less commonly** taste disturbances, dizziness, and hypersensitivity reactions; **rarely** hepatic disorders, headache, hyperglycaemia, acne, and rash; **very rarely** hypo-
tension, nasal dryness, urticaria, and increased white cell count

**Dose**

- See under preparation below

**Omacor** (Solvay)

Capsules, 1 g of omega-3-acid ethyl esters containing eicosapentaenoic acid 460 mg and docosahexaenoic acid 380 mg, net price 28-cap pack = £13.89, 100-cap pack = £49.60. Label: 21

**Dose** hypertriglyceridaemia, initially 2 capsules daily with food, increased if necessary to 4 capsules daily

Secondary prevention after myocardial infarction, 1 capsule daily with food

**OMEGA-3-MARINE TRIGLYCERIDES**

**Indications** adjunct in the reduction of plasma triglycerides in severe hypertriglyceridaemia

**Cautions** haemorrhagic disorders, anticoagulant treatment; aspirin-sensitive asthma; type 2 diabetes

**Side-effects** occasional nausea and belching

**Dose**

- See under preparations below

**Maxepa** (Seven Seas)

Capsules, 1 g (approx. 1.1 mL) concentrated fish oils containing eicosapentaenoic acid 170 mg, docosahexaenoic acid 115 mg. Vitamin A content less than 100 units/g, vitamin D content less than 10 units/g, net price 200-cap pack = £27.28. Label: 21

**Dose** 5 capsules twice daily with food

Liquid, golden-coloured, concentrated fish oils containing eicosapentaenoic acid 170 mg, docosahexaenoic acid 115 mg/g (1.1 mL). Vitamin A content less than 100 units/g, vitamin D content less than 10 units/g, net price 150 mL = £20.46. Label: 21

**Dose** 5 mL twice daily with food

---

**2.13 Local sclerosants**

Ethanolamine oleate and sodium tetradecyl sulphate are used in sclerotherapy of varicose veins, and phenol is used in haemorrhoids (section 1.7.3).

**ETHANOLAMINE OLEATE**

(Monoethanolamine Oleate)

**Indications** sclerotherapy of varicose veins

**Cautions** extravasation may cause necrosis of tissues

**Contra-indications** inability to walk, acute phlebitis, oral contraceptive use, obese legs

**Side-effects** allergic reactions (including anaphylaxis)

**Ethanolamine Oleate** (UCB Pharma) (Non)

**Injection**, ethanolamine oleate 5%, net price 2-mL amp = £3.19, 5-mL amp = £2.28

**Dose** by slow injection into empty isolated segment of vein, 2–5 mL divided between 3–4 sites; repeated at weekly intervals

---

**SODIUM TETRADECYL SULPHATE**

**Indications** sclerotherapy of varicose veins

**Cautions** see under Ethanolamine Oleate

**Contra-indications** see under Ethanolamine Oleate

**Side-effects** see under Ethanolamine Oleate
3 Respiratory system

3.1 Bronchodilators

3.1.1 Adrenoceptor agonists

3.1.1.1 Selective beta₂ agonists

3.1.1.2 Other adrenoceptor agonists

3.1.2 Antimuscarinic bronchodilators

3.1.3 Theophylline

3.1.4 Compound bronchodilator preparations

3.1.5 Peak flow meters, inhaler devices and nebulisers

3.2 Corticosteroids

3.3 Cromoglicate and related therapy and leukotriene receptor antagonists

3.3.1 Cromoglicate and related therapy

3.3.2 Leukotriene receptor antagonists

3.4 Antihistamines, hyposensitisation, and allergic emergencies

3.4.1 Antihistamines

3.4.2 Allergen Immunotherapy

3.4.3 Allergic emergencies

3.5 Respiratory stimulants and pulmonary surfactants

3.5.1 Respiratory stimulants

3.5.2 Pulmonary surfactants

3.6 Oxygen

3.7 Mucolytics

3.8 Aromatic inhalations

3.9 Cough preparations

3.9.1 Cough suppressants

3.9.2 Expectorant and demulcent cough preparations

3.10 Systemic nasal decongestants

Asthma

Drugs used in the management of asthma include beta agonists (section 3.1.1), antimuscarinic bronchodilators (section 3.1.2), theophylline (section 3.1.3), corticosteroids (section 3.2), cromoglicate and nedocromil (section 3.3.1), and leukotriene receptor antagonists (section 3.3.2).

For tables outlining the management of chronic asthma and acute severe asthma see p. 149 and p. 150. For advice on the management of medical emergencies in dental practice, see p. 22.

Administration of drugs for asthma

Inhalation This route delivers the drug directly to the airways; the dose required is smaller than when given by mouth and side-effects are reduced. See also Inhaler Devices, section 3.1.5.

Solutions for nebulisation are available for use in acute severe asthma. They are administered over 5–10 minutes from a nebuliser, usually driven by oxygen in hospital. See also Nebulisers, section 3.1.5.

Oral The oral route is used when administration by inhalation is not possible. Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Drugs given by mouth for the treatment of asthma include beta agonists, corticosteroids, theophylline, and leukotriene receptor antagonists.

Parenteral Drugs such as beta agonists, corticosteroids, and aminophylline can be given by injection in acute severe asthma when administration by nebulisation is inadequate or inappropriate. If the patient is being treated in the community, urgent transfer to hospital should be arranged.

Pregnancy and breast-feeding

It is particularly important that asthma should be well controlled during pregnancy; when this is achieved asthma has no important effects on pregnancy, labour, or on the fetus. Drugs for asthma should preferably be administered by inhalation to minimise exposure of the...
### Management of chronic asthma

Start at step most appropriate to initial severity; before initiating a new drug consider whether diagnosis is correct, check compliance and inhaler technique, and eliminate trigger factors for acute exacerbations.

#### Adult and Child over 5 years

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1. | occasional relief bronchodilator  
Inhaled short-acting beta agonist as required (up to once daily)  
**Note** Move to step 2 if needed more than twice a week, or if night-time symptoms more than once a week, or if exacerbation in the last 2 years requiring systemic corticosteroid or nebulised bronchodilator |
| 2. | regular inhaled preventer therapy  
Inhaled short-acting beta agonist as required plus  
Regular standard-dose inhaled corticosteroid (alternatives are considerably less effective) |
| 3. | inhaled corticosteroid + long-acting inhaled beta agonist  
Inhaled short-acting beta agonist plus  
Regular standard-dose inhaled corticosteroid plus  
Regular inhaled long-acting beta agonist (salmeterol or formoterol)  
**If asthma not controlled** Increase dose of inhaled corticosteroid to upper end of standard dose range and  
**Either** stop long-acting beta agonist if of no benefit  
**Or** continue long-acting beta agonist if of some benefit  
**If asthma still not controlled and long-acting beta agonist stopped, add one of**  
Leukotriene receptor antagonist  
Modified-release oral theophylline  
Modified-release oral beta agonist |
| 4. | high-dose inhaled corticosteroid + regular bronchodilators  
Inhaled short-acting beta agonist as required with  
Regular high-dose inhaled corticosteroid plus  
Inhaled long-acting beta agonist plus  
In adults 6-week sequential therapeutic trial of one or more of  
Leukotriene receptor antagonist  
Modified-release oral theophylline  
Modified-release oral beta agonist |
| 5. | regular corticosteroid tablets  
Inhaled short-acting beta agonist as required with  
Regular high-dose inhaled corticosteroid and  
One or more long-acting bronchodilators (see step 4) plus  
Regular prednisolone tablets (as single daily dose)  
**Note** In addition to regular prednisolone, continue high-dose inhaled corticosteroid (in exceptional cases may exceed licensed doses); these patients should normally be referred to an asthma clinic |

**Stepping down**  
Review treatment every 3 months; if control achieved stepwise reduction may be possible; reduce dose of inhaled corticosteroid slowly (consider reduction every 3 months, decreasing dose by up to 50% each time)

#### Child under 5 years

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1. | occasional relief bronchodilator  
Short-acting beta agonist as required (not more than once daily)  
**Note** Preferably by inhalation (less effective and more side-effects when given by mouth) |
| 2. | regular preventer therapy  
Inhaled short-acting beta agonist as required plus  
Either regular standard-dose inhaled corticosteroid  
**Or** (if inhaled corticosteroid cannot be used) leukotriene receptor antagonist |
| 3. | add-on therapy  
Child under 2 years:  
Refer to respiratory paediatrician  
Child 2–5 years:  
Inhaled short-acting beta agonist as required plus  
Regular inhaled corticosteroid in standard dose  
Leukotriene receptor antagonist |
| 4. | persistent poor control  
Refer to respiratory paediatrician |

**Stepping down**  
Regularly review need for treatment

---

### Inhaled corticosteroids

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **CHILD** Beclometasone dipropionate or budesonide 100–400 micrograms twice daily;  
CHILD under 12 years 200–400 micrograms twice daily  
Fluticasone propionate 50–200 micrograms twice daily;  
CHILD 4–12 years 50–100 micrograms twice daily  
Mometasone furoate (given through a dry-powder inhaler) 200 micrograms twice daily |
| **CHILD** Mometasone furoate 200–400 micrograms twice daily;  
CHILD under 12 years 100–200 micrograms twice daily  
Fluticasone propionate 200–500 micrograms twice daily;  
CHILD 4–12 years 50–100 micrograms twice daily  
Mometasone furoate (given through a dry-powder inhaler) 200–400 micrograms twice daily |
| **CHILD** Beclometasone dipropionate or budesonide 0.4–1 mg twice daily;  
CHILD 5–12 years 200–400 micrograms twice daily  
Fluticasone propionate 200–500 micrograms twice daily;  
CHILD 5–12 years 100–200 micrograms twice daily  
Mometasone furoate (given through a dry powder inhaler) 200–400 micrograms twice daily |

---

### Leukotriene receptor antagonists

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **CHILD** Nedocromil  
**CHILD** Nedocromil  
**CHILD** Leukotriene receptor antagonist |

---

### Other bronchodilators

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
</table>
| **CHILD** Theophylline  
**CHILD** Theophylline |

---

### 1. Standard-dose inhaled corticosteroids (given through a metered-dose inhaler and in children a large-volume spacer):  
**Beclometasone dipropionate or budesonide** 100–400 micrograms twice daily;  
**CHILD** under 12 years 200–400 micrograms twice daily  
**Fluticasone propionate** 50–200 micrograms twice daily;  
**CHILD** 4–12 years 50–100 micrograms twice daily  
**Mometasone furoate** (given through a dry-powder inhaler) 200 micrograms twice daily

2. Alternatives to inhaled corticosteroids are leukotriene receptor antagonists, theophylline, inhaled cromoglicate, or inhaled nedocromil.

3. High-dose inhaled corticosteroids (given through a metered-dose inhaler and a large-volume spacer):  
**Beclometasone dipropionate or budesonide** 0.4–1 mg twice daily;  
**CHILD** 5–12 years 200–400 micrograms twice daily  
**Fluticasone propionate** 200–500 micrograms twice daily;  
**CHILD** 5–12 years 100–200 micrograms twice daily  
**Mometasone furoate** (given through a dry powder inhaler) 200–400 micrograms twice daily

4. Lung-function measurements cannot be used to guide management in those under 5 years.

Advice on the management of chronic asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated May 2008); updates available at [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk)
### Management of acute asthma

#### Important
Patients with severe or life-threatening acute asthma may not be distressed and may not have all of these abnormalities; the presence of any should alert the doctor. Regard each emergency consultation as being for severe acute asthma until shown otherwise.

#### Moderate acute asthma
- Able to talk
- Respiration < 25 breaths/minute; CHILD 2–5 years < 50 breaths/minute, 5–12 years < 30 breaths/minute
- Pulse < 110 beats/minute; CHILD 2–5 years < 130 beats/minute, 5–12 years < 120 beats/minute
- Arterial oxygen saturation ≥ 92%
- Peak flow > 50% of predicted or best; CHILD 5–12 years > 50% of predicted or best

Treat at home or in surgery and assess response to treatment.

#### Severe acute asthma
- Cannot complete sentences in one breath; CHILD too breathless to talk or feed
- Use of accessory breathing muscles in children
- Respiration ≥ 25 breaths/minute; CHILD 2–5 years ≥ 50 breaths/minute; 5–12 years ≥ 30 breaths/minute
- Pulse ≥ 110 beats/minute; CHILD 2–5 years ≥ 130 beats/minute; 5–12 years ≥ 120 beats/minute
- Arterial oxygen saturation < 92%
- Peak flow 33–50% of predicted or best; CHILD 5–12 years < 50% of predicted or best

Send immediately to hospital.

#### Life-threatening acute asthma
- Silent chest, feeble respiratory effort, cyanosis
- Hypotension, bradycardia, dysrhythmia, exhaustion, agitation (in children), confusion, reduced level of consciousness, or coma
- Arterial oxygen saturation < 92%
- Peak flow < 33% of predicted or best; CHILD 5–12 years < 33% of predicted or best

Send immediately to hospital; consult with senior medical staff and refer to intensive care.

#### Treatment

<table>
<thead>
<tr>
<th>Moderate acute asthma</th>
<th>Severe acute asthma</th>
<th>Life-threatening acute asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inhaler</strong></td>
<td><strong>Inhaler</strong></td>
<td><strong>High-flow oxygen</strong> (if available)</td>
</tr>
<tr>
<td><strong>Short-acting beta agonist</strong></td>
<td><strong>Short-acting beta agonist</strong></td>
<td><strong>Short-acting beta agonist</strong> via oxygen-driven nebuliser (if available); give salbutamol 5 mg (CHILD under 5 years 2.5 mg, 5–12 years 2.5–5 mg) or terbutaline 10 mg (CHILD under 5 years 5 mg, 5–12 years 10 mg) and repeat at 10–20 minute intervals if necessary.</td>
</tr>
<tr>
<td><strong>Prednisolone</strong></td>
<td><strong>Prednisolone</strong></td>
<td><strong>Prednisolone</strong> 40–50 mg by mouth as for moderate acute asthma or intravenous hydrocortisone (preferably as sodium succinate) 100 mg (CHILD under 1 year 25 mg, 1–5 years 50 mg, 6–12 years 100 mg) every 6 hours until conversion to oral prednisolone is possible.</td>
</tr>
<tr>
<td><strong>High-flow oxygen</strong> (if available)</td>
<td><strong>Inhaled short-acting beta agonist</strong></td>
<td><strong>Give ipratropium bromide via oxygen-driven nebuliser (if available) 500 micrograms (CHILD under 12 years 250 micrograms) Monitor response for 15–30 minutes.</strong></td>
</tr>
<tr>
<td><strong>Inhaled short-acting beta agonist</strong></td>
<td><strong>Inhaled short-acting beta agonist</strong> via a large-volume spacer or oxygen-driven nebuliser (if available); give 4–10 puffs of salbutamol 100 micrograms metered inhalation each inhaled separately, and repeat at 10–20 minute intervals if necessary or give nebulised salbutamol 5 mg (CHILD under 5 years 2.5 mg, 5–12 years 2.5–5 mg) or terbutaline 10 mg (CHILD under 5 years 5 mg, 5–12 years 10 mg), and repeat at 10–20 minute intervals if necessary.</td>
<td><strong>Consider aminophylline (p. 159) or magnesium sulphate [unlicensed indication] (p. 151) only after consultation with senior medical staff</strong></td>
</tr>
<tr>
<td><strong>Peak flow</strong></td>
<td><strong>Peak flow</strong></td>
<td><strong>If symptoms improve, follow up as for moderate acute asthma</strong></td>
</tr>
</tbody>
</table>

#### Follow up
Monitor symptoms and peak flow
Set up asthma action plan and check inhaler technique
Review by general practitioner within 48 hours; modify treatment according to the Management of Chronic Asthma table, p. 149

Advice on the management of acute asthma is based on the recommendations of the British Thoracic Society and Scottish Intercollegiate Guidelines Network (updated May 2008); updates available at [www.brit-thoracic.org.uk](http://www.brit-thoracic.org.uk).
Management of acute severe asthma

Acute severe asthma can be fatal and must be treated promptly and energetically. All patients with acute severe asthma should be given high-flow oxygen (if available) and an inhaled short-acting beta agonist via a large-volume spacer or nebuliser; give 4–10 puffs of salbutamol 100 micrograms/metered inhalation, each puff inhaled separately via a large-volume spacer, and repeat at 10–20 minute intervals if necessary. If there are life-threatening features, give salbutamol or terbutaline via an oxygen-driven nebuliser every 10–20 minutes, see p. 154 and p. 156. In all cases, a systemic corticosteroid (section 6.3.2) should be given. For adults, give prednisolone 40–50 mg by mouth for at least 5 days, or intravenous hydrocortisone 100 mg (preferably as sodium succinate) every 6 hours until conversion to oral prednisolone is possible. For children, give prednisolone 1–2 mg/kg by mouth (max. 40 mg) for 3–5 days or intravenous hydrocortisone (under 1 year 25 mg, 1–5 years 50 mg, 6–12 years 100 mg) (preferably as sodium succinate) every 6 hours until conversion to oral prednisolone is possible. If the child has been taking an oral corticosteroid for more than a few days, then give prednisolone 2 mg/kg (CHILD under 2 years max. 40 mg, over 2 years max. 50 mg). In life-threatening asthma, also consider initial treatment with ipratropium by nebuliser (section 3.1.2).

Most patients do not require and do not benefit from the addition of intravenous aminophylline or of intravenous beta agonist; both cause more adverse effects than nebulised beta agonists. Nevertheless, an occasional patient who has not been taking theophylline may benefit from aminophylline infusion (see p. 159). Patients with severe asthma may be helped by magnesium sulphate [unlicensed indication] 1.2–2 g given by intravenous infusion over 20 minutes, but evidence of benefit is limited.

Treatment of acute severe asthma is safer in hospital where resuscitation facilities are immediately available. Treatment should never be delayed for investigations, patients should never be sedated, and the possibility of a pneumothorax should be considered.

If the patient's condition deteriorates despite pharmacological treatment, intermittent positive pressure ventilation may be needed.

For a table outlining the management of acute asthma, see p. 150.

Chronic obstructive pulmonary disease

Smoking cessation (section 4.10) reduces the progressive decline in lung function in chronic obstructive pulmonary disease (COPD, chronic bronchitis, or emphysema). Infection can complicate chronic obstructive pulmonary disease and may be prevented by vaccination (pneumococcal vaccine and influenza vaccine, section 14.4).

A trial of a high-dose inhaled corticosteroid or an oral corticosteroid is recommended for patients with moderate airflow obstruction to ensure that asthma has not been overlooked.

Symptoms of chronic obstructive pulmonary disease may be alleviated by an inhaled short-acting beta agonist (section 3.1.1.1) or a short-acting antimuscarinic bronchodilator (section 3.1.2) used as required.

When the airways obstruction is more severe, an inhaled short-acting antimuscarinic bronchodilator (section 3.1.2) given regularly should be added. In those who remain symptomatic or have two or more exacerbations in a year, a long-acting beta agonist or a long-acting antimuscarinic bronchodilator given regularly should be added; a short-acting antimuscarinic bronchodilator should be discontinued when a long-acting antimuscarinic bronchodilator is started. If symptoms persist or if the patient is unable to use an inhaler, oral modified-release aminophylline or theophylline (section 3.1.3) can be used.

In moderate or severe chronic obstructive pulmonary disease, either a combination of a long-acting beta agonist with an inhaled corticosteroid (section 3.2) or a long-acting antimuscarinic bronchodilator should be tried.

A mucolytic drug (section 3.7) may be considered for a patient with a chronic productive cough.

Long-term oxygen therapy (section 3.6) prolongs survival in patients with severe chronic obstructive pulmonary disease and hypoxaemia.

During an exacerbation of chronic obstructive pulmonary disease, bronchodilator therapy can be administered through a nebuliser if necessary and oxygen given if appropriate. Aminophylline can be given intravenously if response to nebulised bronchodilators is poor. A short course of oral corticosteroid (section 6.3.2), such as prednisolone 30 mg daily for 7–14 days, should be given if increased breathlessness interferes with daily activities. Antibacterial treatment (Table 1, section 5.1) is required when sputum becomes purulent or if there are other signs of infection.

Patients who have had an episode of hypercapnic respiratory failure should be given a 24% or 28% Venturi mask and an oxygen alert card (see p. 152) endorsed with the oxygen saturations required during previous exacerbations. Patients and their carers should be instructed to show the card to emergency healthcare providers in the event of an exacerbation, see also section 3.6.
Respiratory system

3.1.1 Adrenoceptor agonists

(Selective beta agonists)

3.1.1.1 Selective beta agonists

The selective beta agonists (selective beta-adrenoceptor agonists, selective beta stimulants) (section 3.1.1.1) such as salbutamol or terbutaline are the safest and most effective short-acting beta agonists for asthma. Less selective beta agonists such as orciprenaline (section 3.1.1.2) should be avoided whenever possible.

Adrenaline (epinephrine) (which has both alpha- and beta-adrenoceptor agonist properties) is used in the emergency management of allergic and anaphylactic reactions (section 3.4.3) and in the management of croup (see above).

Oxygen alert card

Name: ________________________________

I am at risk of type II respiratory failure with a raised CO level.

Please use my ____% Venturi mask to achieve an oxygen saturation of ____% to ____% during exacerbations.

Use compressed air to drive nebulisers (with nasal oxygen at 2 litres/minute). If compressed air not available, limit oxygen-driven nebulisers to 6 minutes.

Oxygen alert card based on British Thoracic Society guidelines for emergency oxygen use in adult patients (October 2008); available at www.brit-thoracic.org.uk

Croup

Mild croup is largely self-limiting, but treatment with a single dose of a corticosteroid (e.g. dexamethasone 150 micrograms/kg) by mouth may be of benefit. More severe croup (or mild croup that might cause complications) calls for hospital admission; a single dose of a corticosteroid (e.g. dexamethasone 150 micrograms/kg or prednisolone 1–2 mg/kg by mouth, section 6.3.2) should be administered before transfer to hospital. In hospital, dexamethasone 150 micrograms/kg (by mouth or by injection) or budesonide 2 mg (by nebulisation, section 3.2) will often reduce symptoms; the dose may need to be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised adrenaline solution 1 in 1000 (1 mg/mL) should be given with close clinical monitoring in a dose of 400 micrograms/kg (max. 5 mg) repeated after 30 minutes if necessary; the effects of nebulised adrenaline last 2–3 hours and the child needs to be monitored carefully for recurrence of the obstruction.

For more severe croup or croup that might cause complications, treatment with a single dose of a corticosteroid (e.g. dexamethasone 150 micrograms/kg or prednisolone 1–2 mg/kg by mouth, section 6.3.2) should be administered before transfer to hospital. In hospital, dexamethasone 150 micrograms/kg (by mouth or by injection) or budesonide 2 mg (by nebulisation, section 3.2) will often reduce symptoms; the dose may need to be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised adrenaline solution 1 in 1000 (1 mg/mL) should be given with close clinical monitoring in a dose of 400 micrograms/kg (max. 5 mg) repeated after 30 minutes if necessary; the effects of nebulised adrenaline last 2–3 hours and the child needs to be monitored carefully for recurrence of the obstruction.

3.1.1.2 Other adrenoceptor agonists

Pressurised-metered dose inhalers are an effective and convenient method of drug administration in mild to moderate asthma. A spacer device (section 3.1.5) may improve drug delivery. At recommended inhaled doses the duration of action of salbutamol, terbutaline and fenoterol is about 3 to 5 hours and for salmeterol and formoterol 12 hours. The dose, the frequency, and the maximum number of inhalations in 24 hours of the beta agonist should be stated explicitly to the patient. The patient should be advised to seek

Short-acting beta agonists

Mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting beta agonist such as salbutamol or terbutaline. If beta agonist inhalation is needed more often than once daily, prophylactic treatment should be considered, using a stepped approach as outlined in the Management of Chronic Asthma table, p. 149. Regular treatment with an inhaled short-acting beta agonist is less effective than ‘as required’ inhalation and is not appropriate prophylactic treatment.

A short-acting beta agonist inhaled immediately before exertion reduces exercise-induced asthma; however, frequent exercise-induced asthma probably reflects poor overall control and calls for reassessment of asthma treatment.

Long-acting beta agonists

Formoterol (efomotorol) and salmeterol are longer-acting beta agonists which are administered by inhalation. Added to regular inhaled corticosteroid treatment, they have a role in the long-term control of chronic asthma (see Chronic Asthma table, p. 149) and they can be useful in nocturnal asthma. Salmeterol should not be used for the relief of an asthma attack; it has a slower onset of action than salbutamol or terbutaline. Formoterol is licensed for short-term symptom relief and for the prevention of exercise-induced bronchospasm; its speed of onset of action is similar to that of salbutamol.

CHM advice

To ensure safe use, the CHM has advised that for the management of chronic asthma, long-acting beta agonists (formoterol and salmeterol) should:

- be added only if regular use of standard-dose inhaled corticosteroids has failed to control asthma adequately;
- not be initiated in patients who have rapidly deteriorating asthma;
- be introduced at a low dose and the effect properly monitored before considering dose increase;
- be discontinued in the absence of benefit;
- be reviewed as clinically appropriate: stepping down therapy should be considered when good long-term asthma control has been achieved.

Patients should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta agonist, see Management of Chronic Asthma table, p. 149.

Inhalation

Pressurised-metered dose inhalers are an effective and convenient method of drug administration in mild to moderate asthma. A spacer device (section 3.1.5) may improve drug delivery. At recommended inhaled doses the duration of action of salbutamol, terbutaline and fenoterol is about 3 to 5 hours and for salmeterol and formoterol 12 hours. The dose, the frequency, and the maximum number of inhalations in 24 hours of the beta agonist should be stated explicitly to the patient. The patient should be advised to seek...
medical advice when the prescribed dose of beta agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the patient may require a prophylactic drug such as an inhaled corticosteroid (see Chronic Asthma table, p. 149).

_Nebuliser (or respirator) solutions_ of salbutamol and terbutaline are used for the treatment of severe acute asthma in hospital or in general practice. Patients with a severe attack of asthma should preferably have oxygen during nebulisation since beta agonists can increase arterial hypoxaemia. For the use of nebulisers in chronic obstructive pulmonary disease, see section 3.1.5. The dose given by nebuliser is substantially higher than that given by inhaler. Patients should therefore be warned that it is dangerous to exceed the prescribed dose and they should seek medical advice if they fail to respond to the usual dose of the respirator solution. See also guidelines in section 3.1.5.

_CFC-free inhalers_ Chlorofluorocarbon (CFC) propellants in pressurised metered-dose inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Patients receiving CFC-free inhalers should be reassured about the efficacy of the new inhalers and counselled that the aerosol may feel and taste different; any difficulty with the new inhaler should be discussed with the doctor or pharmacist.

**Oral** Oral preparations of beta agonists may be used by patients who cannot manage the inhaled route. They are sometimes used for children and the elderly, but inhaled beta agonists are more effective and have fewer side-effects. The longer-acting oral preparations, including bambuterol, may be of value in nocturnal asthma but they have a limited role and inhaled long-acting beta agonists are usually preferred.

**Parenteral** Salbutamol or terbutaline are given by intravenous infusion for severe asthma. The regular use of beta agonists by the subcutaneous route is not recommended since the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started. Patients supplied with a selective beta agonist injection for severe attacks should be advised to attend hospital immediately after using the injection, for further assessment. Beta agonists may also be given by intramascular injection.

**Children** Selective beta agonists are useful even in children under the age of 18 months. They are most effective by the inhaled route; a pressurised metered-dose inhaler should be used with a spacer device in children under 5 years (see NICE guidance, section 3.1.5). A beta agonist may also be given by mouth but administration by inhalation is preferred; a long-acting inhaled beta agonist may be used where appropriate (see Chronic Asthma table, p. 149). In severe attacks nebulisation using a selective beta agonist or ipratropium is advisable (see also Asthma tables, p. 149). For compound preparation containing fenoterol, see section 3.1.4.
Dose
- See under preparations below

Counselling Advise patients not to exceed prescribed dose, and to follow manufacturer's directions; if a previously effective dose of inhaled formoterol fails to provide adequate relief, a doctor's advice should be obtained as soon as possible

Formoterol (Non-proprietary) [AstraZeneca]
Dry powder for inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 120-dose unit = £24.80. Counselling, dose

Brands include Easyhaler Formoterol

Dose
- by inhalation of powder, asthma, ADULT and CHILD over 6 years, 12 micrograms twice daily, increased to 24 micrograms twice daily in more severe airways obstruction

Chronic obstructive pulmonary disease, 12 micrograms twice daily

Atimos Modulite® (Trinity-Chiesi) [Novartis]
Aerosol inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 100-dose unit = £31.28. Counselling, dose

Dose
- by aerosol inhalation, asthma, ADULT and CHILD over 12 years, 12 micrograms twice daily, increased to max. 24 micrograms twice daily in more severe airways obstruction

Chronic obstructive pulmonary disease, ADULT over 18 years, 12 micrograms twice daily; for symptom relief additional doses may be taken to total max. 48 micrograms daily (max. single dose 24 micrograms)

Foradil® (Novartis) [Novartis]
Dry powder for inhalation, formoterol fumarate 12 micrograms/capsule, net price 60-cap pack (with inhaler device) = £29.23. Counselling, dose

Dose
- by inhalation of powder, asthma, ADULT and CHILD over 5 years, 12 micrograms twice daily; increased to 24 micrograms twice daily in more severe airways obstruction

Chronic obstructive pulmonary disease, ADULT over 12 years, 12 micrograms twice daily

Oxis® (AstraZeneca) [AstraZeneca]
Turbolaler® [= dry powder inhaler], formoterol fumarate 6 micrograms/metered inhalation, net price 60-dose unit = £24.80; 12 micrograms/metered inhalation, 60-dose unit = £24.80. Counselling, dose

Dose
- by inhalation of powder, chronic asthma, 6–12 micrograms 1–2 times daily, increased up to 24 micrograms twice daily if necessary; occasionally up to 72 micrograms daily may be needed (max. single dose 36 micrograms); reassess treatment if additional doses required on more than 2 days a week; CHILD 6–18 years, 6–12 micrograms 1–2 times daily; occasionally up to 48 micrograms daily may be needed (max. single dose 12 micrograms)

Relief of bronchospasm, ADULT and CHILD over 6 years, 6–12 micrograms

Prevention of exercise-induced bronchospasm, 12 micrograms; for symptom relief additional doses can be taken to total max. 48 micrograms daily (max. single dose 24 micrograms)

Compound preparations
For compound preparations containing formoterol, see section 3.2

SALBUTAMOL
(Albuterol)

Indications
asthma and other conditions associated with reversible airways obstruction; premature labour (section 7.1.3)

Cautions
see notes above

Side-effects
see notes above

Dose
- by mouth (but use by inhalation preferred), 4 mg (elderly and sensitive patients initially 2 mg) 3–4 times daily; max. single dose 8 mg (but unlikely to provide much extra benefit or to be tolerated); CHILD under 2 years 100 micrograms/kg 4 times daily [unlicensed]; 2–6 years 1–2 mg 3–4 times daily, 6–12 years 2 mg 3–4 times daily

- by subcutaneous or intramuscular injection, 500 micrograms, repeated every 4 hours if necessary

- by slow intravenous injection (dilute to a concentration of 50 micrograms/mL), 250 micrograms, repeated if necessary; CHILD 1 month–2 years 5 micrograms/kg as a single dose [unlicensed]; 2–18 years 15 micrograms/kg (max. 250 micrograms) as a single dose [unlicensed]

- by intravenous infusion, initially 5 micrograms/minute, adjusted according to response and heart rate usually in range 3–20 micrograms/minute, or more if necessary; CHILD 1 month–18 years initially 1–5 micrograms/kg/minute, adjusted according to response and heart rate (doses above 2 micrograms/kg/minute in intensive care setting) [unlicensed]

- by aerosol inhalation (but see also Management of Acute Asthma table, p. 150, or Management of Chronic Asthma table, p. 149), 100–200 micrograms (1–2 puffs); for persistent symptoms up to 4 times daily; CHILD 100 micrograms (1 puff), increased to 200 micrograms (2 puffs) if necessary; for persistent symptoms up to 4 times daily Prophylaxis of allergen- or exercise-induced bronchospasm, 200 micrograms (2 puffs); CHILD 100 micrograms (1 puff), increased to 200 micrograms (2 puffs) if necessary

- by inhalation of powder (but see also Management of Chronic Asthma table, p. 149), 200–400 micrograms; for persistent symptoms up to 4 times daily; CHILD over 5 years 200 micrograms; for persistent symptoms up to 4 times daily (for Asmazal Clickhaler®, Salbulin Novolizer®, and Ventolin Accuhaler® doses, see under preparations) Prophylaxis of allergen- or exercise-induced bronchospasm, 400 micrograms; CHILD 200 micrograms

- by inhalation of nebulised solution, chronic bronchospasm unresponsive to conventional therapy, severe acute asthma (but see also Management of Acute Asthma table, p. 150) or Management of Chronic Asthma table, p. 149), ADULT and CHILD over 18 months 2.5–5 mg, repeated up to 4 times daily; more frequently in severe cases; max. 40 mg daily; CHILD under 18 months (transient hypoxaemia may occur—consider supplemental oxygen), 2.5 mg up to 4 times daily or more frequently in severe cases

Oral
Salbutamol (Non-proprietary) [AstraZeneca]
Tablets, salbutamol (as sulphate) 2 mg, net price 28-tab pack = £12.71; 4 mg, 28-tab pack = £12.20

Oral solution, salbutamol (as sulphate) 2 mg/5 mL, net price 150 mL = £1.27

Brands include Salapin (sugar-free)

Ventmax SR (Trinity) [Trinity]
Capsules, m/r, salbutamol (as sulphate) 4 mg (green/grey), net price 56-cap pack = £8.57; 8 mg (white), 56-cap pack = £10.28. Label: 25

Dose
- 8 mg twice daily; CHILD 3–12 years 4 mg twice daily
Ventolin® (A&H)  
Syrup, sugar-free, salbutamol (as sulphate) 2 mg/5 mL, net price 150 mL = £0.60

Parenteral
Ventolin® (A&H)  
Injection, salbutamol (as sulphate) 500 micrograms/mL, net price 1 mL amp = £0.40
Solution for intravenous infusion, salbutamol (as sulphate) 1 mg/mL. Dilute before use. Net price 5 mL amp = £2.58

Inhalation
Counselling
Advise patients not to exceed prescribed dose and to follow manufacturer's directions: if a previously effective dose of inhaled salbutamol fails to provide at least 3 hours relief, a doctor's advice should be obtained as soon as possible.
Patients receiving CFC-free inhalers should be reassured about their efficacy and counselled that aerosol may feel and taste different

Salbutamol (Non-proprietary)  
Aerosol inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose unit = £2.88.
Counselling, dose
Excipients include CFC propellants
Aerosol inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £5.99. Counselling, dose, change to CFC-free inhaler
Excipients include HFA-134a (a non-CFC propellant)
Brands include Accuhaler® Salbutamol, PulmoNed® Salbutamol
Note
Can be supplied against a generic prescription but if CFC-free not specified will be reimbursed at price for CFC-containing inhaler
Dry powder for inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose unit = £3.46; 200 micrograms/metered inhalation, 100-dose unit = £5.05, 200-dose unit = £6.92. Counselling, dose
Excipients include HFA-134a (a non-CFC propellant)
Brands include Salamol
Dry powder for inhalation, salbutamol micrograms/metered inhalation, net price 200-dose unit = £4.95; 200-dose refill = £2.75. Counselling, dose
Dose
Acute bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 1–2 puffs; for persistent symptoms up to 4 times daily (but see also Management of Chronic Asthma, p. 149).
Prophylaxis of allergen- or exercise-induced bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 1–2 puffs
Salamol Easi-Breathe® (IVAX)  
Aerosol inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose breath-activated unit = £6.30. Counselling, dose
Excipients include HFA-134a (a non-CFC propellant)
Salbutin Novolizer® (Meda)  
Dry powder for inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price refillable 200-dose unit = £4.95, 200-dose refill = £2.75. Counselling, dose
Dose
Acute bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 200 micrograms; for persistent symptoms up to 800 micrograms daily (but see also Management of Chronic Asthma, p. 149).
CHILD 6–12 years 100–200 micrograms; for persistent symptoms up to 400 micrograms daily (but see also Management of Chronic Asthma, p. 149).
Prophylaxis of allergen- or exercise-induced bronchospasm, by inhalation of powder, ADULT 200 micrograms, CHILD 6–12 years 100–200 micrograms
Ventolin® (A&H)  
Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salbutamol (as sulphate) 200 micrograms/b blister with Accuhaler®, device, net price = £5.12. Counselling, dose
Dose
Acute bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 200 micrograms; for persistent symptoms up to 4 times daily (but see also Management of Chronic Asthma, p. 149).
Prophylaxis of allergen- or exercise-induced bronchospasm, by inhalation of powder, ADULT and CHILD over 5 years, 200 micrograms
Evohaler® (aerosol inhalation), salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.50. Counselling, dose, change to CFC-free inhaler
Excipients include HFA-134a (a non-CFC propellant)
Note
Can be supplied against a generic prescription but if CFC-free not specified will be reimbursed at price for CFC-containing inhaler
Nebules® (for use with nebuliser), salbutamol (as sulphate) 1 mg/mL, net price 20 x 2.5 mL (2.5 mg) = £1.75; 2 mg/mL, 20 x 2.5 mL (5 mg) = £2.95. May be diluted with sterile sodium chloride 0.9% if administration time in excess of 10 minutes is required
Respirator solution (for use with a nebuliser or ventilator), salbutamol (as sulphate) 5 mg/mL. Net price 20 mL = £2.27 (hosp. only). May be diluted with sterile sodium chloride 0.9%

Compound preparations
For compound preparations containing salbutamol, see section 3.1.4

Chronic Asthma table, see p. 149
Acute Severe Asthma table, see p. 150.

SALMETEROL
Indications
reversible Airways obstruction (including nocturnal asthma and prevention of exercise-induced bronchospasm) in patients requiring long-term regu-
lary bronchodilator therapy, see also Chronic Asthma table, p. 149; chronic obstructive pulmonary disease

**Note** Not for immediate relief of acute asthma attacks; existing corticosteroid therapy should not be reduced or withdrawn

**Cautions** see notes above

**Side-effects** see notes above; nausea, dizziness, arthralgia, and rash also reported

**Dose**
- **By inhalation,** asthma, 50 micrograms (2 puffs or 1 blister) twice daily; up to 100 micrograms (4 puffs or 2 blisters) twice daily in more severe airways obstruction; **CHILD** 5–12 years, 50 micrograms (2 puffs or 1 blister) twice daily
- Chronic obstructive pulmonary disease 50 micrograms (2 puffs or 1 blister) twice daily

**Counselling** Advise patients that salmeterol should not be used for relief of acute attacks, not to exceed prescribed dose, and to follow manufacturer’s directions; if a previously effective dose of inhaled terbutaline fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible

**Serevent**

**Accuhaler** (dry powder for inhalation), disk containing 60 blisters of salmeterol (as xinafoate) 50 micrograms/blisterr with **Accuhaler** device, net price = £29.26. Counselling, dose

**Evohaler** aerosol inhalation, salmeterol (as xinafoate) 25 micrograms/metered inhalation, net price 120-dose unit = £29.26. Counselling, dose, change to CFC-free inhaler

**Diskhaler** (dry powder for inhalation), disks containing 4 blisters of salmeterol (as xinafoate) 50 micrograms/blisterr with **Diskhaler** device = £35.79, 15-disk refill = £35.15. Counselling, dose

**Compound preparations**

For **compound preparations** containing salmeterol, see section 3.2

**TERBUTALINE SULPHATE**

**Indications** asthma and other conditions associated with reversible airways obstruction; premature labour (section 7.1.3)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**
- **By mouth** (but use by inhalation preferred), initially 2.5 mg 3 times daily for 1–2 weeks, then up to 5 mg 3 times daily; **CHILD** 1 month–7 years 75 micrograms/kg 3 times daily; 7–15 years 2.5 mg 2–3 times daily
- **By subcutaneous or slow intravenous injection,** 250–500 micrograms up to 4 times daily; **CHILD** 2–15 years 10 micrograms/kg to a max. of 300 micrograms
- **By continuous intravenous infusion** as a solution containing 3–5 micrograms/mL, 90–300 micrograms/hour for 8–10 hours; **CHILD** 1 month–18 years, initially 2–4 micrograms/kg as a loading dose, then 1–10 micrograms/kg/hour according to response and heart rate (max. 300 micrograms/hour); high doses with close monitoring
- **By inhalation of powder** (**Turbohaler**), **ADULT** and **CHILD** over 5 years, 500 micrograms (1 inhalation);

for persistent symptoms up to 4 times daily (but see Management of Chronic Asthma table, p. 149)
- **By inhalation of nebulised solution,** 5–10 mg 2–4 times daily; additional doses may be necessary in severe acute asthma; **CHILD**, up to 3 years 2 mg, 3–6 years 3 mg; 6–8 years 4 mg, over 8 years 5 mg, 2–4 times daily

**Oral and parenteral**

**Bricanyl** (AstraZeneca)

**Tablets,** scored, terbutaline sulphate 5 mg, net price 20 = £82p

**Syrup,** sugar-free, terbutaline sulphate 1.5 mg/5 mL, net price 100 mL = £2.00

**Injection,** terbutaline sulphate 50 micrograms/mL, net price 1 mL amp = 30p; 5 mL amp = £1.40

**Inhalation**

**Counselling** Advise patients not to exceed prescribed dose and to follow manufacturer’s directions; if a previously effective dose of inhaled terbutaline fails to provide at least 3 hours relief, a doctor’s advice should be obtained as soon as possible

**Bricanyl** (AstraZeneca)

**Turbohaler** (= dry powder inhaler), terbutaline sulphate 50 micrograms/metered inhalation, net price 100-dose unit = £6.92. Counselling, dose

**Respules** (= single-dose units for nebulisation), terbutaline sulphate 2.5 mg/mL, net price 20 x 2 mL units (5-mg) = £4.04

**3.1.1.2 Other adrenoceptor agonists**

Ephedrine and the partially selective beta agonist, orciprenaline, are less suitable and less safe for use as bronchodilators than the selective beta agonists, because they are more likely to cause arrhythmias and other side-effects. They should be avoided whenever possible.

**Adrenaline (epinephrine) injection** (1 in 1000) is used in the emergency treatment of acute allergic and anaphylactic reactions (section 3.4.3), in angioedema (section 3.4.3), and in cardiopulmonary resuscitation (section 2.7.3). Adrenaline solution (1 in 1000) is used by nebulisation in the management of severe croup (section 3.1).

**EPHEDRINE HYDROCHLORIDE**

**Indications** reversible airways obstruction, but see notes above

**Cautions** hyperthyroidism, diabetes mellitus, ischaemic heart disease, hypertension, renal impairment, elderly; prostatic hypertrophy (risk of acute retention); interaction with MAOIs a disadvantage; **interactions:** Appendix 1 (sympathomimetics)

**Side-effects** tachycardia, anxiety, restlessness, insomnia common; also tremor, arrhythmias, dry mouth, cold extremities

**Dose**
- 15–60 mg 3 times daily; **CHILD** up to 1 year 7.5 mg 3 times daily, 1–5 years 15 mg 3 times daily, 6–12 years 30 mg 3 times daily
3.1.2 Antimuscarinic bronchodilators

Ipratropium can provide short-term relief in chronic asthma, but short-acting beta agonists act more quickly and are preferred. Ipratropium by nebulisation can be added to other standard treatment in life-threatening asthma or if acute asthma fails to improve with standard therapy (see Acute Asthma table, p. 150).

The aerosol inhalation of ipratropium can be used for short-term relief in mild chronic obstructive pulmonary disease in patients who are not using a long-acting antimuscarinic drug. Its maximal effect occurs 30–60 minutes after use; its duration of action is 3 to 6 hours and bronchodilation can usually be maintained with treatment 3 times a day.

Tiotropium, a long-acting antimuscarinic bronchodilator, is effective for the management of chronic obstructive pulmonary disease; it is not suitable for the relief of acute bronchospasm.

Cautions Antimuscarinic bronchodilators should be used with caution in patients with prostatic hyperplasia, bladder outflow obstruction, and those susceptible to angle-closure glaucoma (see below); interactions: Appendix 1 (antimuscarinics)

Glaucoma Acute angle-closure glaucoma reported with nebulised ipratropium, particularly when given with nebulised salbutamol (and possibly other beta agonists); care needed to protect patient’s eyes from nebulised salbutamol (and possibly other beta agonists); care needed to protect patient’s eyes from nebulised ipratropium, particularly when given with 

Side-effects Dry mouth is the most common side-effect of antimuscarinic bronchodilators; less commonly nausea and headache occur. Constipation, tachycardia, palpitation, paradoxical bronchospasm, urinary retention, blurred vision, angle-closure glaucoma, and hypersensitivity reactions including rash, urticaria, pruritus, and angioedema occur rarely.

Ipratropium Bromide

Indications reversible airways obstruction, particularly in chronic obstructive pulmonary disease; rhinitis (section 12.2.2)

Cautions see notes above; pregnancy (see p. 148 and Appendix 4); breast-feeding (see p. 148 and Appendix 5)

Side-effects see notes above

Dose

- By aerosol inhalation, 20–40 micrograms, 3–4 times daily; CHILD up to 6 years 20 micrograms 3 times daily, 6–12 years 20–40 micrograms 3 times daily
- By inhalation of powder, ADULT and CHILD over 12 years, 40 micrograms 3–4 times daily (may be doubled in less responsive patients)
- By inhalation of nebulised solution, reversible airways obstruction in chronic obstructive pulmonary disease, 250–500 micrograms 3–4 times daily

Acute bronchospasm (see also Acute Asthma table, p. 150), 500 micrograms repeated as necessary; CHILD under 5 years 125–250 micrograms, max. 1 mg daily; 6–12 years 250 micrograms, max. 1 mg daily

Counselling Advise patient not to exceed prescribed dose and to follow manufacturer’s directions

Ipratropium Bromide (Non-proprietary) Nebuliser solution, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £6.75, 60 × 1-mL = £21.78; 20 × 2-mL (500-microgram) = £7.43, 60 × 2-mL = £26.97. If dilution is necessary use only sterile sodium chloride 0.9%

Atrovent® (Boehringer Ingelheim) (dry powder for inhalation; for use with Atrovent Aerosolizer®), green, ipratropium bromide 40 micrograms, net price pack of 100 caps with Aerosolizer® = £14.53; 100 caps = £10.53. Counselling, dose

Note One Atrovent Aerocap is equivalent to 2 puffs of Atrovent metered aerosol inhalation

Aerosol inhalation, ipratropium bromide 20 micrograms/unit-dose metered inhaler, net price 200-dose unit = £4.21. Counselling, dose, change to CFC-free inhaler

Excipients include HFA-134a (a non-CFC propellant)

Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL unit-dose vials = £5.18, 60 × 1-mL vials = £15.55; 20 × 2-mL vials = £8.08, 60 × 2-mL vials = £18.24. If dilution is necessary use only sterile sodium chloride 0.9%

Ipratropium Steri-Neb® (IVAX) Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £8.72; 20 × 2-mL (500-microgram) = £9.94. If dilution is necessary use only sterile sodium chloride 0.9%

Respongine® (A&H) Nebuliser solution, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 × 1-mL (250-microgram) unit-dose vials = £5.07; 20 × 2-mL (500-microgram) = £5.95. If dilution is necessary use only sterile sodium chloride 0.9%

Compound ipratropium preparations Section 3.1.4

Tiotropium

Indications maintenance treatment of chronic obstructive pulmonary disease

Cautions see notes above; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)
**THEOPHYLLINE**

**Indications** reversible airways obstruction, acute severe asthma: see also Management of Chronic and Acute Asthma (p. 149 and p. 150)

**Cautions** cardiac disease, hypertension, hyperkalaemia; peptic ulcer; epilepsy; elderly; fever; CSM advice on hypokalaemia risk, p. 153; avoid in acute porphyria (section 9.8.2); monitor plasma-theophylline concentration (see notes above); hepatic impairment (Appendix 2); pregnancy (see p. 148 and Appendix 4); breast-feeding (see p. 148 and Appendix 5); interactions: Appendix 1 (theophylline) and notes above

**Side-effects** tachycardia, palpitation, nausea and other gastro-intestinal disturbances, headache, CNS stimulation, insomnia, arrhythmias, and convulsions especially if given rapidly by intravenous injection; overdosage: see Emergency Treatment of Poisoning, p. 33

**Dose**

- See below

**Note** Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); 4–6 hours after a dose and at least 5 days after starting treatment; narrow margin between therapeutic and toxic dose, see also notes above

**Modified release**

- The rate of absorption from modified-release preparations can vary between brands. The Council of the Royal Pharmaceutical Society of Great Britain advises pharmacists that if a general practitioner prescribes a modified-release oral theophylline preparation without specifying a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

**Theophylline**

Theophylline is a bronchodilator used for asthma and stable chronic obstructive pulmonary disease; it is not generally effective in exacerbations of chronic obstructive pulmonary disease. It may have an additive effect when used in conjunction with small doses of beta agonists; the combination may increase the risk of side-effects, including hypokalaemia (for CSM advice see p. 153).

Theophylline is metabolised in the liver; there is considerable variation in plasma-theophylline concentration particularly in smokers, in patients with hepatic impairment or heart failure, or if certain drugs are taken concurrently. The plasma-theophylline concentration is increased in heart failure, cirrhosis, viral infections, in the elderly, and by drugs that inhibit its metabolism. The plasma-theophylline concentration is decreased in smokers and in chronic alcoholism and by drugs that induce liver metabolism. For other interactions of theophylline see Appendix 1.

Differences in the half-life of theophylline are important because its toxic dose is close to the therapeutic dose; particular care is required when introducing or withdrawing drugs that interact with theophylline. In most individuals a plasma-theophylline concentration of between 10–20 mg/litre is required for satisfactory bronchodilation, although a plasma-theophylline concentration of 10 mg/litre (or less) may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

Theophylline is given by injection as aminophylline, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe attacks of asthma. It must be given by very slow intravenous injection (over at least 20 minutes); it is too irritant for intramuscular use. Measurement of plasma theophylline concentration may be helpful, and is essential if aminophylline is to be given to patients who have been taking theophylline, because serious side-effects such as convulsions and arhythmias can occasionally precede other symptoms of toxicity.

**THEOPHYLLINE**

**Indications** reversible airways obstruction, acute severe asthma: see also Management of Chronic and Acute Asthma (p. 149 and p. 150)

**Cautions** cardiac disease, hypertension, hyperkalaemia; peptic ulcer; epilepsy; elderly; fever; CSM advice on hypokalaemia risk, p. 153; avoid in acute porphyria (section 9.8.2); monitor plasma-theophylline concentration (see notes above); hepatic impairment (Appendix 2); pregnancy (see p. 148 and Appendix 4); breast-feeding (see p. 148 and Appendix 5); interactions: Appendix 1 (theophylline) and notes above

**Side-effects** tachycardia, palpitation, nausea and other gastro-intestinal disturbances, headache, CNS stimulation, insomnia, arrhythmias, and convulsions especially if given rapidly by intravenous injection; overdosage: see Emergency Treatment of Poisoning, p. 33

**Dose**

- See below

**Note** Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); 4–6 hours after a dose and at least 5 days after starting treatment; narrow margin between therapeutic and toxic dose, see also notes above

**Modified release**

- The rate of absorption from modified-release preparations can vary between brands. The Council of the Royal Pharmaceutical Society of Great Britain advises pharmacists that if a general practitioner prescribes a modified-release oral theophylline preparation without specifying a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

**Theophylline**

Theophylline is a bronchodilator used for asthma and stable chronic obstructive pulmonary disease; it is not generally effective in exacerbations of chronic obstructive pulmonary disease. It may have an additive effect when used in conjunction with small doses of beta agonists; the combination may increase the risk of side-effects, including hypokalaemia (for CSM advice see p. 153).

Theophylline is metabolised in the liver; there is considerable variation in plasma-theophylline concentration particularly in smokers, in patients with hepatic impairment or heart failure, or if certain drugs are taken concurrently. The plasma-theophylline concentration is increased in heart failure, cirrhosis, viral infections, in the elderly, and by drugs that inhibit its metabolism. The plasma-theophylline concentration is decreased in smokers and in chronic alcoholism and by drugs that induce liver metabolism. For other interactions of theophylline see Appendix 1.

Differences in the half-life of theophylline are important because its toxic dose is close to the therapeutic dose; particular care is required when introducing or withdrawing drugs that interact with theophylline. In most individuals a plasma-theophylline concentration of between 10–20 mg/litre is required for satisfactory bronchodilation, although a plasma-theophylline concentration of 10 mg/litre (or less) may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

Theophylline is given by injection as aminophylline, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe attacks of asthma. It must be given by very slow intravenous injection (over at least 20 minutes); it is too irritant for intramuscular use. Measurement of plasma theophylline concentration may be helpful, and is essential if aminophylline is to be given to patients who have been taking theophylline, because serious side-effects such as convulsions and arhythmias can occasionally precede other symptoms of toxicity.

**THEOPHYLLINE**

**Indications** reversible airways obstruction, acute severe asthma: see also Management of Chronic and Acute Asthma (p. 149 and p. 150)

**Cautions** cardiac disease, hypertension, hyperkalaemia; peptic ulcer; epilepsy; elderly; fever; CSM advice on hypokalaemia risk, p. 153; avoid in acute porphyria (section 9.8.2); monitor plasma-theophylline concentration (see notes above); hepatic impairment (Appendix 2); pregnancy (see p. 148 and Appendix 4); breast-feeding (see p. 148 and Appendix 5); interactions: Appendix 1 (theophylline) and notes above

**Side-effects** tachycardia, palpitation, nausea and other gastro-intestinal disturbances, headache, CNS stimulation, insomnia, arrhythmias, and convulsions especially if given rapidly by intravenous injection; overdosage: see Emergency Treatment of Poisoning, p. 33

**Dose**

- See below

**Note** Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); 4–6 hours after a dose and at least 5 days after starting treatment; narrow margin between therapeutic and toxic dose, see also notes above

**Modified release**

- The rate of absorption from modified-release preparations can vary between brands. The Council of the Royal Pharmaceutical Society of Great Britain advises pharmacists that if a general practitioner prescribes a modified-release oral theophylline preparation without specifying a brand name, the pharmacist should contact the prescriber and agree the brand to be dispensed. Additionally, it is essential that a patient discharged from hospital should be maintained on the brand on which that patient was stabilised as an in-patient.

**Theophylline**

Theophylline is a bronchodilator used for asthma and stable chronic obstructive pulmonary disease; it is not generally effective in exacerbations of chronic obstructive pulmonary disease. It may have an additive effect when used in conjunction with small doses of beta agonists; the combination may increase the risk of side-effects, including hypokalaemia (for CSM advice see p. 153).

Theophylline is metabolised in the liver; there is considerable variation in plasma-theophylline concentration particularly in smokers, in patients with hepatic impairment or heart failure, or if certain drugs are taken concurrently. The plasma-theophylline concentration is increased in heart failure, cirrhosis, viral infections, in the elderly, and by drugs that inhibit its metabolism. The plasma-theophylline concentration is decreased in smokers and in chronic alcoholism and by drugs that induce liver metabolism. For other interactions of theophylline see Appendix 1.

Differences in the half-life of theophylline are important because its toxic dose is close to the therapeutic dose; particular care is required when introducing or withdrawing drugs that interact with theophylline. In most individuals a plasma-theophylline concentration of between 10–20 mg/litre is required for satisfactory bronchodilation, although a plasma-theophylline concentration of 10 mg/litre (or less) may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase at concentrations above 20 mg/litre.

Theophylline is given by injection as aminophylline, a mixture of theophylline with ethylenediamine, which is 20 times more soluble than theophylline alone. Aminophylline injection is needed rarely for severe attacks of asthma. It must be given by very slow intravenous injection (over at least 20 minutes); it is too irritant for intramuscular use. Measurement of plasma theophylline concentration may be helpful, and is essential if aminophylline is to be given to patients who have been taking theophylline, because serious side-effects such as convulsions and arhythmias can occasionally precede other symptoms of toxicity.
severe, in patients whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as single evening or morning dose

### Aminophylline

**Note** Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine contributes greater solubility in water.

**Indications** reversible airways obstruction, acute severe asthma

**Cautions** see under Theophylline

**Side-effects** see under Theophylline; also allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis.

**Dose**

- See under preparations, below

**Note** Plasma-theophylline concentration for optimum response 10–20 mg/litre (55–110 micromol/litre); measure plasma-theophylline concentration 4–6 hours after dose by mouth and at least 5 days after starting oral treatment, measure plasma-theophylline concentration 4–6 hours after the start of intravenous infusion; narrow margin between therapeutic and toxic dose, see also notes above

**To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal weight for height**

### Aminophylline (Non-proprietary)

**Injection**, aminophylline 25 mg/mL, net price 10-ML amp = 72p

Brands include Minijet Aminophylline

**Dose** acute severe asthma or acute exacerbation of chronic obstructive pulmonary disease not previously treated with theophylline, by slow intravenous injection over at least 20 minutes (with close monitoring), 250–500 mg (5 mg/kg), then see below; **CHILD** 5 mg/kg, then see below

Acute severe asthma or acute exacerbation of chronic obstructive pulmonary disease, by intravenous infusion (with close monitoring), 500 micrograms/kg/hour, adjusted according to plasma-theophylline concentration; **CHILD** 6 months–9 years 1 mg/kg/hour, 10–16 years 800 micrograms/kg/hour, adjusted according to plasma-theophylline concentration

**Note** Patients taking oral theophylline or aminophylline should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage.

**Modified release**

**Note** Advice about modified-release theophylline preparations on p. 158 also applies to modified-release aminophylline preparations

### Phyllocontin Continus® (Napp)

**Tablets**, m/r, yellow, f/c, aminophylline hydrate 225 mg, net price 56-tab pack = £2.58. Label: 25

**Dose** **ADULT** and **CHILD** body-weight over 40 kg initially 1 tablet twice daily, increased after 1 week to 2 tablets twice daily according to plasma-theophylline concentration

**Note** Brands of modified-release tablets containing aminophylline 225 mg include Norphyllin SR

**Forte tablets**, m/r, yellow, f/c, aminophylline hydrate 350 mg, net price 56-tab pack = £4.22. Label: 25

**Dose** initially 1 tablet twice daily, increased after 1 week to 2 tablets twice daily if necessary

**Note** Phyllocontin Continus Forte tablets are for smokers and other patients with shorter theophylline half-life (see notes above)

### 3.1.4 Compound bronchodilator preparations

In general, patients are best treated with single-ingredient preparations, such as a selective beta agonist (section 3.1.1.1) or ipratropium bromide (section 3.1.2), so that the dose of each drug can be adjusted. This flexibility is lost with compound bronchodilator preparations. However, a combination product may be appropriate for patients stabilised on individual components in the same proportion.

**For cautions, contra-indications and side-effects** see under individual drugs.

### Combivent® (Boehringer Ingelheim)

**Nebuliser solution**, isotonic, ipratropium bromide 500 micrograms, salbutamol (as sulphate) 2.5 mg/2.5-mL vial, net price 60 unit-dose vials = £25.08

**Dose** bronchodilation in chronic obstructive pulmonary disease, **by inhalation of nebulised solution**, **ADULT** and **CHILD** over 12 years, 1 vial (2.5 mL) 3–4 times daily

**Glaucoma** In addition to other potential side-effects acute angle-closure glaucoma has been reported with nebulised ipratropium—see also notes above

### Duvent® (Boehringer Ingelheim)

**Nebuliser solution**, isotonic, fenoterol hydrobromide 1.25 mg, ipratropium bromide 500 micrograms/4-mL vial, net price 20 unit-dose vials = £11.00

**Dose** acute severe asthma or acute exacerbation of chronic asthma, **by inhalation of nebulised solution**, **ADULT** and **CHILD** over 14 years, 1 vial (4 mL), may be repeated up to max. 4 vials in 24 hours

### Peak flow meters, inhaler devices and nebulisers

#### 3.1.5 Peak flow meters

Measurement of peak flow is particularly helpful for patients who are ‘poor perceivers’ and hence slow to detect deterioration in their asthma, and for those with moderate or severe asthma.

Standard-range peak flow meters are suitable for both adults and children; low-range peak flow meters are appropriate for severely restricted airflow in adults and children. Patients must be given clear guidelines as to the action they should take if their peak flow falls below a certain level. Patients can be encouraged to adjust some of their own treatment (within specified limits) according to changes in peak flow rate.

**Standard Range Peak Flow Meter**

Conforms to standard EN 13826

- **MicroPeak**, range 60–800 litres/minute, net price = £6.50, replacement mouthpiece = 38p (Micro Medical)
- **Mini-Wright**, range 60–800 litres/minute, net price = £6.86, replacement mouthpiece = 38p (Clement Clarke)
- **Personal Best**, range 60–800 litres/minute, net price = £6.48, replacement mouthpiece = 25p (Respiracare)
- **Piko-1**, range 15–999 litres/minute, net price = £9.50, replacement mouthpiece = 38p (nSPIRE Health)
- **Pocketpeak**, range 60–800 litres/minute, net price = £6.53, replacement mouthpiece = 38p (nSPIRE Health)
- **Vitalograph**, range 50–800 litres/minute, net price = £4.50 (children’s coloured version also available), replacement mouthpiece = 40p (Vitalograph)

**Note** Readings from new peak flow meters are often lower than those obtained from old Wright-scale peak flow meters and the correct recording chart should be used.
Low Range Peak Flow Meter
Compliant to standard EN 13826 except for scale range Mini-Wright, range 50–400 litres/minute, net price = £6.80, replacement mouthpiece = 38p (Clement Clarke)
Pocketpeak, range 50–400 litres/minute, net price = £6.53, replacement mouthpiece = 38p (nSPIRE Health)

Note: Readings from new peak flow meters are often lower than those obtained from old Wright-scale peak flow meters and the correct recording chart should be used.

Drug delivery devices

Inhaler devices
These include pressurised metered-dose inhalers, breath-activated inhalers, and dry powder inhalers. Many patients can be taught to use a pressurised metered-dose inhaler effectively but some patients, particularly the elderly and children, find them difficult to use. Spacer devices (see below) can help such patients because they remove the need to coordinate actuation with inhalation, and are effective particularly for children under 15 years. Alternatively, breath-activated inhalers are suitable for patients over 7 years and dry powder inhalers are suitable for those over 5 years. On changing from a pressurised metered-dose inhaler to a dry powder inhaler, patients may notice a lack of sensation in the mouth and throat previously associated with each actuation. Coughing may also occur.

The patient should be instructed carefully on the use of the inhaler and it is important to check that the inhaler continues to be used correctly because inadequate inhalation technique may be mistaken for a lack of response to the drug.

Able Spacer (Clement Clarke)
Spacer device, small-volume device. For use with all pressurised (aerosol) inhalers, net price standard device = £4.20; with infant, child or adult mask = £6.86

AeroChamber Plus (GSK)
Spacer device, medium-volume device. For use with all pressurised (aerosol) inhalers, net price standard device (blue) = £4.43, with mask (blue) = £7.40; infant device (orange) with mask = £7.40; child device (yellow) with mask = £7.40

Babyhaler (A&H) Spacer device, for paediatric use with Flixotide, Seretide, Seretide and Ventolin inhalers, net price = £11.34

Haleraid (A&H) Inhalation aid, device to place over pressurised (aerosol) inhalers to aid when strength in hands is impaired (e.g. in arthritis). For use with Flixotide, Seretide, Seretide and Ventolin inhalers. Available as Haleraid -120 for 120-dose inhalers and Haleraid -200 for 200-dose inhalers, net price = 80p

Nebuchamber (AstraZeneca)
Spacer device, for use with Pulmicort aerosol inhalers, net price = £8.56

Nebuhaler (AstraZeneca)
Spacer device, large-volume device. For use with Pulmicort inhalers, with paediatric mask = £4.28

Optichamber (Respironics)
Spacer device, for use with all pressurised (aerosol) inhalers, net price = £4.28; with small or medium mask = £7.40

PARI Vortex Spacer (Pari)
Spacer device, medium-volume device. For use with all pressurised (aerosol) inhalers, net price with mouthpiece = £6.07, with mask for infant or child = £7.91; with adult mask = £9.97

Pocket Chamber (nSPIRE Health)
Spacer device, small-volume device. For use with all pressurised (aerosol) inhalers, net price = £4.18; with infant, small, medium, or large mask = £9.75

Volumatic (A&H)
Spacer inhaler, large-volume device. For use with Cenil Modulate, Flixotide, Seretide, Seretide and Ventolin inhalers, net price = £2.75; with paediatric mask = £2.75

Spacer devices
Spacer devices remove the need for co-ordination between actuation of a pressurised metered-dose inhaler and inhalation. The spacer device reduces the velocity of the aerosol and subsequent impaction on the oropharynx. In addition, the device allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Spacer devices are particularly useful for patients with poor inhalation technique, for children, for patients requiring higher doses, for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids. The size of the spacer is important, the larger spacers with a one-way valve (Nebuhaler®, Volumatic®) being most effective. It is important to prescribe a spacer device that is compatible with the metered-dose inhaler, see devices below. Spacer devices should not be regarded as interchangeable; patients should be advised not to switch between spacer devices.

Use and care of spacer devices
Patients should inhale from the spacer device as soon as possible after actuation because the drug aerosol is very short-lived; single-dose actuation is recommended. Tidal breathing is as effective as single breaths. The device should be cleansed once a month in mild detergent and then allowed to dry in air; the mouthpiece should be wiped clean of detergent before use. More frequent cleaning should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

NICE guidance

Inhaler devices for children with chronic asthma (children under 5 years, August 2000; children 6–15 years, March 2002)
A child's needs, ability to develop and maintain effective technique, and likelihood of good compliance should govern the choice of inhaler and spacer device; only then should cost be considered. For children aged under 5 years:
- corticosteroid and bronchodilator therapy should be delivered by pressurised metered-dose inhaler and spacer device, with a facemask if necessary;
- if this is not effective, and depending on the child's condition, nebulised therapy may be considered and, in children over 3 years, a dry powder inhaler may also be considered (but see notes above).

For children aged 5–15 years:
- corticosteroid therapy should be routinely delivered by a pressurised metered-dose inhaler and spacer device;
- children and their carers should be trained in the use of the chosen device; suitability of the device should be reviewed at least annually. Inhaler technique and compliance should be monitored.

Spacer devices
Spacer devices are particularly useful for children under 5 years of age, for patients requiring higher doses of inhaled corticosteroids, for nocturnal asthma, and for patients prone to candidiasis with inhaled corticosteroids. The size of the spacer is important, the larger spacers with a one-way valve (Nebuhaler®, Volumatic®) being most effective. It is important to prescribe a spacer device that is compatible with the metered-dose inhaler, see devices below. Spacer devices should not be regarded as interchangeable; patients should be advised not to switch between spacer devices.
A nebuliser converts a solution of a drug into an aerosol for inhalation. It is used to deliver higher doses of drug to the airways than is usual with standard inhalers. The main indications for use of a nebuliser are:

- to deliver a beta agonist or ipratropium to a patient with an acute exacerbation of asthma or of chronic obstructive pulmonary disease;
- to deliver a beta agonist or ipratropium on a regular basis to a patient with severe asthma or reversible airways obstruction who has been shown to benefit from regular treatment with higher doses;
- to deliver prophylactic medication such as a corticosteroid to a patient unable to use other inhalational devices (particularly to a young child);
- to deliver an antibiotic (such as colistin) to a patient with chronic purulent infection (as in cystic fibrosis or bronchiectasis);
- to deliver budesonide to a child with severe croup;
- to deliver pentamidine for the prophylaxis and treatment of pneumocystis pneumonia.

The proportion of a nebuliser solution that reaches the lungs depends on the type of nebuliser and although it can be as high as 30%, it is more frequently close to 10% and sometimes below 10%. The remaining solution is left in the nebuliser as residual volume or it is deposited in the mouthpiece and tubing. The extent to which the nebulised solution is deposited in the airways or alveoli depends on particle size. Particles with a mass median diameter of 1–5 microns are deposited in the airways and are therefore appropriate for asthma whereas a particle size of 1–2 microns is needed for alveolar deposition of pentamidine to combat pneumocystis infection. The type of nebuliser is therefore chosen according to the deposition required and according to the viscosity of the solution (antibiotic solutions usually being more viscous).

Some jet nebulisers are able to increase drug output during inspiration and hence increase efficiency. The patient should be aware that the dose of a bronchodilator given by nebulisation is usually much higher than that from an aerosol inhaler.

The British Thoracic Society has advised that nebulised treatment. If prescribed, patients must:

- have clear instructions from doctor, specialist nurse or pharmacist on the use of the nebuliser and on peak-flow monitoring;
- be instructed not to treat acute attacks at home without also seeking help;
- receive an education program;
- have regular follow up including peak-flow monitoring and be seen by doctor, specialist nurse or physiotherapist.

Jet nebulisers

Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum gas flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

For patients with chronic obstructive pulmonary disease and hypercapnia, oxygen can be dangerous and the nebuliser should be driven by air (see also p. 153). In exacerbations of chronic obstructive pulmonary disease, the nebuliser should be driven by compressed air in hypercapnia or acidosis. If oxygen is required, it should be given simultaneously by nasal cannula.

### Medics Lifecare Nebuliser Chamber

<table>
<thead>
<tr>
<th>Chamber Description</th>
<th>Net Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>S, D, PARI TurboBOY S, D, and PARI JuniorBOY S, D, AC 2000 Hi Flo, and Econome</td>
<td>£1.00</td>
</tr>
<tr>
<td>Econome</td>
<td>£1.00</td>
</tr>
<tr>
<td>PARI BOY Mobile S, D</td>
<td>£2.10</td>
</tr>
<tr>
<td>Medix Lifecare Nebuliser System</td>
<td>£2.00</td>
</tr>
</tbody>
</table>

Jet nebuliser, disposable; for use with bronchodilators, antimuscarinics, corticosteroids, and antibacterials, replacement recommended every 2–3 months if used 4 times a day. Compatible with AC 2000 Hi Flo, World Traveller Hi Flo, and Econome, net price = £1.00

Jet nebuliser, consisting of mouthpiece, tubing, and nebuliser chamber, net price = £2.20; mask kits with tubing and nebuliser chamber also available, net price (adult) = £2.00; (child) = £1.10

Jet nebuliser, non-disposable, for hospital or home use; for use with bronchodilators, antibacterials, and corticosteroids, replacement recommended yearly if used 4 times a day. Compatible with PARI TurboBOY S, D, PARI JuniorBOY S, D, PAS Mobile S, D, and PARI WALK BOY compressors, net price = £16.05

Jet nebuliser, non-disposable, for hospital or home use; for use with bronchodilators, antibacterials, and corticosteroids, replacement recommended yearly if used 4 times a day. Compatible with PARI TurboBOY S, D, PARI JuniorBOY S, D, PAS Mobile S, D, and PARI WALK BOY compressors. Available separately for children aged less than 1 year, 1–4 years or 4–7 years, net price (with mask and connection tube) = £32.15
**Respiratory system**

**3.1.5 Peak flow meters, inhaler devices and nebulisers**

**BNF 57**

**Sidestream Durable** (Profile Respiratory)

Jet nebuliser, non-disposable, for home use; for use with bronchodilators; yearly replacement recommended if 4 six-minute treatments used per day. Compatible with Freeway Freedom and Porta-Neb, net price year pack = £20.40 (Porta-Neb), £29.00 (Freeway Freedom). Disposable Sidestream nebuliser also available.

**Ventstream** (Profile Respiratory)

Jet nebuliser, closed-system, for use with low flow compressors, compatible with Porta-Neb, and Freeway Freedom compressors; for use with antibacterials, bronchodilators, and corticosteroids, replacement recommended yearly if used 3 times a day, net price year pack with filter = £39.00 (Porta-Neb), £41.00 (Freeway Freedom).

**Home compressors with nebulisers**

**AC 2000 HI FLO** (Medix)

Home and hospital use, containing 1 Jet Nebuliser set with mouthpiece, 1 adult and 1 child mask, 1 spare inlet filter, filter spanner. Mains operated. Nebulises bronchodilators, corticosteroids, and antibacterials, net price = £117.00; carrying case available.

**AC 4000** (Medix)

Home and hospital use, containing 1 Jet Nebuliser set with mouthpiece, 1 adult and 1 child mask, 1 spare inlet filter, filter spanner. Mains operated. Nebulises bronchodilators, corticosteroids, and antibacterials, net price = £80.10.

**Aquilon** (Henleys)

Portable, home use, with 1 adult or 1 child mask and tubing. Mains operated; for use with bronchodilators, corticosteroids and antibacterials, net price = £82.50.

**Econone** (Medix)

Home, clinic and hospital use, used with 1 Jet Nebuliser set with mouthpiece, 1 adult and 1 child mask, 1 spare inlet filter, filter spanner. Mains operated. Nebulises bronchodilators, corticosteroids, and antibacterials. Mains operated, net price = £99.00.

**Freeway Freedom** (Profile Respiratory)

Portable, containing Sidestream Durable nebuliser, 1 adult mask, 1 child mask, 1 angled mouthpiece, 1 coiled Duratube. 4 inlet filters, charger and power lead, net price = £203.20; with Ventstream nebuliser, 1 straight mouthpiece, 1 coiled Duratube, 4 inlet filters, 1 aerosol hose, charger and power lead, net price = £203.20.

**PARI JuniorBOY S** (Pari)

Portable, for hospital or home use, containing PARI LC SPRINT Junior nebuliser with mouthpiece, mask, connection tube, and mains cable. Filter replacement recommended every 12 months. Compatible with PARI LC SPRINT, and PARI LC SPRINT BABY nebulisers, net price = £70.00.

**PARI TurboBOY S** (Pari)

Portable, for hospital or home use, containing PARI LC SPRINT nebuliser with adult mouthpiece, mask, connection tube and mains cable. Filter replacement recommended every 12 months. Compatible with PARI LC SPRINT, and PARI LC SPRINT BABY nebulisers, net price = £55.00.

**PARI BOY Mobile S** (Pari)

Portable, containing PARI LC SPRINT nebuliser with connection tube, mains cable, rechargeable battery, car battery adaptor, and carrying case. Compatible with PARI LC SPRINT, and PARI LC SPRINT BABY nebulisers. Nebulises bronchodilators, corticosteroids, and antibacterials, net price = £180.00.

**Porta-Neb** (Profile Respiratory)

Portable, containing Sidestream Durable nebuliser, 1 adult mask, 1 child mask, 1 angled mouthpiece, 1 coiled Duratube, 4 inlet filters. Mains operated, net price = £94.00; with Ventstream nebuliser, 1 straight mouthpiece, 1 coiled Duratube, 4 inlet filters, aerosol hose. Mains operated, net price = £104.80.

**De Vilbiss 5650** (De Vilbiss)

Home, clinic use, containing disposable nebuliser set, mouthpiece, mask, mains lead, tubing, thumb-valve. For use with bronchodilators, net price = £142.14.

**De Vilbiss 4650** (De Vilbiss)

Home, clinic and hospital use; with mouthpiece. Mains operated, net price = £93.95.

**Tourer** (Henleys)

Portable, home use, mains/car battery operated; for use with bronchodilators, corticosteroids and antibacterials, net price = £101.25.

**Ultima** (Henleys)

Portable, home use, rechargeable or mains/car battery operated. Nebulises bronchodilators and corticosteroids, net price = £156.00 (includes case).

**World Traveller HI FLO** (Medix)

Portable, containing 1 Jet Nebuliser set with mouthpiece, 1 adult and 1 child mask, 1 spare inlet filter, filter spanner. Battery, car, and mains operated; rechargeable battery pack available. Nebulises bronchodilators, corticosteroids, and antibacterials, net price excluding battery = £166.00; with battery = £216.00; carrying case available.

**Compressors**

**Omron CX3** (Omron)

Home and hospital use, mains operated, net price = £48.75.

**Omron compAIR CX** (Omron)

Home and hospital use, mains operated, net price = £56.78 (includes 1 adult mask, child mask, 5 spare filters, and carrying case).

**System 22 CR60** (Profile Respiratory)

Hospital use, high flow compressor. Mains operated, net price = £199.90. Also compatible with System 22 Antibiotic Tee for nebulisation of high viscosity drugs such as antibacterials.

**Turboneb** (Medix)

Home use, high flow compressor. Nebulises bronchodilators, corticosteroids, antibacterials, and pentamidine. Mains operated, net price = £125.00.

**Ultrasonic nebulisers**

Ultrasonic nebulisers produce an aerosol by ultrasonic vibration of the drug solution and therefore do not require a gas flow.

**F16 Wave** (Parkside)

Portable, adjustable delivery rate. Mains/car battery operated or rechargeable battery pack (supplied), net price = £130.00.

**Liberty** (Medix)

Portable, home and clinic use, containing disposable mouthpiece and chamber cover. Mains and car battery operated. Nebulises bronchodilators and antibacterials, net price £112.49.

**Omron MicroAIR** (Omron)

Portable, battery operated, net price = £149.96 (includes 1 adult mask, 1 child mask, and carrying case; mains adaptor also available).

**Omron NE-U17** (Omron)

Clinic and hospital use, mains operated, net price = £650.17.

**Ultra Neb 2000** (De Vilbiss)

Hospital, clinic, and home use, delivery rate adjustable. Supplied with stand, net price = £1205.00.

**Nebuliser diluent**

Nebulisation may be carried out using an undiluted nebuliser solution or it may require dilution beforehand. The usual diluent is sterile sodium chloride 0.9% (physiological saline).

**Sodium Chloride** (Non-proprietary)

Nebuliser solution, sodium chloride 0.9%, net price 20 × 2.5 mL = £5.49. Brands include Saline Steripoule, Saline Steri-Neb.
Corticosteroids

Corticosteroids are used for the management of reversible and irreversible airways disease. An inhaled corticosteroid used for 3–4 weeks may help to distinguish asthma from chronic obstructive pulmonary disease; clear improvement over 3–4 weeks suggests asthma.

Asthma Corticosteroids are effective in asthma; they reduce airway inflammation (and hence reduce oedema and secretion of mucus into the airway).

An inhaled corticosteroid is used regularly for prophylaxis of asthma when patients require a beta agonist more than twice a week, or if symptoms disturb sleep more than once a week, or if the patient has suffered exacerbations in the last 2 years requiring a systemic corticosteroid or a nebulised bronchodilator (see Management of Chronic Asthma table, p. 149). Regular use of inhaled corticosteroids reduces the risk of exacerbation of asthma.

Current and previous smoking reduces the effectiveness of inhaled corticosteroids and higher doses may be necessary.

Corticosteroid inhalers must be used regularly for maximum benefit; alleviation of symptoms usually occurs 3 to 7 days after initiation. Beclometasone dipropionate (beclometasone dipropionate), budesonide, fluticasone propionate, and mometasone furoate appear to be equally effective. Preparations that combine a corticosteroid with a long-acting beta agonist may be helpful for patients stabilised on the individual components in the same proportion.

In adults using an inhaled corticosteroid and a long-acting beta agonist for the prophylaxis of asthma (see step 3 of the Management of Chronic Asthma table, p. 149) but who are poorly controlled, Symbicort® (budesonide with formoterol) is licensed for use as a reliever (instead of a short-acting beta agonist), in addition to its regular use for the prophylaxis of asthma. Patients must be carefully instructed on the appropriate dose and management of exacerbations before initiating this therapy, see Symbicort® p. 166. This management approach has not been investigated with combination inhalers containing other corticosteroids and long-acting beta agonists.

Patients taking long-term oral corticosteroids for asthma can often be transferred to an inhaled corticosteroid but the transfer must be slow, with gradual reduction in the dose of the oral corticosteroid, and at a time when the asthma is well controlled.

High doses of inhaled corticosteroid can be prescribed for patients who respond only partially to standard doses with a long-acting beta agonist or another long-acting bronchodilator (see Management of Chronic Asthma table, p. 149). High doses should be continued only if there is clear benefit over the lower dose. The recommended maximum dose of an inhaled corticosteroid should not generally be exceeded. However, if a higher dose is required, then it should be initiated and supervised by a specialist. The use of high doses of inhaled corticosteroid can minimise the requirement for an oral corticosteroid.

Systemic corticosteroid therapy may be necessary during episodes of infection or if the asthma is worsening, when higher doses are needed and access of inhaled drug to small airways may be reduced; patients may need a reserve supply of tablets.

**Side-effects of inhaled corticosteroids** Inhaled corticosteroids have considerably fewer systemic effects than oral corticosteroids (section 6.3.2), but adverse effects have been reported.

High doses of inhaled corticosteroids (see Management of Chronic Asthma table, p. 149) used for prolonged periods can induce adrenal suppression. Inhaled corticosteroids have been associated with adrenal crisis and coma in children; excessive doses should be avoided. Patients using high doses of inhaled corticosteroids should be given a ‘steroid card’ (section 6.3.2) and specific written advice to consider corticosteroid replacement during an episode of stress, such as severe intercurrent illness or an operation.

**MHRA/CHM advice (July 2008)**

- Beclometasone dipropionate CFC-free pressurised metered-dose inhalers (Qvar® and Clenil Modulite®) are not interchangeable and should be prescribed by brand name; Qvar® has extra-fine particles, is more potent than traditional CFC-containing inhalers, and is approximately twice as potent as Clenil Modulite®
- Fostair® is a combination beclometasone dipropionate and formoterol fumarate CFC-free pressurised metered-dose inhaler; Fostair® has extra-fine particles and is more potent than traditional beclometasone dipropionate CFC-free inhalers

**3.2 Corticosteroids**

**Chronic obstructive pulmonary disease** In chronic obstructive pulmonary disease inhaled corticosteroid treatment may reduce exacerbations. An inhaled corticosteroid [unlicensed indication] should be considered (in addition to bronchodilator treatment) if the forced expiratory volume in 1 second (FEV1) is less than 50% of the predicted value and if the patient has had 2 or more exacerbations in a year which require antibacterial treatment or an oral corticosteroid.

**Cautions of inhaled corticosteroids** Systemic therapy may be required during periods of stress or when either airways obstruction or mucus prevent drug access to smaller airways. For advice on the use of corticosteroids in women with asthma who are pregnant or breast-feeding, see p. 148, and Appendix 4 and Appendix 5; interactions: Appendix 1 (corticosteroids)

**Paradoxical bronchospasm** The potential for paradoxical bronchospasm (calling for discontinuation and alternative therapy) should be borne in mind—mild bronchospasm may be prevented by inhalation of a short-acting beta agonist beforehand (or by transfer from an aerosol inhalation to a dry powder inhalation). CFC-free inhalers Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Patients receiving CFC-free inhalers should be reassured about the efficacy of the new inhalers and counselled that the aerosol may feel and taste different; any difficulty with the new inhaler should be discussed with the doctor or pharmacist.

Doses for CFC-free corticosteroid inhalers may be different from those that contain CFCs, see also MHRA/CHM advice below.
High doses of inhaled corticosteroids have been associated with lower respiratory tract infections, including pneumonia, in older patients with chronic obstructive pulmonary disease.

Bone mineral density may be reduced following long-term inhalation of higher doses of corticosteroids, predisposing patients to osteoporosis (section 6.6). It is therefore sensible to ensure that the dose of an inhaled corticosteroid is no higher than necessary to keep a patient’s asthma under good control. Treatment with an inhaled corticosteroid can usually be stopped after a mild exacerbation as long as the patient knows that it is necessary to reinstate it should the asthma deteriorate or the peak flow rate fall.

In children, growth restriction associated with systemic corticosteroid therapy does not seem to occur with recommended doses of inhaled therapy; although initial growth velocity may be reduced, there appears to be no effect on achieving normal adult height. However, the CSM has recommended that the height of children receiving prolonged treatment of inhaled corticosteroid is monitored; if growth is slowed, referral to a paediatrician should be considered. Large-volume spacer devices should be used for administering inhaled corticosteroids in children under 5 years (see NICE guidance, section 3.1.5); they are also useful in older children and adults, particularly if high doses are required. Spacer devices increase airway deposition and reduce oropharyngeal deposition.

A small risk of glaucoma with prolonged high doses of inhaled corticosteroids has been reported; cataracts have also been reported with inhaled corticosteroids. Hoarseness and candidiasis of the mouth or throat have been reported, usually only with large doses (see also below). Hypersensitivity reactions (including rash and angioedema) have been reported rarely. Other side-effects that have been reported very rarely include paradoxical bronchospasm, anxiety, depression, sleep disturbances, and behavioural changes including hyperactivity and irritability.

Candidiasis The risk of oral candidiasis can be reduced by using a spacer device with the corticosteroid inhaler; rinsing the mouth with water (or cleaning a child’s teeth) after inhalation of a dose may also be helpful. Antifungal oral suspension or lozenges (section 12.3.2) can be used to treat oral candidiasis without discontinuing therapy.

Oral An acute attack of asthma should be treated with a short course of an oral corticosteroid starting with a high dose, e.g. prednisolone 40–50 mg daily for a few days. Patients whose asthma has deteriorated rapidly usually respond quickly to corticosteroids. The dose can usually be stopped abruptly in a mild exacerbation of asthma (see also Withdrawal of Corticosteroids, section 6.3.2) but it should be reduced gradually in those with poorer asthma control, to reduce the possibility of serious relapse. For the use of corticosteroids in the emergency treatment of acute severe asthma, see Management of Acute Asthma table, p. 150.

In chronic continuing asthma, when the response to other drugs has been inadequate, longer term administration of an oral corticosteroid may be necessary; in such cases high doses of an inhaled corticosteroid should be continued to minimise oral corticosteroid requirements. In chronic obstructive pulmonary disease prednisolone 30 mg daily should be given for 7–14 days; treatment can be stopped abruptly. Prolonged treatment with oral prednisolone is of no benefit and maintenance treatment is not normally recommended.

An oral corticosteroid should normally be taken as a single dose in the morning to reduce the disturbance to circadian cortisol secretion. Dosage should always be titrated to the lowest dose that controls symptoms. Regular peak-flow measurements help to optimise the dose.

**Parenteral** For the use of hydrocortisone injection in the emergency treatment of acute severe asthma, see Management of Acute Asthma table, p. 150.

---

**BECLOMETASONE DIPROPIONATE** (Becloethasone Dipropionate)

**Indications** prophylaxis of asthma (see also Management of Chronic Asthma table, p. 149)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- By aerosol inhalation, see Management of Chronic Asthma table, p. 149 (important: for Clenil Modulite® and Qvar®, see under preparations)
- By inhalation of dry powder (important: for Asmacet® and Becodisks®, see under preparations), 200–400 micrograms twice daily; adjusted as necessary up to 800 micrograms twice daily; CHILD over 5 years 100–200 micrograms twice daily, adjusted as necessary

**Beclometasone** (Non-proprietary) \[\text{BECLOMETASONE DICLOFILMATE}\]

Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £5.69; 100 micrograms/metered inhalation, 200-dose unit = £9.91; 200 micrograms/metered inhalation, 200-dose unit = £17.25; 250 micrograms/metered inhalation, 200-dose unit = £22.88. Label: 8, counselling, dose; also 10 and steroid card with high doses

Excipients include CFC propellants

**Brand include Beclozone**

Dry powder for inhalation, beclometasone dipropionate 100 micrograms/metered inhalation, net price 100-dose unit = £5.58; 200 micrograms/metered inhalation, 100-dose unit = £10.29, 200-dose unit = £15.60; 400 micrograms/metered inhalation, 100-dose unit = £20.41. Label: 8, counselling, dose; also 10 and steroid card with high doses

Excipients include Pulvinal beclometasone Dipropionate, Easyhaler beclometasone Dipropionate

**Inhalation powder, hard capsule** (for use with Cyclohaler® device), beclometasone dipropionate 100 micrograms, net price 120-cap pack = £15.99; 200 micrograms, 120-cap pack = £25.00; 400 micrograms, 120-cap pack = £32.25. Label: 8, counselling, dose; also 10 and steroid card with high doses

**Brand include Beclometasone Cyclocaps**

Asmabec Clickhaler® (UCB Pharma) \[\text{BECLOMETASONE DICLOFILMATE}\]

Dry powder for inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £6.68; 100 micrograms/metered inhalation, 200-dose unit = £9.81; 250 micrograms/metered inhalation, 100-dose unit = £12.31. Label: 8, counselling, dose; also 10 and steroid card with high doses

**Dose** by inhalation of powder; prophylaxis of asthma, 100–400 micrograms twice daily, adjusted as necessary, max. 1 mg twice daily; CHILD 6–12 years 50–200 micrograms twice daily, adjusted as necessary
Clenil Modulite® (Trinity-Chiesi) ▼ (Inh)<br>Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £3.26; 100 micrograms/metered inhalation, 200-dose unit = £10.30; 250 micrograms/metered inhalation, 200-dose unit = £20.25. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Excipients include CFC propellants.<br><br>Becodisks® (A&H) ▼ (Inh)<br>Dry powder for inhalation, disks containing 8 blisters of beclometasone dipropionate 100 micrograms/blistter, net price 15 disks with Diskhaler® device = £12.00, 15-disk refill = £11.42; 200 micrograms/blistter, 15 disks with Diskhaler® device = £22.87, 15-disk refill = £22.28; 400 micrograms/blistter, 15 disks with Diskhaler® device = £45.14, 15-disk refill = £44.57. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Dose by inhalation of powder, prophylaxis of asthma, 400 micrograms twice daily, adjusted as necessary to 800 micrograms twice daily, CHILD 5–12 years 100–200 micrograms twice daily, adjusted as necessary.<br><br>Clenil Modulite® (Trinity-Chiesi) ▼ (Inh)<br>Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £3.85; 100 micrograms/metered inhalation = £7.72; 200 micrograms/metered inhalation = £16.83; 250 micrograms/metered inhalation = £16.95. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Excipients include HFA-134a (a non-CFC propellant)<br>Dose by aerosol inhalation, 200–400 micrograms twice daily, adjusted as necessary up to 1 mg twice daily; CHILD under 12 years 100–200 micrograms twice daily<br>Note Clenil Modulite is not interchangeable with other CFC-free beclometasone dipropionate inhalers; the MHRA has advised (August 2006 and July 2008) that CFC-free beclometasone dipropionate inhalers should be prescribed by brand name.<br>Dental prescribing on NHS Clenil Modulite 50 micrograms/ metered inhalation may be prescribed.<br><br>Qvar® (IVAX) ▼ (Inh)<br>Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.87; 100 micrograms/metered inhalation, 200-dose unit = £17.21. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Excipients include HFA-134a (a non-CFC propellant)<br><br>Autohaler® (breath-actuated aerosol inhalation), beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.87; 100 micrograms/metered inhalation, 200-dose unit = £17.21. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Excipients include HFA-134a (a non-CFC propellant)<br><br>Easi-Breathe® (breath-actuated aerosol inhalation), beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £7.74; 100 micrograms/metered inhalation, 200-dose unit = £16.95. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Excipients include HFA-134a (a non-CFC propellant)<br><br>When switching a patient with poorly controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of Qvar should be prescribed for 100 micrograms of beclometasone dipropionate, budesonide, or fluticasone propionate, the dose of Qvar should be adjusted according to response<br>Note The MHRA has advised (August 2006 and July 2008) that beclometasone dipropionate CFC-free inhalers should be prescribed by brand name.<br><br>**Budesonide**<br><br>Indications prophylaxis of asthma (see also Management of Chronic Asthma table, p. 149); croup<br>Cautions see notes above<br>Side-effects see notes above<br>Dose see preparations below<br><br>Budesonide (Non-proprietary) ▼ (Inh)<br>Dry powder for inhalation, budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £9.25; 200 micrograms/metered inhalation, 200-dose unit = £18.50; 400 micrograms/metered inhalation, 100-dose unit = £18.50. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Brands include Easyhaler, Budesonide.<br><br>Inhalation powder, hard capsule (for use with Cyclohaler® device), budesonide 200 micrograms, net price 100-cap pack = £15.48; 400 micrograms, 50-cap pack = £15.48. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Brands include Budesonide Cyclospore.<br><br>Dose by inhalation of powder, ADULT and CHILD over 12 years, 100–800 micrograms twice daily, adjusted as necessary, alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening; CHILD 6–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening.<br><br>Dose by inhalation of powder, ADULT and CHILD over 12 years, 200–800 micrograms twice daily, adjusted as necessary, alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening; CHILD 6–12 years 200–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening.<br><br>Novolizer® (Viatris) ▼ (Inh)<br>Dry powder for inhalation, budesonide 200 micrograms, net price refillable inhaler device and 100-dose cartridge = £14.86; 100-dose refill cartridge = £9.59. Label: 8, counselling, dose; also 10 and steroid card with high doses<br>Dose by inhalation of powder, ADULT and CHILD over 12 years, 100–800 micrograms twice daily, adjusted as necessary, alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening; CHILD 6–12 years 200–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening.
Pulmicort® (AstraZeneca) [NH]
Aerosol inhalation, budesonide 200 micrograms/metered inhalation, net price 200-dose unit = £20.90. Label: 8, counselling, dose; also 10 and steroid card with high doses
Excipients include CFC propellants
Dose: by aerosol inhalation, ADULT and CHILD over 12 years, 200–400 micrograms twice daily, adjusted as necessary; max. 800 micrograms twice daily. CHILD 6–12 years, 50–400 micrograms twice daily adjusted as necessary

Turbohaler® (= dry powder inhaler), budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £18.50; 200 micrograms/metered inhalation, 100-dose unit = £18.50; 400 micrograms/metered inhalation, 50-dose unit = £18.50. Label: 8, counselling, dose; also 10 and steroid card with high doses
Dose: by inhalation of powder, ADULT and CHILD over 12 years, 100–800 micrograms twice daily, adjusted as necessary, alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms (max. 800 micrograms) as a single dose in the evening. CHILD 5–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, for patients previously stabilised on a twice daily dose, 200–400 micrograms as a single dose in the evening

Respules® (= single-dose units for nebulisation), budesonide 250 micrograms/mL, net price 20 × 2 mL (500-microgram) unit = £32.00; 500 micrograms/mL, 20 × 2 mL (1-mg) unit = £44.64. May be diluted with sterile sodium chloride 0.9%. Label: 8, counselling, dose, 10, steroid card
Dose: prophylaxis of asthma, by inhalation of nebulised suspension, ADULT and CHILD over 12 years, 1–2 mg twice daily, reduced to 0.5–1 mg twice daily; CHILD 3 months–12 years, 0.5–1 mg twice daily, reduced to 250–500 micrograms twice daily. Group, by inhalation of nebulised solution, 2 mg as a single dose (or as two 1-mg doses separated by 30 minutes)

Symbicort® (AstraZeneca) [NH]
Symbicort 100/6 Turbohaler® (= dry powder inhaler), budesonide 100 micrograms, formoterol fumarate 6 micrograms/metered inhalation, net price 120-dose unit = £33.00. Label: 8, counselling, dose
Dose: by inhalation of powder, asthma maintenance therapy, 1–2 puffs twice daily increased if necessary to max. 4 puffs twice daily, reduced to 1 puff once daily if control maintained. CHILD 6–12 years, 2 puffs twice daily reduced to 1 puff once daily if control maintained. 12–17 years, 1–2 puffs twice daily reduced to 1 puff once daily if control maintained. Asthma, maintenance and reliever therapy, ADULT over 18 years, 2 puffs daily in 1–2 divided doses, for relief of symptoms, 1 puff as needed up to max. 6 puffs at a time; max. 8 puffs daily; up to 12 puffs can be used for a limited time but medical assessment should be considered
Symbicort 200/6 Turbohaler® (= dry powder inhaler), budesonide 200 micrograms, formoterol fumarate 6 micrograms/metered inhalation, net price 120-dose unit = £38.00. Label: 8, counselling, dose; also 10 and steroid card with high doses
Dose: by inhalation of powder, asthma maintenance therapy, 1–2 puffs twice daily increased if necessary to max. 4 puffs twice daily, reduced to 1 puff once daily if control maintained. CHILD 12–17 years 1–2 puffs twice daily reduced to 1 puff once daily if control maintained. Asthma, maintenance and reliever therapy, ADULT over 18 years, 2 puffs daily in 1–2 divided doses, increased if necessary to 2 puffs twice daily; for relief of symptoms, 1 puff as needed up to max. 6 puffs at a time; max. 8 puffs daily; up to 12 puffs can be used for a limited time but medical assessment should be considered. Chronic obstructive pulmonary disease, 2 puffs twice daily
Symbicort 400/12 Turbohaler® (= dry powder inhaler), budesonide 400 micrograms, formoterol fumarate 12 micrograms/metered inhalation, net price 60-dose unit = £38.00. Label: 8, counselling, dose; also 10 and steroid card with high doses
Dose: by inhalation of powder, asthma maintenance therapy, 1 puff twice daily increased if necessary to max. 2 puffs twice daily, reduced to 1 puff once daily if control maintained. CHILD 12–17 years 1 puff twice daily reduced to 1 puff once daily if control maintained. Chronic obstructive pulmonary disease, 1 puff twice daily

Ciclesonide
Indications prophylaxis of asthma
Cautions see notes above
Side-effects see notes above
Dose
• By aerosol inhalation, ADULT and CHILD over 12 years, 160 micrograms daily as a single dose reduced to 80 micrograms daily if control maintained
Alvesco® (Nycomed) [NH]
Aerosol inhalation, ciclesonide 80 micrograms/metered inhalation, net price 120-dose unit = £28.56; 160 micrograms/metered inhalation, 60-dose unit = £16.80. 120-dose unit = £33.60. Label: 8, counselling, dose
Excipients include HFA-134a (a non-CFC propellant)

Fluticasone Propionate
Indications prophylaxis of asthma (see also Management of Chronic Asthma table, p. 149)
Cautions see notes above
Side-effects see notes above; also very rarely dyspepsia, hyperglycaemia, and arthralgia
Dose
• See preparations below
Flixotide® (A&H) [NH]
Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 50 micrograms/blister with Accuhaler® device, net price = £6.38; 100 micrograms/blister with Accuhaler® device = £8.93; 250 micrograms/blister with Accuhaler® device = £21.28; 500 micrograms/blister with Accuhaler® device = £36.14. Label: 8, counselling, dose; also label 10 and steroid card with high doses
Note: Flixotide Accuhaler 250 micrograms and 500 micrograms are not indicated for children
Dose: by inhalation of powder, prophylaxis of asthma, ADULT and CHILD over 16 years, 100–500 micrograms twice daily, increased according to severity of asthma (max. 1 mg twice daily). CHILD 5–16 years, 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily

Diskhaler® (dry powder for inhalation), fluticasone propionate 50 micrograms/blister, net price 15 disks of 4 blisters with Diskhaler® device = £8.17, 15-disk refill = £7.64; 100 micrograms/blister, 15 disks of 4 blisters with Diskhaler® device = £12.71, 15-disk refill = £12.18; 250 micrograms/blister, 15 disks of 4 blisters with Diskhaler® device = £24.11, 15-disk refill = £23.58; 500 micrograms/blister, 15 disks of 4 blisters with Diskhaler® device = £40.05, 15-disk refill = £39.52. Label: 8, counselling, dose; also label 10 and steroid card with high doses
Note: Flixotide Diskhaler 250 micrograms and 500 micrograms are not indicated for children
Dose: by inhalation of powder, prophylaxis of asthma, ADULT and CHILD over 16 years, 100–500 micrograms twice daily, increased according to severity of asthma (max. 1 mg twice daily). CHILD 5–16 years, 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily
Evohaler® aerosol inhalation, fluticasone propionate 50 micrograms/metered inhalation, net price 120-dose unit = £5.44; 125 micrograms/metered inhalation, 120-dose unit = £21.26; 250 micrograms/metered inhalation, 120-dose unit = £36.14. Label: 8, counselling, dose, change to CFC-free inhaler; also label 10 and steroid card with high doses

Exipients include HFA-134a (a non-CFC propellant)

Note Flutotide Evohaler 125 micrograms and 250 micrograms not indicated for children

Dose by aerosol inhalation, prophylaxis of asthma, ADULT and CHILD over 16 years, 100–500 micrograms twice daily increased according to severity of asthma (max. 1 mg twice daily). CHILD 4–16 years, 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily

Nebulés® (=single-dose units for nebulisation) fluticasone propionate 250 micrograms/mL, net price 10 × 2-mL (500-microgram) unit = £9.34; 1 mg/mL, 10 × 2-mL (2-mg) unit = £37.35. May be diluted with sterile sodium chloride 0.9%. Label: 8, counselling, dose, 10, steroid card

Dose by inhalation of nebulised suspension, prophylaxis of asthma, ADULT and CHILD over 16 years, 0.5–2 mg twice daily; CHILD 4–16 years, 1 mg twice daily

**3.3.1 Cromoglicate and related therapy**

**MOMETASONE FURONATE**

**Indications** prophylaxis of asthma (see also Management of Chronic Asthma table, p. 149)

**Cautions** see notes above

**Side-effects** see notes above; also pharyngitis, headache; less commonly palpitation

**Dose**

- By inhalation of powder, 200–400 micrograms as a single dose in the evening or in 2 divided doses; dose increased to 400 micrograms twice daily if necessary; CHILD not recommended

Asmanex® (Schering-Plough) ▼ (Puff)

Twisthaler (= dry powder inhaler), mometasone furoate 200 micrograms/metered inhalation, net price 30-dose unit = £16.00, 60-dose unit = £24.00, 400 micrograms/metered inhalation, 30-dose unit = £22.20, 60-dose unit = £36.75. Label: 8, counselling, dose, 10, steroid card

Note The Scottish Medicines Consortium has advised (November 2003) that Asmanex is restricted for use following failure of first-line inhaled corticosteroids

**3.3.2 Leukotriene receptor antagonists**

**3.3.3 Cromoglicate and related therapy and leukotriene receptor antagonists**

**3.3.3.1 Cromoglicate and related therapy**

The mode of action of sodium cromoglicate and nedocromil is not completely understood. They may be of value in asthma with an allergic basis, but, in practice, it is difficult to predict who will benefit; they could probably be given for 4 to 6 weeks to assess response. Dose frequency is adjusted according to response but is usually 3 to 4 times a day initially; this may subsequently be reduced.

In general, prophylaxis with sodium cromoglicate is less effective than prophylaxis with corticosteroid inhalations (see Chronic Asthma table, p. 149). There is evidence of efficacy of nedocromil in children aged 5–12 years. Sodium cromoglicate is of no value in the treatment of acute attacks of asthma.
Sodium cromoglicate can prevent exercise-induced asthma. However, exercise-induced asthma may reflect poor overall control and the patient should be assessed. If inhalation of sodium cromoglicate causes bronchospasm, a selective beta agonist such as salbutamol or terbutaline should be inhaled a few minutes beforehand.

**SODIUM CROMOGLICATE**
(Sodium Cromoglycate)

**Indications** prophylaxis of asthma (see also Management of Chronic Asthma table, p. 149); food allergy (section 1.5); allergic conjunctivitis (section 11.4.2); allergic rhinitis (section 12.2.1)

**Cautions** discontinue if eosinophilic pneumonia occurs

**Side-effects** coughing, transient bronchospasm, and throat irritation; very rarely hypersensitivity reactions (including angioedema); rhinitis and headache also reported

**Dose**
- By aerosol inhalation, ADULT and CHILD, 10 mg (2 puffs) 4 times daily, increased in severe cases or during periods of risk to 6–8 times daily; additional doses may also be taken before exercise; maintenance 5 mg (1 puff) 4 times daily

Intel® (Sanofi-Aventis) [W]
Aerosol inhalation, sodium cromoglicate 5 mg/ metered inhalation, net price 112-dose unit = £15.44.
Label: 8, counselling, change to CFC-free inhaler
Excipients include HFA-227 (a non-CFC propellant)

**NEDOCROMIL SODIUM**

**Indications** prophylaxis of asthma (see also Management of Chronic Asthma table, p. 149)

**Side-effects** see under Sodium Cromoglicate; also headache, nausea, vomiting, dyspepsia and abdominal pain; bitter taste (masked by mint flavour)

**Dose**
- By aerosol inhalation, ADULT and CHILD over 6 years 4 mg (2 puffs) 4 times daily, when control achieved may be possible to reduce to twice daily
- Counselling Regular use is necessary

Tilade CFC-free Inhaler® (Sanofi-Aventis) ▼ [N]
Aerosol inhalation, mint-flavoured, nedocromil sodium 2 mg/metered inhalation. Net price 112-dose unit = £39.94. Label: 8, counselling, change to CFC-free inhaler
Excipients include HFA-227 (a non-CFC propellant)

**3.3.2 Leukotriene receptor antagonists**

The leukotriene receptor antagonists, montelukast and zafirlukast, block the effects of cysteinyl leukotrienes in the airways. They are effective in asthma when used alone or with an inhaled corticosteroid (see Chronic Asthma table, p. 149). Montelukast has not been shown to be more effective than a standard dose of inhaled corticosteroid but the two drugs appear to have an additive effect. The leukotriene receptor antagonists may be of benefit in exercise-induced asthma and in those with concomitant rhinitis but they are less effective in those with severe asthma who are also receiving high doses of other drugs.

Churg-Strauss syndrome has occurred very rarely in association with the use of leukotriene receptor antagonists; in many of the reported cases the reaction followed the reduction or withdrawal of oral corticosteroid therapy. The CSM has advised that prescribers should be alert to the development of eosinophilia, vasculitic rash, worsening pulmonary symptoms, cardiac complications, or peripheral neuropathy.

**MONTELUKAST**

**Indications** prophylaxis of asthma, see notes above and Chronic Asthma table, p. 149; symptomatic relief of seasonal allergic rhinitis in patients with asthma

**Cautions** pregnancy (see p. 148 and Appendix 4); breast-feeding (see p. 148 and Appendix 5); interactions: Appendix 1 (leukotriene antagonists)

**Side-effects** abdominal pain, thirst; hyperkinesia (in young children), headache; very rarely Churg-Strauss syndrome (see notes above); dry mouth, diarrhoea, dyspepsia, nausea, vomiting, hepatic disorders, pitting, oedema, increased bleeding, hypersensitivity reactions (including anaphylaxis and skin reactions), depression, suicidal thoughts and behaviour, tremor, asthenia, dizziness, hallucinations, paraesthesia, hypoaesthesia, sleep disturbances, abnormal dreams, agitation, aggression, seizures, arthralgia, and myalgia, also reported

**Dose**
- Prophylaxis of asthma, ADULT and CHILD over 15 years, 10 mg once daily in the evening. CHILD 6 months–6 years 4 mg once daily in the evening, 6–15 years 5 mg once daily in the evening
- Seasonal allergic rhinitis, ADULT and CHILD over 15 years, 10 mg once daily in the evening

Singular® (MSD) [N]
Chewable tablets, pink, cherry-flavoured, montelukast (as sodium salt) 4 mg, net price 28-tab pack = £25.69. Label: 23, 24
Excipients include aspartame equivalent to phenylalanine 674 micrograms/4-mg tablet and 842 micrograms/5-mg tablet (section 9.4.1)

Granules; montelukast (as sodium salt) 4 mg, net price 28-sachet pack = £25.69. Counselling, administration

Counselling Granules may be swallowed or mixed with cold food (but not fluid) and taken immediately

Tablets, beige, 10 mg. Montelukast (as sodium salt) 10 mg, net price 28-tab pack = £26.97

Note The Scottish Medicines Consortium has advised (June 2007) that Singular chewable tablets and granules are restricted for use as an alternative to low-dose inhaled corticosteroids for children 2-14 years with mild persistent asthma who have not recently had serious asthma attacks that required oral corticosteroid use and who are not capable of using inhaled corticosteroids; Singular chewable tablets and granules should be initiated by a specialist in paediatric asthma.

**ZAFIRLUKAST**

**Indications** prophylaxis of asthma, see notes above and Chronic Asthma table, p. 149

**Cautions** elderly, renal impairment (Appendix 3); pregnancy (see p. 148 and Appendix 4); interactions: Appendix 1 (leukotriene antagonists)

Hepatic disorders Patients or their carers should be told how to recognise development of liver disorder and advised
to seek medical attention if symptoms or signs such as persistent nausea, vomiting, malaise, or jaundice develop.

**Contra-indications** hepatic impairment; breast-feeding (see p. 148 and Appendix 5)

**Side-effects** gastro-intestinal disturbances, headache, insomnia, malaise; rarely bleeding disorders, hypersensitivity reactions including angioedema and skin reactions, arthralgia, myalgia, hepatitis, hyperbilirubinaemia, thrombocytopenia; very rarely Churg-Strauss syndrome (see notes above), agranulocytosis

**Dose**
- **ADULT** and **CHILD** over 12 years, 20 mg twice daily

**Accolate**
- **Tablets,** f/c, zafirlukast 20 mg, net price 56-tab pack = £28.26. Label: 23

# 3.4 Antihistamines, hyposensitisation, and allergic emergencies

## 3.4.1 Antihistamines

All antihistamines are of potential value in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hay fever), and they may be of some value in vasomotor rhinitis. They reduce rhinorrhea and sneezing but are usually less effective for nasal congestion. Antihistamines are used topically in the eye (section 11.4.2), in the nose (section 12.2.1), and on the skin (section 13.3).

Oral antihistamines are also of some value in preventing urticaria and are used to treat urticarial rashes, pruritus, and insect bites and stings; they are also used in drug allergies. Injections of chlorphenamine (chlorpheniramine) or promethazine are used as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis and angioedema (section 3.4.3). For the use of antihistamines (including cinnarizine, cyclizine, and promethazine teoclate) in nausea and vomiting, see section 4.6. Buclizine is included as an anti-emetic in a preparation for migraine (section 4.7.4.1). For reference to the use of antihistamines for occasional insomnia, see section 4.1.1.

All older antihistamines cause sedation but **alimemazine** (trimeprazine) and promethazine may be more sedating whereas chlorphenamine and cyclizine (section 4.6) may be less so. This sedating activity is sometimes used to manage the pruritus associated with some allergies. There is little evidence that any one of the older, ‘sedating’ antihistamines is superior to another. Patients vary widely in their response. The sedating activity is sometimes used to manage the pruritus associated with some allergies. There is little evidence that any one of the older antihistamines is superior to another. Patients vary widely in their response. The sedating activity is some-

**Non-sedating antihistamines**

**Driving** Although drowsiness is rare, nevertheless patients should be advised that it can occur and may affect performance of skilled tasks (e.g. driving); excess alcohol should be avoided.

**CETIRIZINE HYDROCHLORIDE**

**Indications** symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

**Cautions** see notes above; also renal impairment (Appendix 3)

**Contra-indications** see notes above; also pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see notes above

**Dose**
- **ADULT** and **CHILD** over 6 years, 10 mg once daily or 5 mg twice daily; **CHILD** 1–2 years see **BNF for Children**, 2–6 years, hay fever, 5 mg once daily or 2.5 mg twice daily

**Cetirizine**
- **Tablets,** cetirizine hydrochloride 10 mg, net price 30-tab pack = 97p. Counselling, driving

**Cetirizine (Non-proprietary)**
- **Tablets,** cetirizine hydrochloride 10 mg, net price 30-tab pack = 97p. Counselling, driving

**Oral solution,** cetirizine hydrochloride 5 mg/5 mL, net price 200 mL = £2.43. Counselling, driving

**DESLORATADINE**

**Note** Desloratadine is a metabolite of loratadine

**Indications** symptomatic relief of allergic rhinitis and urticaria
**Respiratory system**

**Cautions** see notes above; also renal impairment (Appendix 3)

**Contra-indications** see notes above; also hypersensitivity to loratadine; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see notes above; rarely myalgia; very rarely hallucinations

**Dose**
- 5 mg once daily; **CHILD** 1–6 years 1.25 mg once daily, 6–12 years 2.5 mg once daily

**Neoclarityn** *(Schering-Plough)*

**Tablets**, blue, f/c, desloratadine 5 mg, net price 30-tab pack = £7.04. Counselling, driving

**Syrup**, desloratadine 2.5 mg/5 mL, net price 100 mL (bubblegum-flavour) = £7.04. Counselling, driving

**FEXOFENADINE HYDROCHLORIDE**

**Note** Fexofenadine is a metabolite of terfenadine

**Indications** see under Dose

**Cautions** see notes above; also pregnancy (Appendix 4)

**Contra-indications** see notes above; also breast-feeding (Appendix 5)

**Side-effects** see notes above

**Dose**
- Seasonal allergic rhinitis, 120 mg once daily; **CHILD** 6–12 years, 30 mg twice daily
- Chronic idiopathic urticaria, **ADULT** and **CHILD** over 12 years, 180 mg once daily

**Fexofenadine** *(Non-proprietary)*

**Tablets**, f/c, fexofenadine hydrochloride 120 mg, net price 30-tab pack = £5.92; 180 mg, 30-tab pack = £7.49. Label: 5, counselling, driving

**Telfast** *(Aventis Pharma)*

**Tablets**, f/c, peach, fexofenadine hydrochloride 30 mg, net price 60-tab pack = £5.68; 120 mg, 30-tab pack = £6.23; 180 mg, 30-tab pack = £7.89. Label: 5, counselling, driving

**LEVOCETIRIZINE HYDROCHLORIDE**

**Note** Levocetirizine is an isomer of cetirizine

**Indications** symptomatic relief of allergy such as hay fever, urticaria

**Cautions** see notes above; also renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above; very rarely weight gain

**Dose**
- **ADULT** and **CHILD** over 6 years, 5 mg once daily; **CHILD** 2–6 years 1.25 mg twice daily

**Xyzal** *(UCB Pharma)*

**Tablets**, f/c, levocetirizine hydrochloride 5 mg, net price 30-tab pack = £5.20. Counselling, driving

**Oral solution**, levocetirizine hydrochloride 2.5 mg/5 mL, net price 200 mL = £6.00. Counselling, driving

**LORATADINE**

**Indications** symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

**Cautions** see notes above

**Contra-indications** see notes above; also pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** see notes above

**Dose**
- **ADULT** and **CHILD** over 6 years 10 mg once daily; **CHILD** 2–6 years 5 mg once daily

**Loratadine** *(Non-proprietary)*

**Tablets**, loratadine 10 mg, net price 30-tab pack = £1.24. Counselling, driving

**Dental prescribing on NHS** Loratadine 10 mg may be prescribed

**Syrup**, loratadine 5 mg/5 mL, net price 100 mL = £5.16. Counselling, driving

**MIZOLASTINE**

**Indications** symptomatic relief of allergy such as hay fever, urticaria

**Cautions** see notes above

**Contra-indications** see notes above; also susceptibility to QT-interval prolongation (including cardiac disease and hypokalaemia); significant hepatic impairment; pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** see notes above; weight gain; anxiety, asthenia; less commonly arthralgia and myalgia

**Dose**
- **ADULT** and **CHILD** over 12 years, 10 mg once daily

**Mizollen** *(Sanofi-Aventis)*

**Tablets**, m/r, f/c, scored, mizolastine 10 mg, net price 30-tab pack = £5.77. Label: 25, counselling, driving

**Sedating antihistamines**

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); sedating effects enhanced by alcohol.

**ALIMEMAZINE TARTRATE** *(Trimeprazine tartrate)*

**Indications** urticaria and pruritus, premedication

**Cautions** see notes above; pregnancy (Appendix 4); see also section 4.2.1

**Contra-indications** see notes above; also renal impairment; breast-feeding (Appendix 5); see also section 4.2.1

**Side-effects** see notes above; see also section 4.2.1

**Dose**
- Urticaria and pruritus, 10 mg 2–3 times daily, in severe cases up to max. 100 mg daily has been used; **ELDERLY** 10 mg 1–2 times daily; **CHILD** under 2 years, see **BNF for Children**, 2–5 years 2.5 mg 3–4 times daily, 5–12 years 5 mg 3–4 times daily
- Premedication, **CHILD** 2–7 years up to 2 mg/kg 1–2 hours before operation

**Vallegan** *(Sanofi-Aventis)*

**Tablets**, blue, f/c, alimemazine tartrate 10 mg, net price 28-tab pack = £3.89. Label: 2

**Syrup**, straw-coloured, alimemazine tartrate 7.5 mg/5 mL, net price 100 mL = £4.44. Label: 2

**Syrup forte**, alimemazine tartrate 30 mg/5 mL, net price 100 mL = £6.86. Label: 2

**BNF 57**
CHLORPHENAMINE MALEATE
(Chlorpheniramine maleate)

**Indications** symptomatic relief of allergy such as hay fever, urticaria; emergency treatment of anaphylactic reactions (section 3.4.3)

**Cautions** see notes above; also pregnancy (Appendix 4) and breastfeeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- By mouth, 4 mg every 4–6 hours, max. 24 mg daily; CHILD under 1 year see BNF for Children, 1–2 years 1 mg twice daily; 2–6 years 1 mg every 4–6 hours, max. 6 mg daily; 6–12 years 2 mg every 4–6 hours, max. 12 mg daily
- By intramuscular injection or by intravenous injection over 1 minute, 10 mg, repeated if required up to 4 times in 24 hours; CHILD 1–6 months 250 micrograms/kg, repeated if required up to 4 times in 24 hours; 6 months–6 years 2.5 mg, repeated if required up to 4 times in 24 hours; 6–12 years 5 mg, repeated if required up to 4 times in 24 hours

Chlorphenamine (Non-proprietary)

**Tablets**, chlorphenamine maleate 4 mg, net price 28 = £1.12. Label: 2

**Dental prescribing on NHS** Chlorphenamine tablets may be prescribed

**Oral solution**, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.25. Label: 2

**Dental prescribing on NHS** Chlorphenamine oral solution may be prescribed

**Injection**, chlorphenamine maleate 10 mg/mL, net price 1-mL amp = £1.62

1. (TM) restriction does not apply where administration is for saving life in emergency

Piriton® (GSK Consumer Healthcare)

**Tablets**, yellow, scored, chlorphenamine maleate 4 mg, net price 28 = £1.62. Label: 2

**Syrup**, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.39. Label: 2

CLEMASTINE

**Indications** symptomatic relief of allergy such as hay fever, urticaria

**Cautions** see notes above; also pregnancy (Appendix 4) and breastfeeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- 1 mg twice daily, increased up to 6 mg daily if required; INFANT under 1 year not recommended, CHILD 1–3 years 250–500 micrograms twice daily; 3–6 years 500 micrograms twice daily; 6–12 years 0.5–1 mg twice daily

Tavegil® (Novartis Consumer Health)

**Tablets**, scored, clemastine (as hydrogen fumarate) 1 mg, Net price 60-tab pack = £2.35. Label: 2

CYPROHEPATIDNE HYDROCHLORIDE

**Indications** symptomatic relief of allergy such as hay fever, urticaria; migraine (section 4.7.4.2)

**Cautions** see notes above; also pregnancy (Appendix 4) and breastfeeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Allergy, usual dose 4 mg 3–4 times daily; usual range 4–20 mg daily, max. 32 mg daily; INFANT under 2 years not recommended, CHILD 2–6 years 2 mg 2–3 times daily, max. 12 mg daily; 7–14 years 4 mg 2–3 times daily, max. 16 mg daily
- Migraine, 4 mg with a further 4 mg after 30 minutes if necessary; maintenance, 4 mg every 4–6 hours

Periactin® (MSD)

**Tablets**, scored, cyproheptadine hydrochloride 4 mg, net price 30-tab pack = 86p. Label: 2

HYDROXYZINE HYDROCHLORIDE

**Indications** pruritus, anxiety (short-term) (section 4.1.2)

**Cautions** see notes above

**Contra-indications** see notes above; also pregnancy (Appendix 4) and breastfeeding (Appendix 5)

**Side-effects** see notes above

**Dose**
- Pruritus, initially 25 mg at night increased if necessary to 25 mg 3–4 times daily; CHILD 6 months–6 years initially 5–15 mg daily increased if necessary to 50 mg daily in divided doses; over 6 years initially 15–25 mg daily increased if necessary to 50–100 mg daily in divided doses
- Anxiety (adults only), 50–100 mg 4 times daily

Atarax® (Alliance) (TM)

**Tablets**, both s/c, hydroxyzine hydrochloride 10 mg (orange), net price 84-tab pack = £1.82; 25 mg (green), 28-tab pack = £1.22. Label: 2

Ucerax® (UCB Pharma) (TM)

**Tablets**, f/c, scored, hydroxyzine hydrochloride 25 mg, net price 25-tab pack = £1.22. Label: 2

**Syrup**, hydroxyzine hydrochloride 10 mg/5 mL. Net price 200-mL pack = £1.78. Label: 2

KETOTIFEN

**Indications** allergic rhinitis

**Cautions** see notes above

**Contra-indications** pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Side-effects** see notes above; also excitation, irritability, nervousness; less commonly cystitis, rarely weight gain; very rarely Stevens-Johnson syndrome

**Dose**
- 1 mg twice daily with food increased if necessary to 2 mg twice daily; initial treatment in readily sedated patients 0.5–1 mg at night; CHILD 3 years and over, 1 mg twice daily

Zaditen® (Novartis) (TM)

**Tablets**, scored, ketotifen (as hydrogen fumarate) 1 mg, net price 60-tab pack = £10.75. Label: 2, 21

**Elirx**, ketotifen (as hydrogen fumarate), 1 mg/5 mL, net price 300 mL (strawberry-flavoured) = £12.73. Label: 2, 21
3.4.2 Allergen Immunotherapy

Immunotherapy using allergen vaccines containing house dust mite, animal dander (cat or dog), or extracts of grass and tree pollen can reduce symptoms of asthma and allergic rhinoconjunctivitis. A vaccine containing extracts of wasp and bee venom is used to reduce the risk of severe anaphylaxis and systemic reactions in individuals with hypersensitivity to wasp or bee venom. Desensitising vaccines should be avoided in pregnant women, in children under five years old, and in those taking beta-blockers (adrenaline may be ineffective in case of a hypersensitivity reaction), or ACE inhibitors (risk of severe anaphylactoid reactions).

Hypersensitivity reactions to immunotherapy (especially to wasp and bee venom extracts) can be life-threatening; bronchospasm usually develops within 1 hour and anaphylaxis within 30 minutes of injection. Therefore patients need to be monitored for 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), even when mild, the patient should be observed until these have resolved completely.

For details of the management of anaphylactic shock, see section 3.4.3.

Each set of allergen extracts usually contains vials for the administration of graded amounts of allergen to patients undergoing hyposensitisation. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

BEE AND WASP ALLERGEN EXTRACTS

Indications hypersensitivity to wasp or bee venom (see notes above)

Cautions see notes above and consult product literature

CSM advice The CSM has advised that facilities for cardiopulmonary resuscitation must be immediately available and patients monitored closely for one hour after each injection

Contra-indications see notes above and consult product literature

Side-effects consult product literature

Dose

- By subcutaneous injection, consult product literature

Pharmalgen® (ALK-Abelló)®

Bee venom extract (Apis mellifera) or wasp venom extract (Vespula spp.), net price initial treatment set = £59.77 (bee), £73.28 (wasp); maintenance treatment set = £69.54 (bee), £89.45 (wasp)

GRASS AND TREE POLLEN EXTRACTS

Indications treatment of seasonal allergic hay fever due to grass or tree pollen in patients who have failed to respond to anti-allergy drugs (see notes above)

Cautions see notes above and consult product literature

CSM advice The CSM has advised that facilities for cardiopulmonary resuscitation must be immediately available and patients monitored closely for one hour after each injection

Contra-indications see notes above and consult product literature

Side-effects see notes above and consult product literature

Dose

- See under preparations, below

Pollinex® (Allergy)®

Grasses and rye or tree pollen extract, net price initial treatment set (3 vials) and extension course treatment (1 vial) = £320.00

Dose By subcutaneous injection, consult product literature
Grass pollen extract

Grazax® (ALK-Abello®) \[\text{\footnotesize ALK-Abello®}\] Oral lyophilisates (= freeze-dried tablets), grass pollen extract 75 000 units, net price 30-tab pack = £67.50. Counselling, administration

Dose ADULT over 18 years, 1 tablet daily; start treatment at least 4 months before start of pollen season and continue for up to 3 years

Counselling Tablets should be placed under the tongue and allowed to disperse

Omalizumab

Omalizumab is a monoclonal antibody that binds to immunoglobulin E (IgE). It is licensed for use as additional therapy in individuals with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high-dose inhaled corticosteroid therapy. Omalizumab should be initiated by physicians experienced in the treatment of severe persistent asthma.

Churg-Strauss syndrome has occurred rarely in patients given omalizumab; the reaction is usually associated with the reduction of oral corticosteroid therapy. Churg-Strauss syndrome can present as eosinophilia, vasculitic rash, cardiac complications, worsening pulmonary symptoms, or peripheral neuropathy. Hypersensitivity reactions can also occur immediately following treatment with omalizumab or sometimes more than 24 hours after the first injection.

For details on the management of anaphylactic shock, see section 3.4.3.

NICE guidance

Omalizumab for severe persistent allergic asthma (November 2007)

Omalizumab is recommended as additional therapy for the prophylaxis of severe persistent allergic asthma in adults and children over 12 years, who cannot be controlled adequately with high-dose inhaled corticosteroids and long-acting beta agonists in addition to leukotriene receptor antagonists, theophylline, oral corticosteroids, oral beta agonists, and smoking cessation where clinically appropriate. The following conditions apply:

- confirmation of IgE-mediated allergy to a perennial allergen by clinical history and allergy skin testing;
- either 2 or more severe exacerbations of asthma requiring hospital admission within the previous year, or 3 or more severe exacerbations of asthma within the previous year, at least one of which required hospital admission, and a further 2 which required treatment or monitoring in excess of the patient’s usual regimen, in an accident and emergency unit.

Omalizumab should be initiated and monitored by a physician experienced in both allergy and respiratory medicine in a specialist centre, and discontinued at 16 weeks in patients who have not shown an adequate response to therapy.

OMALIZUMAB

Indications prophylaxis of allergic asthma (see notes above)

Cautions autoimmune disease; susceptibility to bemith infection—discontinue if infection does not respond to antihelminitic; hepatic impairment; renal impairment; pregnancy (Appendix 4)

Contra-indications breast-feeding (Appendix 5)

Side-effects headache; injection-site reactions; less commonly nausea, diarrhoea, dyspepsia, flushing, fatigue, dizziness, drowsiness, paraesthesia, weight gain, influenza-like symptoms, photosensitivity, hypersensitivity reactions (including hypotension, bronchospasm, laryngoeudema, rash, pruritus, and anaphylaxis); Churg-Strauss syndrome (see notes above), thrombocytopenia, arthralgia, myalgia, and alopecia also reported

Dose

- By subcutaneous injection, ADULT and CHILD over 12 years, according to immunoglobulin E concentration and body-weight, consult product literature

Xolair® (Novartis) \[\text{\footnotesize Novartis}\] Injection, powder for reconstitution, omalizumab, net price 150-mg vial = £256.15 (with solvent)

Excipients include sucrose 108 mg/vial

3.4.3 Allergic emergencies

Adrenaline (epinephrine) provides physiological reversal of the immediate symptoms (such as laryngeal oedema, bronchospasm, and hypotension) associated with hypersensitivity reactions such as anaphylaxis and angioedema.

Anaphylaxis

Anaphylactic shock requires prompt treatment of laryngeal oedema, bronchospasm, and hypotension. Atopic individuals are particularly susceptible. Insect stings are a recognised risk (in particular wasp and bee stings). Latex and certain foods, including eggs, fish, cow’s milk protein, peanuts, and tree nuts may also precipitate anaphylaxis. Medicinal products particularly associated with anaphylaxis include blood products, vaccines, hyposensitising (allergen) preparations, antibacterials, aspirin and other NSAIDs, heparin, and neuromuscular blocking drugs. In the case of drugs, anaphylaxis is more likely after parenteral administration; resuscitation facilities must always be available for injections associated with special risk. Anaphylactic reactions may also be associated with additives and excipients in foods and medicines. Reashed arachis (peanut) oil, which may be present in some medicinal products, is unlikely to cause an allergic reaction—nevertheless it is wise to check the full formula of preparations which may contain allergenic fats or oils.

First-line treatment of anaphylaxis includes securing the airway, restoration of blood pressure (laying the patient flat and raising the legs, or in the recovery position if unconscious or nauseated and at risk of vomiting) and administration of adrenaline (epinephrine) injection. Adrenaline is given intramuscularly in a dose of 500 micrograms \(0.5\text{ mL adrenaline injection 1 in 1000}\); a dose of 300 micrograms \(0.3\text{ mL adrenaline injection 1 in 1000}\) may be appropriate for immediate self-administration. The dose is repeated if necessary at
3.4.3 Allergic emergencies

5-minute intervals according to blood pressure, pulse, and respiratory function (important: possible need for intravenous route using dilute solution, see below). High-flow oxygen administration and intravenous fluids (section 9.2.2) are also of primary importance. An antihistamine (e.g. chlorphenamine), given by slow intravenous injection or intramuscular injection in a dose of 10 mg, see p. 171) is a useful adjunctive treatment, given after adrenaline injection and continued for 24 to 48 hours according to clinical response to prevent relapse. Patients receiving beta-blockers require special consideration (see under Adrenaline, p. 175).

Continuing respiratory deterioration requires further treatment with bronchodilators including inhaled or intravenous salbutamol (see p. 154), inhaled ipratropium (see p. 157), intravenous aminophylline (see p. 159), or intravenous magnesium sulphate [unlicensed indication] (see under Acute Severe Asthma, p. 151); in addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary.

An intravenous corticosteroid e.g. hydrocortisone (as sodium succinate) in a dose of 200 mg (section 6.3.2) is of secondary value in the initial management of anaphylactic shock because the onset of action is delayed for several hours, but should be given to prevent further deterioration in severely affected patients and continued for 24 to 48 hours according to clinical response.

When a patient is so ill that there is doubt about the adequacy of the circulation, the initial injection of adrenaline may need to be given as a dilute solution by the intravenous route; for details of cautions, dose, and strength, see under Intravenous Adrenaline (Epinephrine), below.

Cardiopulmonary arrest may follow an anaphylactic reaction; resuscitation should be started immediately (see p. 123).

For advice on the management of medical emergencies in dental practice, see p. 21.

Patients who are suspected of having had an anaphylactic reaction should be referred to a specialist for specific allergy diagnosis; avoidance of the allergen is the principal treatment.

Intramuscular adrenaline (epinephrine)

The intramuscular route is the first choice route for the administration of adrenaline (epinephrine) in the management of anaphylactic shock. Adrenaline has a rapid onset of action after intramuscular administration and in the shocked patient its absorption from the intramuscular site is faster and more reliable than from the subcutaneous site (the intravenous route should be reserved for extreme emergency when there is doubt about the adequacy of the circulation; for details of cautions, dose and strength see under Intravenous Adrenaline (Epinephrine), below).

Patients with severe allergy should ideally be instructed in the self-administration of adrenaline by intramuscular injection (for details see under Self-administration of Adrenaline (Epinephrine), below).

Prompt injection of adrenaline is of paramount importance. The following adrenaline doses are based on the revised recommendations of the Working Group of the Resuscitation Council (UK).

### Dose of intramuscular injection of adrenaline (epinephrine) for anaphylactic shock

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose</th>
<th>Volume of adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child under 6 years</td>
<td>150 micrograms</td>
<td>0.15 mL¹</td>
</tr>
<tr>
<td>Child 6–12 years</td>
<td>300 micrograms</td>
<td>0.3 mL²</td>
</tr>
<tr>
<td>Adult and child 12–18 years</td>
<td>500 micrograms</td>
<td>0.5 mL²</td>
</tr>
</tbody>
</table>

¹ These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function.
² For advice on the use of the intravenous route for cardiac resuscitation, see section 2.7.3.

### Intravenous adrenaline (epinephrine)

When the patient is severely ill and there is real doubt about the adequacy of the circulation and absorption after intramuscular injection, adrenaline (epinephrine) can be given by slow intravenous injection in a dose of 50 micrograms (0.5 mL of the dilute 1 in 10 000 adrenaline injection) repeated according to response; if multiple doses are required, adrenaline should be given as a slow intravenous infusion stopping when a response has been obtained; children may respond to as little as 1 microgram/kg (0.01 mL/kg of the dilute 1 in 10 000 adrenaline injection) by slow intravenous injection over several minutes.

Intravenous adrenaline should be given only by those experienced in its use, in a setting where patients can be carefully monitored; it should only be given to children when intravenous access is already available.

Great vigilance is needed to ensure that the correct strength of adrenaline injection is used; anaphylactic shock kits need to make a very clear distinction between the 1 in 10 000 strength and the 1 in 1000 strength. It is also important that, where intramuscular injection might still succeed, time should not be wasted seeking intravenous access.

For reference to the use of the intravenous route for cardiac resuscitation, see section 2.7.3.

### Self-administration of adrenaline (epinephrine)

Individuals at considerable risk of anaphylaxis need to carry adrenaline (epinephrine) at all times and need to be instructed in advance how to inject it. In addition, the packs need to be labelled so that in the case of rapid collapse someone else is able to administer the adrenaline. It is important to ensure that an adequate supply is provided to treat symptoms until medical assistance is available.

Adrenaline for administration by intramuscular injection is available in ‘auto-injectors’, pre-assembled syringes fitted with a needle suitable for very rapid administration (if necessary by a bystander or a healthcare provider if it is the only preparation available). Anapen® and EpiPen® consist of a fully assembled syringe and needle delivering a dose of 300 micrograms of adrenaline by intramuscular injection; 150-microgram versions (Anapen® Junior, EpiPen® Jr) are also available for use in children.
ADRENALINE/EPINEPHRINE

Indications  emergency treatment of acute anaphylaxis; angioedema; cardiopulmonary resuscitation (section 2.7.3); priapism [unlicensed indication] (section 7.4.5)

Cautions heart disease, hypertension, arrhythmias, cerebrovascular disease, phaeochromocytoma, diabetes mellitus, hyperthyroidism; susceptibility to angle-closure glaucoma; elderly

Interactions Severe anaphylaxis in patients taking non-cardioselective beta-blockers may not respond to adrenaline, calling for intravenous salbutamol (see p. 154); adrenaline can cause severe hypertension and bradycardia in those taking non-cardioselective beta-blockers. Other interactions, see Appendix 1 (sympathomimetics).

Side-effects nausea, vomiting; tachycardia, arrhythmias, palpitation, cold extremities, hypertension (risk of cerebral haemorrhage); dyspnoea, pulmonary oedema (on excessive dosage or extreme sensitivity); anxiety, tremor, restlessness, headache, weakness, dizziness; hyperglycaemia; urinary retention; sweating; tissue necrosis at injection site and angle-closure glaucoma also reported

Dose
• Acute anaphylaxis, by intramuscular injection (preferably midline in anterolateral thigh) of 1 in 1000 (1 mg/mL) solution, see notes and table above
• Acute anaphylaxis when there is doubt as to the adequacy of the circulation, by slow intravenous injection of 1 in 10 000 (100 micrograms/mL) solution (extreme caution—specialist use only), see notes above

Important Intravenous route should be used with extreme care by specialists only, see notes above

Intramuscular or subcutaneous

1 Adrenaline/Epinephrine 1 in 1000 (Non-proprietary) [FW]

Injection, adrenaline (as acid tartrate) 1 mg/mL, net price 0.5-mL amp = 49p; 1-mL amp = 56p

1 Minijet® Adrenaline 1 in 1000 (UCB Pharma) [FW]

Injection, adrenaline (as hydrochloride) 1 in 1000 (1 mg/mL), net price 1 mL (with 25 gauge × 0.25 inch needle for subcutaneous injection) = £9.81, 1 mL (with 21 gauge × 1.5 inch needle for intramuscular injection) = £5.78 (both disposable syringes)

Excipients include sulphites

Intravenous

Extreme caution, see notes above

Adrenaline/Epinephrine 1 in 10 000, Dilute (Non-proprietary) [FW]

Injection, adrenaline (as acid tartrate) 100 micrograms/mL, 10-mL amp, 1-mL and 10-mL prefilled syringe

Minijet® Adrenaline 1 in 10 000 (UCB Pharma) [FW]

Injection, adrenaline (as hydrochloride) 1 in 10 000 (100 micrograms/mL), net price 3-mL prefilled syringe = £5.70; 10-mL prefilled syringe = £5.30

Excipients include sulphites

1. [FW] restriction does not apply to adrenaline injection 1 mg/mL where administration is for saving life in emergency

Intramuscular injection for self-administration

Anapen® (Lincoln Medical) [FW]

1 Anapen® 0.3 mg solution for injection (delivering a single dose of adrenaline 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 1.05-mL auto-injector device = £30.67

Excipients include sulphites

Note 0.75 mL of the solution remains in the auto-injector device after use

Dose by intramuscular injection, ADULT and CHILD over 30 kg, 300 micrograms repeated after 10–15 minutes as necessary

Anapen® Junior 0.15 mg solution for injection (delivering a single dose of adrenaline 150 micrograms), adrenaline 500 micrograms/mL (1 in 2000), net price 1.05-mL auto-injector device = £30.67

Excipients include sulphites

Note 0.75 mL of the solution remains in the auto-injector device after use

Dose by intramuscular injection, CHILD 15–30 kg, 150 micrograms repeated after 10–15 minutes as necessary

EpiPen® (ALK-Abelló) [FW]

EpiPen® Auto-Injector 0.3 mg (delivering a single dose of adrenaline 300 micrograms), adrenaline 1 mg/mL (1 in 1000), net price 2-mL auto-injector = £28.05

Excipients include sulphites

Note 1.7 mL of the solution remains in the Auto-injector after use

Dose by intramuscular injection, ADULT and CHILD over 30 kg, 300 micrograms repeated after 5–15 minutes as necessary

EpiPen® Jr Auto-injector 0.15 mg (delivering a single dose of adrenaline 150 micrograms), adrenaline 500 micrograms/mL (1 in 2000), net price 2-mL auto-injector = £28.05

Excipients include sulphites

Note 1.7 mL of the solution remains in the Auto-injector after use

Dose by intramuscular injection, CHILD 15–30 kg, 150 micrograms (but on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children) repeated after 5–15 minutes as necessary

Angioedema

Angioedema is dangerous if laryngeal oedema is present. In this circumstance adrenaline (epinephrine) injection and oxygen should be given as described under Anaphylaxis (see above); antihistamines and corticosteroids should also be given (see again above). Tracheal intubation may be necessary.

Hereditary angioedema The administration of C1 esterase inhibitor (in fresh frozen plasma or in partially purified form) can terminate acute attacks of hereditary angioedema, but is not practical for long-term prophylaxis. Icatibant is licensed for the treatment of acute attacks of hereditary angioedema in adults with C1 esterase inhibitor deficiency.

Tranexamic acid (section 2.11) and danazol (section 6.7.2) [unlicensed indication] are used for short-term and long-term prophylaxis of hereditary angioedema. Short-term prophylaxis is started several days before planned procedures (e.g. dental work) and continued for 2–5 days afterwards. Danazol should be avoided in children because of its androgenic effects.

ICATIBANT

Indications acute attacks of hereditary angioedema in patients with C1 esterase inhibitor deficiency

Cautions ischaemic heart disease, stroke; pregnancy (Appendix 4); breast-feeding (Appendix 5)
Side-effects  
nausea, abdominal pain; nasal congestion; headache, dizziness; asthena; rash, injection-site reactions; less commonly vomiting, weight gain, cough, asthma, fatigue, pyrexia, pharyngitis, flushing, and pruritus

Dose  
- By subcutaneous injection, ADULT over 18 years, 30 mg as a single dose, repeated after 6 hours if necessary; a third dose may be given after a further 6 hours (max. 3 doses in 24 hours)

Firazyr® (gerini) ▼ [H]
Injection, icatibant (as acetate) 10 mg/mL, net price 3-mL prefilled syringe = £1395.00

3.5 Respiratory stimulants and pulmonary surfactants

3.5.1 Respiratory stimulants

Respiratory stimulants (analectic drugs) have a limited place in the treatment of ventilatory failure in patients with chronic obstructive pulmonary disease. They are effective only when given by intravenous injection or infusion and have a short duration of action. Their use has largely been replaced by ventilatory support including nasal intermittent positive pressure ventilation. However, occasionally when ventilatory support is contra-indicated and in patients with hypercapnic respiratory failure who are becoming drowsy or comatose, respiratory stimulants in the short term may arouse patients sufficiently to co-operate and clear their secretions.

Respiratory stimulants can also be harmful in respiratory failure since they stimulate non-respiratory as well as respiratory muscles. They should only be given under expert supervision in hospital and must be combined with active physiotherapy. There is at present no oral respiratory stimulant available for long-term use in chronic respiratory failure.

Doxapram is given by continuous intravenous infusion. Frequent arterial blood gas and pH measurements are necessary during treatment to ensure correct dosage.

Doxapram Hydrochloride

Indications  see under Dose

Cautions  give with oxygen in severe irreversible airways obstruction or severely decreased lung compliance (because of increased work load of breathing); give with beta agonist in bronchoconstriction; hypertension (avoid if severe), impaired cardiac reserve; hepatic impairment, pregnancy (compelling reasons only); interactions: Appendix 1 (doxapram)

Contra-indications  severe hypertension, status asthmaticus, coronary artery disease, thyrotoxicosis, epilepsy, physical obstruction of respiratory tract

Side-effects  perineal warmth, dizziness, sweating, moderate increase in blood pressure and heart rate; side-effects reported in postoperative period (causal effect not established) include muscle fasciculation, hyperactivity, confusion, hallucinations, cough, dyspnoea, laryngospasm, bronchospasm, sinus tachycardia, bradycardia, extrasystoles, nausea, vomiting and salivation

Dose  
- Postoperative respiratory depression, by intravenous injection over at least 30 seconds, 1–1.5 mg/kg repeated if necessary after intervals of 1 hour or alternatively by intravenous infusion, 2–3 mg/minute adjusted according to response; CHILD not recommended

- Acute respiratory failure, by intravenous infusion, 1.5–4 mg/minute adjusted according to response (given concurrently with oxygen and whenever possible monitor with frequent measurement of blood gas tensions); CHILD not recommended

- Neonatal apnoea, see BNF for Children

Dopram® (Anpharm) ▼ [H]
Injection, doxapram hydrochloride 20 mg/mL. Net price 5-mL amp = £3.00

Intravenous infusion, doxapram hydrochloride 2 mg/mL in glucose 5%. Net price 500-mL bottle = £21.13

3.5.2 Pulmonary surfactants

Pulmonary surfactants are used in the management of respiratory distress syndrome (hyaline membrane disease) in neonates and preterm neonates. They may also be given prophylactically to those considered at risk of developing the syndrome.

Cautions  Continuous monitoring is required to avoid hyperoxaemia caused by rapid improvement in arterial oxygen concentration.

Side-effects  Pulmonary haemorrhage has been rarely reported. Pulmonary surfactants are used in the management of respiratory distress syndrome (hyaline membrane disease) in neonates and preterm neonates. They may also be given prophylactically to those considered at risk of developing the syndrome.

BERACTANT

Indications  treatment of respiratory distress syndrome in preterm neonates over 700 g; prophylaxis of respiratory distress syndrome in preterm neonates less than 32 weeks post-menstrual age

Cautions  see notes above

Side-effects  see notes above

Dose  
- By endotracheal tube, phospholipid 100 mg/kg equivalent to a volume of 4 mL/kg, preferably within 8 hours of birth; may be repeated within 48 hours at intervals of at least 6 hours for up to 4 doses

Survanta® (Abbott) ▼ [H]
Suspension, beractant (bovine lung extract) providing phospholipid 25 mg/mL, with lipids and proteins, net price 8-mL vial = £306.43
Oxygen should be regarded as a drug. It is prescribed for hypoxaemic patients to increase alveolar oxygen tension and decrease the work of breathing. The concentration of oxygen required depends on the condition being treated; the administration of an inappropriate concentration of oxygen can have serious or even fatal consequences.

Oxygen is probably the most common drug used in medical emergencies. It should be prescribed initially to achieve a normal or near-normal oxygen saturation; in most acutely ill patients with a normal or low arterial carbon dioxide ($P_{CO_2}$), oxygen saturation should be 94–98% oxygen saturation. However, in some clinical situations such as cardiac arrest and carbon monoxide poisoning (see also Emergency Treatment of Poisoning, p. 35) it is more appropriate to aim for the highest possible oxygen saturation until the patient is stable. A lower target of 88–92% oxygen saturation is indicated for patients at risk of hypercapnic respiratory failure, see below.

High concentration oxygen therapy, with concentrations of up to 60%, is safe in uncomplicated cases of conditions such as pneumonia, pulmonary thromboembolism, fibrosing alveolitis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions low arterial oxygen ($P_O_2$) is usually associated with low or normal arterial carbon dioxide ($P_{CO_2}$), and therefore there is little risk of hyperventilation and carbon dioxide retention.

In acute severe asthma, the arterial carbon dioxide ($P_{CO_2}$) is usually subnormal but as asthma deteriorates it may rise steeply (particularly in children). These patients usually require high concentrations of oxygen and if the arterial carbon dioxide ($P_{CO_2}$) remains high despite other treatment, intermittent positive-pressure ventilation needs to be considered urgently. Where facilities for blood gas measurement are not immediately available, for example while transferring the patient to hospital, 40–60% oxygen delivered through a high-flow mask is recommended.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for patients at risk of hypercapnic respiratory failure, which is more likely in those with:

- chronic obstructive pulmonary disease;
- cystic fibrosis;
- non-cystic fibrosis bronchiectasis;
- severe kyphoscoliosis or severe ankylosing spondylitis;
- severe lung scarring caused by tuberculosis;
- musculoskeletal disorders with respiratory weakness, especially if on home ventilation;
- an overdose of opioids, benzodiazepines, or other drugs causing respiratory depression.

Treatment should be initiated in hospital because repeated blood gas measurements are required to determine the correct concentration. Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target oxygen saturation of 88–92%. The aim is to provide the patient with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis. Patients may carry an oxygen alert card, see section 3.1.

### Domiciliary oxygen
Oxygen should only be prescribed for use in the home after careful evaluation in hospital by respiratory experts.

Patients should be advised of the risks of continuing to smoke when receiving oxygen therapy, including the risk of fire. Smoking cessation therapy (section 4.10) should be tried before home oxygen prescription.

### Air travel
Some patients with arterial hypoxaemia require supplementary oxygen for air travel. The patient’s requirement should be discussed with the airline before travel.

### Long-term oxygen therapy
Long-term administration of oxygen (usually at least 15 hours daily) prolongs survival in some patients with chronic obstructive pulmonary disease.

For assessment of long-term oxygen therapy requirements measurement of arterial blood gas tensions. Measurements should be taken on 2 occasions at least 3 weeks apart to demonstrate clinical stability, and not sooner than 4 weeks after an acute exacerbation of the disease. Long-term oxygen therapy should be considered for patients with:

- chronic obstructive pulmonary disease with $P_O_2 < 7.3$ kPa when breathing air during a period of clinical stability;
- chronic obstructive pulmonary disease with $P_O_2 7.3–8$ kPa in the presence of secondary polycythaemia, nocturnal hypoxaemia, peripheral oedema, or evidence of pulmonary hypertension;
- severe chronic asthma with $P_O_2 < 7.3$ kPa or persistent disabling breathlessness;
- interstitial lung disease with $P_O_2 < 8$ kPa and in patients with $P_O_2 > 8$ kPa with disabling dyspnoea;
- cystic fibrosis when $P_O_2 < 7.3$ kPa or if $P_O_2 7.3–8$ kPa in the presence of secondary polycythaemia.
3 Respiratory system

• nocturnal hypoxaemia, pulmonary hypertension, or peripheral oedema;
• pulmonary hypertension, without parenchymal lung involvement when $P O_2 < 8$ kPa;
• neuromuscular or skeletal disorders, after specialist assessment;
• obstructive sleep apnoea despite continuous positive airways pressure therapy, after specialist assessment;
• pulmonary malignancy or other terminal disease with disabling dyspnoea;
• heart failure with daytime $P O_2 < 7.3$ kPa when breathing air or with nocturnal hypoxaemia;
• paediatric respiratory disease, after specialist assessment.

Increased respiratory depression is seldom a problem in patients with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; patients and relatives should be warned to call for medical help if drowsiness or confusion occur.

### Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness not relieved by other treatment in patients with severe chronic obstructive pulmonary disease, interstitial lung disease, heart failure, and in palliative care. It is important, however, that the patient does not rely on oxygen instead of obtaining medical help or taking more specific treatment. Short-burst oxygen therapy can be used to improve exercise capacity and recovery; it should only be continued if there is proven improvement in breathlessness or exercise tolerance.

### Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for patients on long-term oxygen therapy who need to be away from home on a regular basis. Patients who are not on long-term oxygen therapy can be considered for ambulatory oxygen therapy if there is evidence of exercise-induced oxygen desaturation and of improvement in blood oxygen saturation and exercise capacity with oxygen. Ambulatory oxygen therapy is not recommended for patients with heart failure or those who smoke.

### Oxygen therapy equipment

Under the NHS oxygen may be supplied as oxygen cylinders. Oxygen flow can be adjusted as the cylinders are equipped with an oxygen flow meter with ‘medium’ (2 litres/minute) and ‘high’ (4 litres/minute) settings.

Oxygen concentrators are more economical for patients who require oxygen for long periods, and in England and Wales can be ordered on the NHS on a regional tendering basis (see below). A concentrator is recommended for a patient who requires oxygen for more than 8 hours a day (or 21 cylinders per month). Exceptionally, if a higher concentration of oxygen is required the output of 2 oxygen concentrators can be combined using a ‘Y’ connection.

A nasal cannula is usually preferred for long-term oxygen therapy from an oxygen concentrator. It can, however, produce dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the patient to talk, eat, and drink, but the concentration of oxygen is not controlled; this may not be appropriate for acute respiratory failure. When oxygen is given through a nasal cannula at a rate of 1–2 litres/minute the inspiratory oxygen concentration is usually low, but it varies with ventilation and can be high if the patient is under-ventilating.

### Arrangements for supplying oxygen

The following oxygen services may be ordered in England and Wales:

• emergency oxygen;
• short-burst (intermittent) oxygen therapy;
• long-term oxygen therapy;
• ambulatory oxygen.

The type of oxygen service (or combination of services) should be ordered on a Home Oxygen Order Form (HOOF); the amount of oxygen required (hours per day) and flow rate should be specified. The supplier will determine the appropriate equipment to be provided. Special needs or preferences should be specified on the HOOF.

The clinician should obtain the patient’s consent to pass on the patient’s details to the supplier and the fire brigade. The supplier will contact the patient to make arrangements for delivery, installation, and maintenance of the equipment. The supplier will also train the patient to use the equipment.

The clinician should send order forms to the supplier by facsimile (see below); a copy of the HOOF should be sent to the Primary Care Trust or Local Health Board. The supplier will continue to provide the service until a revised order is received, or until notified that the patient no longer requires the home oxygen service.

#### Oxygen concentrators

- **England**: BOC Medical
  - to order: Tel: 0800 136 603, Fax: 0800 169 9989
  - North East: Air Liquide
    - to order: Tel: 0500 823 773, Fax: 0800 781 4610
- **Scotland**: Air Products
  - to order: Tel: 0800 373 580, Fax: 0800 214 709

In **Scotland** refer the patient for assessment by a respiratory consultant. If the need for a concentrator is confirmed the consultant will arrange for the provision of a concentrator through the Common Services Agency. In **Northern Ireland** oxygen concentrators and cylinders should be prescribed on form HS21; oxygen concentrators are supplied by a local contractor. In **Scotland** and **Northern Ireland** prescriptions for oxy-
3.7 Mucolytics

Mucolytics are prescribed to facilitate expectoration by reducing sputum viscosity. In some patients with chronic obstructive pulmonary disease and a chronic productive cough, mucolytics can reduce exacerbations; mucolytic therapy should be stopped if there is no benefit after a 4-week trial. Steam inhalation with postural drainage is effective in bronchiectasis and in some cases of chronic bronchitis. Mucolytics should be used with caution in those with a history of peptic ulceration because they may disrupt the gastric mucosal barrier. For reference to dornase alfa and hypertonic saline, see below.

**CARBOCISTEINE**

**Indications**  
reduction of sputum viscosity, see notes above

**Cautions**  
see notes above; pregnancy (Appendix 4)

**Contra-indications**  
active peptic ulceration

**Side-effects**  
rarely  
active peptic ulceration; hyper-sensitivity reactions (including rash and anaphylaxis) also reported

**Dose**  
Initially 2.25 g daily in divided doses, then 1.5 g daily in divided doses as condition improves; CHILD 2–5 years 62.5–125 mg 4 times daily, 5–12 years 250 mg 3 times daily

**Carbocisteine** (Sanofi-Aventis)  
**Capsules**, carbocisteine 375 mg, net price 120-cap pack = £16.68  
**Brands include** Mucodyne

**Oral liquid**, carbocisteine 125 mg/5 mL, net price 300 mL = £4.57; 250 mg/5 mL, 300 mL = £5.84  
**Brands include** Mucodyne (cherry- and raspberry-flavoured) and Mucodyne (cinnamon- and rum-flavoured)

**ERDOSTEINE**

**Indications**  
symptomatic treatment of acute exacerbations of chronic bronchitis

**Cautions**  
see notes above; hepatic impairment (avoid if severe—Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4)

**Contra-indications**  
brainfeeding (Appendix 5)

**Side-effects**  
very rarely nausea, vomiting, diarrhoea, abdominal pain, taste disturbance, headache, rash, and urticaria

**Dose**  
**ADULT** over 18 years, 300 mg twice daily for up to 10 days

**Erdotin®** (KoGEN)  
**Capsules**, yellow/green, erdosteine 300 mg, net price 20-cap pack = £5.00  
**Note** The Scottish Medicines Consortium (October 2007) has advised that erdosteine (Erdotin®) is not recommended for the symptomatic treatment of acute exacerbations of chronic bronchitis

**MECYSTEINE HYDROCHLORIDE**  
(Methyl Cysteine Hydrochloride)

**Indications**  
reduction of sputum viscosity

**Cautions**  
see notes above

**Contra-indications**  
pregnancy; breast-feeding

**Dose**  
- 200 mg 4 times daily for 2 days, then 200 mg 3 times daily for 6 weeks, then 200 mg twice daily; **CHILD** 5–12 years 100 mg 3 times daily

**Visclease®** (Ranbaxy)  
**Tablets**, yellow, s/c, e/c, mecysteine hydrochloride 100 mg, net price 100 = £17.65. Label: 5, 22, 25

**Dornase alfa**

Dornase alfa is a genetically engineered version of a naturally occurring human enzyme which cleaves extra-cellular deoxyribonucleic acid (DNA). It is used in cystic fibrosis and is administered by inhalation using a jet nebuliser (section 3.1.5).

**DORNASE ALFA**

**Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase)**

**Indications**  
management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function

**Cautions**  
pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**  
pharyngitis, voice changes, chest pain; occasionally laryngitis, rashes, urticaria, conjunctivitis

**Dose**  
**ADULT** and **CHILD** over 5 years, by inhalation of nebulised solution (by jet nebuliser), 2500 units (2.5 mg) once daily (patients over 21 years may benefit from twice daily dosage)

**Pulmozyme®** (Roche)  
**Nebuliser solution**, dornase alfa 1000 units (1 mg)/mL. Net price 2.5-mL (2500 units) vial = £17.57  
**Note** For use undiluted with jet nebulisers only; ultrasonic nebulisers are unsuitable

**Hypertonic sodium chloride**

Nebulised hypertonic sodium chloride solution is used to mobilise lower respiratory tract secretions in mucous consolidation (e.g. cystic fibrosis).

**MucoClear®** (Pari)  
**Nebuliser solution**, sodium chloride 6%, net price 20 × 4 mL = £12.98; 60 × 4 mL = £29.98  
**Dose** by inhalation of nebulised solution, 4 mL twice daily

3.8 Aromatic inhalations

Inhalations containing volatile substances such as eucalyptus oil are traditionally used and although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting in bronchitis; boiling water should not be used owing to the risk of scalding. Inhalations are also used for the relief of nasal obstruction in acute rhinitis or sinusitis. Menthol and eucalyptus inhalation is used to
Cough preparations

3.9 Cough suppressants

Cough may be a symptom of an underlying disorder, such as asthma (section 3.1.1), gastro-oesophageal reflux disease (section 1.1), or rhinitis (section 12.2.1), which should be addressed before prescribing cough suppressants. Cough may be a side-effect of another drug, such as an ACE inhibitor (section 2.5.5.1), or it can be associated with smoking or environmental pollutants. Cough can also have a significant habit component. When there is no identifiable cause, cough suppressants may be effective, for example if sleep is disturbed. They may cause sputum retention and this may be harmful in patients with chronic bronchitis and bronchiectasis.

Codeine may be effective but it is constipating and can cause dependence; dextromethorphan and pholcodine have fewer side-effects.

Sedating antihistamines are used as the cough suppressant component of many compound cough preparations on sale to the public; all tend to cause drowsiness which may reflect their main mode of action.

Children The use of cough suppressants containing codeine or similar opioid analgesics is not generally recommended in children and should be avoided altogether in children under 2 years.

MHRA/CHM advice (March 2008)
Children under 2 years should not be given over-the-counter cough and cold medicines containing the following ingredients:
- brompheniramine, chlorphenamine, or diphenhydramine (antihistamines);
- dextromethorphan or pholcodine (cough suppressants);
- guaifenesin or ipecacuanha (expectorants);
- phenylephrine, pseudoephedrine, ephedrine, oxymetazoline, or xylometazoline (decongestants).
Children over 2 years should not be given more than 1 cough or cold preparation at a time because different brands may contain the same active ingredient; care should be taken to give the correct dose.

CODEINE PHOSPHATE

Indications dry or painful cough; diarrhoea (section 1.4.2); pain (section 4.7.2)
Cautions see notes above and section 4.7.2
Contra-indications see section 4.7.2
Side-effects see section 4.7.2

Codeine Linctus, BP

Linctus (= oral solution), codeine phosphate 15 mg/5 mL. Net price 100 mL = 62p (diabetic, 34p)
Brands include Galcodine
Dose 5–10 mL 3–4 times daily; CHILD (but not generally recommended) 5–12 years, 2.5–5 mL
Note BP directs that when Diabetic Codeine Linctus is prescribed, Codeine Linctus formulated with a vehicle appropriate for administration to diabetics, whether or not labelled ‘Diabetic Codeine Linctus’, shall be dispensed or supplied

1. Can be sold to the public provided the maximum single dose does not exceed 5 mL.

Codeine Linctus, Paediatric, BP

Linctus (= oral solution), codeine phosphate 3 mg/5 mL. Net price 100 mL = 18p
Brands include Galcodine Paediatric
Dose CHILD (but not generally recommended) 2–5 years 5 mL 3–4 times daily
Note BP directs that Paediatric Codeine Linctus may be prepared extemporaneously by diluting Codeine Linctus with a suitable vehicle in accordance with the manufacturer’s instructions

Other preparations
Tablets, syrup, and injection section 4.7.2

PHOLCODINE

Indications dry or painful cough
Cautions see under Codeine Phosphate
Contra-indications see under Codeine Phosphate
Side-effects see under Codeine Phosphate

Pholcodine Linctus, BP

Linctus (= oral solution), pholcodine 5 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 1%. Net price 100 mL = 43p
Brands include Pavacol-D (sugar-free), Galenolph (sugar-free)
Dose 5–10 mL 3–4 times daily; CHILD (but not generally recommended, see notes above) 5–12 years 2.5–5 mL
Pholcodine Linctus, Strong, BP

Linctus (= oral solution), pholcodine 10 mg/5 mL in a suitable flavoured vehicle, containing citric acid monohydrate 2%. Net price 100 mL = 35p

Dose 5 mL 3–4 times daily

Brands include Galenphol

Galenphol® (Thornton & Ross)

Paediatric linctus (= oral solution), orange, sugar-free, pholcodine 2 mg/5 mL. Net price 90-mL pack = £1.11

Dose CHILD (but not generally recommended, see notes above) 2–5 years 5–10 mL 3 times daily; 6–12 years 10 mL 3 times daily

Palliative care

Diamorphine and methadone have been used to control distressing cough in terminal lung cancer although morphine is now preferred (see p. 16). In other circumstances they are contra-indicated because they induce sputum retention and ventilatory failure as well as causing opioid dependence. Methadone linctus should be avoided because it has a long duration of action and tends to accumulate.

**METHADONE HYDROCHLORIDE**

**Indications** cough in terminal disease

**Cautions** see notes in section 4.7.2

**Contra-indications** see notes in section 4.7.2

**Side-effects** see notes in section 4.7.2; longer-acting than morphine therefore effects may be cumulative

**Dose**

- See below

Methadone Linctus

Linctus (= oral solution), methadone hydrochloride 2 mg/5 mL in a suitable vehicle with a tolu flavour. Label: 2

Dose 2.5–5 mL every 4–6 hours, reduced to twice daily on prolonged use

**MORPHINE HYDROCHLORIDE**

**Indications** cough in terminal disease (see also Prescribing in Palliative Care p. 16)

**Cautions** see notes in section 4.7.2

**Contra-indications** see notes in section 4.7.2

**Side-effects** see notes in section 4.7.2

**Dose**

- Initially 5 mg every 4 hours

**Preparation**

Section 4.7.2

**3.9.2 Expectorant and demulcent cough preparations**

Expectorants are claimed to promote expulsion of bronchial secretions but there is no evidence that any drug can specifically facilitate expectoration. The assumption that sub-emetic doses of expectorants, such as ammonium chloride, ipecacuanha, and squill promote expectoration is a myth. However, a simple expectorant mixture may serve a useful placebo function and has the advantage of being inexpensive.

Demulcent cough preparations contain soothing substances such as syrup or glycerol and some patients believe that such preparations relieve a dry irritating cough. Preparations such as simple linctus have the advantage of being harmless and inexpensive; paediatric simple linctus is particularly useful in children.

Compound preparations are on sale to the public for the treatment of cough and colds but should not be used in children under 2 years; the rationale for some is dubious. Care should be taken to give the correct dose and to not use more than one preparation at a time, see MHRA/CHM advice, p. 180.

Ammonia and Ipecacuanha Mixture, BP

Mixture, ammonium bicarbonate 200 mg, liquorex liquid extract 0.5 mL, ipecacuanha tincture 0.3 mL, concentrated camphor water 0.1 mL, concentrated anise water 0.05 mL, double-strength chloroform water 5 mL, water to 10 mL. It should be recently prepared

Dose ADULT and CHILD over 12 years, 10–20 mL up to 4 times daily

Simple Linctus, BP

Linctus (= oral solution), citric acid monohydrate 2.5% in a suitable vehicle with an anise flavour. Net price 200 mL = 42p

Dose ADULT and CHILD over 12 years 5 mL 3–4 times daily

A sugar-free version is also available

Simple Linctus, Paediatric, BP

Linctus (= oral solution), citric acid monohydrate 0.625% in a suitable vehicle with an anise flavour. Net price 200 mL = 72p

Dose CHILD 1 month–12 years 5–10 mL 3–4 times daily

A sugar-free version is also available

**3.10 Systemic nasal decongestants**

Nasal decongestants for administration by mouth may not be as effective as preparations for local application (section 12.2.2) but they do not give rise to rebound nasal congestion on withdrawal. Pseudoephedrine is available over the counter; it has few sympathomimetic effects.

Systemic decongestants should be used with caution in diabetes, hypertension, hyperthyroidism, susceptibility to angle-closure glaucoma, prostatic hypertrophy, renal impairment (Appendix 3), pregnancy (Appendix 4), and ischaemic heart disease, and should be avoided in patients taking monoamine oxidase inhibitors; interactions: Appendix 1 (sympathomimetics).

**PSEUDOEPHEDRINE HYDROCHLORIDE**

**Indications** see notes above

**Cautions** see notes above

**Side-effects** tachycardia, anxiety, restlessness, insomnia; rarely hallucinations, rash; very rarely angle-closure glaucoma; urinary retention also reported

**Dose**

- 60 mg 3–4 times daily; CHILD 2–6 years 15 mg 3–4 times daily; 6–12 years 30 mg 3–4 times daily
3.10 Systemic nasal decongestants

1 **Galpseud** (Thornton & Ross)
   - Tablets, pseudoephedrine hydrochloride 60 mg, net price 20 = £1.06
   - Linctus, orange, sugar-free, pseudoephedrine hydrochloride 30 mg/5 mL, net price 100 mL = 69p

2 **Sudafed** (Pfizer Consumer)
   - Tablets, red, f/c, pseudoephedrine hydrochloride 60 mg, net price 24 = £2.12
   - Elixir, red, pseudoephedrine hydrochloride 30 mg/5 mL, net price 100 mL = £1.48

1 Can be sold to the public provided no more than 720 mg of pseudoephedrine salts are supplied, and ephedrine base (or salts) are not supplied at the same time; for details see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available)
4 Central nervous system

4.1 Hypnotics and anxiolytics

4.1.1 Hypnotics

4.1.2 Anxiolytics

4.1.3 Barbiturates

4.2 Drugs used in psychoses and related disorders

4.2.1 Antipsychotic drugs

4.2.2 Antipsychotic depot injections

4.2.3 Antimanic drugs

4.3 Antidepressant drugs

4.3.1 Tricyclic and related antidepressant drugs

4.3.2 Monoamine-oxidase inhibitors

4.3.3 Selective serotonin re-uptake inhibitors

4.3.4 Other antidepressant drugs

4.4 CNS stimulants and drugs used for attention deficit hyperactivity disorder

4.5 Drugs used in the treatment of obesity

4.5.1 Anti-obesity drugs acting on the gastro-intestinal tract

4.5.2 Centrally acting appetite suppressants

4.6 Drugs used in nausea and vertigo

4.7 Analgesics

4.7.1 Non-opioid analgesics

4.7.2 Opioid analgesics

4.7.3 Neuropathic pain

4.7.4 Antimigraine drugs

4.7.4.1 Treatment of acute migraine

4.7.4.2 Prophylaxis of migraine

4.7.4.3 Cluster headache

4.8 Antiepileptic drugs

4.8.1 Control of epilepsy

4.8.2 Drugs used in status epilepticus

4.8.3 Febrile convulsions

4.9 Drugs used in parkinsonism and related disorders

4.9.1 Dopaminergic drugs used in parkinsonism

4.9.2 Antimuscarinic drugs used in parkinsonism

4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

4.10 Drugs used in substance dependence

4.11 Drugs for dementia

Most anxiolytics (‘sedatives’) will induce sleep when given at night and most hypnotics will sedate when given during the day. Prescribing of these drugs is widespread but dependence (both physical and psychological) and tolerance occurs. This may lead to difficulty in withdrawing the drug after the patient has been taking it regularly for more than a few weeks (see Dependence and Withdrawal, below). Hypnotics and anxiolytics should therefore be reserved for short courses to alleviate acute conditions after causal factors have been established.

Benzodiazepines are the most commonly used anxiolytics and hypnotics; they act at benzodiazepine receptors which are associated with gamma-aminobutyric acid (GABA) receptors. Older drugs such as meprobamate and barbiturates (section 4.1.3) are not recommended—they have more side-effects and interactions than benzodiazepines and are much more dangerous in overdosage.

Paradoxical effects A paradoxical increase in hostility and aggression may be reported by patients taking benzodiazepines. The effects range from talkativeness and excitement to aggressive and antisocial acts. Adjustment of the dose (up or down) sometimes attenuates the impulses. Increased anxiety and perceptual disorders are other paradoxical effects. Increased hostility and aggression after barbiturates and alcohol usually indicates intoxication.

Driving Hypnotics and anxiolytics may impair judgement and increase reaction time, and so affect ability to drive or operate machinery; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair driving on the following day. See also Drugs and Driving under General Guidance, p. 3.

Dependence and withdrawal Withdrawal of a benzodiazepine should be gradual because abrupt withdrawal may produce confusion, toxic psychosis, convulsions, or a condition resembling delirium tremens.
A abrupt withdrawal of a barbiturate (section 4.1.3) is even more likely to have serious effects.

The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks after stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one. It is characterised by insomnia, anxiety, loss of appetite and of body-weight, tremor, perspiration, tinnitus, and perceptual disturbances. Some symptoms may be similar to the original complaint and encourage further prescribing; some symptoms may continue for weeks or months after stopping benzodiazepines.

A benzodiazepine can be withdrawn in steps of about one-eighth (range one-tenth to one-quarter) of the daily dose every fortnight. A suggested withdrawal protocol for patients who have difficulty is as follows:

1. Transfer patient to equivalent daily dose of diazepam preferably taken at night
2. Reduce diazepam dose every 2-3 weeks in steps of 2 or 2.5 mg if withdrawal symptoms occur, maintain this dose until symptoms improve
3. Reduce dose further, if necessary in smaller steps it is better to reduce too slowly rather than too quickly
4. Stop completely; time needed for withdrawal can vary from about 4 weeks to a year or more

Counselling may help; beta-blockers should only be tried if other measures fail; antidepressants should be used only where depression or panic disorder co-exist or emerge; avoid antipsychotics (which may aggravate withdrawal symptoms).

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.
2. The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate and unsuitable.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

**CSM advice**

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe, disabling, or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.
2. The use of benzodiazepines to treat short-term ‘mild’ anxiety is inappropriate and unsuitable.
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or subjecting the individual to extreme distress.

**4.1.1 Hypnotics**

Before a hypnotic is prescribed the cause of the insomnia should be established and, where possible, underlying factors should be treated. However, it should be noted that some patients have unrealistic sleep expectations, and others underestimate their alcohol consumption which is often the cause of the insomnia.

**Transcript**

- **Short-term insomnia** is usually related to an emotional problem or serious medical illness. It may last for a few weeks and may recur; a hypnotic can be useful but should not be given for more than three weeks (preferably only one week). Intermittent use is desirable with omission of some doses. A rapidly eliminated drug is generally appropriate.

- **Chronic insomnia** is rarely benefited by hypnotics and is sometimes due to mild dependence caused by injudicious prescribing of hypnotics. Psychiatric disorders such as anxiety, depression, and abuse of drugs and alcohol are common causes. Sleep disturbance is very common in depressive illness and early waking is often a useful pointer. The underlying psychiatric complaint should be treated, adapting the drug regimen to alleviate insomnia. For example, clomipramine or mirtazapine prescribed for depression will also help to promote sleep if taken at night. Other causes of insomnia include daytime cat-napping and physical causes such as pain, pruritus, and dyspnoea. Hypnotics should not be prescribed indiscriminately and routine prescribing is undesirable. They should be reserved for short courses in the acutely distressed. Tolerance to their effects develops within 3 to 14 days of continuous use and long-term efficacy cannot be assured. A major drawback of long-term use is that withdrawal can cause rebound insomnia and a withdrawal syndrome (section 4.1).

Where prolonged administration is unavoidable hypnotics should be discontinued as soon as feasible and the patient warned that sleep may be disturbed for a few days before normal rhythm is re-established; broken sleep with vivid dreams may persist for several weeks.

**Children** The prescribing of hypnotics to children, except for occasional use such as for night terrors and somnambulism (sleep-walking), is not justified.

**Elderly** Hypnotics should be avoided in the elderly, because the elderly are at greater risk of becoming ataxic and confused and so liable to fall and injure themselves.

**Dental procedures** Some anxious patients may benefit from the use of a hypnotic for 1 to 3 nights before the dental appointment. Hypnotics do not relieve pain, and if pain interferes with sleep an appropriate analgesic should be given. **Diazepam** (section 4.1.2), **nitrazepam** or **temazepam** are used at night for dental patients. Temazepam is preferred when it is important to minimise any residual effect the following day. For information on anxiolytics for dental procedures, see section 15.1.4.1.

**Benzodiazepines**

Benzodiazepines used as hypnotics include **nitrazepam** and **flurazepam** which have a prolonged action and may give rise to residual effects on the following day; repeated doses tend to be cumulative.
Loprazolam, lormetazepam, and temazepam act for a shorter time and they have little or no hangover effect. Withdrawal phenomena are more common with the short-acting benzodiazepines.

If insomnia is associated with daytime anxiety then the use of a long-acting benzodiazepine anxiolytic such as diazepam given as a single dose at night may effectively treat both symptoms.

For general guidelines on benzodiazepine prescribing see section 4.1.2 and for benzodiazepine withdrawal see section 4.1.

**NITRAZEPAM**

**Indications** insomnia (short-term use; see CSM advice, p. 184)

**Cautions** respiratory disease, muscle weakness and myasthenia gravis, history of drug or alcohol abuse, marked personality disorder (Appendix 4), breast-feeding (Appendix 5); reduce dose in elderly and debilitated, and in hepatic impairment (avoid if severe; Appendix 2) and renal impairment (Appendix 3); avoid prolonged use (and abrupt withdrawal thereafter); acute porphyria (section 9.8.2); **interaction:** Appendix 1 (anxiolytics and hypnotics)

**Driving** Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; severe hepatic impairment; sleep apnoea syndrome; not for use alone to treat depression or anxiety associated with depression) or chronic psychosis

**Side-effects** drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia may occur; dependence; see also section 15.1.4.1 for perioperative use

**Overdosage:** see Emergency Treatment of Poisoning, p. 32

**Dose**
- 5–10 mg at bedtime; **ELDERLY** (or debilitated) 2.5–5 mg; **CHILD** 1 month–2 years (infantile spasms) see BNF for Children

**Nitrazepam** (Non-proprietary) [FN]

| Tablets, nitrazepam 5 mg, net price 28 = £9.8p. | Label: 19 |
| Brains include Mogadon, Remnos |
| Dental prescribing on NHS Nitrazepam Tablets may be prescribed |
| Oral suspension, nitrazepam 2.5 mg/5 mL. Net price 150 mL = £5.30. | Label: 19 |
| Brains include Somnice |

**FLURAZEPAM**

**Indications** insomnia (short-term use; see CSM advice, p. 184)

**Cautions** see under Nitrazepam

**Contra-indications** see under Nitrazepam

**Side-effects** see under Nitrazepam

**Dose**
- 15–30 mg at bedtime; **ELDERLY** (or debilitated) 15 mg; **CHILD** not recommended

**Dalmame** (Valeant) [FN]

| Capsules, flurazepam (as hydrochloride), 15 mg (grey/yellow), net price 30-cap pack = £5.44; 30 mg (black/grey), 30-cap pack = £6.98. | Label: 19 |

**LORMETAZEPAM**

**Indications** insomnia (short-term use; see CSM advice, p. 184)

**Cautions** see under Nitrazepam

**Contra-indications** see under Nitrazepam

**Side-effects** see under Nitrazepam; shorter acting

**Dose**
- 1 mg at bedtime, increased to 1.5 or 2 mg if required; **ELDERLY** (or debilitated) 0.5 or 1 mg; **CHILD** not recommended

**Lormetazepam** (Non-proprietary) [FN]

| Tablets, lormetazepam 1 mg (as mesilate). Net price 28-tab pack = £18.00. | Label: 19 |

**TEMAZEPAM**

**Indications** insomnia (short-term use; see CSM advice, p. 184); see also section 15.1.4.1 for perioperative use

**Cautions** see under Nitrazepam

**Contra-indications** see under Nitrazepam

**Side-effects** see under Nitrazepam; shorter acting

**Dose**
- 10–20 mg at bedtime, exceptional circumstances 30–40 mg; **ELDERLY** (or debilitated) 10 mg at bedtime, exceptional circumstances 20 mg; **CHILD** not recommended

**Temazepam** (Non-proprietary) [FN]

| Tablets, temazepam 10 mg, net price 28-tab pack = £3.89; 20 mg, 28-tab pack = £1.64. | Label: 19 |
| Oral solution, sugar-free, temazepam 10 mg/5 mL, net price 300 mL = £18.96. | Label: 19 |
| Dental prescribing on NHS Temazepam Tablets or Oral Solution may be prescribed |

**Zaleplon, zolpidem, and zopiclone**

Zaleplon, zolpidem and zopiclone are non-benzodiazepine hypnotics, but they act at the benzodiazepine receptor. Zolpidem and zopiclone have a short duration of action; zaleplon is very short acting. All three drugs are not licensed for long-term use; dependence has been reported in a small number of patients.
Central nervous system

Stilnoct
Zolpidem (Non-proprietary)

ADULT
Dose
• ADULT over 18 years, 10 mg at bedtime; ELDERLY 5 mg

Side-effects
• diarrhoea, nausea, vomiting, vertigo,

Contra-indications
• sleep apnoea syndrome, marked neuromuscular respiratory weakness including unstable myasthenia gravis

Side-effects
• amnesia, paraesthesia, drowsiness; dysmenorrhoea; less commonly nausea, anorexia, asthma, incoordination, confusion, impaired concentration, depression, depersonalisation, dizziness, hallucinations, disturbances of smell, hearing, speech, and vision; photosensitivity; paradoxical effects (see p. 183) and sleep-walking also reported

Contra-indications
• sleep apnoea syndrome, marked neuromuscular respiratory weakness including unstable myasthenia gravis

Side-effects
• amnesia, paraesthesia, drowsiness; dysmenorrhoea; less commonly nausea, anorexia, asthma, incoordination, confusion, impaired concentration, depression, depersonalisation, dizziness, hallucinations, disturbances of smell, hearing, speech, and vision; photosensitivity; paradoxical effects (see p. 183) and sleep-walking also reported

Contra-indications
• marked neuromuscular respiratory weakness including unstable myasthenia gravis

Side-effects
• taste disturbance; less commonly nausea, vomiting; dizziness, drowsiness, dry mouth, headache; rarely amnesia, confusion, depression, hallucinations, nightmares; very rarely light headedness, incoordination; paradoxical effects (see p. 183) and sleep-walking also reported

Dose
• ADULT over 18 years, 7.5 mg at bedtime; ELDERLY initially 3.75 mg at bedtime increased if necessary

Zopiclon (Non-proprietary)

Indications
• insomnia (short-term use—up to 4 weeks)

Cautions
• sleep apnoea, marked neuromuscular respiratory weakness including unstable myasthenia gravis

Side-effects
• light headedness, incoordination, confusion, alterations of vision; photosensitivity; less commonly nightmares; abdominal distention, flatulence, headache, skin reactions, changes in libido; paradoxical effects (see p. 183) and sleep-walking also reported

Contra-indications
• obstructive sleep apnoea, acute or severe respiratory depression, marked neuromuscular respiratory weakness including unstable myasthenia gravis, severe hepatic impairment, psychotic illness, pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects
• diarrhoea, nausea, vomiting, vertigo, dizziness, headache, drowsiness, asthenia, amnesia; dependence, memory disturbances, nightmares, nocturnal restlessness, depression, confusion, perceptual disturbances or diplopia, tremor, ataxia, falls, skin reactions, changes in libido; paradoxical effects (see p. 183) and sleep-walking also reported

Dose
• ADULT over 18 years, 10 mg at bedtime; ELDERLY (or debilitated) 5 mg

Zopidem (Non-proprietary)

Tablets, zopidem tartrate 5 mg, net price 28-tab pack = £1.63; 10 mg, 28-tab pack = £1.70. Label: 19

Stilnot® (Sanofi-Synthelabo)

Tablets, both f/c, zolpidem tartrate 5 mg, net price 28-tab pack = £3.08; 10 mg, 28-tab pack = £4.48. Label: 19

4.1.1 Hypnotics BNF 57

ZOPICLONE

Indications
• insomnia (short-term use—up to 4 weeks)

Cautions
• elderly; muscle weakness and myasthenia gravis, history of drug abuse, psychiatric illness; avoid prolonged use (risk of tolerance and withdrawal symptoms); hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (anxiolytics and hypnotics)

Driving
Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications
• marked neuromuscular respiratory weakness including unstable myasthenia gravis, respiratory failure, severe sleep apnoea syndrome; breast-feeding (Appendix 5)

Side-effects
• taste disturbance; less commonly nausea, vomiting; dizziness, drowsiness, dry mouth, headache; rarely amnesia, confusion, depression, hallucinations, nightmares; very rarely light headedness, incoordination; paradoxical effects (see p. 183) and sleep-walking also reported

Dose
• ADULT over 18 years, 7.5 mg at bedtime; ELDERLY initially 3.75 mg at bedtime increased if necessary

Zopiclon (Non-proprietary)

Indications
• insomnia (short-term use—up to 4 weeks)

Cautions
• sleep apnoea, marked neuromuscular respiratory weakness including unstable myasthenia gravis

Side-effects
• light headedness, incoordination, confusion, alterations of vision; photosensitivity; less commonly nightmares; abdominal distention, flatulence, headache, skin reactions, changes in libido; paradoxical effects (see p. 183) and sleep-walking also reported

Contra-indications
• obstructive sleep apnoea, acute or severe respiratory depression, marked neuromuscular respiratory weakness including unstable myasthenia gravis, severe hepatic impairment, psychotic illness, pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects
• diarrhoea, nausea, vomiting, vertigo, dizziness, headache, drowsiness, asthenia, amnesia; dependence, memory disturbances, nightmares, nocturnal restlessness, depression, confusion, perceptual disturbances or diplopia, tremor, ataxia, falls, skin reactions, changes in libido; paradoxical effects (see p. 183) and sleep-walking also reported

Dose
• ADULT over 18 years, 10 mg at bedtime; ELDERLY (or debilitated) 5 mg

Zopidem (Non-proprietary)

Tablets, zopidem tartrate 5 mg, net price 28-tab pack = £1.63; 10 mg, 28-tab pack = £1.70. Label: 19

Stilnot® (Sanofi-Synthelabo)

Tablets, both f/c, zolpidem tartrate 5 mg, net price 28-tab pack = £3.08; 10 mg, 28-tab pack = £4.48. Label: 19

CHLORAL HYDRATE

Indications
• insomnia (short-term use)

Cautions
• reduce dose in elderly and debilitated; avoid prolonged use (and abrupt withdrawal thereafter); avoid contact with skin and mucous membranes; hepatic impairment (avoid if severe—Appendix 2); interactions: Appendix 1 (anxiolytics and hypnotics)

Driving
Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications
• severe cardiac disease, gastritis, renal impairment (avoid if creatinine clearance less than 10 mL/minute); pregnancy; breast-feeding (Appendix 5); acute porphyria (section 9.8.2)

Side-effects
• gastric irritation (nausea and vomiting reported), abdominal distention, flatulence, headache, tolerance, dependence, excitement, delirium (especially on abrupt withdrawal), ketonuria, and rash

Dose
• See under preparations below
Chloral Mixture, BP 2000 (Chloral Oral Solution)

*Mixture*, chloral hydrate 500 mg/5 mL in a suitable vehicle. Extemporaneous preparations should be recently prepared according to the following formula: chloral hydrate 1 g, syrup 2 mL, water to 10 mL. Net price 100 mL = £5.3 p. Label: 19, 27

**Dose** 5–20 mL; **CHILD** 1–12 years 30–50 mg/kg (max. 1 g), taken well diluted with water at bedtime

Chloral Elixir, Paediatric, BP 2000 (Chloral Oral Solution, Paediatric)

*Elixir*, chloral hydrate 200 mg/5 mL (4%) in a suitable vehicle with a black currant flavour. Extemporaneous preparations should be recently prepared according to the following formula: chloral hydrate 200 mg, water 0.1 mL, black currant syrup 1 mL, syrup to 5 mL. Net price 100 mL = £1.02. Label: 1, 27

**Dose** CHILD 1 month–1 year 30–50 mg/kg, taken well diluted with water at bedtime

**Cloral betaine**

**Wellldorm** (Alphashow)

**Tablets**, blue-purple, 1/5, cloral betaine 707 mg (cloral hydrate 414 mg). Net price 30-tab pack = £7.90. Label: 19, 27

**Dose** ADULT and CHILD over 12 years, 1–2 tablets with water or milk at bedtime, max. 5 tablets (cloral hydrate 2 g) daily

**Elixir**, red, chloral hydrate 143.3 mg/5 mL. Net price 150-mL pack = £6.67. Label: 19, 27

**Dose** 15–45 mL (chloral hydrate 0.4–1.3 g) with water or milk, at bedtime, max. 70 mL (chloral hydrate 2 g) daily. CHILD 1 month–12 years, 1–1.75 mL/kg (chloral hydrate 30–50 mg/kg), max. 35 mL (chloral hydrate 1 g) daily

**TRICLOFOS SODIUM**

**Indications** insomnia (short-term use)

**Cautions** avoid prolonged use (and abrupt withdrawal thereafter); elderly; hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (anxiolytics and hypnotics)

**Driving** Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** cardiac disease; gastritis; acute porphyria (section 9.8.2); pregnancy; breast-feeding (Appendix 5)

**Side-effects** abdominal distension, flatulence, gastric irritation including nausea and vomiting, dependence, malaise, ataxia, drowsiness, headache, lightheadedness, vertigo, confusion, paranoiac excitement, nightmares, delirium (especially on abrupt withdrawal), ketonuria, blood disorders, skin reactions, and urticaria

**Dose**

- See under preparation below

Triclofos Oral Solution, BP (Triclofos Elixir)

**Oral solution**, triclofos sodium 500 mg/5 mL. Net price 300 mL = £28.23. Label: 19

**Dose** 10–20 mL; **CHILD** up to 1 year 25–30 mg/kg, 1–5 years 2–5 mL (250–500 mg triclofos sodium), 6–12 years 5–10 mL (0.5–1 g triclofos sodium)

**Clomethiazole** (Chlormethiazole) may be a useful hypnotic for elderly patients because of its freedom from hangover but, as with all hypnotics, routine administration is undesirable and dependence occurs. It is licensed for use as a hypnotic only in the elderly (and for very short-term use in younger adults to attenuate alcohol withdrawal symptoms, section 4.10).

**CLOMETHIAZOLE** (Chlormethiazole)

**Indications** see under Dose; alcohol withdrawal (section 4.10)

**Cautions** cardiac and respiratory disease (confusional state may indicate hypoxia), chronic pulmonary insufficiency, sleep apnoea syndrome; history of drug abuse; avoid prolonged use (and abrupt withdrawal thereafter); marked personality disorder; elderly; excessive sedation may occur (particularly with higher doses); hepatic impairment (especially if severe because sedation can mask hepatic coma; Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (anxiolytics and hypnotics)

**Driving** Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** acute pulmonary insufficiency; alcohol-dependent patients who continue to drink

**Side-effects** nasal congestion and irritation (increased nasopharyngeal and bronchial secretions), conjunctival irritation, headache; rarely gastro-intestinal disturbances, paradoxical excitement, confusion, dependence, rash, urticaria, bullous eruption, anaphylaxis, alterations in liver enzymes

**Dose**

- Severe insomnia in the elderly (short-term use), 1–2 capsules (or 5–10 mL syrup) at bedtime; **CHILD** not recommended

- Restlessness and agitation in the elderly, 1 capsule (or 5 mL syrup) 3 times daily

- Alcohol withdrawal, initially 2–4 capsules, if necessary repeated after some hours; day 1 (first 24 hours), 9–12 capsules in 3–4 divided doses; day 2, 6–8 capsules in 3–4 divided doses; day 3, 4–6 capsules in 3–4 divided doses; then gradually reduced over days 4–6; total treatment for not more than 9 days

Heminevrin® (AstraZeneca)

**Capsules**, grey-brown, clomethiazole base 192 mg in an oily basis. Net price 60-cap pack = £4.78. Label: 19

**Syrup**, sugar-free, clomethiazole edisilate 250 mg/5 mL. Net price 300-mL pack = £4.00. Label: 19

**Note** For an equivalent therapeutic effect 1 capsule = 5 mL syrup

**Antihistamines**

Some antihistamines (section 3.4.1) such as promethazine are on sale to the public for occasional insomnia; their prolonged duration of action can often cause drowsiness the following day. The sedative effect of antihistamines may diminish after a few days of continued treatment; antihistamines are associated with headache, psychomotor impairment and antimuscarinic effects.

Promethazine is also popular for use in children, but the use of hypnotics in children is not usually justified.
4.1.2 Anxiolytics

**PROMETHAZINE HYDROCHLORIDE**

**Indications** night sedation and insomnia (short-term use); other indications (section 3.4.1, section 4.6)

**Cautions** section 3.4.1

**Contra-indications** section 3.4.1

**Side-effects** section 3.4.1

**Dose**
- **By mouth**, 25 mg at bedtime increased to 50 mg if necessary; **CHILD** under 2 years not recommended, 2–5 years 15–20 mg, 5–10 years 20–25 mg, at bedtime

**Preparations** Section 3.4.1

**Alcohol**

Alcohol is a poor hypnotic because the diuretic action interferes with sleep during the latter part of the night. Alcohol also disturbs sleep patterns, and so can worsen sleep disorders; **interactions**: Appendix 1 (alcohol).

**SODIUM OXYBATE**

**Indications** narcolepsy with cataplexy (under specialist supervision)

**Cautions** history of drug abuse or depression; epilepsy; elderly; respiratory disorders; heart failure and hypertension (high sodium content); risk of discontinuation effects including rebound cataplexy and withdrawal symptoms; acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); renal impairment (Appendix 3); breast-feeding (Appendix 4); **interactions**: Appendix 1 (sodium oxybate)

**Contra-indications** pregnancy (Appendix 4)

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain, anorexia; hypertension, peripheral oedema; dyspnoea; sleep disorders, confusion, disorientation, paraesthesia, hypoesthesia, impaired attention, depression, drowsiness, anxiety, dizziness, headache, tremor, asthenia, fatigue; urinary incontinence, nocturnal enuresis; arthralgia, muscle cramps; blurred vision; sweating; **less commonly** faecal incontinence, myoclonus, psychosis, paranoia, hallucination, agitation, amnesia, and rash; respiratory depression, dependence, seizures, suicidal ideation, and urticaria also reported

**Dose**
- **ADULT** over 18 years, initially 2.25 g on retiring and repeated 2.5–4 hours later, increased according to response in steps of 1.5 g daily in 2 divided doses at intervals of 1–2 weeks; max. 9 g daily in two divided doses

**Note** Dose titration should be repeated if restarting after interval of more than 14 days

**Counselling** Dilute each dose with 60 mL water; prepare both doses before retiring. Observe the same time interval (2–3 hours) each night between the last meal and the first dose

**BNF 57**

**Melatonin**

Melatonin is a pineal hormone; it is licensed for the short-term treatment of insomnia in adults over 55 years.

**MELATONIN**

**Indications** insomnia (short-term use)

**Cautions** renal impairment (Appendix 3); **interactions**: Appendix 1 (melatonin)

**Contra-indications** autoimmune disease; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** pharyngitis; back pain, headache, asthenia; **less commonly** abdominal pain, constipation, dry mouth, weight gain, drowsiness, dizziness, sleep disorders, restlessness, nervousness, irritability, and sweating; **rarely** flattulence, halitosis, hypersalivation, vomiting, hypertriglyceridaemia, aggression, agitation, fatigue, impaired memory, mood changes, hot flushes, priapism, increased libido, leucopenia, thrombocytopenia, muscle cramp, skin reaction, lacrimation, and visual disturbances

**Dose**
- **ADULT** over 55 years, 2 mg once daily 1–2 hours before bedtime for 3 weeks

**Circadin** (Lundbeck) ▼ ▼ ▼

Tablets, m/r, melatonin 2 mg, net price 21-tab pack = £10.77. Label: 2, 21, 25

**BNF 57**

**4.1.2 Anxiolytics**

Benzodiazepine anxiolytics can be effective in alleviating anxiety states. Although these drugs are often prescribed to almost anyone with stress-related symptoms, unhappiness, or minor physical disease, their use in many situations is unjustified. In particular, they are not appropriate for treating depression or chronic psychosis. In bereavement, psychological adjustment may be inhibited by benzodiazepines. In children anxiolytic treatment should be used only to relieve acute anxiety (and related insomnia) caused by fear (e.g. before surgery).

Anxiolytic treatment should be limited to the lowest possible dose for the shortest possible time (see CSM advice, section 4.1). Dependence is particularly likely in patients with a history of alcohol or drug abuse and in patients with marked personality disorders.

Anxiolytics, particularly the benzodiazepines, have been termed ‘minor tranquillisers’. This term is misleading because not only do they differ markedly from the antipsychotic drugs (‘major tranquillisers’) but their use is by no means minor. Antipsychotics, in low doses, are also sometimes used in severe anxiety for their sedative action but long-term use should be
avoided in view of a possible risk of tardive dyskinesia (section 4.2.1).

Some antidepressants (section 4.3) are licensed for use in anxiety and related disorders; see section 4.3 for a comment on their role in chronic anxiety, generalised and social anxiety disorder, and panic disorder. The use of antihistamines (e.g. hydroxyzine, section 3.4.1) for their sedative effect in anxiety is not appropriate.

**Beta-blockers** (section 2.4) do not affect psychological symptoms of anxiety, such as worry, tension, and fear, but they do reduce autonomic symptoms, such as palpitation and tremor; they do not reduce non-autonomic symptoms, such as muscle tension. Beta-blockers are therefore indicated for patients with predominantly somatic symptoms; this, in turn, may prevent the onset of worry and fear.

### Benzodiazepines

Benzodiazepines are indicated for the **short-term relief of severe anxiety**; long-term use should be avoided (see CSM advice, p. 184). Diazepam, alprazolam, clordiazepoxide, and clobazam have a sustained action. Shorter-acting compounds such as lorazepam and oxazepam may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms.

In **panic disorders** (with or without agoraphobia) resistant to antidepressant therapy (section 4.3), a benzodiazepine (lorazepam 3–5 mg daily or clonazepam 1–2 mg daily (section 4.8.1) [both unlicensed]) may be used; alternatively, a benzodiazepine may be used as short-term adjunctive therapy at the start of antidepressant treatment to prevent the initial worsening of symptoms.

Diazepam or lorazepam are very occasionally administered intravenously for the control of panic attacks. This route is the most rapid but the procedure is not without risk (section 4.8.2) and should be used only when alternative measures have failed. The intramuscular route has no advantage over the oral route.

For guidelines on benzodiazepine withdrawal, see p. 183.

### DIAZEPAM

**Indications** short-term use in anxiety or insomnia (see CSM advice, p. 184); adjunct in acute alcohol withdrawal; status epilepticus (section 4.8.2); febrile convulsions (section 4.8.3); muscle spasm (section 10.2.2); peri-operative use (section 15.1.4.1)

**Cautions** respiratory disease, muscle weakness and myasthenia gravis, history of drug or alcohol abuse, marked personality disorder, pregnancy (Appendix 4), breast-feeding (Appendix 5); reduce dose in elderly and debilitated, and in hepatic impairment (avoid if severe; Appendix 2), renal impairment (Appendix 3); avoid prolonged use (and abrupt withdrawal thereafter); special precautions for intravenous injection (section 4.8.2); acute porphyria (section 9.8.2); when given parenterally, close observation required until full recovery from sedation; **interactions**: Appendix 1 (anxiolytics and hypnotics)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** respiratory depression; marked neuromuscular respiratory weakness including unstable myasthenia gravis; acute pulmonary insufficiency; sleep apnoea syndrome; severe hepatic impairment; not for chronic psychosis; should not be used alone in depression or in anxiety with depression; avoid injections containing benzyl alcohol in neonates (see under preparations below)

**Side-effects** drowsiness and lightheadedness the next day; confusion and ataxia (especially in the elderly); amnesia; dependence; paradoxical increase in aggression (see also section 4.1); muscle weakness; **occasionally**: headache, vertigo, hypotension, salivation changes, gastro-intestinal disturbances, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention; blood disorders and jaundice reported; skin reactions; on intravenous injection, pain, thrombophlebitis, and rarely apnoea; **overdose**: see Emergency Treatment of Poisoning, p. 32

**Dose**

- **By mouth**, anxiety, 2 mg 3 times daily increased if necessary to 15–30 mg daily in divided doses; **ELDERLY** (or debilitated) half adult dose

- **By intramuscular injection or slow intravenous injection** (into a large vein, at a rate of not more than 5 mg/minute), for severe acute anxiety, control of acute panic attacks, and acute alcohol withdrawal, 10 mg, repeated if necessary after not less than 4 hours

**Note** Only use intramuscular route when oral and intravenous routes not possible; special precautions for intravenous injection section 4.8.2.

- **By rectum** as rectal solution, acute anxiety and agitation, 500 micrograms/kg repeated after 12 hours as required; **ELDERLY** 250 micrograms/kg; **CHILD** not recommended

As suppositories, anxiety when oral route not appropriate, 10–30 mg (higher dose divided); dose form not appropriate for less than 10 mg

**Diazepam** (Non-proprietary) (SWN)

- **Tablets**, diazepam 2 mg, net price 28 = 95p; 5 mg, 28 = 98p; 10 mg, 28 = £1.08. Label: 2 or 19
  - Brands include Rimplap, Tensium

- **Oral solution**, diazepam 2 mg/5 mL, net price 100 mL = £6.75. Label: 2 or 19
  - Brands include Dialar

- **Strong oral solution**, diazepam 5 mg/5 mL, net price 100 mL-pack = £6.38. Label: 2 or 19
  - Brands include Dialar

**Injection** (solution), diazepam 5 mg/mL. Do not dilute (except for intravenous infusion, see Appendix 6). Net price 2-mL amp = 45p

- **Excipients** may include benzyl alcohol (avoid in neonates, see Excipients, p. 2), ethanol, propylene glycol

**Injection** (emulsion), diazepam 5 mg/mL. For intravenous injection or infusion, see Appendix 6. Net price 2-mL amp = 84p

- Brands include Diazemuls

**Rectal tubes** (= rectal solution), diazepam 2 mg/mL, net price 1.25-ML (2.5-mg) tube = 90p, 2.5-ML (5-mg) tube = £1.27; 4 mg/mL, 2.5-ML (10-mg) tube = £1.65

- Brands include Diazepam Rectubes, Stesolid

**Suppositories**, diazepam 10 mg, net price 6 = £10.20. Label: 2 or 19

- Brands include Valclor

**Dental prescribing on NHS** Diazepam Tablets or Diazepam Oral Solution 2 mg/5 mL may be prescribed
**ALPRAZOLAM**

**Indications**  
anxiety (short-term use; see CSM advice, p. 184)

**Cautions**  
see under Diazepam

**Contra-indications**  
see under Diazepam

**Side-effects**  
see under Diazepam

**Dose**

- 250–500 micrograms 3 times daily (ELDERLY or debilitated 250 micrograms 2–3 times daily), increased if necessary to a total of 3 mg daily; CHILD not recommended

**Alprazolam (Non-proprietary)**

- **Tablets**, alprazolam 250 micrograms, net price 60-tab pack = £2.97; 500 micrograms, 60-tab pack = £5.69. Label: 2
- **Brands** include Xanax

**CHLORDIAZEPoxide HYDROCHLORIDE**

**Indications**  
anxiety (short-term use; see CSM advice, p. 184); adjunct in acute alcohol withdrawal (section 4.10)

**Cautions**  
see under Diazepam

**Contra-indications**  
see under Diazepam

**Side-effects**  
see under Diazepam

**Dose**

- Anxiety: 10 mg 3 times daily increased if necessary to 60–100 mg daily in divided doses; ELDERLY (or debilitated) half adult dose; CHILD not recommended

**Chlordiazepoxide (Non-proprietary)**

- **Capsules**, chlordiazepoxide hydrochloride 5 mg, net price 20 = 50p; 10 mg, 20 = 84p. Label: 2
- **Brands** include Librium, Tropium

**Chlordiazepoxide Hydrochloride (Non-proprietary)**

- **Tablets**, chlordiazepoxide hydrochloride 5 mg, net price 20 = £1.58; 10 mg, 20 = £3.19. Label: 2

**LORAZEPAM**

**Indications**  
short-term use in anxiety or insomnia (see CSM advice, p. 184); status epilepticus (section 4.8.2); peri-operative (section 15.1.4.1)

**Cautions**  
see under Diazepam; short acting; when given parenterally, facilities for managing respiratory depression with mechanical ventilation must be at hand

**Contra-indications**  
see under Diazepam

**Side-effects**  
see under Diazepam

**Dose**

- **By mouth**, anxiety, 1–4 mg daily in divided doses; ELDERLY (or debilitated) half adult dose  
  Insomnia associated with anxiety, 1–2 mg at bedtime; CHILD not recommended

- **By intramuscular or slow intravenous injection** (into a large vein), acute panic attacks, 25–30 micrograms/kg (usual range 1.5–2.5 mg), repeated every 6 hours if necessary; CHILD not recommended

**Note** 
Only use intramuscular route when oral and intravenous routes not possible

**Lorazepam (Non-proprietary)**

- **Tablets**, lorazepam 1 mg, net price 28-tab pack = £8.28; 2.5 mg, 28-tab pack = £15.08. Label: 2 or 19

**Injection**, lorazepam 4 mg/mL. Net price 1-mL amp = 37p

**Excipients** include benzyl alcohol, propylene glycol (see Excipients, p. 2)

**Brands** include Ativan

**Note** 
For intramuscular injection it should be diluted with an equal volume of water for injections or physiological saline (but only use when oral and intravenous routes not possible)

**OXAZEPAM**

**Indications**  
anxiety (short-term use; see CSM advice, p. 184)

**Cautions**  
see under Diazepam; short acting

**Contra-indications**  
see under Diazepam

**Side-effects**  
see under Diazepam

**Dose**

- Anxiety, 15–30 mg (elderly or debilitated 10–20 mg) 3–4 times daily; CHILD not recommended

- Insomnia associated with anxiety, 15–25 mg (max. 50 mg) at bedtime; CHILD not recommended

**Oxazepam (Non-proprietary)**

- **Tablets**, oxazepam 10 mg, net price 28-tab pack = £6.17; 15 mg, 28-tab pack = £6.52. Label: 2

**Buspirone**

Buspirone is thought to act at specific serotonin (5HT) receptors. Response to treatment may take up to 2 weeks. It does not alleviate the symptoms of benzodiazepine withdrawal. Therefore a patient taking a benzodiazepine still needs to have the benzodiazepine withdrawn gradually; it is advisable to do this before starting buspirone. The dependence and abuse potential of buspirone is low; it is, however, licensed for short-term use only (but specialists occasionally use it for several months).

**BUSBIRONE HYDROCHLORIDE**

**Indications**  
anxiety (short-term use)

**Cautions**  
does not alleviate benzodiazepine withdrawal (see notes above); hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3); interactions: Appendix 1 (anxiolytics and hypnotics)

**Driving**  
May affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

**Contra-indications**  
epilepsy; acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**  
nausea; dizziness, headache, nervousness, excitement; rarely dry mouth, tachycardia, palpitation, chest pain, drowsiness, confusion, seizures, fatigue, and sweating

**Dose**

- **ADULT** over 18 years, 5 mg 2–3 times daily, increased as necessary every 2–3 days; usual range 15–30 mg daily in divided doses; max. 45 mg daily

**Buspirone Hydrochloride (Non-proprietary)**

- **Tablets**, buspirone hydrochloride 5 mg, net price 30-tab pack = £17.34; 10 mg, 30-tab pack = £19.67. Counselling, driving
The very short-acting barbiturate thiopental is used in anaesthesia (section 4.8.1) but its use as a sedative is unjustified. Avoid prolonged use, abrupt withdrawal may precipitate convulsions; interactions: Appendix 1 (anxiolytics and hypnotics).

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Contra-indications insomnia caused by pain; acute porphyria (section 9.8.2); children, young adults, elderly and debilitated patients, also patients with history of drug or alcohol abuse; pregnancy (Appendix 4); breast-feeding (Appendix 5).

Side-effects drowsiness, incoordination; less commonly nausea, vomiting, constipation, liver damage, bradycardia, hypotension, syncope, hyperventilation, anorexia, respiratory depression, agitation, confusion, hyperkinesia, ataxia, CNS depression, sleep disorders, hallucinations, anxiety, dizziness, headache, paradoxical excitement, impaired memory, fever, and megaloblastic anaemia.

Dose • See under preparations below.

Sodium Amytal® (Flynn) Capsules, blue, amobarbital (amobarbitone) sodium 60 mg, net price 20 = £3.43. Label: 19.

Dose 60–200 mg at bedtime (important: but see also contra-indications).

Soneryl® (Flynn) Tablets, pink, scored, butobarbital (butobarbitone) 100 mg. Net price 56-tab pack = £10.65. Label: 19.

Dose 100–200 mg at bedtime (important: but see also contra-indications).

Preparations containing secobarbital (quinalbarbitone) Seconal Sodium® (Flynn) Capsules, orange, secobarbital (quinalbarbitone) sodium 100 mg, 20 = £6.96. Label: 19.

Dose 100 mg at bedtime (important: but see also contra-indications).

Tuinal® (Flynn) Capsules, orange/blue, a mixture of amobarbital (amobarbitone) sodium 50 mg, secobarbital (quinalbarbitone) sodium 50 mg. Net price 20 = £3.88. Label: 19.

Dose 1–2 capsules at bedtime (important: but see also contra-indications).

Note Prescriptions need only specify ‘Tuinal capsules’.

4.1.3 Barbiturates

The intermediate-acting barbiturates have a place only in the treatment of severe intractable insomnia in patients already taking barbiturates; they should be avoided in the elderly. The long-acting barbiturate phenobarbital is still sometimes of value in epilepsy (section 4.8.1) but its use as a sedative is unjustified. The very short-acting barbiturate thiopental is used in anaesthesia (section 15.1.1).

BARBITURATES

Indications severe intractable insomnia only in patients already taking barbiturates; see also notes above.

Cautions avoid use where possible; dependence and tolerance readily occur; abrupt withdrawal may precipitate serious withdrawal syndrome (rebound insomnia, anxiety, tremor, dizziness, nausea, convulsions, delirium, and death); repeated doses are cumulative and can cause excessive sedation; depression and suicidal ideation; shock; respiratory disease (avoid if dyspnoea or obstruction present); hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (barbiturates).

Driving Drowsiness may persist the next day and affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Contra-indications insomnia caused by pain; acute porphyria (section 9.8.2); children, young adults, elderly and debilitated patients, also patients with history of drug or alcohol abuse; pregnancy (Appendix 4); breast-feeding (Appendix 5).

Side-effects drowsiness, incoordination; less commonly nausea, vomiting, constipation, liver damage, bradycardia, hypotension, syncope, hyperventilation, anorexia, respiratory depression, agitation, confusion, hyperkinesia, ataxia, CNS depression, sleep disorders, hallucinations, anxiety, dizziness, headache, paradoxical excitement, impaired memory, fever, and megaloblastic anaemia.

Dose • See under preparations below.

Sodium Amytal® (Flynn) Capsules, blue, amobarbital (amobarbitone) sodium 60 mg, net price 20 = £3.43. Label: 19.

Dose 60–200 mg at bedtime (important: but see also contra-indications).

Soneryl® (Flynn) Tablets, pink, scored, butobarbital (butobarbitone) 100 mg. Net price 56-tab pack = £10.65. Label: 19.

Dose 100–200 mg at bedtime (important: but see also contra-indications).

Preparations containing secobarbital (quinalbarbitone) Seconal Sodium® (Flynn) Capsules, orange, secobarbital (quinalbarbitone) sodium 100 mg, 20 = £6.96. Label: 19.

Dose 100 mg at bedtime (important: but see also contra-indications).

Tuinal® (Flynn) Capsules, orange/blue, a mixture of amobarbital (amobarbitone) sodium 50 mg, secobarbital (quinalbarbitone) sodium 50 mg. Net price 20 = £3.88. Label: 19.

Dose 1–2 capsules at bedtime (important: but see also contra-indications).

Note Prescriptions need only specify ‘Tuinal capsules’.

4.2 Drugs used in psychoses and related disorders

4.2.1 Antipsychotic drugs

4.2.2 Antipsychotic depot injections

4.2.3 Antimanic drugs

Advice of Royal College of Psychiatrists on doses above BNF upper limit. Unless otherwise stated, doses in the BNF are licensed doses—any higher dose is...
4.2.1 Antipsychotic drugs

Antipsychotic drugs are also known as 'neuroleptics' and (misleadingly) as 'major tranquillisers'. Antipsychotic drugs generally tranquillise without impairing consciousness and without causing paradoxical excitement but they should not be regarded merely as tranquillisers. For conditions such as schizophrenia the tranquillising effect is of secondary importance. In the short term they are used to calm disturbed patients whatever the underlying psychopathology, which may be schizophrenia, brain damage, mania, toxic delirium, or agitated depression. Antipsychotic drugs are used to alleviate severe anxiety but this too should be a short-term measure.

Schizophrenia Antipsychotic drugs relieve florid psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse. Although they are usually less effective in apathetic withdrawn patients, they sometimes appear to have an activating influence. Patients with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a patient with a definite diagnosis of schizophrenia may be necessary even after the first episode of illness in order to prevent the illness from becoming chronic. Withdrawal of drug treatment requires careful surveillance because the patient who appears well on medication may suffer a disastrous relapse if treatment is withdrawn inappropriately. In addition the need for continuation of treatment may not become immediately evident because relapse is often delayed for several weeks after cessation of treatment.

Antipsychotic drugs are considered to act by interfering with dopaminergic transmission in the brain by blocking dopamine D receptors, which may give rise to the extrapyramidal effects described below, and also to hyperprolactinaemia. Antipsychotic drugs may also affect cholinergic, alpha-adrenergic, histaminergic, and serotoninergic receptors.

Cautions and contra-indications Antipsychotics should be used with caution in patients with hepatic impairment (Appendix 2), renal impairment (Appendix 3), cardiovascular disease, Parkinson's disease (may be exacerbated by antipsychotics), epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, prostatic hypertrophy, or a susceptibility to angle-closure glaucoma. Caution is also required in severe respiratory disease and in patients with a history of jaundice or who have blood dyscrasias (perform blood counts if unexplained infection or fever develops). As photosensitisation may occur with higher dosages, patients should avoid direct sunlight.

Antipsychotic drugs may be contra-indicated in comatose states, CNS depression, and phaeochromocytoma. Most antipsychotics are best avoided during pregnancy, unless essential (Appendix 4) and it is advisable to discontinue breast-feeding during treatment (Appendix 5). Interactions: Appendix 1 (antipsychotics).

Prescribing for the elderly The balance of risks and benefit should be considered before prescribing antipsychotic drugs for elderly patients. In elderly patients with dementia, antipsychotic drugs are associated with a small increased risk of mortality and an increased risk of stroke or transient ischaemic attack. Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper- and hypothermia in hot or cold weather.

It is recommended that:

- Antipsychotic drugs should not be used in elderly patients to treat mild to moderate psychotic symptoms.
- Treatment should be reviewed regularly.

Driving Drowsiness may affect performance of skilled tasks (e.g. driving or operating machinery), especially at start of treatment; effects of alcohol are enhanced.

Withdrawal Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse.

Side-effects Extrapyramidal symptoms are the most troublesome. They occur most frequently with the piperazine phenothiazines (fluphenazine, perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (benperidol and haloperidol), and the depot preparations. They are easy to recognise but cannot be predicted accurately because they depend on the dose, the type of drug, and on individual susceptibility.
Extrapyramidal symptoms consist of:

- **parkinsonian symptoms** (including tremor), which may occur more commonly in adults or the elderly and may appear gradually;
- **dystonia** (abnormal face and body movements) and **dyskinesia**, which occur more commonly in children or young adults and appear after only a few doses;
- **akathisia** (restlessness), which characteristically occurs after large initial doses and may resemble an exacerbation of the condition being treated; and
- **tardive dyskinesia** (rhythmic, involuntary movements of tongue, face, and jaw), which usually develops on long-term therapy or with high dosage, but it may develop on short-term treatment with low doses—short-lived tardive dyskinesia may occur after withdrawal of the drug.

**Parkinsonian symptoms** remit if the drug is withdrawn and may be suppressed by the administration of **antimuscarinic** drugs (section 4.9.2). However, routine administration of such drugs is not justified because not all patients are affected and because they may unmask or worsen tardive dyskinesia.

**Tardive dyskinesia** is of particular concern because it may be irreversible on withdrawing therapy and treatment is usually ineffective. However, some manufacturers suggest that drug withdrawal at the earliest signs of tardive dyskinesia (fine vermiform movements of the tongue) may halt its full development. Tardive dyskinesia occurs fairly frequently, especially in the elderly, and treatment must be carefully and regularly reviewed.

**Hypotension** and **interference with temperature regulation** are dose-related side-effects and are liable to cause dangerous falls and hypothermia or hyperthermia in the elderly.

**Neuroleptic malignant syndrome** (hyperthermia, fluctuating level of consciousness, muscle rigidity, and autonomic dysfunction with pallor, tachycardia, labile blood pressure, sweating, and urinary incontinence) is a rare but potentially fatal side-effect of some drugs. Discontinuation of the antipsychotic is essential because there is no proven effective treatment, but cooling, bromocriptine, and dantrolene have been used. The syndrome, which usually lasts for 5–7 days after drug discontinuation, may be unduly prolonged if depot preparations have been used.

Other side-effects include: drowsiness; apathy; agitation, excitement and insomnia; convulsions; dizziness; headache; confusion; gastro-intestinal disturbances; nasal congestion; antimuscarinic symptoms (such as dry mouth, constipation, difficulty with micturition, and blurred vision; very rarely, precipitation of angle-closure glaucoma); cardiovascular symptoms (such as hypertension, tachycardia, and arrhythmias); ECG changes (cases of sudden death have occurred); endocrine effects such as menstrual disturbances, galactorrhoea, gynaecomastia, impotence, and weight gain; blood dyscrasias (such as agranulocytosis and leucopenia), photosensitisation, contact sensitisation and rashes, and jaundice (including cholestatic); corneal and lens opacities, and purplish pigmentation of the skin, cornea, conjunctiva, and retina.

**Overdosage**: for poisoning with phenothiazines and related compounds, see Emergency Treatment of Poisoning, p. 33.

**Classification of antipsychotics**

The **phenothiazine** derivatives can be divided into 3 main groups.

**Group 1**: chlorpromazine, levomepromazine (methotrimeprazine), and promazine, generally characterised by pronounced sedative effects and moderate antimuscarinic and extrapyramidal side-effects.

**Group 2**: pericyazine and pipotiazine, generally characterised by moderate sedative effects, marked antimuscarinic effects, but fewer extrapyramidal side-effects than groups 1 or 3.

**Group 3**: fluphenazine, perphenazine, prochlorperazine, and trifluoperazine, generally characterised by fewer sedative effects, fewer antimuscarinic effects, but more pronounced extrapyramidal side-effects than groups 1 and 2.

Drugs of other chemical groups resemble the phenothiazines of group 3 in their clinical properties. They include the **butyrophenones** (benperidol and haloperidol); **diphenylbutylpiperidines** (pimozide); **thioxanthenes** (flupentixol and zuclopenthixol); and the **substituted benzamides** (salpine). For details of the newer antipsychotic drugs amisulpride, clozapine, olanzapine, quetiapine, risperidone, sertindole, and zotepine, see under Atypical Antipsychotics, p. 197.

**Choice** As indicated above, the various drugs differ somewhat in predominant actions and side-effects. Selection is influenced by the degree of sedation required and the patient’s susceptibility to extrapyramidal side-effects. However, the differences between antipsychotic drugs are less important than the great variability in patient response; moreover, tolerance to secondary effects such as sedation usually develops. The atypical antipsychotics may be appropriate if extrapyramidal side-effects are a particular concern (see under Atypical Antipsychotics, below). Clozapine is used for schizophrenia when other antipsychotics are ineffective or not tolerated.

Prescribing of more than one antipsychotic at the same time is not recommended; it may constitute a hazard and there is no significant evidence that side-effects are minimised.

**Chlorpromazine** is still widely used despite the wide range of adverse effects associated with it. It has a marked sedating effect and is useful for treating violent patients without causing stupor. Agitated states in the elderly can be controlled without confusion, a dose of 10 to 25 mg once or twice daily usually being adequate.

**Flupentixol** (flupentixol) and **pimozide** (see CSM warning, p. 196) are less sedating than chlorpromazine.

**Sulpiride** in high doses controls florid positive symptoms, but in lower doses it can have an alerting effect on apathetic withdrawn schizophrenics.

**Fluphenazine**, **haloperidol**, and **trifluoperazine** are also of value but their use is limited by the high incidence of extrapyramidal symptoms. Haloperidol may be preferred for the rapid control of hyperactive psychotic states; it causes less hypotension than chlorpromazine and is therefore also popular for agitation and restlessness in the elderly, despite the high incidence of extrapyramidal side-effects.
Promazine is not sufficiently active by mouth to be used as an antipsychotic drug; it has been used to treat agitation and restlessness in the elderly (see Other uses, below).

Other uses Nausea and vomiting (section 4.6), choreas, motor tics (section 4.9.3), and intractable hiccup (see under Chlorpromazine Hydrochloride and under Haloperidol). 
Benperidol is used in deviant antisocial sexual behaviour but its value is not established; see also section 6.4.2 for the role of cyproterone acetate.

Psychomotor agitation should be investigated for an underlying cause; it can be managed with low doses of chlorpromazine or haloperidol used for short periods. Antipsychotic drugs can be used with caution for the short-term treatment of severe agitation and restlessness in the elderly (but see p. 192).

### Equivalent doses of oral antipsychotics

These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication.

<table>
<thead>
<tr>
<th>Antipsychotic drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>100 mg</td>
</tr>
<tr>
<td>Clozapine</td>
<td>50 mg</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2–3 mg</td>
</tr>
<tr>
<td>Pimozide</td>
<td>2 mg</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5–1 mg</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>200 mg</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

**Important** These equivalences must not be extrapolated beyond the maximum dose for the drug. Higher doses require careful titration in specialist units and the equivalences shown here may not be appropriate.

### Dosage

After an initial period of stabilisation, in most patients, the total daily oral dose can be given as a single dose. For the advice of The Royal College of Psychiatrists on doses above the BNF upper limit, see p. 191.

### BENPERIDOL

**Indications** control of deviant antisocial sexual behaviour (but see notes above)

**Cautions** see notes above; also manufacturer advises regular blood counts and liver function tests during long-term treatment

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- 0.25–1.5 mg daily in divided doses, adjusted according to response; ELDERLY (or debilitated) initially half adult dose; CHILD not recommended

Anquil® (Concord)

| Tablets, scored, benperidol 250 micrograms, net price 112-tab pack = £104.00. Label: 2 |

**Note** The proprietary name Anquil has been used for benperidol tablets

---

### Chlorpromazine Hydrochloride

**Warning** Owing to the risk of contact sensitisation, pharmacists, nurses, and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care

**Indications** see under Dose; antiemetic in palliative care (section 4.6)

**Cautions** see notes above; also patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection

**Contra-indications** see notes above

**Side-effects** see notes above; also intramuscular injection may be painful, cause hypotension and tachycardia, and give rise to nodule formation

**Dose**

- **By mouth**, schizophrenia and other psychoses, mania, short-term Adjunctive management of severe anxiety, psychomotor agitation, excitement, and violent or dangerously impulsive behaviour initially 25 mg 3 times daily (or 75 mg at night), adjusted according to response, to usual maintenance dose of 75–300 mg daily (but up to 1 g daily may be required in psychoses); ELDERLY (or debilitated) third to half adult dose; CHILD (childhood schizophrenia and autism) 1–6 years 500 micrograms/kg every 4–6 hours (max. 40 mg daily); 6–12 years 10 mg 3 times daily (max. 75 mg daily)

Intractable hiccup, 25–50 mg 3–4 times daily

- **By deep intramuscular injection**, (for relief of acute symptoms but see also Cautions and Side-effects), 25–50 mg every 6–8 hours; CHILD, 1–6 years 500 micrograms/kg every 6–8 hours (max. 40 mg daily); 6–12 years 500 micrograms/kg every 6–8 hours (max. 75 mg daily)

Induction of hypothermia (to prevent shivering), 25–50 mg every 6–8 hours; CHILD 1–12 years, initially 0.5–1 mg/kg, followed by maintenance 500 micrograms/kg every 4–6 hours

- **By rectum** in suppositories as chlorpromazine base 100 mg every 6–8 hours [unlicensed]

**Note** For equivalent therapeutic effect 100 mg chlorpromazine base given rectally as a suppository = 20–25 mg chlorpromazine hydrochloride by intramuscular injection = 40–50 mg of chlorpromazine base or hydrochloride by mouth

**Chlorpromazine (Non-proprietary)**

| Tablets, coated, chlorpromazine hydrochloride 25 mg, 28-tab pack = £3.35; 50 mg, 28-tab pack = £3.40; 100 mg, 28-tab pack = £3.57. Label: 2, 11 |

**Brands include** Chloractil

**Oral solution**, chlorpromazine hydrochloride 25 mg/5 mL, net price 150 mL = £1.47, 100 mg/5 mL, 150 mL = £3.57. Label: 2, 11

**Injection**, chlorpromazine hydrochloride 25 mg/mL, net price 1 mL amp = 60p; 2 mL amp = 63p

**Suppositories**, chlorpromazine 25 mg and 100 mg. Label: 2, 11

Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

**Largactil** (Sanofi-Aventis)

**Injection**, chlorpromazine hydrochloride 25 mg/mL. Net price 2 mL amp = 63p
**FLUPENTIXOL**  
(Flupenthixol)

**Indications**  
schizophrenia and other psychoses, particularly with apathy and withdrawal but not mania or psychomotor hyperactivity; depression (section 4.3.4)

**Cautions**  
see notes above; avoidance in acute porphyria (section 9.8.2)

**Contra-indications**  
see notes above; also subarachnoid

**Side-effects**  
see notes above; occasionally raised

**Dose**
- Psychosis, initially 3–9 mg twice daily adjusted according to the response; max. 18 mg daily; **ELDERLY** (or debilitated) initially quarter to half adult dose; **CHILD** not recommended

**Depixol**® (Lundbeck)

Tablets, yellow, s/c, flupentixol 3 mg (as dihydrochloride). Net price 20 = £2.78. Label: 2

**Depot preparation**
Section 4.2.2

---

**HALOPERIDOL**

**Indications**  
see under Dose; motor tics (section 4.9.3)

**Cautions**  
see notes above; also subarachnoid

**Contra-indications**  
see notes above

**Side-effects**  
see notes above, but less sedating and fewer antimuscarinic or hypotensive symptoms; pigmentation and photosensitivity reactions rare; extrapyramidal symptoms, particularly dystonic reactions rare; weight loss; hypoglycaemia; inappropriate antidiuretic hormone secretion

**Dose**
- Schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, **ADULT** and **CHILD** over 12 years, **by mouth**, initially 0.5–3 mg 2–3 times daily or 3–5 mg 2–3 times daily in severely affected or resistant patients; in resistant schizophrenia up to 30 mg daily may be needed; adjusted according to response to lowest effective maintenance dose (as low as 5–10 mg daily); **ELDERLY** (or debilitated) initially half adult dose
- **By intramuscular** or **by intravenous injection**, **ADULT** over 18 years, initially 2–10 mg, then every 4–8 hours according to response to total max. 18 mg daily; severely disturbed patients may require initial dose of up to 18 mg; **ELDERLY** (or debilitated) initially half adult dose
- Agitation and restlessness in the elderly, **by mouth**, initially 0.5–1.5 mg once or twice daily
- Short-term adjunctive management of severe anxiety, **by mouth**, **ADULT** over 18 years, 500 micrograms twice daily
- Intractable hiccup, **by mouth**, **ADULT** over 18 years, 1.5 mg 3 times daily adjusted according to response
- Nausea and vomiting, see Prescribing in Palliative Care, p. 17
- **By intramuscular** or **by intravenous injection**, 1–2 mg

**Haloperidol** (Non-proprietary)

Tablets, haloperidol 500 micrograms, net price 28-tab pack = £1.73; 5 mg, 28 = £0.98. Label: 2

**Docz**® (Rosemont)

Oral liquid, sugar-free, haloperidol 1 mg/mL. Net price 100-mL pack = £4.72. Label: 2

**Haldol**® (Janssen-Cilag)

Tablets, both scored, haloperidol 5 (blue), net price 20 = £1.53; 10 mg (yellow), 20 = £2.99. Label: 2

Oral liquid, sugar-free, haloperidol 2 mg/mL. Net price 100-mL pack (with pipette) = £4.72. Label: 2

**Injection**, haloperidol 5 mg/mL. Net price 1-mL amp = 30p

**Serenace**® (IVAX)

Capsules, green, haloperidol 500 micrograms, net price 30-cap pack = £8.81. Label: 2

Tablets, haloperidol 1.5 mg, net price 30-tab pack = £1.73; 5 mg (pink), 30-tab pack = £4.90; 10 mg (pale pink), 30-tab pack = £8.81. Label: 2

Oral liquid, sugar-free, haloperidol 2 mg/mL. Net price 500-mL pack = £43.83. Label: 2

**Depot preparation**
Section 4.2.2

---

**LEVOMEPROMAZINE**  
(Methotrimeprazine)

**Indications**  
see under Dose

**Cautions**  
see notes above; patients receiving large initial doses should remain supine

**Elderly**  
**Risk of postural hypotension**; not recommended for ambulant patients over 50 years unless risk of hypotensive reaction assessed

**Contra-indications**  
see notes above

**Side-effects**  
see notes above; occasionally raised erythrocyte sedimentation rate occurs

**Dose**
- Schizophrenia, **by mouth** initially 25–50 mg daily in divided doses increased as necessary; bedpatients initially 100–200 mg daily usually in 3 divided doses, increased if necessary to 1 g daily; **ELDERLY**; see Cautions
- Pain in palliative care, see p. 16
- Restlessness and confusion in palliative care, see p. 18; **CHILD** 1–18 years, see BNF for Children
- Nausea and vomiting in palliative care, by mouth, see p. 17, or by subcutaneous infusion, see p. 18; **CHILD** 1 month–18 years, see BNF for Children

**Noziman**® (Link)

Tablets, scored, levomepromazine maleate 25 mg, net price 84-tab pack = £20.26. Label: 2

**Injection**, levomepromazine hydrochloride 25 mg/mL, net price 1-mL amp = £2.01

---

**PERICYAZINE**  
(Periciazine)

**Indications**  
see under Dose

**Cautions**  
see notes above

**Contra-indications**  
see notes above; renal impairment
Side-effects see notes above; more sedating; hypotension common when treatment initiated; respiratory depression

Dose

- Schizophrenia and other psychoses, initially 75 mg daily in divided doses increased at weekly intervals by steps of 25 mg according to response; usual max. 300 mg daily (elderly initially 15–30 mg daily); CHILD and INFANT over 1 year (schizophrenia or behavioural disorders only), initially, 500 micrograms daily for 10-kg child, increased by 1 mg for each additional 5 kg body-weight to max. total daily dose of 10 mg; dose may be gradually increased according to response but maintenance should not exceed twice initial dose

- Short-term adjunctive management of severe anxiety, psychomotor agitation, and violent or dangerously impulsive behaviour, initially 15–30 mg (elderly 5–10 mg) daily divided into 2 doses, taking the larger dose at bedtime, adjusted according to response; CHILD not recommended

Neulactil® (Winthrop) Tablets, all yellow, scored, pericyazine 2.5 mg, net price 84-tab pack = £9.23; 10 mg, 84-tab pack = £24.95. Label: 2

Syrup forte, brown, pericyazine 10 mg/5 mL. Net price 100-mL pack = £12.08. Label: 2

PERPHENAZINE

Indications see under Dose; antiemetic (section 4.6)

Cautions see notes above

Contra-indications see notes above; also agitation and restlessness in the elderly

Side-effects see notes above; less sedating; extrapyramidal symptoms, especially dystonia, more frequent, particularly at high dosage; rarely systemic lupus erythematosus

Dose

- Schizophrenia and other psychoses, mania, short-term adjunctive management of anxiety, severe psychomotor agitation, excitement, and violent or dangerously impulsive behaviour, initially 4 mg 3 times daily adjusted according to the response; max. 24 mg daily; ELDERLY quarter to half adult dose (but see Cautions); CHILD under 14 years not recommended

Fentazin® (Goldshield) Tablets, both s/c, perphenazine 2 mg, net price 20 = £4.48; 4 mg, 20 = £5.27. Label: 2

PROMAZINE HYDROCHLORIDE

Indications see under Dose

Cautions see notes above; also cerebral arteriosclerosis

Contra-indications see notes above

Side-effects see notes above; also haemolytic anaemia

Dose

- Short-term adjunctive management of psychomotor agitation, 100–200 mg 4 times daily; CHILD not recommended

- Agitation and restlessness in elderly, 25–50 mg 4 times daily; CHILD not recommended

Promazine (Non-proprietary) Tablets, coated, promazine hydrochloride 25 mg, net price 20 = £1.32; 50 mg, 20 = £3.48. Label: 2

Orap® (Janssen-Cilag) Tablets, scored, green, pimozide 4 mg, net price 20 = £5.70. Label: 2

PIMOZIDE

Indications see under Dose

Cautions see notes above

CSM warning Following reports of sudden unexplained death, the CSM recommends ECG before treatment. The CSM also recommends that patients on pimozide should have an annual ECG (if the QT interval is prolonged, treatment should be reviewed and either withdrawn or dose reduced under close supervision) and that pimozide should not be given with other antipsychotic drugs (including depot preparations), tricyclic antidepressants or other drugs which prolong the QT interval, such as certain antimalarials, antihistamines and certain antihistamines and should not be given with drugs which cause electrolyte disturbances (especially diuretics)

Contra-indications see notes above; history of arrhythmias or congenital QT prolongation

Side-effects see notes above; less sedating; serious arrhythmias reported; glycosuria and, rarely, hypotension reported

Dose

- Schizophrenia, ADULT and CHILD over 12 years, initially 2 mg daily, increased according to response in steps of 2–4 mg at intervals of not less than 1 week; usual dose range 2–20 mg daily; ELDERLY half usual starting dose

- Monosymptomatic hypochondriacal psychosis, paranoid psychosis, ADULT and CHILD over 12 years, initially 4 mg daily, increased according to response in steps of 2–4 mg at intervals of not less than 1 week; max. 16 mg daily; ELDERLY half usual starting dose
SULPIRIDE

**Indications** schizophrenia

**Cautions** see notes above; also excited, agitated, or aggressive patients (even low doses may aggravate symptoms); renal impairment (avoid if creatinine clearance less than 10 mL/minute)

**Contra-indications** see notes above; also acute porphyria (section 9.8.2)

**Side-effects** see notes above; also hepatitis

**Dose**
- **ADULT** and **CHILD** over 14 years, 200–400 mg twice daily; max. 800 mg daily in predominantly negative symptoms, and 2.4 g daily in mainly positive symptoms; **ELDERLY**, lower initial dose, increased gradually according to response

Sulpiride (Non-proprietary)

- **Tablets**, sulpiride 200 mg, net price 30-tab pack = £6.92, 56-tab pack = £6.46; 400 mg, 30-tab pack = £12.12. Label: 2

Dolmatil® (Sanofi-Synthelabo)

- **Tablets**, both scored, sulpiride 200 mg, net price 100-tab pack = £13.85; 400 mg, 100-tab pack = £36.29. Label: 2

Sulpor® (Rosemont)

- **Oral solution**, sugar-free, lemon- and aniseed-flavoured, sulpiride 200 mg/5 mL, net price 150 mL = £25.38. Label: 2

TRIFLUOPERAZINE

**Indications** see under Dose; antiemetic (section 4.6)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; extrapyramidal symptoms more frequent, especially at doses exceeding 6 mg daily; pancytopenia; thrombocytopenia; hypopyrexia; anorexia

**Dose**
- **Schizophrenia and other psychoses**, short-term adjunctive management of psychomotor agitation, excitement, and violent or dangerous impulsive behaviour, **ADULT** and **CHILD** over 12 years, initially 5 mg twice daily, increased by 5 mg daily after 1 week, then at intervals of 3 days, according to the response; **ELDERLY** reduce initial dose by at least half
- **Short-term adjunctive management of severe anxiety**, **ADULT** and **CHILD** over 12 years, 2–4 mg daily in divided doses, increased if necessary to 6 mg daily; **CHILD** 3–5 years up to 1 mg daily, 6–12 years up to 4 mg daily; **ELDERLY** reduce initial dose by at least half

Trifluoperazine (Non-proprietary)

- **Tablets**, coated, trifluoperazine (as hydrochloride) 1 mg, net price 20 = £1.22; 5 mg, 20 = £1.06. Label: 2
- **Oral solution**, trifluoperazine (as hydrochloride) 5 mg/5 mL. Net price 150 mL = £9.33. Label: 2

Stelazine® (Goldshield)

- **Tablets**, both blue, f/c, trifluoperazine (as hydrochloride) 1 mg, net price 20 = 61p; 5 mg, 20 = 87p. Label: 2
- **Syrup**, sugar-free, yellow, trifluoperazine (as hydrochloride) 1 mg/5 mL, net price 200-mL pack = £2.95. Label: 2

ZUCLOPENTHIXOL ACETATE

**Indications** short-term management of acute psychosis, mania, or exacerbations of chronic psychosis

**Cautions** see notes above; avoid in acute porphyria (section 9.8.2)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- By deep intramuscular injection into the gluteal muscle or lateral thigh, 50–150 mg **ELDERLY** 50–100 mg, if necessary repeated after 2–3 days (1 additional dose may be needed 1–2 days after the first injection); max. cumulative dose 400 mg per course and max. 4 injections; max. duration of treatment 2 weeks—if maintenance treatment necessary change to an oral antipsychotic 2–3 days after last injection, or to a longer acting antipsychotic depot injection given concomitantly with last injection of zuclopenthixol acetate; **CHILD** not recommended

Clopixol Acuphase® (Lundbeck)

- **Injection** (oily), zuclopenthixol acetate 50 mg/mL, net price 1-mL amp = £4.84; 2-mL amp = £9.33

**Depot preparation** Section 4.2.2

ZUCLOPENTHIXOL

**Indications** schizophrenia and other psychoses

**Cautions** see notes above; avoid in acute porphyria (section 9.8.2)

**Contra-indications** see notes above; apathetic or withdrawn states

**Side-effects** see notes above; urinary frequency or incontinence; weight loss (less common than weight gain)

**Dose**
- **By mouth**, initially 20–30 mg daily in divided doses, increasing to a max. of 150 mg daily if necessary; usual maintenance dose 20–50 mg daily; **ELDERLY** (or debilitated) initially quarter to half adult dose; **CHILD** not recommended

Clopixol® (Lundbeck)

- **Tablets**, f/c, pink, zuclopenthixol (as dihydrochloride) 2 mg, net price 100 = £2.99; 10 mg, 100 = £8.06; 25 mg, 100 = £16.12. Label: 2

**Depot preparation** Section 4.2.2

Atypical antipsychotic drugs

The ‘atypical’ antipsychotic drugs amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone, and zotepine may be better tolerated than other antipsychotic drugs; extrapyramidal symptoms may be less frequent than with older antipsychotic drugs.

Aripiprazole, clozapine, olanzapine, quetiapine, and serindole cause little or no elevation of prolactin concentrations; when changing from other antipsychotic drugs, a reduction in prolactin may increase fertility.
Clozapine is licensed for the treatment of schizophrenia only in patients unresponsive to, or intolerant of, conventional antipsychotic drugs. It can cause agranulocytosis and its use is restricted to patients registered with a clozapine patient monitoring service (see under preparations, below).

Sertindole has been reintroduced following an earlier suspension of the drug because of concerns about arrhythmias; its use is restricted to patients who are enrolled in clinical studies and who are intolerant of at least one other antipsychotic.

The Scottish Medicines Consortium (p. 3) has advised (March 2008) that paliperidone (Invega®) is not recommended for use within NHS Scotland.

<table>
<thead>
<tr>
<th>NICE guidance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical antipsychotics for schizophrenia (June 2002)</td>
</tr>
<tr>
<td>NICE has recommended:</td>
</tr>
<tr>
<td>● the atypical antipsychotics (amisulpride, olanzapine, quetiapine, risperidone, and zotepine) should be considered when choosing first-line treatment of newly diagnosed schizophrenia;</td>
</tr>
<tr>
<td>● an atypical antipsychotic is considered the treatment option of choice for managing an acute schizophrenic episode when discussion with the individual is not possible;</td>
</tr>
<tr>
<td>● an atypical antipsychotic should be considered for an individual who is suffering unacceptable side-effects from a conventional antipsychotic;</td>
</tr>
<tr>
<td>● an atypical antipsychotic should be considered for an individual in relapse whose symptoms were previously inadequately controlled;</td>
</tr>
<tr>
<td>● changing to an atypical antipsychotic is not necessary if a conventional antipsychotic controls symptoms adequately and the individual does not suffer unacceptable side-effects;</td>
</tr>
<tr>
<td>● clozapine should be introduced if schizophrenia is inadequately controlled despite the sequential use of two or more antipsychotics (one of which should be an atypical antipsychotic) each for at least 6–8 weeks.</td>
</tr>
</tbody>
</table>

Cautions and contra-indications While atypical antipsychotics have not generally been associated with clinically significant prolongation of the QT interval, they should be used with care if prescribed with other drugs that increase the QT interval. Atypical antipsychotics should be used with caution in patients with cardiovascular disease, or a history of epilepsy; they should be used with great caution in the elderly (see p. 192); interactions: Appendix 1 (antipsychotics).

Driving Atypical antipsychotics may affect performance of skilled tasks (e.g. driving); effects of alcohol are enhanced.

Withdrawal Withdrawal of antipsychotic drugs after long-term therapy should always be gradual and closely monitored to avoid the risk of acute withdrawal syndromes or rapid relapse.

Side-effects Side-effects of the atypical antipsychotics include weight gain, dizziness, postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some patients, extrapyramidal symptoms (usually mild and transient and which respond to dose reduction or to an antimuscarinic drug), and occasionally tardive dyskinesia on long-term administration (discontinue drug on appearance of early signs). Hyperglycaemia and sometimes diabetes can occur, particularly with clozapine and olanzapine; monitoring weight and plasma glucose may identify the development of hyperglycaemia. Neuroleptic malignant syndrome has been reported rarely. Hypersalivation associated with clozapine therapy can be treated with hyoscine hydrobromide (unlicensed indication) (p. 228).

### AMISULPRIDE

**Indications** schizophrenia

**Contra-indications** see notes above; also phaeochromocytoma, prolactin-dependent tumours; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see notes above; also insomnia, anxiety, agitation, drowsiness, gastro-intestinal disorders such as constipation, nausea, vomiting, and dry mouth; hyperprolactinaemia; occasionally bradycardia; rarely seizures

**Dose**

- Acute psychotic episode, 400–800 mg daily in 2 divided doses, adjusted according to response; max. 1.2 g daily; CHILD under 15 years not recommended
- Predominantly negative symptoms, 50–300 mg daily; CHILD under 15 years not recommended

**Amisulpride (Non-proprietary)**

- **Tablets**, amisulpride 50 mg, net price 60-tab pack = £19.00; 100 mg, 60-tab pack = £33.73; 200 mg, 60-tab pack = £56.47; 400 mg, 60-tab pack = £112.45. Label: 2

**Solan®** (Sanofi-Synthelabo)

- **Tablets**, scored, amisulpride 50 mg, net price 60-tab pack = £23.69; 100 mg, 60-tab pack = £36.72; 200 mg, 60-tab pack = £61.38; 400 mg, 60-tab pack = £122.76. Label: 2

**Solution**, 100 mg/mL, net price 60 mL (caramel flavour) = £30.69. Label: 2

### ARIPIPRAZOLE

**Indications** see under Dose

**Contra-indications** see notes above; cerebrovascular disease; elderly (reduce initial dose); hepatic impairment (Appendix 2); pregnancy (Appendix 4)

**Side-effects** see notes above; breast-feeding (Appendix 5)

**AMISULPRIDE**

**Cautions** see notes above; also Parkinson’s disease; renal impairment (Appendix 3)

**AMISULPRIDE**

**Indications** schizophrenia

**Contra-indications** see notes above; also phaeochromocytoma, prolactin-dependent tumours; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see notes above; also insomnia, anxiety, agitation, drowsiness, gastro-intestinal disorders such as constipation, nausea, vomiting, and dry mouth; hyperprolactinaemia; occasionally bradycardia; rarely seizures

**Dose**

- Acute psychotic episode, 400–800 mg daily in 2 divided doses, adjusted according to response; max. 1.2 g daily; CHILD under 15 years not recommended
- Predominantly negative symptoms, 50–300 mg daily; CHILD under 15 years not recommended

**Amisulpride (Non-proprietary)**

- **Tablets**, amisulpride 50 mg, net price 60-tab pack = £19.00; 100 mg, 60-tab pack = £33.73; 200 mg, 60-tab pack = £56.47; 400 mg, 60-tab pack = £112.45. Label: 2

**Solan®** (Sanofi-Synthelabo)

- **Tablets**, scored, amisulpride 50 mg, net price 60-tab pack = £23.69; 100 mg, 60-tab pack = £36.72; 200 mg, 60-tab pack = £61.38; 400 mg, 60-tab pack = £122.76. Label: 2

**Solution**, 100 mg/mL, net price 60 mL (caramel flavour) = £30.69. Label: 2

### ARIPIPRAZOLE

**Indications** see under Dose

**Cautions** see notes above; cerebrovascular disease; elderly (reduce initial dose); hepatic impairment (Appendix 2); pregnancy (Appendix 4)

**Contra-indications** see notes above; breast-feeding (Appendix 5)

**Side-effects** see notes above; gastro-intestinal disturbances; tachycardia; fatigue, insomnia, akathisia; drowsiness, restlessness, tremor, headache, asthenia; blurred vision; less commonly depression; very rarely anorexia, dysphagia, oropharyngeal spasm, laryngospasm, hepatitis, jaundice, hypersalivation, pancreatitis, oedema, thromboembolism, arrhythmias, bradycardia, hypertension, chest pain, agitation, anxiety, speech disorder, suicidal ideation, seizures, hyponatraemia, stiffness, myalgia, rhabdomyolysis, priapism, urinary retention and incontinence, blood disorders, sweating, alopecia, photosensitivity reactions, rash, weight loss, and impaired temperature regulation; with injection, dry mouth
**Dose**

- **Schizophrenia, by mouth, ADULT** over 18 years 10–15 mg once daily, usual maintenance 15 mg once daily; max. 30 mg once daily
- **Mania, by mouth, ADULT** over 18 years, 15 mg once daily, increased if necessary; max. 30 mg once daily
- **Control of agitation and disturbed behaviour in schizophrenia, by intramuscular injection, ADULT** over 18 years, initially 5.25–15 mg (usual dose 9.75 mg) as a single dose followed by 5.25–15 mg after 2 hours if necessary; max. 3 injections daily; max. daily combined oral and parenteral dose 30 mg

**Abilify**® (Bristol-Myers Squibb) (BNF)

| Tablets | aripiprazole 5 mg (blue), net price 28-tab pack = £101.63; 10 mg (pink), 28-tab pack = £101.63; 15 mg (yellow), 28-tab pack = £101.63; 30 mg (pink), 28-tab pack = £203.26. Label: 2 |
| Orodispersible tablets | aripiprazole 10 mg (pink), net price 28-tab pack = £101.63; 15 mg (yellow), 28-tab pack = £101.63. Label: 2, counselling, administration |

**CLOZAPINE**

**Indications** schizophrenia (including psychosis in Parkinson’s disease) in patients unresponsive to, or intolerant of, conventional antipsychotic drugs

**Cautions** see notes above; elderly; monitor leucocyte and differential blood counts (see Agranulocytosis, (Appendix 5)); hypersalivation, dry mouth, nausea, vomiting, anorexia; tachycardia, ECG changes, hypertension; drowsiness, headache, tremor, seizures, fatigue, impaired temperature regulation; urinary incontinence and retention; leucopenia, eosinophilia, leucocytosis; blurred vision; sweating; less commonly agranulocytosis (important: see Cautions); rarely dysphagia, hepatitis, cholestatic jaundice, pancreatitis, circulatory collapse, arrhythmia, myocardiitis (important: see Cautions), pericarditis, thrombomembolism, agitation, confusion, delirium, anaemia; very rarely parotid gland enlargement, intestinal obstruction (see Cautions), cardiomyopathy, myocardial infarction, respiratory depression, priapism, interstitial nephritis, thrombocytopenia, thrombocytopenia, hyperlipidaemia, angle-closure glaucoma, fulminating hepatic necrosis, and skin reactions

**Dose**

- **Schizophrenia, ADULT** over 16 years, 12.5 mg once or twice (ELDERLY 12.5 mg once) on first day then 25–50 mg (ELDERLY 25–37.5 mg) on second day then increased gradually (if well tolerated) in steps of 25–50 mg daily (ELDERLY max. increment 25 mg daily) over 14–21 days up to 300 mg daily in divided doses (larger dose at night, up to 200 mg daily may be taken as a single dose at bedtime); if necessary may be further increased in steps of 50–100 mg once (preferably) or twice weekly; usual dose 200–450 mg daily (max. 900 mg daily)

**Note** Restarting after interval of more than 2 days, 12.5 mg once or twice on first day (but may be feasible to increase more quickly than on initiation)—extreme caution if previous respiratory or cardiac arrest with initial dosing

- **Psychosis in Parkinson’s disease, ADULT** over 16 years, 12.5 mg at bedtime then increased according to response in steps of 12.5 mg up to twice weekly; usual dose range 25–37.5 mg at bedtime, usual max. 50 mg daily; exceptionally, dose may be increased further in steps of 12.5 mg weekly to max. 100 mg daily in 1–2 divided doses

**Clozaril**® (Novartis) (BNF)

| Tablets | both yellow, clozapine 25 mg (scored), net price 28-tab pack = £6.17, 84-tab pack (hosp. only) = £18.49; 100 mg, 28-tab pack = £24.64, 84-tab pack (hosp. only) = £73.92. Label: 2, 10, patient information leaflet |

**Note** Patient, prescriber, and supplying pharmacist must be registered with the Clozaril Patient Monitoring Service—takes several days to do this
### Denzapine (Merz) \( ^{\text{TM}} \)

**Tablets**, both yellow, scored, clozapine 25 mg, net price 28-tab pack = £6.17, 84-tab pack = £18.49; 100 mg, 28-tab pack = £24.64, 84-tab pack = £73.92. Label: 2, 10, patient information leaflet

**Note** Patient, prescriber, and supplying pharmacist must be registered with the Denzapine Patient Monitoring Service—takes several days to do this

**Zaponex** (IVAX) \( ^{\text{TM}} \)

**Tablets**, both yellow, scored, clozapine 25 mg, net price 84-tab pack = £22.17; 100 mg, 84-tab pack = £50.00. Label: 2, 10, patient information leaflet

**Note** Patient, prescriber, and supplying pharmacist must be registered with the Zaponex Treatment Access System—takes several days to do this

### OLANZAPINE

**Indications** see under Dose

**Cautions** see notes above; also prostatic hypertrophy, susceptibility to angle-closure glaucoma, paralytic ileus, diabetes mellitus (risk of exacerbation or keto-acidosis), low leucocyte or neutrophil count, bone-marrow depression, hypersesinophilic disorders, myeloproliferative disease, Parkinson's disease; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4)

**CNS and respiratory depression** Blood pressure, pulse and respiratory rate should be monitored for at least 4 hours after intramuscular injection, particularly in those also receiving another antipsychotic or benzodiazepine

**Contra-indications** breast-feeding (Appendix 5); for injection, acute myocardial infarction, unstable angina, severe hypotension or bradycardia, sick sinus syndrome, recent heart surgery

**Side-effects** see notes above; also mild, transient abdominal pain, diaphoresis, bradycardia, first-degree AV block, bundle branch block; drowsiness, headache, asthenia; less commonly tachycardia, arrhythmias, ischaemia, oedema, seizures, nightmare, syncope, menstrual disturbances, erectile dysfunction, galactorrhoea, and gynaecomastia

**Dose**

- **ADULT** over 18 years, 6 mg once daily in the morning, adjusted if necessary; usual range 3–12 mg daily
- **Counselling** Always take with breakfast or always take on an empty stomach

**Invega** (Janssen-Cilag) \( ^{\text{TM}} \)

**Tablets**, m/r, paliperidone 3 mg (white), net price 28-tab pack = £97.28; 6 mg (beige), 28-tab pack = £97.28; 9 mg (pink), 28-tab pack = £145.92. Label: 2, 25, counselling, administration

### PALPERIDONE

**Note** Paliperidone is a metabolite of risperidone

**Indications** schizophrenia

**Cautions** see notes above; predisposition to gastrointestinal obstruction; elderly patients with dementia and risk factors for stroke; Parkinson’s disease; severe hepatic impairment; renal impairment (avoid if creatinine clearance less than 10 mL/minute); pregnancy (Appendix 4)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** see notes above; also abdominal pain, dry mouth, hypersalivation, vomiting; tachycardia, bradycardia, first-degree AV block, bundle branch block; drowsiness, headache, asthenia; less commonly palpitation, arrhythmias, ischaemia, oedema, seizures, nightmare, syncope, menstrual disturbances, erectile dysfunction, galactorrhoea, and gynaecomastia

**Dose**

- **ADULT** over 18 years, 5 mg/mL, net price 10-mg vial = £3.48

### QUETIAPINE

**Indications** schizophrenia; treatment of episodes ofmania either alone or with mood stabilisers

**Cautions** see notes above; also hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); cerebrovascular disease

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** see notes above; also dry mouth, constipation, dyspepsia; tachycardia, peripheral oedema; drowsiness, headache, asthenia; leucopenia, neutropenia; rhinitis; less commonly elevated plasma-triglyceride and -cholesterol concentrations, seizures, and eosinophilia; rarely jaundice and priapism; very rarely hepatitis, angioedema, and Stevens-Johnson syndrome

---

**Note** When one or more factors present that might result in slower metabolism (e.g. female gender, elderly, non-smoker) consider lower initial dose and more gradual dose increase

**Zyprexa** (Lilly) \( ^{\text{TM}} \)

**Tablets**, 1/c, olanzapine 2.5 mg, net price 28-tab pack = £33.29; 5 mg, 28-tab pack = £48.78; 7.5 mg, 56-tab pack = £146.34; 10 mg, 28-tab pack = £79.45, 15 mg (blue), 28-tab pack = £119.18; 20 mg (pink), 28-tab pack = £158.90. Label: 2

**Ondispersible tablet** (Velotab)\(^{\text{TM}}\), yellow, olanzapine 5 mg, net price 28-tab pack = £48.78; 10 mg, 28-tab pack = £79.45; 15 mg, 28-tab pack = £119.18; 20 mg, 28-tab pack = £158.90. Label: 2, counselling, administration

**Excipients** include aspartame (section 9.4.1)

**Counselling** Velotab may be placed on the tongue and allowed to dissolve or dispersed in water, orange juice, apple juice, milk, or coffee

**Injection**, powder for reconstitution, olanzapine 5 mg/mL, net price 10-mg vial = £3.48
Dose

- Schizophrenia, ADULT over 18 years, 25 mg twice daily on day 1, 50 mg twice daily on day 2, 100 mg twice daily on day 3, 150 mg twice daily on day 4, then adjusted according to response, usual range 300–450 mg daily in 2 divided doses; max. 750 mg daily; ELDERLY initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses; CHILD 12–18 years, see BNF for Children

- Mania, ADULT over 18 years, 50 mg twice daily on day 1, 100 mg twice daily on day 2, 150 mg twice daily on day 3, 200 mg twice daily on day 4, then adjusted according to response in steps of up to 200 mg daily to max. 800 mg daily; usual range 400–800 mg daily in 2 divided doses; ELDERLY initially 25 mg daily as a single dose, increased in steps of 25–50 mg daily in 2 divided doses

Seroquel® (AstraZeneca) Tablets, f/c, quetiapine (as fumarate) 25 mg (peach), net price 60-tab pack = £33.83; 100 mg (yellow), 60-tab pack = £113.10; 150 mg (pale yellow), 60-tab pack = £113.10; 200 mg (white), 60-tab pack = £113.10; 300 mg (white), 60-tab pack = £170.00. Label: 2

Modiﬁed release Seroquel® XL (AstraZeneca) Tablets, m/r, quetiapine (as fumarate) 50 mg (peach), net price 60-tab pack = £67.66; 200 mg (yellow), 60-tab pack = £113.10; 300 mg (pale yellow), 60-tab pack = £170.00; 400 mg (white), 60-tab pack = £226.20. Label: 2, 23, 25

Dose schizophrenia, mania, ADULT over 18 years, 300 mg once daily on day 1, then 600 mg once daily on day 2, then adjusted according to response; dose range 400–800 mg daily; ELDERLY initially 50 mg once daily adjusted according to response in steps of 50 mg daily

Risperdal® (Janssen-Cilag) Tablets, f/c, scored, risperidone 500 micrograms (brown-red), net price 20-tab pack = £7.06; 1 mg (white), 20-tab pack = £11.61, 60-tab pack = £34.84; 2 mg (orange), 60-tab pack = £68.69; 3 mg (yellow), 60-tab pack = £101.01; 4 mg (green), 60-tab pack = £133.34; 6 mg (yellow), 28-tab pack = £94.28. Label: 2

Orodispensible tablets (Quicklet®), pink, risperidone 500 micrograms, net price 28-tab pack = £11.43; 1 mg, 28-tab pack = £18.39; 2 mg, 28-tab pack = £34.66; 3 mg, 28-tab pack = £50.34; 4 mg, 28-tab pack = £64.84. Label: 2, counselling, administration

Excipients include aspartame (section 9.4.1)

Counselling Tablets should be placed on the tongue, allowed to dissolve and swallowed

Liquid, risperidone 1 mg/mL, net price 100 mL = £56.12. Label: 2

Note Liquid may be diluted with mineral water, orange juice or black coffee (should be taken immediately)

Depot preparation Section 4.2.2

SERTINDOLE

Indications schizophrenia, see also notes above

Cautions see notes above; hepatic impairment (Appendix 2); correct hypokalaemia or hypomagnesaemia before treatment; monitor ECG during treatment; monitor blood pressure during dose titration and early maintenance therapy (risk of postural hypotension)

Contra-indications see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5), severe hepatic impairment. QT interval prolongation (ECG required before and during treatment—consult product literature); concomitant administration of drugs which prolong QT interval (see interactions); uncorrected hypokalaemia or hypomagnesaemia

Side-effects see notes above; prolonged QT interval, peripheral oedema, dry mouth, rhi­nitis, nasal congestion, dyspnoea, paraesthesia, abnormal ejaculation (decreased volume); rarely seizures, hyperglycaemia

Dose

- Psychoses, 2 mg in 1–2 divided doses on first day then 4 mg in 1–2 divided doses on second day (slower titration appropriate in some patients); usual dose range 4–6 mg daily; doses above 10 mg daily only if benefit considered to outweigh risk (max. 16 mg daily); ELDERLY initially 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily; CHILD 12–15 years see BNF for Children

- Mania, initially 2 mg once daily, increased if necessary in steps of 1 mg daily; usual dose range 1–6 mg daily; ELDERLY initially 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily

ZOTEPINE

Indications schizophrenia

Cautions see notes above; personal or close family history of epilepsy; withdrawal of concomitantly prescribed CNS depressants; QT interval prolongation—ECG required (before treatment and at each dose increase) in patients at risk of arrhythmias; monitor plasma electrolytes particularly before treatment and at each dose increase; hepatic impairment (Appendix 2); renal impairment (Appendix 3); prostatic hyper-
Central nervous system

4.2.2 Antipsychotic depot injections

Long-acting depot injections are used for maintenance therapy especially when compliance with oral treatment is unreliable. However, depot injections of conventional antipsychotics may give rise to a higher incidence of extrapyramidal reactions than oral preparations; extrapyramidal reactions occur less frequently with atypical antipsychotics such as risperidone.

**Dose**
- Initially 25 mg 3 times daily increased according to response at intervals of 4 days to max. 100 mg 3 times daily; **ELDERLY** initially 25 mg twice daily increased according to response to max. 75 mg twice daily; **CHILD** and **ADOLESCENT** under 18 years not recommended**

Zoleptil® (Healthcare Logistics) (BNF 57)
Tablets, s/c, zotepine 25 mg (white), net price 30-tab pack = £21.50, 90-tab pack = £42.98, 50 mg (yellow), 30-tab pack = £28.65, 90-tab pack = £57.30; 100 mg (pink), 30-tab pack = £47.28, 90-tab pack = £94.55. Label: 2

**Choice** There is no clear-cut division in the use of the conventional antipsychotics, but **zuclopenthixol** may be suitable for the treatment of agitated or aggressive patients whereas **flupentixol** can cause over-excitement in such patients. The incidence of extrapyramidal reactions is similar for the conventional antipsychotics.

**Cautions** See section 4.2.1. Treatment requires careful monitoring for optimum effect. When transferring from oral to depot therapy, dosage by mouth should be reduced gradually.

**Contra-indications** See section 4.2.1. Do not use in children.

**Side-effects** See section 4.2.1. Pain may occur at injection site and occasionally erythema, swelling, and nodules. For side-effects of specific antipsychotics see under the relevant drug.

**FLUPENTIXOL DECANOATE** (Flupenthixol Decanoate)

**Indications** maintenance in schizophrenia and other psychoses

**Cautions** see notes on p. 192 and also under Flupentixol (section 4.2.1) and notes above; an alternative antipsychotic may be necessary if symptoms such as aggression or agitation appear

**Contra-indications** see notes on p. 192 and also under Flupentixol (section 4.2.1) and notes above

**Side-effects** see notes on p. 192 and also under Flupentixol (section 4.2.1) and notes above, but may have a mood elevating effect

**Dose**
- By deep intramuscular injection into the upper outer buttock or lateral thigh, test dose 20 mg, then after at least 7 days 20–40 mg repeated at intervals

**Dosage** Individual responses to neuroleptic drugs are very variable and to achieve optimum effect, dosage and dosage interval must be titrated according to the patient’s response. For the advice of The Royal College of Psychiatrists on doses above the BNF upper limit, see p. 192.

**Equivalent doses of depot antipsychotics**

These equivalences are intended only as an approximate guide; individual dosage instructions should also be checked; patients should be carefully monitored after any change in medication

<table>
<thead>
<tr>
<th>Antipsychotic drug</th>
<th>Dose (mg)</th>
<th>Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flupentixol decanoate</td>
<td>40</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>25</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Haloperidol (as decanoate)</td>
<td>100</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Pipotazine palmitate</td>
<td>50</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Zuclopenthixol decanoate</td>
<td>200</td>
<td>2 weeks</td>
</tr>
</tbody>
</table>

**Important** These equivalences must not be extrapolated beyond the maximum dose for the drug.
of 2–4 weeks, adjusted according to response; max. 400 mg weekly; usual maintenance dose 50 mg every 4 weeks to 300 mg every 2 weeks; **ELDERLY** initially quarter to half adult dose; **CHILD** not recommended

**Depixol**® (Lundbeck) [monograph]

**Injection** (oily), flupentixol decanoate 20 mg/mL. Net price 1-mL amp = £1.52; 2-mL amp = £2.54

**Depixol Conc.**® (Lundbeck) [monograph]

**Injection** (oily), flupentixol decanoate 100 mg/mL. Net price 0.5-mL amp = £3.42; 1-mL amp = £6.25

**Depixol Low Volume**® (Lundbeck) [monograph]

**Injection** (oily), flupentixol decanoate 200 mg/mL. Net price 1-mL amp = £19.52

**FLUPHENAZINE DECANOATE**

**Indications** maintenance in schizophrenia and other psychoses

**Cautions** see notes on p. 192 and also notes above; also marked cerebral atherosclerosis

**Side-effects** see notes on p. 192 and notes above; less sedating and fewer antimuscarinic or hypotensive symptoms, particularly dystonic reactions and akathisia, more frequent; systemic lupus erythematosus, inappropriate anti-diuretic hormone secretion, oedema, also reported; extrapyramidal symptoms usually appear a few hours after injection and continue for about 2 days but may be delayed

**Dose**

- By deep intramuscular injection into the gluteal muscle, test dose 12.5 mg (6.25 mg in elderly), then after 4–7 days 12.5–100 mg repeated at intervals of 14–35 days, adjusted according to response; **CHILD** not recommended

**Fluphenazine decanoate** (Non-proprietary) [monograph]

**Injection** (oily), fluphenazine decanoate 25 mg/mL. Net price 1-mL amp = £2.35; 100 mg/mL, 0.5-mL amp = £4.50, 1-mL amp = £8.79

Exipients include sesame oil

**Moducate**® (Sanofi-Synthelabo) [monograph]

**Injection** (oily), fluphenazine decanoate 25 mg/mL. Net price 0.5-mL amp = £1.35, 1-mL amp = £2.35, 2-mL amp = £4.62

Exipients include sesame oil

**Moducate Concentrate**® (Sanofi-Synthelabo) [monograph]

**Injection** (oily), fluphenazine decanoate 100 mg/mL. Net price 0.5-mL amp = £4.66, 1-mL amp = £9.10

Exipients include sesame oil

**HALOPERIDOL**

**Indications** maintenance in schizophrenia and other psychoses

**Cautions** see notes on p. 192 and also under Haloperidol (section 4.2.1) and notes above

**Contra-indications** see notes on p. 192 and also under Haloperidol (section 4.2.1) and notes above

**Side-effects** see notes on p. 192 and also under Haloperidol (section 4.2.1) and notes above

**Dose**

- By deep intramuscular injection into the gluteal muscle, initially 50 mg every 4 weeks, if necessary increasing by 50-mg increments to 300 mg every 4 weeks; higher doses may be needed in some patients; **ELDERLY** initially 12.5–25 mg every 4 weeks; **CHILD** not recommended

**Note** If 2-weekly administration preferred, doses should be halved

**Haldol Decanoate**® (Janssen-Cilag) [monograph]

**Injection** (oily), haloperidol (as decanoate) 50 mg/mL. Net price 1-mL amp = £4.05; 100 mg/mL, 1-mL amp = £5.36

Exipients include sesame oil

**ZUCLOPENTHIXOL DECANOATE**

**Indications** maintenance in schizophrenia and paranoid psychoses

**Cautions** see notes on p. 192 and notes above

**Contra-indications** see notes on p. 192 and notes above

**Side-effects** see notes on p. 192 and notes above

**Dose**

- By deep intramuscular injection into the gluteal muscle, patients taking oral risperidone up to 4 mg daily, initially 25 mg every 2 weeks; patients taking oral risperidone over 4 mg daily, initially 37.5 mg every 2 weeks; dose adjusted at intervals of at least 4 weeks in steps of 12.5 mg to max. 50 mg (**ELDERLY** initial 5–10 mg; **CHILD** not recommended)

**Note** During initiation risperidone by mouth may need to be continued for 4–6 weeks; risperidone by mouth may also be used during dose adjustment of depot injection

**Risperdal Consta**® (Janssen-Cilag) [monograph]

**Injection**, powder for reconstitution, risperidone 25-mg vial, net price = £82.92; 37.5-mg vial = £115.84; 50-mg vial = £148.55 (all with diluent)

**Central nervous system**
### Antimanic drugs

**Side-effects** see notes on p. 192 and notes above

**Dose**
- By deep intramuscular injection into the upper outer buttock or lateral thigh, test dose 100 mg, followed after at least 7 days by 200–500 mg or more, repeated at intervals of 1–4 weeks, adjusted according to response; max. 600 mg weekly; **ELDERLY** quarter to half usual starting dose; **CHILD** not recommended

**Clopixol** *(Lundbeck)*
- **Injection** (oily), zuclopenthixol decanoate 200 mg/mL, net price 1-mL amp = £3.15
- **Clopixol Conc.** *(Lundbeck)*
- **Injection** (oily), zuclopenthixol decanoate 500 mg/mL, net price 1-mL amp = £7.44

### Benzodiazepines

Use of benzodiazepines (section 4.1) may be helpful in the initial stages of treatment until lithium achieves its full effect; they should not be used for long periods because of the risk of dependence.

### Antipsychotic drugs

In an acute attack of mania, treatment with an antipsychotic drug (section 4.2.1) is usually required because it may take a few days for lithium to exert its antimanic effect. Lithium may be given concurrently with the antipsychotic drug, and treatment with the antipsychotic gradually tailed off as lithium becomes effective. Alternatively, lithium therapy may be commenced once the patient’s mood has been stabilised with the antipsychotic. The adjunctive use of atypical antipsychotics such as olanzapine (section 4.2.1) and risperidone with either lithium or valproic acid may also be of benefit.

High doses of haloperidol or flupentixol may be hazardous when used with lithium; irreversible toxic encephalopathy has been reported.

### Carbamazepine

Carbamazepine (section 4.8.1) may be used for the prophylaxis of bipolar disorder (manic-depressive disorder) in patients unresponsive to lithium; it seems to be particularly effective in patients with rapid-cycling manic-depressive illness (4 or more affective episodes per year).

### Valproic acid

Valproic acid (as the semisodium salt) is licensed for the treatment of manic episodes associated with bipolar disorder. It may be useful in patients unresponsive to lithium.

Sodium valproate (section 4.8.1) has also been used, but it is unlicensed for this indication.
**Interactions** Lithium toxicity is made worse by sodium depletion, therefore concurrent use of diuretics (particularly thiazides) is hazardous and should be avoided. For other interactions with lithium, see Appendix 1 (lithium).

**Withdrawal** While there is no clear evidence of withdrawal or rebound psychosis, abrupt discontinuation of lithium increases the risk of relapse. If lithium is to be discontinued, the dose should be reduced gradually over a period of a few weeks and patients should be warned of possible relapse if it is discontinued abruptly.

**LITHIUM CARBONATE**

**Indications** treatment and prophylaxis of mania, bipolar disorder, and recurrent depression (see also notes above); aggressive or self-mutilating behaviour

**Cautions** measure serum-lithium concentration regularly (every 3 months on stabilised regimens), measure renal function and thyroid function every 6–12 months on stabilised regimens and advise patient to seek attention if symptoms of hypothyroidism develop (women at greater risk) e.g. lethargy, feeling cold; maintain adequate sodium and fluid intake; test renal function before initiating and if evidence of toxicity, avoid in renal impairment (Appendix 3), cardiac disease, and conditions with sodium imbalance such as Addison's disease; reduce dose or discontinue in diaphoresis, vomiting and intercurrent infection (especially if sweating profusely); psoriasis (risk of exacerbation); pregnancy (Appendix 4), breast-feeding (Appendix 5), elderly (reduce dose), diuretic treatment, myasthenia gravis; surgery (section 15.1); avoid abrupt withdrawal (see notes above); interactions: Appendix 1 (lithium)

**Counselling** Patients should maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake; lithium treatment cards are available from pharmacies (see above)

**Side-effects** gastrointestinal disturbances, fine tremor, renal impairment (particularly impaired urinary concentration and polyuria), polydipsia, leucocytosis; also weight gain and oedema (may respond to dose reduction); hyperparathyroidism and hypercalcaemia reported; signs of intoxication are blurred vision, increasing gastrointestinal disturbances (anorexia, vomiting, diarrhoea), muscle weakness, increased CNS disturbances (mild drowsiness and sluggishness increasing to giddiness with ataxia, coarse tremor, lack of co-ordination, dysarthria), and require withdrawal of treatment; with severe overdosage (serum-lithium concentration above 2 mmol/litre) hyperreflexia and hyperextension of limbs, convulsions, toxic psychoses, syncope, renal failure, circulatory failure, coma, and occasionally, death; goitre, raised anti-diuretic hormone concentration, hypothyroidism, hypokalaemia, ECG changes, and kidney changes may also occur; see also Emergency Treatment of Poisoning, p. 33

**Dose**

- See under preparations below, adjusted to achieve a serum-lithium concentration of 0.4–1 mmol/litre 12 hours after a dose on days 4–7 of treatment, then every week until dosage has remained constant for 4 weeks and every 3 months thereafter; doses are initially divided throughout the day, but once daily administration is preferred when serum-lithium concentration stabilised

**Note** Preparations vary widely in bioavailability, changing the preparation requires the same precautions as initiation of treatment

**Note** Lithium carbonate 200 mg = lithium citrate 509 mg

**Camcolit** (Norgine) Tablets, f/c, scored, lithium carbonate 250 mg (Li+ 6.8 mmol), net price 20 = 64p. Label: 10, lithium card, counselling, see above

**Camcolit 400** tablets, m/r, f/c, scored, lithium carbonate 400 mg (Li+ 10.8 mmol), net price 20 = 86p. Label: 10, lithium card, 25, counselling, see above

**Dose** (see Dose above for advice on bioavailability and serum monitoring)

**Note** Camcolit 400 also available as Lithionate (TEVA UK)

**Liskonum** (GSK) Tablets, m/r, f/c, scored, lithium carbonate 450 mg (Li+ 12.2 mmol), net price 60-tab pack = £2.88. Label: 10, lithium card, 25, counselling, see above

**Dose** (see Dose above for advice on bioavailability and serum monitoring)

**Note** Liskonum 450 also available as Lithionate (GSK)

**Priadel** (Sanofi-Synthelabo) Tablets, m/r, both scored, lithium carbonate 200 mg (Li+ 5.4 mmol), net price 20 = 48p; 400 mg (Li+ 10.8 mmol), 20 = 70p. Label: 10, lithium card, 25, counselling, see above

**Dose** (see Dose above for advice on bioavailability and serum monitoring)

**Note** Priadel 400 also available as Lithonate (TEVA UK)

**Liquid**, see under Lithium Citrate below

**LITHIUM CITRATE**

**Indications** see under Lithium Carbonate and notes above

**Cautions** see under Lithium Carbonate and notes above

**Counselling** Patients should maintain an adequate fluid intake and should avoid dietary changes which might reduce or increase sodium intake; lithium treatment cards are available from pharmacies (see above)

**Side-effects** see under Lithium Carbonate and notes above

**Dose**

- See under preparations below, adjusted to achieve serum-lithium concentration of 0.4–1 mmol/litre as described under Lithium Carbonate

**Note** Preparations vary widely in bioavailability, changing the preparation requires the same precautions as initiation of treatment

**Note** Lithium carbonate 200 mg = lithium citrate 509 mg
Antidepressants are effective for treating moderate to severe depression associated with psychomotor and physiological changes such as loss of appetite and sleep disturbance; improvement in sleep is usually the first benefit of therapy. They are also effective for dysthymia (lower grade chronic depression). Antidepressant drugs are not generally effective in mild depression, and cognitive behavioural therapy should be considered initially; however, a trial of antidepressant therapy may be considered in cases refractory to psychological treatments or those associated with psychosocial or medical problems. Drug treatment of mild depression may also be considered in patients with a history of moderate or severe depression.

**Choice** The major classes of antidepressants include the tricyclics and related antidepressants, the selective serotonin re-uptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs). A number of antidepressants cannot be accommodated easily into this classification; these are included in section 4.3.4.

There is little to choose between the different classes of antidepressants in terms of efficacy, so choice should be based on the individual patient’s requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy. Since there may be an interval of 2 weeks before the antidepressant action takes place, electroconvulsive treatment may be required in severe depression when delay is hazardous or intolerable.

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants and should be considered first-line for treating depression. In patients with unstable angina or who have had a recent myocardial infarction, sertraline has been shown to be safe.

Tricyclic antidepressants have similar efficacy to SSRIs but are more likely to be discontinued because of side-effects; toxicity in overdose is also a problem. See section 4.3.1 for more details.

MAOIs have dangerous interactions with some foods and drugs, and should be reserved for use by specialists. Although anxiety is often present in depressive illness (and may be the presenting symptom), the use of an antipsychotic or an anxiolytic may mask the true diagnosis. Anxiolytics (section 4.1.2) or antipsychotics (section 4.2.1) should therefore be used with caution in depression but they are useful adjuncts in agitated patients.

See also section 4.2.3 for references to the management of bipolar disorders.

**St John’s wort** (*Hypericum perforatum*) is a popular unlicensed herbal remedy for treating mild depression. However, preparations of St John’s wort can induce drug metabolising enzymes and a number of important interactions with conventional drugs have been identified, see Appendix 1 (St John’s wort). The amount of active ingredient can vary between different preparations of St John’s wort and switching from one to another can change the degree of enzyme induction. Furthermore, when a patient stops taking St John’s wort, concentrations of interacting drugs may increase, leading to toxicity. Antidepressants should not be used with St John’s wort because of the potential for interaction.

**Hyponatraemia and antidepressant therapy**

Hyponatraemia (usually in the elderly and possibly due to inappropriate secretion of antidiuretic hormone) has been associated with all types of antidepressants; however, it has been reported more frequently with SSRIs than with other antidepressants. The CSM has advised that hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.

**Suicidal behaviour and antidepressant therapy**

The use of antidepressants has been linked with suicidal thoughts and behaviour; children, young adults, and patients with a history of suicidal behaviour are particularly at risk. Where necessary patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

**Management** Patients should be reviewed every 1–2 weeks at the start of antidepressant treatment. Treatment should be continued for at least 4 weeks (6 weeks in the elderly) before considering whether to switch antidepressant due to lack of efficacy. In cases of partial response, continue for a further 2 weeks (elderly patients may take longer to respond).

Following remission, antidepressant treatment should be continued at the same dose for at least 6 months (about 12 months in the elderly). Patients with a history of recurrent depression should continue to receive maintenance treatment for at least 2 years.
Failure to respond Failure to respond to initial treatment with an SSRI may require an increase in the dose, or switching to a different SSRI or mirtazapine; in patients with atypical depression, an MAOI such as phenelzine may be effective. Other second-line choices include mianserin, moclobemide, and reboxetine. Other tricyclic antidepressants and venlafaxine should be considered for more severe forms of depression; dosulepin (dothiepin) and irreversible MAOIs should only be prescribed by specialists. Failure to respond to a second antidepressant may require the addition of another antidepressant of a different class, or an augmenting agent such as lithium, but such adjunctive treatment should be initiated only by doctors with special experience of these combinations. Electroconvulsive therapy may be initiated in severe refractory depression.

Withdrawal Gastro-intestinal symptoms of nausea, vomiting, and anorexia, accompanied by headache, dizziness, ‘chills’, and insomnia, and sometimes by hypomania, panic-anxiety, and extreme motor restlessness may occur if an antidepressant (particularly an MAOI) is stopped suddenly after regular administration for 8 weeks or more. The dose should preferably be reduced gradually over about 4 weeks, or longer if withdrawal symptoms emerge (6 months in patients who have been on long-term maintenance treatment). SSRIs have been associated with a specific withdrawal syndrome (section 4.3.3).

Anxiety disorders and obsessive-compulsive disorder Management of acute anxiety generally involves the use of a benzodiazepine or buspirone (section 4.1.2). For chronic anxiety (of longer than 4 weeks’ duration) it may be appropriate to use an antidepressant. Combined therapy with a benzodiazepine may be required until the antidepressant takes effect. Generalised anxiety disorder, a form of chronic anxiety, is treated with an SSRI such as escitalopram or paroxetine; pregabalin and venlafaxine are also licensed for the treatment of generalised anxiety disorder. Panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and phobic states such as social anxiety disorder are treated with SSRIs. Clomipramine or imipramine can be used second-line in panic disorder (unlicensed); clomipramine can also be used second-line for obsessive-compulsive disorder. Moclobemide is licensed for the treatment of social anxiety disorder.

Choice Tricyclic and related antidepressants block the re-uptake of both serotonin and noradrenaline, although to different extents. For example, clomipramine is more selective for serotonergic transmission, and imipramine is more selective for noradrenergic transmission. Tricyclic and related antidepressant drugs can be roughly divided into those with additional sedative properties and those that are less sedating. Agitated and anxious patients tend to respond best to the sedative compounds, whereas withdrawn and apathetic patients will often obtain most benefit from the less sedating ones. Those with sedative properties include amitriptyline, clomipramine, dosulepin (dothiepin), doxepin, mianserin, trazodone, and trimipramine. Those with less sedative properties include imipramine, lofepramine, and nortriptyline.

Tricyclic and related antidepressants also have varying degrees of antimuscarinic side-effects and cardio toxicity in overdosage, which may be important in individual patients. Lofepramine has a lower incidence of side-effects and is less dangerous in overdosage but is infrequently associated with hepatic toxicity. Imipramine is also well established, but has more marked antimuscarinic side-effects than other tricyclic and related antidepressants. Amitriptyline and dosulepin (dothiepin) are effective but they are particularly dangerous in overdosage (see Overdosage, below) and are not recommended for the treatment of depression; doxepin (dothiepin) should only be prescribed by specialists.

Children and adolescents Evidence of the efficacy of tricyclic antidepressants for depression in children has not been established; see also CSM advice, p. 212.

Side-effects Arrhythmias and heart block occasionally follow the use of tricyclic antidepressants, particularly amitriptyline, and may be a factor in the sudden death of patients with cardiac disease. They are also sometimes associated with convulsions (and should be prescribed with special caution in epilepsy as they lower the convulsive threshold). Hepatic and haematological reactions may occur and have been particularly associated with mianserin.

Other side-effects of tricyclic and related antidepressants include drowsiness, dry mouth, blurred vision (very rarely precipitation of angle-closure glaucoma), constipation, and urinary retention (all attributed to antimuscarinic activity), and sweating. The patient should be encouraged to persist with treatment as some tolerance to these side-effects seems to develop. They are reduced if low doses are given initially and then gradually increased, but this must be balanced against the need to obtain a full therapeutic effect as soon as possible. Gradual introduction of treatment is particularly important in the elderly, who, because of the hypoensive effects of these drugs, are prone to attacks of dizziness or even syncope. Another side-effect to which
the elderly are particularly susceptible is hyponatraemia
(see Hyponatraemia and Antidepressant Therapy on p. 206).

Neuroleptic malignant syndrome (section 4.2.1) may, very rarely, arise in the course of antidepressant treatment. Suicide risk has been linked with antidepressants (see p. 206).

Overdosage Limited quantities of tricyclic antidepressants should be prescribed at any one time because their cardiovascular effects are dangerous in overdose. In particular, overdose with dosulepin (dothiepin) and amitriptyline is associated with a relatively high rate of fatality. For advice on overdosage see Emergency Treatment of Poisoning, p. 31.

Withdrawal If possible tricyclic and related antidepressants should be withdrawn slowly (see also section 4.3).

Interactions A tricyclic or related antidepressant (or an SSRI or related antidepressant) should not be started until 2 weeks after stopping an MAOI (3 weeks if starting clomipramine or imipramine). Conversely, an MAOI should not be started until at least 7–14 days after a tricyclic or related antidepressant (3 weeks in the case of clomipramine or imipramine). For guidance relating to the reversible monoamine oxidase inhibitors, moclobemide, see p. 212. For other tricyclic antidepressant interactions, see Appendix 1 (antidepressants, tricyclic and antidepressants, tricyclic (related)).

Tricyclic antidepressants

**AMITRIPTYLINE HYDROCHLORIDE**

**Indications** depressive illness (but not recommended, see notes above); nocturnal enuresis in children (section 7.4.2); neuropathic pain [unlicensed] (section 4.7.3); migraine prophylaxis [unlicensed] (section 4.7.4.2)

**Cautions** cardiac disease (particularly with arrhythmias, see Contra-indications below), history of epilepsy, pregnancy (Appendix 4), breast-feeding (Appendix 5), elderly, hepatic impairment (avoid if severe; Appendix 2), thyroid disease, phaeochromocytoma, history of mania, psychoses (may aggravate psychotic symptoms), susceptibility to angle-closure glaucoma, history of urinary retention, concurrent electroconvulsive therapy; if possible avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension, see surgery section 15.1); acute porphyria (section 9.8.2); see section 7.4.2 for additional nocturnal enuresis warnings; interactions: Appendix 1 (antidepressants, tricyclic)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** recent myocardial infarction, arrhythmias (particularly heart block), not indicated in manic phase, severe liver disease

**Side-effects** dry mouth, sedation, blurred vision (disturbance of accommodation, increased intra-ocular pressure), constipation, nausea, difficulty with micturition; cardiovascular side-effects (such as ECG changes, arrhythmias, postural hypotension, tachycardia, syncope, particularly with high doses); sweating, tremor, rashes and hypersensitivity reactions (including urticaria, photosensitivity), behavioural disturbances (particularly children), hypomania or mania, confusion or delirium (particularly elderly), headache, interference with sexual function, blood sugar changes; increased appetite and weight gain (occasionally weight loss); endocrine side-effects such as testicular enlargement, gynaecomastia, galactorrhoea; also convulsions (see also Cautions), movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, agranulocytosis, leucopenia, eosinophilia, purpura, thrombocytopenia, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 206), abnormal liver function tests (jaundice); for a general outline of side-effects see also notes above; **overdosage:** see Emergency Treatment of Poisoning, p. 31 (high rate of fatality—see notes above)

**Dose**

- Depression (but not recommended, see notes above), initially 75 mg (elderly and adolescents 30–75 mg) daily in divided doses or as a single dose at bedtime increased gradually as necessary to 150–200 mg.
- **CHILD** under 16 years not recommended for depression
- Nocturnal enuresis, **CHILD** 7–10 years 10–20 mg, 11–16 years 25–50 mg at night; max. period of treatment (including gradual withdrawal) 3 months—full physical examination before further course
- Neuropathic pain [unlicensed indication], initially 10–25 mg daily at night, increased if necessary to 75 mg daily; higher doses under specialist supervision
- Migraine prophylaxis [unlicensed indication], initially 10 mg at night, increased if necessary to maintenance of 50–75 mg at night

**Amitriptyline** (Non-proprietary) (PM)

**Tablets**, coated, amitriptyline hydrochloride 10 mg, net price 28 = 97p; 25 mg, 28 = 97p; 50 mg, 28 = £1.12. Label: 2

**Oral solution**, amitriptyline hydrochloride 25 mg/5 mL, net price 150 mL = £13.30; 50 mg/5 mL, 150 mL = £14.48. Label: 2

**Compound preparations**

**Triptafen®** (Goldshield) (PM)

**Tablets**, pink, s/c, amitriptyline hydrochloride 25 mg, perphenazine 2 mg. Net price 20 = £5.10. Label: 2

**Dose** depression with anxiety, **ADULT** and **CHILD** over 14 years, 1 tablet 3 times daily, increased if necessary to 4 tablets daily (with last dose at bedtime); review treatment if no response within 4 weeks; discontinue after 3 months

**Triptafen-M®** (Goldshield) (PM)

**Tablets**, pink, s/c, amitriptyline hydrochloride 10 mg, perphenazine 2 mg. Net price 20 = £4.56. Label: 2

**Dose** mild to moderate depression with anxiety, **ADULT** and **CHILD** over 14 years, 1 tablet 3 times daily, increased if necessary to 4 tablets daily (with last dose at bedtime); review treatment if no response within 4 weeks; discontinue after 3 months

**CLOMIPRAMINE HYDROCHLORIDE**

**Indications** depressive illness, phobic and obsessional states; adjunctive treatment of cataplexy associated with narcolepsy

**Cautions** see under Amitriptyline Hydrochloride
Adjunctive treatment of cataplexy associated with
Prothiaden (Non-proprietary)
Initially 75 mg (Dose)
Side-effects see under Amitriptyline Hydrochloride
Contra-indications see under Amitriptyline Hydrochloride
see under Amitriptyline Hydrochloride

Clomipramine (Non-proprietary) (Novartis)
Capsules, clomipramine hydrochloride 10 mg, net price 28-cap pack = £2.27; 25 mg, 28-cap pack = £2.65; 50 mg, 28-cap pack = £3.38. Label: 2

Anafranil® (Novartis) (Flm)
Capsules, clomipramine hydrochloride 10 mg (yellow/caramel), net price 84-cap pack = £3.23; 25 mg (orange/caramel), 84-cap pack = £6.35; 50 mg (grey/caramel), 56-cap pack = £8.06. Label: 2

Modified release
Anafranil SR® (Novartis) (Flm)
Tablets, m/r, grey-red, l/c, clomipramine hydrochloride 75 mg. Net price 28-tab pack = £8.83. Label: 2, 25
Dose see above, to be taken once daily

DOSULEPIN HYDROCHLORIDE (Dothiepin hydrochloride)
Indications depressive illness, particularly where sedation is required
Cautions see under Amitriptyline Hydrochloride
Contra-indications see under Amitriptyline Hydrochloride
Side-effects see under Amitriptyline Hydrochloride (high rate of fatality—see notes above)
Dose

DOXEPIN
Indications depressive illness, particularly where sedation is required; pruritus in eczema (section 13.3)
Cautions see under Amitriptyline Hydrochloride
Contra-indications see under Amitriptyline Hydrochloride
Side-effects see under Amitriptyline Hydrochloride

Dose

IMIPRAMINE HYDROCHLORIDE
Indications depressive illness; nocturnal enuresis in children (section 7.4.2)
Cautions see under Amitriptyline Hydrochloride
Contra-indications see under Amitriptyline Hydrochloride
Side-effects see under Amitriptyline Hydrochloride, but less sedating

Dose

LOFEPRAMINE
Indications depressive illness
Cautions see under Amitriptyline Hydrochloride
Contra-indications see under Amitriptyline Hydrochloride; hepatic and severe renal impairment
Side-effects see under Amitriptyline Hydrochloride, but less sedating, lower incidence of antimuscarinic effects and less dangerous in overdosage; hepatic disorders reported
Dose

Lofepramine (Non-proprietary) (Flm)
Tablets, lofepramine 70 mg (as hydrochloride). Net price 56-tab pack = £20.35. Label: 2
Brands include Fropax

Oral suspension, lofepramine 70 mg/5 mL (as hydrochloride). Net price 150 mL = £22.22. Label: 2
Brands include Lomont (sugar-free)
4 Central nervous system

**4.3.1 Tricyclic and related antidepressant drugs**

---

### Nortriptyline

**Indications**
- Depressive illness; nocturnal enuresis in children (section 7.4.2); neuropathic pain (section 4.7.3)

**Cautions**
- See under Amitriptyline Hydrochloride; manufacturer advises plasma-nortriptyline concentration monitoring if dose above 100 mg daily; but evidence of practical value uncertain

**Contra-indications**
- See under Amitriptyline Hydrochloride

**Side-effects**
- See under Amitriptyline Hydrochloride, but less sedating

**Dose**
- Depression, low dose initially increased as necessary to 75–100 mg daily in divided doses or as a single dose (max. 150 mg daily); ADOLESCENT and ELDERLY 30–50 mg daily in divided doses; CHILD not recommended for depression
- Nocturnal enuresis, child 7 years 10 mg, 8–11 years 10–20 mg, over 11 years 25–35 mg at night; max period of treatment (including gradual withdrawal) 3 months—full physical examination and ECG before further course
- Neuropathic pain [unlicensed], initially 10–25 mg daily at night, increased if necessary to 75 mg daily; higher doses under specialist supervision

**Allergon** (King) Tablets, nortriptyline (as hydrochloride) 10 mg, net price 20 = £2.48; 25 mg (orange, scored), 20 = £4.80. Label: 2

---

### Trimipramine

**Indications**
- Depressive illness, particularly where sedation is required

**Cautions**
- See under Amitriptyline Hydrochloride

**Contra-indications**
- See under Amitriptyline Hydrochloride

**Side-effects**
- See under Amitriptyline Hydrochloride

**Dose**
- Initially 50–75 mg daily in divided doses or as a single dose at bedtime, increased as necessary to 150–300 mg daily; ELDERLY initially 10–25 mg 3 times daily, maintenance half adult dose may be sufficient; CHILD not recommended

**Surmontil** (Aventis Pharma) Tablets, green/white, trimipramine 50 mg (as maleate). Net price 28-caps pack = £7.91. Label: 2

---

### Related antidepressants

Tricyclic-related antidepressant drugs have a lower incidence of antimuscarinic side-effects than older tricyclics. The tricyclic-related antidepressant drugs may also be associated with a lower risk of cardiotoxicity in overdosage.

---

### Mianserin Hydrochloride

**Indications**
- Depressive illness, particularly where sedation is required

**Cautions**
- See under Amitriptyline Hydrochloride; interactions: Appendix 1 (antidepressants, tricyclic (related))

**Blood counts**
- A full blood count is recommended every 4 weeks during the first 3 months of treatment; clinical monitoring should continue subsequently and treatment should be stopped and a full blood count obtained if fever, sore throat, stomatitis, or other signs of infection develop.

**Contra-indications**
- See under Amitriptyline Hydrochloride

**Side-effects**
- See under Amitriptyline Hydrochloride, fewer and milder antimuscarinic and cardiovascular effects; leucopenia, agranulocytosis and aplastic anaemia (particularly in the elderly); jaundice; arthritides, arthralgia

**Dose**
- Initially 30–40 mg (elderly 30 mg) daily in divided doses or as a single dose at bedtime, increased gradually as necessary; usual dose range 50–90 mg; CHILD not recommended

**Mianserin** (Non-proprietary) Tablets, mianserin hydrochloride 10 mg, net price 28-caps pack = £7.10; 20 mg, 28-caps pack = £4.12; 30 mg, 28-caps pack = £11.23. Label: 2, 25

---

### Trazodone Hydrochloride

**Indications**
- Depressive illness, particularly where sedation is required; anxiety

**Cautions**
- See under Amitriptyline Hydrochloride; interactions: Appendix 1 (antidepressants, tricyclic (related))

**Contra-indications**
- See under Amitriptyline Hydrochloride

**Side-effects**
- See under Amitriptyline Hydrochloride but fewer antimuscarinic and cardiovascular effects; rarely priapism (discontinue immediately)

**Dose**
- Depression, initially 150 mg (elderly 100 mg) daily in divided doses after food or as a single dose at bedtime; may be increased to 300 mg daily; hospital patients up to max. 600 mg daily in divided doses; CHILD not recommended
- Anxiety, 75 mg daily, increasing if necessary to 300 mg daily; CHILD not recommended

**Trazodone** (Non-proprietary) Tablets, trazodone hydrochloride 50 mg, net price 84-caps pack = £8.07; 100 mg, 56-caps pack = £8.00. Label: 2, 21

---

### Molinepaxin

**Indications**
- Anxiety, 75 mg daily, increasing if necessary to 300 mg daily; CHILD not recommended

**Contra-indications**
- See under Amitriptyline Hydrochloride, interactions: Appendix 1 (antidepressants, tricyclic (related))

**Blood counts**
- A full blood count is recommended every 4 weeks during the first 3 months of treatment; clinical monitoring should continue subsequently and treatment should be stopped and a full blood count obtained if fever, sore throat, stomatitis, or other signs of infection develop.

**Contra-indications**
- See under Amitriptyline Hydrochloride

**Side-effects**
- See under Amitriptyline Hydrochloride, fewer and milder antimuscarinic and cardiovascular effects; leucopenia, agranulocytosis and aplastic anaemia (particularly in the elderly); jaundice; arthritides, arthralgia

**Dose**
- Initially 30–40 mg (elderly 30 mg) daily in divided doses or as a single dose at bedtime, increased gradually as necessary; usual dose range 50–90 mg; CHILD not recommended

**Mianserin** (Non-proprietary) Tablets, mianserin hydrochloride 10 mg, net price 28-caps pack = £7.10; 20 mg, 28-caps pack = £4.12; 30 mg, 28-caps pack = £11.23. Label: 2, 25

---

### Related antidepressants

Tricyclic-related antidepressant drugs have a lower incidence of antimuscarinic side-effects than older tricyclics. The tricyclic-related antidepressant drugs may also be associated with a lower risk of cardiotoxicity in overdosage.

---

### Mianserin Hydrochloride

**Indications**
- Depressive illness, particularly where sedation is required
Monoamine-oxidase inhibitors (MAOIs)

Monoamine-oxidase inhibitors are used much less frequently than tricyclic and related antidepressants, or SSRIs and related antidepressants because of the dangers of dietary and drug interactions and the fact that it is easier to prescribe MAOIs when tricyclic antidepressants have been unsuccessful than vice versa. Tranylcypromine is the most hazardous of the MAOIs because of its stimulant action. The drugs of choice are phенел зине or isocarboxazid which are less stimulant and therefore safer.

Phobic patients and depressed patients with atypical, hypochondriacal, or hysterical features are said to respond best to MAOIs. However, MAOIs should be tried in any patients who are refractory to treatment with other antidepressants as there is occasionally a dramatic response. Response to treatment may be delayed for 3 weeks or more and may take an additional 1 or 2 weeks to become maximal.

Withdrawal If possible MAOIs should be withdrawn slowly (see also section 4.3).

Interactions MAOIs inhibit monoamine oxidase, thereby causing an accumulation of amine neurotransmitters. The metabolism of some amine drugs such as indirect-acting sympathomimetics (present in many cough and decongestant preparations, section 3.10) is also inhibited and their pressor action may be potentiated; the pressor effect of tyramine (in some foods, such as mature cheese, pickled herring, broad bean pods, and Bovril®, Oxet®, Marmite® or any similar meat or yeast extract or fermented soya bean extract) may also be dangerously potentiated. These interactions may cause a dangerous rise in blood pressure. An early warning symptom may be a throbbing headache. Patients should be advised to eat only fresh foods and avoid food that is suspected of being stale or ‘going off’. This is especially important with meat, fish, poultry or offal; game should be avoided. The danger of interaction persists for up to 2 weeks after treatment with MAOIs is discontinued. Patients should also avoid alcoholic drinks or de-alcoholised (low alcohol) drinks.

Other antidepressants should not be started for 2 weeks after treatment with MAOIs has been stopped (3 weeks if starting clomipramine or imipramine). Some psychiatrists use selected tricyclics in conjunction with MAOIs but this is hazardous, indeed potentially lethal, except in experienced hands and there is no evidence that the combination is more effective than when either constituent is used alone. The combination of tranylcypromine with clomipramine is particularly dangerous.

Conversely, an MAOI should not be started until at least 7–14 days after a tricyclic or related antidepressant (3 weeks in the case of clomipramine or imipramine) has been stopped.

In addition, an MAOI should not be started for at least 2 weeks after a previous MAOI has been stopped (then started at a reduced dose).

For other interactions with MAOIs including those with opioid analgesics (notably pethidine), see Appendix 1 (MAOIs). For guidance on interactions relating to the reversible monoamine oxidase inhibitor, moclobemide, see p. 212; for guidance on interactions relating to SSRIs, see p. 213.

4.3.2 Monoamine-oxidase inhibitors

Indications depressive illness

Cautions diabetes mellitus, cardiovascular disease, epilepsy, blood disorders, concurrent electroconvulsive therapy; elderly (great caution); monitor blood pressure (risk of postural hypotension and hypertensive responses—discontinue if palpitations or frequent headaches); if possible avoid abrupt withdrawal; severe hypertensive reactions to certain drugs and foods; avoid in agitated patients; acute porphyria (section 9.8.2); pregnancy (Appendix 4) and breastfeeding; surgery (section 15.1); interactions: Appendix 1 (MAOIs)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications hepatic impairment or abnormal liver function tests (Appendix 2); cerebrovascular disease, phaeochromocytoma; not indicated in manic phase

Side-effects commonly postural hypotension (especially in elderly) and dizziness; less common side-effects include drowsiness, insomnia, headache, weakness and fatigue, dry mouth, constipation and other gastro-intestinal disturbances, oedema, myoclonic movement, hyperreflexia, elevated liver enzymes; agitation and tremors, nervousness, euphoria, arrhythmias, blurred vision, ny statmus, difficulty in micturition, sweating, convulsions, rashes, purpura, leucopenia, sexual disturbances, and weight gain with inappropriate appetite may also occur; psychotic episodes with hypomanic behaviour, confusion, and hallucinations may be induced in susceptible persons; suicidal behaviour (see p. 206); jaundice has been reported and, on rare occasions, fatal progressive hepatic necrosis; paraesthesia, peripheral neuritis, peripheral neuropathy may be due to pyridoxine deficiency; hyponatraemia (see Hypo- nataemia and Antidepressant Therapy, p. 206)

Dose

• 15 mg 3 times daily, increased if necessary to 4 times daily after 2 weeks (hospital patients, max. 30 mg 3 times daily), then reduced gradually to lowest possible maintenance dose (15 mg on alternate days may be adequate); CHILD not recommended

Nardil® (Concord) tablets, oral, f/c, phenelzine (as sulphate) 15 mg, net price 20 = £3.99. Label: 3, 10, patient information leaflet

Phenelzine

Indications depressive illness

Cautions see under Phenelzine

Contra-indications see under Phenelzine

Side-effects see under Phenelzine

Dose

• Initially 30 mg daily in single or divided doses until improvement occurs (increased after 4 weeks if necessary to max. 60 mg daily for 4–6 weeks under close supervision), then reduced to usual maintenance dose 10–20 mg daily (but up to 40 mg daily may
4.3.3 Selective serotonin re-uptake inhibitors

Moclobemide

Moclobemide is indicated for major depression and social anxiety disorder; it is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant. It is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant. It is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant.

Interactions Moclobemide is claimed to cause less inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant more frequent than with other MAOIs; liver damage less frequent than with phenelzine.

Dose

- Initially 10 mg twice daily not later than 3 p.m., increasing the second daily dose to 20 mg after 1 week if necessary; doses above 30 mg daily under close supervision only; usual maintenance dose 10 mg daily.
- CHILD not recommended

Tranylcypromine

Tranylcypromine is indicated for major depression and related antidepressants. For a general comment on the management of depression and on the comparison between tricyclic and related antidepressants and the SSRIs and related antidepressants, see section 4.3.4

Reversible MAOIs

Moclobemide

Moclobemide is indicated for major depression and social anxiety disorder; it is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant.

Interactions Moclobemide is claimed to cause less inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant more frequent than with other MAOIs; liver damage less frequent than with phenelzine.

Dose

- Initially 10 mg twice daily not later than 3 p.m., increasing the second daily dose to 20 mg after 1 week if necessary; doses above 30 mg daily under close supervision only; usual maintenance dose 10 mg daily.
- CHILD not recommended

Tranylcypromine

Tranylcypromine is indicated for major depression and related antidepressants. For a general comment on the management of depression and on the comparison between tricyclic and related antidepressants and the SSRIs and related antidepressants, see section 4.3.

Reversible MAOIs

Moclobemide is indicated for major depression and social anxiety disorder; it is reported to act by reversible inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant.

Interactions Moclobemide is claimed to cause less inhibition of monoamine oxidase type A (it is therefore termed a RIMA). It should be reserved as a second-line antidepressant more frequent than with other MAOIs; liver damage less frequent than with phenelzine.

Dose

- Initially 10 mg twice daily not later than 3 p.m., increasing the second daily dose to 20 mg after 1 week if necessary; doses above 30 mg daily under close supervision only; usual maintenance dose 10 mg daily.
- CHILD not recommended

Tranylcypromine

Tranylcypromine is indicated for major depression and related antidepressants. For a general comment on the management of depression and on the comparison between tricyclic and related antidepressants and the SSRIs and related antidepressants, see section 4.3.
Cautions SSRIs should be used with caution in patients with epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastro-intestinal bleeding), and if used with other drugs that increase the risk of bleeding, hepatic impairment (Appendix 2), renal impairment (Appendix 3), pregnancy (Appendix 4), and breast-feeding (Appendix 5). They should also be used with caution in those receiving concurrent electroconvulsive therapy (prolonged seizures reported with fluoxetine). SSRIs may also impair performance of skilled tasks (e.g. driving). Interactions: see below and Appendix 1 (antidepressants, SSRI).

Withdrawal Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal of an SSRI or marked reduction of the dose; the dose should be tapered over a few weeks to avoid these effects.

Interactions An SSRI or related antidepressant should not be started until 2 weeks after stopping an MAOI. Conversely, an MAOI should not be started until at least a week after an SSRI or related antidepressant has been stopped (2 weeks in the case of sertraline, at least 5 weeks in the case of fluoxetine). For guidance relating to the reversible monoamine oxidase inhibitor, moclobemide, see above. For other SSRI antidepressant interactions, see Appendix 1 (antidepressants, SSRI).

Contra-indications SSRIs should not be used if the patient enters a manic phase.

Side-effects SSRIs are less sedating and have fewer antimuscarinic and cardiotoxic effects than tricyclic antidepressants (section 4.3). Side-effects of the SSRIs include gastro-intestinal effects (dose-related and fairly common)—include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation); anorexia with weight loss (increased appetite and weight gain also reported) and hypersensitivity reactions including rash (consider discontinuation—may be sign of impending serious systemic reaction, possibly associated with vasculitis), urticaria, angioedema, anaphylaxis, arthralgia, myalgia and photosensitivity; other side-effects include dry mouth, nervousness, anxiety, headache, insomnia, tremor, dizziness, asthenia, hallucinations, drowsiness, convulsions (see Cautions above), galactorrhoea, sexual dysfunction, urinary retention, sweating, hypomana or mania (see Cautions above), movement disorders and dyskinesias, visual disturbances, hypotension (see Hypotension and Antidepressant Therapy, p. 206), and bleeding disorders including ecchymoses and purpura. Suicidal behaviour has been linked with antidepressants (see p. 206). Angle-closure glaucoma may very rarely be precipitated by treatment with SSRIs.

Dose
- Depressive illness, 20 mg once daily increased if necessary in steps of 20 mg daily at intervals of 3–4 weeks; max. 60 mg daily (ELDERLY over 65 years, max. 40 mg daily); CHILD under 18 years, see BNF for Children and CSM advice, p. 212
- Panic disorder, ADULT over 18 years, initially 10 mg daily increased gradually if necessary in steps of 10 mg daily, usual dose 20–30 mg daily; max. 60 mg daily (ELDERLY over 65 years, max. 40 mg daily)

Note 8 mg (4 drops) Cipramil oral drops is equivalent in therapeutic effect to 10-mg citalopram tablet

Citalopram (Non-proprietary) Tablets, citalopram (as hydrobromide) 10 mg, net price 28-tab pack = £1.08; 20 mg, 28-tab pack = £1.25; 40 mg, 28-tab pack = £1.46. Counselling, driving

Cipramil® (Lundbeck) Tablets, f/c, citalopram (as hydrobromide) 10 mg, net price 28-tab pack = £8.97; 20 mg (scored), 28-tab pack = £14.91; 40 mg, 28-tab pack = £25.20. Counselling, driving

Oral drops, sugar-free, citalopram (as hydrochloride) 40 mg/mL, net price 15 mL = £20.16. Counselling, driving, administration

Dose depressive illness, 16 mg daily as a single dose increased if necessary in steps of 16 mg daily at intervals of 3–4 weeks; max. 48 mg daily (ELDERLY over 65 years, max. 32 mg daily); CHILD under 18 years, see BNF for Children and CSM advice, p. 212

Panic disorder, initially 8 mg daily as a single dose increased gradually if necessary in steps of 8 mg, usual dose 16–24 mg daily, max. 48 mg daily, (ELDERLY over 65 years, max. 32 mg daily); CHILD under 18 years not recommended.

Excipients include alcohol

Note 8 mg (4 drops) Cipramil oral drops can be considered equivalent in therapeutic effect to 10-mg citalopram tablet

Mix with water, orange juice, or apple juice before taking

ESCITALOPRAM

Note Escitalopram is the active enantiomer of citalopram

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; also sinusitis, yawning; fatigue, restlessness, abnormal dreams, paraesthesia; pyrexia; less commonly taste disturbance, bruxism, syncope, tachycardia, oedema, confusion, menstrual disturbances, epistaxis, mydriasis, tinnitus, pruritus, and alopecia; rarely bradycardia, aggression, and depersonalisation; hepatitis, postural hypotension, QT interval prolongation, and thrombocytopenia also reported; paradoxical increased anxiety during initial treatment of panic disorder (reduce dose)

Dose
- ADULT over 18 years, depressive illness, generalised anxiety disorder, and obsessive-compulsive disorder, 10 mg once daily increased if necessary to max. 20 mg daily; ELDERLY initially half adult dose, lower maintenance dose may be sufficient; CHILD not recommended (see CSM advice, p. 212)
- ADULT over 18 years, panic disorder, initially 5 mg once daily increased to 10 mg daily after 7 days; max. 20 mg daily; ELDERLY initially half adult dose, lower maintenance dose may be sufficient
Central nervous system

• ADULT over 18 years, social anxiety disorder, initially 10 mg once daily adjusted after 2–4 weeks; usual dose 5–20 mg daily

Cipralex® (Lundbeck) 

Tablets, f/c, escitalopram (as oxalate) 5 mg, net price 28-tab pack = £8.97; 10 mg (scored), 28-tab pack = £14.91; 20 mg (scored), 28-tab pack = £25.20. Counselling, driving

Oral drops, sugar-free, escitalopram (as oxalate) 10 mg/mL, net price 28 mL = £18.82. Counselling, driving, administration

Note: Can be mixed with water, orange juice, or apple juice before taking

The Scottish Medicines Consortium (p. 3) has advised that escitalopram (Cipralex®) is not recommended within NHS Scotland for the treatment of social anxiety disorder (April 2008)

FLUOXETINE

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; also vasodilatation, postural hypotension, pharyngitis, dyspnoea, chills, taste disturbances, sleep disturbances, euphoria, confusion, yawning, impaired concentration, changes in blood sugar, alopecia, urinary frequency; rarely pulmonary inflammation and fibrosis; very rarely hepatitis, toxic epidermal necrolysis, and neuroleptic malignant syndrome-like event

Dose

• Major depression, 20 mg once daily increased after 3–4 weeks if necessary, and at appropriate intervals thereafter; max. 60 mg once daily (ELDERLY usual max. 40 mg once daily but 60 mg can be used); CHILD 8–18 years, 10 mg once daily increased after 1–2 weeks if necessary, max. 20 mg once daily (but see also CSM advice, p. 212)

• Bulimia nervosa, ADULT over 18 years, 60 mg once daily

• Obsessive-compulsive disorder, ADULT over 18 years, 20 mg once daily; if inadequate response after 2 weeks increase gradually to max. 60 mg once daily (ELDERLY usual max. 40 mg once daily but 60 mg can be used)

Long duration of action Consider the long half-life of fluoxetine when adjusting dosage (or in overdosage)

Fluoxetine (Non-proprietary) 

Capsules, fluoxetine (as hydrochloride) 20 mg, net price 30-cap pack = £1.02; 60 mg, 30-cap pack = £5.76. Counselling, driving

Brands include: Oxitin

Liquid, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £7.41. Counselling, driving

Brands include: Prasep

Prozac® (Lilly) 

Capsules, fluoxetine (as hydrochloride) 20 mg (green/yellow), net price 30-cap pack = £14.21. Counselling, driving

Liquid, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £13.26. Counselling, driving

FLUOXETINE MALEATE

Indications depressive illness, obsessive-compulsive disorder

Cautions see notes above

CSM advice The CSM has advised that concomitant use of fluvoxamine and theophylline or aminophylline should usually be avoided; see also interactions: Appendix 1 (antidepressants, SSRIs)

Contra-indications see notes above

Side-effects see notes above; palpititation, tachycardia (may also cause bradycardia); rarely postural hypotension, confusion, ataxia, paraesthesia, malaise, taste disturbances, neuroleptic malignant syndrome-like event, abnormal liver function tests, usually symptomatic (discontinue treatment)

Dose

• Depression, ADULT over 18 years, initially 50–100 mg daily in the evening, increased gradually if necessary to max. 300 mg daily (over 150 mg in divided doses); usual maintenance dose 100 mg daily

• Obsessive-compulsive disorder, initially 50 mg in the evening increased gradually if necessary after some weeks to max. 300 mg daily (over 150 mg in divided doses); usual maintenance dose 100–300 mg daily;

CHILD over 8 years initially 25 mg daily increased if necessary in steps of 25 mg every 4–7 days to max. 200 mg daily (over 50 mg in 2 divided doses)

Note: If no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered

Fluvoxamine (Non-proprietary) 

Tablets, fluvoxamine maleate 50 mg, net price 60-tab pack = £6.80; 100 mg, 30-tab pack = £8.34. Counselling, driving

Faverin® (Solvay) 

Tablets, f/c, scored, fluvoxamine maleate 50 mg, net price 60-tab pack = £17.10; 100 mg, 30-tab pack = £17.10. Counselling, driving

PAROXETINE

Indications major depression, obsessive-compulsive disorder, panic disorder; social anxiety disorder; post-traumatic stress disorder; generalised anxiety disorder

Cautions see notes above; also achlorhydria or high gastric pH (reduced absorption of oral suspension)

CSM advice Extrapyramidal reactions (including orofacial dyskinesia) and withdrawal syndrome are reported to the CSM more commonly with paroxetine than with other SSRIs

Contra-indications see notes above

Side-effects see notes above; also yawning; raised cholesterol; less commonly arrhythmias, transient changes in blood pressure, confusion, urinary incontinence; rarely panic attacks and paradoxical increased anxiety during initial treatment of panic disorder (reduce dose), depersonalisation, and neuroleptic malignant syndrome-like event; very rarely peripheral oedema, acute glaucoma, hepatic disorders (e.g. hepatitis), and priapism

Dose

• Major depression, social anxiety disorder, post-traumatic stress disorder, generalised anxiety disorder, ADULT over 18 years, usually 20 mg each morning, higher doses on specialist advice only (see also CSM advice, below); max. 50 mg daily (ELDERLY 40 mg daily);

CHILD not recommended (see CSM advice, p. 212)

• Obsessive-compulsive disorder, ADULT over 18 years, initially 20 mg each morning, increased gradually in steps of 10 mg to usual dose of 40 mg daily, higher doses on specialist advice only (see also CSM advice, below); max. 60 mg daily (ELDERLY 40 mg daily)
● Panic disorder, **ADULT** over 18 years, initially 10 mg each morning, increased gradually in steps of 10 mg to usual dose of 40 mg daily; higher doses on specialist advice only (see also CSM advice; below); max. 60 mg daily (**ELDERLY** 40 mg daily)

**CSM advice** The recommended dose for the treatment of depression, social anxiety disorder, generalised anxiety disorder, and post-traumatic stress disorder is 20 mg daily and for obsessive-compulsive disorder and panic disorder it is 40 mg daily. There is no evidence that higher doses are more effective

**Paroxetine** (Non-proprietary) *(Pfizer)*

**Tablets**, paroxetine (as hydrochloride) 20 mg, net price 30-tab pack = £2.92; 30 mg, 30-tab pack = £6.46. Label: 21, counselling, driving

**Seroxat** *(GSK)* *(Pfizer)*

**Tablets**, f/c, scored, paroxetine (as hydrochloride) 10 mg, net price 28-pc pack = £12.32; 20 mg, 30-tab pack = £13.21; 30 mg (blue), 30-tab pack = £23.18. Label: 21, counselling, driving

**Oral suspension**, orange, sugar-free, paroxetine (as hydrochloride) 10 mg/5 mL. Net price 150-mL pack = £9.49. Label: 5, 21, counselling, driving

---

**SERTRALINE**

**Indications** depressive illness, obsessive-compulsive disorder (under specialist supervision in children), post-traumatic stress disorder in women

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; pancreatitis, hepatitis, jaundice, liver failure, tachycardia, postural hypotension, amnesia, paraesthesia, aggression, urinary incontinence, and menstrual irregularities also reported

**Dose**

- Depressive illness, initially 50 mg daily, increased if necessary by increments of 50 mg over several weeks to max. 200 mg daily; usual maintenance dose 50 mg daily; **CHILD** under 18 years, see **BNF for Children** and CSM advice, p. 212
- Obsessive-compulsive disorder, **ADULT** and **CHILD** over 12 years initially 50 mg daily, increased if necessary in steps of 50 mg over several weeks; usual dose range 50–200 mg daily; **CHILD** 6–12 years initially 25 mg daily, increased to 50 mg daily after 1 week, further increased if necessary in steps of 50 mg at intervals of at least 1 week (max. 200 mg daily)
- Post-traumatic stress disorder, **ADULT** over 18 years, initially 25 mg daily, increased after 1 week to 50 mg daily; if response is partial and if drug tolerated, dose increased in steps of 50 mg over several weeks to max. 200 mg daily

**Sertraline** (Non-proprietary) *(Pfizer)*

**Tablets**, sertraline (as hydrochloride) 50 mg, net price 28-tab pack = £1.37; 100 mg, 28-tab pack = £1.80. Counselling, driving

**Lustral** *(Pfizer)*

**Tablets**, f/c, sertraline (as hydrochloride) 50 mg (scored), net price 28-tab pack = £17.82; 100 mg, 28-tab pack = £29.16. Counselling, driving

---

**DULOXETINE**

**Indications** major depressive disorder; generalised anxiety disorder; diabetic neuropathy (section 6.1.5); stress urinary incontinence (section 7.4.2)

**Cautions** section 7.4.2; pregnancy (Appendix 4)

**Contra-indications** section 7.4.2

**Side-effects** section 7.4.2

**Note** In diabetic neuropathy, discontinue if inadequate response after 2 months; review treatment at least every 3 months

**Cymbalta** *(Lilly)* *(Pfizer)*

**Capsules**, duloxetine (as hydrochloride) 30 mg (white/blue), net price 28-cp pack = £22.40; 60 mg (green/blue), 28-cp pack = £27.72. Label: 2

**Note** The Scottish Medicines Consortium has advised (September 2006) that duloxetine (Cymbalta) should be restricted for use by specialists when other treatments for diabetic peripheral neuropathic pain are unsuitable or inadequate

**Yentreve** *(Lilly)* *(Pfizer)*

Section 7.4.2 (stress urinary incontinence)

---

**FLUPENTIXOL** *(Flupenthixol)* *(Lilly)*

**Indications** depressive illness; psychoses (section 4.2.1)
4 Central nervous system

**Mirtazapine** (Non-proprietary) (BNF 57)

- **Indications** - major depression
- **Cautions** - cardiovascular disease (including cardiac disorders and cerebral arteriosclerosis), senile confusional states, parkinsonism, hepatic impairment (Appendix 2); renal impairment (Appendix 3); avoid in excitable and overactive patients; acute porphyria (section 9.8.2); see also section 4.2.1; **interactions**: Appendix 1 (antipsychotics)
- **Side-effects** - restlessness, insomnia; hypomania reported; rarely dizziness, tremor, visual disturbances, headache, hyperprolactinaemia, extrapyramidal symptoms; suicidal behaviour (see p. 206)
- **Dose**
  - **ADULT** over 18 years, initially 1 mg (elderly 500 micrograms) in the morning, increased after 1 week to 2 mg (elderly 1 mg) if necessary; max. 3 mg (elderly 2 mg) daily, doses above 2 mg (elderly 1 mg) being divided in 2 portions, second dose not after 4 p.m. Discontinue if no response after 1 week at max. dosage
  - **CHILD** under 18 years not recommended (see Appendix 4; breast-feeding (Appendix 5); **interactions**: Appendix 1 (mirtazapine)
- **Contra-indications** - pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Fluanxol** (Lundbeck) (BNF 57)

- **Tablets**, yellow, s/c, flupentixol (as dihydrochloride) 500 micrograms, net price 60-tab pack = £2.88; 1 mg, 60-tab pack = £4.86. Label: 2, counselling, administration

**Zispin SolTab** (Organon) (BNF 57)

- **Orodispersible tablets**, mirtazapine 15 mg, net price 6-tab pack = £3.84, 30-tab pack = £19.19; 30 mg, 30-tab pack = £19.19; 45 mg, 30-tab pack = £19.19. Label: 2, counselling, administration

**REBOXETINE**

- **Indications** - major depression
- **Cautions** - history of cardiovascular disease and epilepsy; bipolar disorder; urinary retention; prostatic hypertrophy; susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; hepatic impairment (Appendix 2); renal impairment (Appendix 3); **interactions**: Appendix 1 (reboxetine)
- **Contra-indications** - pregnancy (Appendix 4); breast-feeding (Appendix 5)
- **Side-effects** - nausea, dry mouth, constipation, anorexia; tachycardia, palpitation, vasodilation, postural hypotension; headache, insomnia, dizziness; chills; impotence; urinary retention; impaired visual accommodation; sweating; lowering of plasma-potassium concentration on prolonged administration in the elderly; very rarely angle-closure glaucoma: also reported vomiting, hypertension, paraesthesia, agitation, anxiety, irritability, hallucinations, aggression, cold extremities, and rash; suicidal behaviour (see p. 206)
- **Dose**
  - 4 mg twice daily increased if necessary after 3–4 weeks to 10 mg daily in divided doses, max. 12 mg daily; **CHILD** under 18 years and **ELDERLY** not recommended

**Edronax** (Pharmacia) (BNF 57)

- **Tablets**, scored, reboxetine (as mesilate) 4 mg, net price 60-tab pack = £18.91. Counselling, driving

**TRYPТОPHAN** (L-Tryptophan)

- **Indications** - see notes above
- **Cautions** - eosinophilia-myalgia syndrome has been reported (withhold treatment if increased eosinophil count, myalgia, arthralgia, fever, dyspnoea, neuro-pathy, oedema or skin lesions develop until possibility of eosinophilia-myalgia syndrome excluded); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (tryptophan)
- **Contra-indications** - history of eosinophilia-myalgia syndrome following use of tryptophan
- **Side-effects** - drowsiness, nausea, headache, light-headedness, suicidal behaviour (see p. 206); eosinophilia-myalgia syndrome, see Cautions

**Dose**

- 1 g 3 times daily; max. 6 g daily; **ELDERLY** lower dose may be appropriate especially in renal or hepatic impairment; **CHILD** not recommended

**Optimax** (Merck) (BNF 57)

- **Tablets**, scored, tryptophan 500 mg. Net price 84-tab pack = £23.47. Label: 3

---

**Central nervous system**

**4** Other antidepressant drugs

**216**
**VENLAFAXINE**

**Indications** major depression, generalised anxiety disorder

**Cautions** heart disease (monitor blood pressure); history of epilepsy; susceptibility to angle-closure glaucoma; concomitant use of drugs that increase risk of bleeding, history of bleeding disorders; hepatic impairment (avoid if severe—Appendix 2); renal impairment (avoid if severe—Appendix 3); breastfeeding (Appendix 5); interactions: Appendix 1 (venlafaxine)

**Driving** May affect performance of skilled tasks (e.g. driving)

**Withdrawal** Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, tremor, sleep disturbances, and sweating are most common features of withdrawal if treatment stopped abruptly or if dose reduced markedly; dose should be reduced over several weeks

**Contra-indications** conditions associated with high risk of cardiac arrhythmia, uncontrolled hypertension; pregnancy (Appendix 4)

**Side-effects** constipation, nausea, anorexia, weight changes, diarrhoea, dyspepsia, vomiting, abdominal pain; hypertension, palpitation, vasodilatation, changes in serum cholesterol; chills, pyrexia, dysphonia, yawning; dizziness, dry mouth, insomnia, nervousness, drowsiness, asthenia, headache, abnor-mal dreams, agitation, anxiety, confusion, hypertonia, paraesthesia, tremor; urinary frequency, sexual dys-function, menstrual disturbances; arthralgia, myalgia; visual disturbances, mydriasis (very rarely angle-closure glaucoma); tinnitus; sweating, pruritus, rash; less commonly bruxism, taste disturbance, hypotension and postural hypotension, arrhythmias, syndrome of inappropriate anti-diuretic hormone secretion (see Hyponatraemia and Antidepressant Therapy, p. 206), apathy, hallucinations, myoclonus, urinary retention, bleeding disorders (including ecchymosis and rarely haemorrhage), alopecia, hypersensitivity reactions including angioedema, urticaria, photosensitivity; rarely hepatitis, ataxia, incoordination, speech disor-der, mania and hypomania, seizures, and neuroleptic malignant syndrome, Stevens-Johnson syndrome; very rarely pancreatitis, QT interval prolongation, aggression, delirium, extrapyramidal symptoms including akathisia, hyperprolactinaemia, blood dys-crasias, rhadomyolysis; suicidal behaviour (doses over 300 mg under specialist supervision; see also p. 206)

**Dose**

- Depression. **ADULT** over 18 years, initially 75 mg daily in 2 divided doses increased if necessary after at least 3–4 weeks to 150 mg daily in 2 divided doses; severely depressed or hospitalised patients, increased further if necessary in steps of up to 75 mg every 2–3 days; max. 375 mg daily; **CHILD** under 18 years not recommended (see CSM advice, p. 212)
- Generalised anxiety disorder and social anxiety dis-order, see under preparations below

**Efexor®** (Wyeth) Tablets, peach, venlafaxine (as hydrochloride) 37.5 mg, net price 28-tab pack = £11.71, 56-tab pack = £23.41; 75 mg, 28-tab pack = £19.52, 56-tab pack = £39.03. Label: 3, counselling, driving

**Modified release**

**Efexor® XL** (Wyeth) Capsules, m/r, venlafaxine (as hydrochloride) 75 mg (peach), net price 14-cap pack = £11.71, 28-cap pack = £23.41; 150 mg (orange) 14–cap pack = £19.52, 28-cap pack = £39.03. Label: 3, 25, counselling, driving

**Dose** depression, **ADULT** over 18 years, 75 mg once daily; increased if necessary after at least 2 weeks to 150 mg once daily; max. 225 mg once daily; **CHILD** under 18 years not recommended (see CSM advice, p. 212)

**Generalised anxiety disorder, ADULT** over 18 years, 75 mg once daily; discontinue if no response after 8 weeks

**Social anxiety disorder, ADULT** over 18 years, 75 mg once daily; discontinue if no response after 12 weeks

Central nervous system stimulants include the amphetamines (notably dexamfetamine) and related drugs (e.g. methylphenidate). They have very few indications in particular, should **not** be used to treat depression, obesity, senility, debility, or for relief of fatigue. Methylphenidate and atomoxetine are used for the management of attention deficit hyperactivity disorder (ADHD) in children and adolescents as part of a comprehensive treatment programme. Growth is not generally affected but it is advisable to monitor growth during treatment. Dexamfetamine (dexamphetamine) is an alternative in children who do not respond to other drugs. CNS stimulants should only be prescribed to children with severe and persistent symptoms and when the diagnosis of ADHD has been confirmed by a specialist; treatment may be continued by general prac-titioners, under a shared-care arrangement. Treatment often needs to be continued into adolescence, and may need to be continued into adulthood.

**NICE guidance**

Methylphenidate, atomoxetine, and dexamfetamine for attention deficit hyperactivity disorder (March 2006) Methylphenidate, atomoxetine, and dexamfetamine are options for the treatment of ADHD in children and adolescents as part of a comprehensive treatment programme. Choice of drug should take into consideration:

- co-morbid conditions (such as tic disorders, Tourette syndrome, and epilepsy);
- different adverse effects of the drugs;
- potential for drug misuse;
- preferences of the child and carers.

**Modafinil** is used for the treatment of daytime sleepi-ness associated with narcolepsy or obstructive sleep apnoea syndrome; dependence with long-term use cannot be excluded and it should therefore be used with caution. Dexamfetamine and methylphenidate [unlicensed indi-cation] are also used to treat narcolepsy.

**ATOMOXETINE**

**Indications** attention deficit hyperactivity disorder (initiated by a specialist physician experienced in managing the condition)
**Central nervous system**

**Cautions** cardiovascular disease including hypertension and tachycardia; monitor growth in children; QT interval prolongation (avoid concomitant administration of drugs that prolong QT interval); history of seizures; susceptibility to angle-closure glaucoma; hepatic impairment (see Hepatic Disorders below; Appendix 2); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (atomoxetine) Hepatic disorders Following rare reports of hepatic disorders, the CSM has advised that patients and carers should be advised of the risk and be told how to recognise symptoms; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine or jaundice.

Suicidal ideation Following reports of suicidal thoughts and behaviour, the CSM has advised that patients and their carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression.

**Side-effects** anorexia, dry mouth, nausea, vomiting, abdominal pain, constipation, dyspepsia, flatulence; palpitation, tachycardia, increased blood pressure, postural hypotension, hot flushes; sleep disturbance, dizziness, headache, fatigue, lethargy, depression, anxiety, irritability, tremor, rigors; urinary retention, prostatitis, sexual dysfunction, menstrual disturbances; mydriasis, conjunctivitis; dermatitis, pruritus, rash, sweating, weight changes; less commonly suicidal ideation (see Suicidal Ideation, above), cold extremities; very rarely hepatic disorders (see Hepatic Disorders, above), seizures, angle-closure glaucoma, and Raynaud’s phenomenon.

**Dose**

- **ADOLESCENT** body-weight over 70 kg, initially 40 mg daily for 7 days then increased according to response to usual maintenance dose 80 mg daily; max. 100 mg daily; **CHILD** over 6 years and **ADOLESCENT** body-weight up to 70 kg, initially 500 micrograms/kg daily for 7 days then increased according to response to usual maintenance dose 1.2 mg/kg daily (higher dose unlikely to be beneficial).

Note Total daily dose may be given either as a single dose in the morning or in 2 divided doses with last dose no later than early evening.

**Special cautions in children** Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdraw slowly to avoid inducing depression or renewed hyperactivity). In psychotic children may exacerbate behavioural disturbances and thought disorder.

**Driving** May affect performance of skilled tasks (e.g. driving); effects of alcohol unpredictable.

**Contra-indications** cardiovascular disease including moderate to severe hypertension, hyperexcitability or agitated states, hyperthyroidism, history of drug or alcohol abuse; pregnancy (Appendix 4); breast-feeding (Appendix 5).

**Side-effects** insomnia, restlessness, irritability and excitability, nightmares, nervousness, night terrors, euphoria, tremor, dizziness, headache; convulsions (see also Cautions); dependence and tolerance, sometimes psychosis; anorexia, gastro-intestinal symptoms, growth restriction in children (see also under Cautions); dry mouth, sweating, tachycardia (and anginal pain), palpitation, increased blood pressure; visual disturbances; cardiomyopathy reported with chronic use; central stimulants have provoked choreoathetoid movements, tics and Tourette syndrome in predisposed individuals (see also Cautions above); very rarely angle-closure glaucoma; overdosage: see Emergency Treatment of Poisoning, p. 33.

**Dose**

- Narcolepsy, 10 mg (ELDERLY, 5 mg) daily in divided doses increased by 10 mg (ELDERLY, 5 mg) daily at intervals of 1 week to a max. of 60 mg daily.
- Refractory attention deficit hyperactivity disorder, 10 mg (older children have received max. 40 mg daily); maintenance dose given in 2–3 divided doses.

**Dexedrine®** (UCB Pharma) Tablets, scored, dexamfetamine sulphate 5 mg. Net price 28-tab pack = £3.00. Counselling, driving.

---

**METHYLPHENIDATE HYDROCHLORIDE**

**Indications** attention deficit hyperactivity disorder (under specialist supervision); narcolepsy [unlicensed indication].

**Cautions** monitor growth (if prolonged treatment), blood pressure and full blood count; epilepsy (discontinue if increased seizure frequency); susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; pregnancy (Appendix 4); interactions: Appendix 1 (sympathomimetics).

**Contra-indications** anxiety or agitation; severe depression, suicidal ideation; tics or a family history of Tourette syndrome; drug or alcohol dependence; psychosis; hyperthyroidism; cardiovascular disease; breast-feeding (Appendix 5).

**Side-effects** abdominal pain, nausea, vomiting, dyspepsia, dry mouth, anorexia, reduced weight gain; tachycardia, palpitation, arrhythmias, changes in blood pressure; cough, nasopharyngitis; tics (very rarely Tourette Syndrome), insomnia, nervousness, asthenia, depression, irritability, aggression, headache, drowsiness, dizziness, movement disorders; fever; arthralgia; rash, pruritus, alopecia; less commonly diarrhoea, dyspnoea, abnormal dreams, confusion, suicidal ideation, urinary frequency, haematuria, muscle cramps, epistaxis; rarely angina, growth

---

**Dexamfetamine SULPHATE**

(Dexamphetamine sulphate)

**Indications** narcolepsy, refractory attention deficit hyperactivity disorder (under specialist supervision).

**Cautions** mild hypertension (contra-indicated if moderate or severe)—monitor blood pressure; history of epilepsy (discontinue if convulsions occur); tics and Tourette syndrome (use with caution)—discontinue if tics occur; monitor growth in children (see also below); susceptibility to angle-closure glaucoma; avoid abrupt withdrawal; data on safety and efficacy of long-term use not complete; acute porphyria (section 9.8.2); interactions: Appendix 1 (sympathomimetics).

**Special cautions in children** Monitor height and weight as growth restriction may occur during prolonged therapy.

---

**Central nervous system**

**218 4.4 CNS stimulants and drugs used for ADHD**

**BNF 57**
restriction, visual disturbances; very rarely hepatic dysfunction, myocardial infarction, cerebral arteritis, psychosis, neuroleptic malignant syndrome, tolerance and dependence, blood disorders including leucopenia and thrombocytopenia, angle-closure glaucoma, exfoliative dermatitis, erythema multiforme

**Dose**

- Attention deficit hyperactivity disorder, CHILD 4–6 years [unlicensed], 2.5 mg twice daily increased if necessary at weekly intervals by 2.5 mg daily to max. 14.4 mg/kg daily in divided doses; CHILD over 6 years, initially 5 mg 1–2 times daily, increased if necessary at weekly intervals by 5–10 mg daily to max. 60 mg daily in divided doses; discontinue if no response after 1 month, also suspend every 1–2 years to assess child's condition

**Evening dose** If effect wears off in evening (with rebound hyperactivity) a dose at bedtime may be appropriate (establish need with trial bedtime dose)

- Narcolepsy [unlicensed indication], 10–60 mg (usually 20–30 mg) daily in divided doses before meals

**Methylphenidate Hydrochloride** (Non-proprietary)

<table>
<thead>
<tr>
<th>Brand</th>
<th>Formulation</th>
<th>Dosage</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medikinet XL</td>
<td>Tablets, methylphenidate hydrochloride 10 mg, net price 30-tab pack = £9.98</td>
<td>10 mg</td>
<td>£9.98</td>
</tr>
<tr>
<td>Concerta</td>
<td>Tablets, scored, methylphenidate hydrochloride 10 mg, net price 30-tab pack = £3.57</td>
<td>10 mg</td>
<td>£3.57</td>
</tr>
</tbody>
</table>

**MODAFINIL**

**Indications** daytime sleepiness associated with narcolepsy, obstructive sleep apnoea syndrome, and chronic shift work

**Cautions** monitor blood pressure and heart rate in hypertensive patients (but see Contra-indications); history of psychosis, depression, mania, alcohol or drug abuse; discontinue treatment if psychiatric symptoms develop; possibility of dependence; discontinue treatment if rash develops; hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (modafinil)

**Contra-indications** moderate to severe uncontrolled hypertension, arrhythmia; history of left ventricular hypertrophy, cor pulmonale, or of clinically significant signs of CNS stimulant-induced mitral valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** dry mouth, appetite changes, gastrointestinal disturbances (including nausea, diarrhoea, constipation, and dyspepsia), abdominal pain; tachycardia, vasodilatation, chest pain, palpitation; head-ache (uncommonly migraine), anxiety, sleep disturb-ances, dizziness, drowsiness, depression, confusion, paraesthesia, asthenia; visual disturbances; less com-monly flatulence, reflux, vomiting, mouth ulcers, glossitis, dysphagia, taste disturbance, weight changes, hypertension, hypotension, bradycardia, arrhythmia, peripheral oedema, hypercholesterol-aeemia, rhi-nitis, dyspnoea, epistaxis, dyskinesia, amnesia, emotional lability, tremor, decreased libido, agitation, aggression, hyperglycaemia, thirst, urinary frequency, menstrual disturbances, eosinophilia, leucopenia, myasthenia, muscle cramps, hyperton-ia, myalgia, arthralgia, dry eye, sinusitis, acne, sweating, rash, and pruritus; also reported: psychosis, mania, delusions, hallucinations, suicidal ideation, Stevens-Johnson syndrome, and toxic epidermal necrolysis

**Dose**

- Narcolepsy and obstructive sleep apnoea syndrome, ADULT over 12 years, initially 200 mg daily, either in 2 divided doses morning and at noon or as a single dose in the morning, dose adjusted according to response to 200–400 mg daily in 2 divided doses or as a single dose; ELDERLY initiate at 100 mg daily; CHILD 5–12 years, see BNF for Children

**Cocaine**

Cocaine is a drug of addiction which causes central nervous stimulation. Its clinical use is mainly as a topical local anaesthetic (section 15.2). It has been included in
4.5 Drugs used in the treatment of obesity

4.5.1 Anti-obesity drugs acting on the gastro-intestinal tract

Obesity is associated with many health problems including cardiovascular disease, diabetes mellitus, gallstones and osteoarthritis. Factors that aggravate obesity may include depression, other psychosocial problems, and some drugs.

The main treatment of the obese individual is a suitable diet, carefully explained to the individual, with appropriate support and encouragement; the individual should also be advised to increase physical activity. Smoking cessation (while maintaining body weight) may be worthwhile before attempting supervised weight loss since cigarette smoking may be more harmful than obesity. Attendance at groups (e.g. 'weight-watchers') helps some individuals.

Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity; the individual should receive advice on diet and lifestyle modification and be monitored for changes in weight as well as in blood pressure, blood lipids and other associated conditions.

An anti-obesity drug should be considered only for those with a body mass index (BMI, individual’s body-weight divided by the square of the individual's height) of 30 kg/m² or greater in whom at least 3 months of managed care involving supervised diet, exercise and behaviour modification fails to achieve a realistic reduction in weight. In the presence of risk factors (such as diabetes, coronary heart disease, hypertension, and obstructive sleep apnoea), it may be appropriate to choose orlistat for those who have a high BMI and lifestyle modification and be monitored for changes in weight as well as in blood pressure, blood lipids and other associated conditions.

Drugs specifically licensed for the management of obesity are orlistat (section 4.5.1), sibutramine and rimonabant (both section 4.5.2). There is little evidence to guide selection between these drugs, but it may be appropriate to choose orlistat for those who have a high intake of fats whereas sibutramine or rimonabant may be chosen for those who cannot control their eating.

Combination therapy involving more than one anti-obesity drug is contra-indicated until further information about efficacy and long-term safety is available.

Thyroid hormones have no place in the treatment of obesity except in biochemically proven hypothyroid patients. The use of diuretics, cholinic gonadotrophin, or amphetamines is not appropriate for weight reduction.

4.5.2 Centrally acting appetite suppressants

Orlistat, a lipase inhibitor, reduces the absorption of dietary fat. It is used in conjunction with a mildly hypocaloric diet in individuals with a body mass index (BMI) of 30 kg/m² or more or in individuals with a BMI of 28 kg/m² in the presence of other risk factors such as type 2 diabetes, hypertension, or hypercholesterolaemia.

Orlistat should be used in conjunction with other lifestyle measures to manage obesity (section 4.5); treatment should only be continued beyond 12 months after discussing potential benefits and risks with the patient. On stopping orlistat, there may be a gradual reversal of weight loss.

Some of the weight loss in those taking orlistat probably results from individuals reducing their fat intake to avoid severe gastro-intestinal effects including steatorrhoea. Vitamin supplementation (especially of vitamin D) may be considered if there is concern about deficiency of fat-soluble vitamins.

The most commonly used bulk-forming drug is methylcellulose (section 1.6.1). It is claimed to reduce intake by producing a feeling of satiety but there is little evidence to support its use in the management of obesity.

**ORLISTAT**

*Indications* adjunct in obesity (see notes above)

*Caution* may impair absorption of fat-soluble vitamins; pregnancy (Appendix 4); *interactions*: Appendix 1 (orlistat)

*Multivitamins* If a multivitamin supplement is required, it should be taken at least 2 hours after orlistat dose or at bedtime

*Contra-indications* chronic malabsorption syndrome; cholestasis; breast-feeding (Appendix 5)

*Side-effects* oily leakage from rectum, flatulence, faecal urgency, liquid or oily stools, faecal incontinence, abdominal distension and pain (gastro-intestinal effects minimised by reduced fat intake), tooth and gingival disorders; respiratory infections; fatigue, anxiety, headache; menstrual disturbances, urinary-tract infection; hypoglycaemia; rarely rectal bleeding; very rarely diverticulitis, cholelithiasis, hepatitis, and bullous eruptions

**Dose**

- **ADULT** over 18 years, 120 mg taken immediately before, during, or up to 1 hour after each main meal (up to max. 360 mg daily); continue treatment beyond 12 weeks only if weight loss since start of treatment exceeds 5% (target for initial weight loss may be lower in patients with type 2 diabetes);

- **CHILD** over 12 years, initiated by specialist only [unlicensed use]

*Note* If a meal is missed or contains no fat, the dose of orlistat should be omitted

**Xenical** (Roche) (NH)

*Capsules* turquoise, orlistat 120 mg, net price 84-cap pack = £33.58
Sibutramine inhibits the re-uptake of noradrenaline and serotonin. It is used in the adjunctive management of obesity in individuals with a body mass index (BMI) of 30 kg/m² or more (and no associated co-morbidity) or in individuals with a BMI of 27 kg/m² or more in the presence of other risk factors such as type 2 diabetes or dyslipidaemia. Sibutramine is not licensed for use for longer than 1 year; on stopping sibutramine, there may be a gradual reversal of weight loss.

Rimonabant is a cannabinoid receptor antagonist for the adjunctive management of obesity in individuals with a BMI of 30 kg/m² or more, or in individuals with a BMI above 27 kg/m² in the presence of other risk factors such as type 2 diabetes or dyslipidaemia. On stopping rimonabant, there may be a gradual reversal of weight loss.

Dose

Side-effects

nausea, vomiting, diarrhoea, dry mouth, anorexia, depression (see above), anxiety, irritability, nervousness, sleep disorders, impaired memory, dizziness, paraesthesia, hypoesthesia, sciatica, hot flush, asthenia, impaired attention; tendonitis, muscle cramp; pruritus, hyperhidrosis; less commonly hicups, anger, aggression, suicidal ideation; rarely hallucinations

Dose

● Initially 10 mg daily in the morning, increased if weight loss less than 2 kg after 4 weeks to 15 mg daily; discontinue if weight loss less than 2 kg after 4 weeks at higher dose (see also Discontinuation of Treatment below); max. period of treatment 1 year; CHILD over 12 years, initiated by specialist only [unlicensed use]; ELDERLY over 65 years not recommended

Discontinuation of treatment Discontinue treatment if:

● weight loss after 3 months less than 5% of initial body-weight;
● weight loss stabilises at less than 5% of initial body-weight;
● individuals regain 3 kg or more after previous weight loss

In individuals with co-morbid conditions, treatment should be continued only if weight loss is associated with other clinical benefits

SiBUTRAMINE HYDROCHLORIDE

Indications adjunct in obesity (see notes above)

Cautions monitor blood pressure and pulse rate (every 2 weeks for first 3 months then monthly for 3 months then at least every 3 months)—discontinue if blood pressure exceeds 145/90 mmHg or if systolic or diastolic pressure raised by more than 10 mmHg or if pulse rate raised by 10 beats per minute at 2 consecutive visits; sleep apnoea syndrome (increased risk of hypertension); epilepsy; open-angle glaucoma, susceptibility to angle-closure glaucoma; history of ocular hypertension; monitor for pulmonary hypertension; family history of motor or vocal tics, history of depression; predisposition to bleeding, concomitant use of drugs that increase risk of bleeding; hepatic impairment (avoid if severe; Appendix 2); renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); interactions: Appendix 1 (sibutramine)

Contra-indications history of major eating disorders; psychiatric illness, Tourette syndrome; history of coronary artery disease, congestive heart failure, tachycardia, peripheral arterial occlusive disease, arrhythmias, and of cerebrovascular disease; uncontrolled hypertension; hypertrophy; prostatic hypertrophy; phaeochromocytoma; history of drug or alcohol abuse; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects constipation, dry mouth, nausea, taste disturbances, diarrhoea, vomiting, gastro-intestinal haemorrhage, haemorrhoid aggregation; tachycardia, palpitation, arrhythmias, hypertension, flushing; insomnia, lightheadedness, paraesthesia, headache, anxiety, depression, seizures, transient memory disturbance; sexual dysfunction, menstrual disturbances, urinary retention; thrombocytopenia; blurred vision; sweating, alopecia, cutaneous bleeding disorders, hypersensitivity reactions including Henoch-Schönlein purpura, rash, urticaria, angioedema and anaphylaxis; interstitial nephritis, glomerulonephritis; rarely headache and increased appetite on withdrawal; very rarely angle-closure glaucoma

Dose

● Initially 10 mg daily in the morning, increased if weight loss less than 2 kg after 4 weeks to 15 mg daily; discontinue if weight loss less than 2 kg after 4 weeks at higher dose (see also Discontinuation of Treatment below); max. period of treatment 1 year; CHILD over 12 years, initiated by specialist only [unlicensed use]; ELDERLY over 65 years not recommended

Discontinuation of treatment Discontinue treatment if:

● weight loss after 3 months less than 5% of initial body-weight;
● weight loss stabilises at less than 5% of initial body-weight;
● individuals regain 3 kg or more after previous weight loss

In individuals with co-morbid conditions, treatment should be continued only if weight loss is associated with other clinical benefits
4.6 Drugs used in nausea and vertigo

Antiemetics should be prescribed only when the cause of vomiting is known because otherwise they may delay diagnosis, particularly in children. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin or anti-epileptic overdose.

If antiemetic drug treatment is indicated, the drug is chosen according to the aetiology of vomiting.

**Antihistamines** are effective against nausea and vomiting resulting from many underlying conditions. There is no evidence that any one antihistamine is superior to another but their duration of action and incidence of adverse effects (drowsiness and antimuscarinic effects) differ.

The phenothiazines are dopamine antagonists and act centrally by blocking the chemoreceptor trigger zone. They are of considerable value for the prophylaxis and treatment of nausea and vomiting associated with diffuse neoplastic disease, radiation sickness, and the emesis caused by drugs such as opioids, general anaesthetics, and cytotoxics. Prochlorperazine, perphenazine, and trifluoperazine are less sedating than chlorpromazine; severe dystonic reactions sometimes occur with phenothiazines, especially in children. Other antipsychotic drugs including haloperidol and levomepromazine (methotrimeprazine) are also used for the relief of nausea (see Palliative Care, p. 17). Some phenothiazines are available as rectal suppositories, which can be useful in patients with persistent vomiting or with severe nausea; prochlorperazine can also be administered as a buccal tablet which is placed between the upper lip and the gum.

**Metoclopramide** is an effective antiemetic and its activity closely resembles that of the phenothiazines. Metoclopramide also acts directly on the gastro-intestinal tract and it may be superior to the phenothiazines for emesis associated with gastroduodenal, hepatic, and biliary disease. In postoperative nausea and vomiting, metoclopramide in a dose of 10 mg has limited efficacy. High-dose metoclopramide injection is now less commonly used for cytotoxic-induced nausea and vomiting. As with the phenothiazines, metoclopramide can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculargic crises. These dystonic effects are more common in the young (especially girls and young women) and the very old; they usually occur shortly after starting treatment with metoclopramide and subside within 24 hours of stopping it. Injection of an antiparkinsonian drug such as procyclidine (section 4.9.2) will abort dystonic attacks.

**Domperidone** acts at the chemoreceptor trigger zone; it is used for the relief of nausea and vomiting, especially when associated with cytotoxic therapy. It has the advantage over metoclopramide and the phenothiazines of being less likely to cause central effects such as sedation and dystonic reactions because it does not readily cross the blood-brain barrier. In Parkinson’s disease, it is used to prevent nausea and vomiting during treatment with apomorphine and also to treat nausea caused by other dopaminergic drugs (section 4.9.1). Domperidone is also used to treat vomiting due to emergency hormonal contraception (section 7.3.5).

**Dolasetron, granisetron, and ondansetron**, are specific 5HT antagonists which block 5HT receptors in the gastro-intestinal tract and in the CNS. They are of value in the management of nausea and vomiting in patients receiving cytotoxics and in postoperative nausea and vomiting. **Palonosetron** is licensed for prevention of nausea and vomiting associated with moderately or highly emetogenic cytotoxic chemotherapy.

**Dexamethasone** (section 6.3.2) has antiemetic effects and it is used in vomiting associated with cancer chemotherapy. It can be used alone or with metoclopramide, prochlorperazine, lorazepam, or a 5HT antagonist (section 8.1).

**Aprepitant** and fosaprepitant are neurokinin 1 receptor antagonists licensed for the prevention of acute and delayed nausea and vomiting associated with cisplatin-based cytotoxic chemotherapy; they are given with dexamethasone and a 5HT antagonist.

**Nabilone** is a synthetic cannabinoid with antiemetic properties. It may be used for nausea and vomiting caused by cytotoxic chemotherapy that is unresponsive to conventional antiemetics. Side-effects such as drowsiness and dizziness occur frequently with standard doses.

**Vomiting during pregnancy**

Nausea in the first trimester of pregnancy is generally mild and does not require drug therapy. On rare occasions if vomiting is severe, short-term treatment with an antihistamine, such as promethazine, may be required. **Prochlorperazine or metoclopramide** may be considered as second-line treatments. If symptoms do not settle in 24 to 48 hours then specialist opinion should be sought. Hyperemesis gravidarum is a more serious condition, which requires intravenous fluid and electrolyte replacement and sometimes nutritional support. Supplementation with thiamine must be considered in order to reduce the risk of Wernicke’s encephalopathy.

**Postoperative nausea and vomiting**

The incidence of postoperative nausea and vomiting depends on many factors including the anaesthetic used, the type and duration of surgery, and the patient’s sex. The aim is to prevent postoperative nausea and vomiting from occurring. Drugs used include some phenothiazines (e.g. prochlorperazine), metoclopramide (but 10-mg dose has limited efficacy and higher parenteral doses associated with greater side-effects), 5HT antagonists, antihistamines (such as cyclizine), and dexamethasone. A combination of two antiemetic drugs acting at different sites may be needed in resistant postoperative nausea and vomiting.

**Motion sickness**

Antiemetics should be given to prevent motion sickness rather than after nausea or vomiting develop. The most effective drug for the prevention of motion sickness is hyoscine. A transdermal hyoscine patch provides prolonged activity but it needs to be applied several hours before travelling. The sedating antihistamines are slightly less effective against motion sickness, but are generally better tolerated than hyoscine. If a sedative
effect is desired promethazine is useful, but generally a slightly less sedating antihistamine such as cyclizine or cinnarizine is preferred. The 5HT agonists, domperidone, metoclopramide, and the phenothiazines (except the antihistamine phenothiazine promethazine) are ineffectivemotion sickness.

Other vestibular disorders

Management of vestibular diseases is aimed at treating the underlying cause as well as treating symptoms of the balance disturbance and associated nausea and vomiting. Vertigo and nausea associated with Ménière’s disease and middle-ear surgery can be difficult to treat.

Betahistine is an analogue of histamine and is claimed to reduce endolymphatic pressure by improving the microcirculation. Betahistine is licensed for vertigo, tinnitus, and hearing loss associated with Ménière’s disease.

A diuretic alone or combined with salt restriction may provide some benefit in vertigo associated with Ménière’s disease; antihistamines (such as cinnarizine), and phenothiazines (such as prochlorperazine) are also used. Where possible, prochlorperazine should be reserved for the treatment of acute symptoms.

For advice to avoid the inappropriate prescribing of drugs (notably phenothiazines) for dizziness in the elderly, see Prescribing for the Elderly, p. 19.

Cytotoxic chemotherapy

For the management of nausea and vomiting induced by cytotoxic chemotherapy, see section 8.1.

Palliative care

For the management of nausea and vomiting in palliative care, see p. 17 and p. 18.

Migraine

For the management of nausea and vomiting associated with migraine, see p. 247.

Antihistamines

Cinnarizine

**Indications** vestibular disorders, such as vertigo, tinnitus, nausea, and vomiting in Ménière’s disease; motion sickness

**Cautions** section 3.4.1; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications** section 3.4.1

**Side-effects** section 3.4.1; also rarely weight gain, sweating, lichen planus, and lupus-like skin reactions

**Dose**

- Vestibular disorders, 30 mg 3 times daily; CHILD 5–12 years 15 mg 3 times daily
- Motion sickness, 30 mg 2 hours before travel then 15 mg every 8 hours during journey if necessary;

Cyclizine

**Indications** nausea, vomiting, vertigo, motion sickness, labyrinthine disorders

**Cautions** section 3.4.1; severe heart failure; may counteract haemodynamic benefits of opioids; interactions: Appendix 1 (antihistamines)

**Contra-indications** section 3.4.1

**Side-effects** section 3.4.1

**Dose**

- By mouth, cyclizine hydrochloride 50 mg up to 3 times daily; CHILD 6–12 years 25 mg up to 3 times daily
- By intramuscular or intravenous injection, cyclizine lactate 50 mg 3 times daily

Valoid® (Amphipharm)

**Tablets**, scored, cyclizine hydrochloride 50 mg. Net price 20 = £1.48. Label: 2

Injection, cyclizine lactate 50 mg/mL. Net price 1-mL amp = 49p

Promethazine Hydrochloride

**Indications** nausea, vomiting, vertigo, labyrinthine disorders, motion sickness; other indications (section 3.4.1, section 4.1.1, section 15.1.4.1)

**Cautions** section 3.4.1; also pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Contra-indications** section 3.4.1

**Side-effects** section 3.4.1 but more sedating; intramuscular injection may be painful

**Dose**

- Motion sickness prevention, 20–25 mg at bedtime on night before travel, repeat following morning if necessary; CHILD under 2 years not recommended, 2–5 years 5 mg at night and following morning if necessary, 5–10 years 10 mg at night and following morning if necessary

Preparations

Section 3.4.1

Promethazine Teocluate

**Indications** nausea, vertigo, labyrinthine disorders, motion sickness (acts longer than the hydrochloride)

**Cautions** section 3.4.1; also pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Contra-indications** section 3.4.1
PROCHLORPERAZINE

Indications severe nausea, vomiting, vertigo, labyrinthine disorders (see notes above); other indications section 4.2.1

Cautions see under Prochlorperazine (section 4.2.1); oral route only for children (avoid if under 10 kg); elderly (see notes above)

Contra-indications see under Prochlorperazine (section 4.2.1)

Side-effects see under Prochlorperazine (section 4.2.1); extrapyramidal symptoms, particularly in children, elderly, and debilitated

Dose
Note Doses are expressed as prochlorperazine maleate or mesilate; 1 mg prochlorperazine maleate = 1 mg prochlorperazine mesilate

By mouth, nausea and vomiting, acute attack, 20 mg initially then 10 mg after 2 hours; prevention 5–10 mg 2–3 times daily; CHILD (over 10 kg only) 250 micrograms/kg 2–3 times daily

Labyrinthine disorders, 5 mg 3 times daily, gradually increased if necessary to 30 mg daily in divided doses, then reduced after several weeks to 5–10 mg daily; CHILD not recommended

By deep intramuscular injection, nausea and vomiting, 12.5 mg when required followed if necessary after 6 hours by an oral dose, as above; CHILD and ADOLESCENT under 18 years, see BNF for Children

Prochlorperazine (Non-proprietary)  
Tablets, prochlorperazine maleate 5 mg, net price 28 = £2.09, 84 = £4.14. Label: 2

Stemetil® (Castlemead)  
Tablets, prochlorperazine maleate 5 mg (off-white), net price 84-tab pack = £6.18. Label: 2

Syrup, straw-coloured, prochlorperazine mesilate 5 mg/5 mL. Net price 100-mL pack = £3.48. Label: 2

Injection, prochlorperazine mesilate 12.5 mg/mL. Net price 1-mL amp = 54p

Buccal preparation

1 Buccastem® (R&C)  
Tablets (buccal), pale yellow, prochlorperazine maleate 3 mg. Net price 5 x 10-tab pack = £5.75. Label: 2, counselling, administration, see under Dose below

Dose ADULT and CHILD over 12 years, 1–2 tablets twice daily, tablets are placed high between upper lip and gum and left to dissolve

1. Prochlorperazine maleate can be sold to the public for adults over 18 years (provided packs do not contain more than 24 mg) for the treatment of nausea and vomiting in previously diagnosed migraine only (max. daily dose 12 mg)

TRIFLUOPERAZINE

Indications severe nausea and vomiting (see notes above); other indications section 4.2.1

Cautions section 4.2.1

Contra-indications section 4.2.1

Side-effects section 4.2.1; extrapyramidal symptoms, particularly in children, elderly, and debilitated
**Domperidone and metoclopramide**

### Domperidone

**Indications**
- Nausea and vomiting, dyspepsia, gastrointestinal reflux

**Cautions**
- Children; renal impairment (Appendix 3); breastfeeding (Appendix 5); interactions: Appendix 1 (domperidone)

**Contra-indications**
- Prolactinoma, hepatic impairment; where increased gastrointestinal motility harmful; pregnancy (Appendix 4)

**Side-effects**
- Rarely gastrointestinal disturbances (including cramps) and hyperprolactinaemia; very rarely extrapyramidal effects and rashes

**Dose**
- By mouth, adult and child body-weight over 35 kg, 10–20 mg 3–4 times daily; max. 80 mg daily; child body-weight 35 kg (nausea and vomiting only), 250–500 micrograms/kg 3–4 times daily; max. 2.4 mg/kg daily
- By rectum, adult and child body-weight over 35 kg, 60 mg twice daily; child 15–35 kg (nausea and vomiting only), 30 mg twice daily; child body-weight under 15 kg, not recommended

**Motilium**
- Tablets, 10 mg (as maleate), net price 30-tab pack = £1.37, 100-tab pack = £2.55

**DOMPERIDONE**
- Tablets, 10 mg (as maleate), net price 30-tab pack = £1.37, 100-tab pack = £2.55

**Note**
- Daily dose of motoclopramide should not normally exceed 500 micrograms/kg, particularly for children and young adults (restricted use, see above)

### Metoclopramide Hydrochloride

**Indications**
- Adults, nausea and vomiting, particularly in gastrointestinal disorders (section 1.2) and treatment with cytotoxics or radiotherapy; migraine (section 4.7.4.1)

**Patients under 20 years**
- Use restricted to severe intractable vomiting of known cause, vomiting of radiotherapy and cytotoxics, aid to gastrointestinal intubation, premedication; dose should be determined on the basis of body-weight

**Cautions**
- Elderly, young adults, and children (measure dose accurately, preferably with a pipette); atopic allergy (including asthma); may mask underlying disorders such as cerebral irritation; acute porphyria (section 9.8.2); epilepsy; hepatic impairment (Appendix 2), renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (metoclopramide)

**Contra-indications**
- Gastro-intestinal obstruction, perforation or haemorrhage; 3–4 days after gastro-intestinal surgery; phaeochromocytoma; breastfeeding (Appendix 5)

**Side-effects**
- Extrapyramidal effects (especially in children and young adults—see p. 222), hyperprolactinaemia, occasionally tardive dyskinesia on prolonged administration; also reported, anxiety, confusion, drowsiness, restlessness, diarrhoea, depression, neuroleptic malignant syndrome, rashes, pruritus, oedema; cardiac conduction abnormalities reported following intravenous administration; rarely methaemoglobinemia (more severe in G6PD deficiency)

**Dose**
- By mouth or by intramuscular injection or by intravenous injection over 1–2 minutes, nausea and vomiting, 10 mg (5 mg in young adults) 15–19 years under 60 kg) 3 times daily; child up to 1 year (up to 10 kg) 100 micrograms/kg (max. 1 mg) twice daily; 1–3 years (10–14 kg) 1 mg 2–3 times daily, 3–5 years (15–19 kg) 2 mg 2–3 times daily; 5–9 years (20–29 kg) 2.5 mg 3 times daily, 9–15 years (30 kg and over) 5 mg 3 times daily

- **Note**
- Daily dose of metoclopramide should not normally exceed 500 micrograms/kg, particularly for children and young adults (restricted use, see above)

- For diagnostic procedures, as a single dose 5–10 minutes before examination, 10–20 mg (10 mg in young adults 15–19 years); child under 3 years of age, 3–5 years 2 mg, 5–9 years 2.5 mg, 9–14 years 5 mg

**Metoclopramide**
- Tablets, metoclopramide hydrochloride 10 mg, net price 28-tab pack = 80p
- Oral solution, metoclopramide hydrochloride 5 mg/5 mL, net price 200-mL pack = £3.83
- Note Sugar-free versions are available and can be ordered by specifying ‘sugar-free’ on the prescription

**Injection**, metoclopramide hydrochloride 5 mg/mL, net price 2-mL amp = 26p

**Maxolon**
- Tablets, scored, metoclopramide hydrochloride 10 mg, net price 84-tab pack = £5.25
- Syrup, sugar-free, metoclopramide hydrochloride 5 mg/5 mL, net price 200-mL pack = £3.83
- Paediatric liquid, sugar-free, metoclopramide hydrochloride 1 mg/mL, net price 15-mL pack with pipette = £1.51. Counselling, use of pipette

**Injection**, metoclopramide hydrochloride 5 mg/mL, net price 2-mL amp = 27p

**High-dose (with cytotoxic chemotherapy only)**

**Maxolon High Dose**
- Injection, metoclopramide hydrochloride 5 mg/mL, net price 20-mL amp = £2.67

- For dilution and use as an intravenous infusion in nausea and vomiting associated with cytotoxic chemotherapy only
- **Dose** by continuous intravenous infusion (preferred method), initially (before starting chemotherapy), 2–4 mg/kg over 15–20 minutes, then 3–5 mg/kg over 8–12 hours; max. in 24 hours, 10 mg/kg

- **By intermittent intravenous infusion,** initially (before starting chemotherapy), up to 2 mg/kg over at least 15 minutes then up to 2 mg/kg every 15 minutes every 2 hours; max. in 24 hours, 10 mg/kg
4 Central nervous system

4.6 Drugs used in nausea and vertigo

DOLASETRON MESILATE

Indications see under Dose

Contra-indications prolonged QT interval, cardiac conduction disorders

Side-effects diarrhoea, constipation, dyspepsia, abdominal pain, flatulence, anorexia, taste disturbance; tachycardia, bradycardia, ECG changes, flushing; fever, shivering; headache, sleep disorder, fatigue, dizziness, drowsiness, hypersensitivity reactions including rash, rarely intestinal obstruction, pancreatitis, jaundice, oedema, cardiac arrhythmia, bronchospasm, seizures, very rarely severe hypotension following intravenous injection

Dose
• Prevention of nausea and vomiting induced by cytotoxic chemotherapy, by intravenous injection (over 30 seconds) or by intravenous infusion, ADULT over 18 years, 100 mg 30 minutes before treatment
• Prevention of postoperative nausea and vomiting by intravenous injection (over 30 seconds) or by intravenous infusion, ADULT over 18 years, 12.5 mg at cessation of anaesthesia,
• Treatment of postoperative nausea and vomiting, by intravenous injection (over 30 seconds) or by intravenous infusion, ADULT over 18 years, 12.5 mg

Anzemet® (Amdipharm) ▼ (FM)
Injection, dolasetron mesilate 20 mg/mL, net price 0.625-mL (12.5-mg) amp = £4.00, 5-mL (100-mg) amp = £13.00

GRANISETRON

Indications see under Dose

Contra-indications pregnancy (Appendix 4) and breast-feeding (Appendix 5)

Side-effects constipation, headache, rash; hypersensitivity reactions reported; rarely movement disorders

Dose
• Nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy, by mouth, 1–2 mg within 1 hour before start of treatment, then 2 mg daily in 1–2 divided doses during treatment; when intravenous infusion also used, max. combined total 9 mg in 24 hours; CHILD 20 micrograms/kg (max. 1 mg) within 1 hour before start of treatment, then 20 micrograms/kg (max. 1 mg) twice daily for up to 5 days during treatment

By intravenous injection (diluted in 15 mL sodium chloride 0.9% and given over not less than 30 seconds) or by intravenous infusion (over 5 minutes), prevention, 3 mg before start of cytotoxic therapy (up to 2 additional 3-mg doses may be given within 24 hours); treatment, as for prevention (the two additional doses must not be given less than 10 minutes apart); max. 9 mg in 24 hours; CHILD, by intravenous infusion, (over 5 minutes), prevention, 40 micrograms/kg (max. 3 mg) before start of cytotoxic therapy; treatment, as for prevention—one additional dose of 40 micrograms/kg (max. 3 mg) may be given within 24 hours (not less than 10 minutes after initial dose)
• Postoperative nausea and vomiting, by intravenous injection (diluted to 5 mL and given over 30 seconds), prevention, 1 mg before induction of anaesthesia, treatment, 1 mg, given as for prevention; max. 2 mg in one day; CHILD not recommended

Kyrtil® (Roche) ▼ (FM)
Tablets, 1, c, granisetron (as hydrochloride) 1 mg, net price 10-tab pack = £65.49; 2 mg, 5-tab pack = £65.49
Sterile solution, granisetron (as hydrochloride) 1 mg/mL, for dilution and use as injection or infusion, net price 1-mL amp = £8.60, 3-mL amp = £25.79

ONDANSETRON

Indications see under Dose

Contra-indications QT interval prolongation (avoid concomitant administration of drugs that prolong QT interval); hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (ondansetron)

Side-effects constipation; headache; flushing; injection site-reactions; less commonly hiccups, hypotension, bradycardia, chest pain, arrhythmias, movement disorders, seizures; on intravenous administration, rarely dizziness, transient visual disturbances (very rarely transient blindness); suppositories may cause rectal irritation

Dose
• Moderately emetogenic chemotherapy or radiotherapy, by mouth, 8 mg 1–2 hours before treatment or by rectum, 16 mg 1–2 hours before treatment or by intramuscular injection or slow intravenous injection, 8 mg immediately before treatment then by mouth, 8 mg every 12 hours for up to 5 days or by rectum, 16 mg daily for up to 5 days; CHILD, by slow intravenous injection or by intravenous infusion over 15 minutes, 5 mg/m immediately before chemotherapy then 4 mg by mouth every 12 hours for up to 5 days
• Severely emetogenic chemotherapy, by intramuscular injection or slow intravenous injection, 8 mg immediately before treatment, where necessary followed by 2 further doses of 8 mg at intervals of 2–4 hours (or followed by 1 mg/hour by continuous intravenous infusion for up to 24 hours) then by mouth, 8 mg every 12 hours for up to 5 days or by rectum, 16 mg daily for up to 5 days; CHILD, by slow intravenous injection or by intravenous infusion over at least 15 minutes, 32 mg immediately before treatment or by rectum, 16 mg 1–2 hours before treatment then by mouth, 8 mg every 12 hours for up to 5 days or by rectum, 16 mg daily for up to 5 days; CHILD, by slow intravenous injection, 5 mg/m immediately

Modified release

Maxolon SR® (Shire) ▼ (FM)
Capsules, m/r, clear, enclosing white granules, metoclopramide hydrochloride 15 mg. Net price 56-cap pack = £7.01. Label: 25

Dose patients over 20 years, 1 capsule twice daily

Compound preparations (for migraine)

Section 4.7.4.1

5HT3 antagonists
before chemotherapy then 4 mg by mouth every 12 hours for up to 5 days

- Prevention of postoperative nausea and vomiting, by mouth, 16 mg 1 hour before anaesthesia or 8 mg 1 hour before anaesthesia followed by 8 mg at intervals of 8 hours for 2 further doses
- Alternatively, by intramuscular or slow intravenous injection, 4 mg at induction of anaesthesia; CHILD over 2 years, by slow intravenous injection, 100 micrograms/kg (max. 4 mg) before, during, or after induction of anaesthesia

- Treatment of postoperative nausea and vomiting, by intramuscular or slow intravenous injection, 4 mg; CHILD over 2 years, by slow intravenous injection, 100 micrograms/kg (max. 4 mg)

### Ondansetron

**Ondansetron (Non-proprietary)**

- Tablets, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £89.69; 8 mg, 10-tab pack = £59.71
  - Brands include Ondemet
- Injection, ondansetron (as hydrochloride) 2 mg/mL, net price 2-mL amp = £5.39, 4-mL amp = £10.79
  - Brands include Ondemet

### Zofran® (GSK)

- Tablets, yellow, f/c, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £107.91; 8 mg, 10-tab pack = £71.94
- Oral lyophilisates (Zofran Mel®), ondansetron 4 mg, net price 10-tab pack = £35.97; 8 mg, 10-tab pack = £71.94. Counselling, administration
  - Excipients include aspartame (section 9.4.1)
- Counselling Tablets should be placed on the tongue, allowed to disperse and swallowed

### Syrup

- Sugar-free, strawberry-flavoured, ondansetron (as hydrochloride) 4 mg/5 mL, net price 50-mL pack = £35.97
- Injection, ondansetron (as hydrochloride) 2 mg/mL, net price 2-mL amp = £5.99; 4-mL amp = £11.99
- Suppositories, ondansetron 16 mg, net price 1 = £14.39

### PALONOSETRON

**Indications** prevention of nausea and vomiting induced by moderately and severely emetogenic chemotherapy

**Caution** history of constipation; intestinal obstruction; concomitant administration of drugs that prolong QT interval; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Driving** Dizziness or drowsiness may affect performance of skilled tasks (e.g. driving)

**Side-effects** diarrhoea, constipation; headache, dizziness; less commonly dyspepsia, abdominal pain, dry mouth, flatulence, changes in blood pressure, tachycardia, bradycardia, arrhythmia, myocardial ischaemia, hiccups, drowsiness, asthenia, insomnia, anxiety, euphoria, paraesthesia, peripheral neuropathy, anorexia, motion sickness, influenza-like symptoms, urinary retention, glycosuria, hyperglycaemia, electrolyte disturbance, arthralgia, eye irritation, amiblopyria, tinitus, rash, pruritus

**Dose**

- By intravenous injection (over 30 seconds), 250 micrograms as a single dose 30 minutes before treatment; do not repeat dose within 7 days; CHILD and ADOLESCENT under 18 years not recommended

**Aloxi® (IS Pharmaceuticals)**

- Injection, palonosetron (as hydrochloride) 50 micrograms/mL, net price 5-mL amp = £55.89

### Neurokinin receptor antagonist

#### Aprepitant

**Indications** adjunct to dexamethasone and a 5HT antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

**Caution** hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (aprepitant)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** hiccups, dyspepsia, diarrhoea, constipation, anorexia; asthenia, headache, dizziness; less commonly weight changes, dry mouth, colitis, flatulence, stomatitis, abdominal pain, gastro-oesophageal reflux, duodenal ulcer, oedema, bradycardia, cough, disorientation, euphoria, anxiety, confusion, thirst, abnormal dreams, hyperglycaemia, polyuria, anaemia, dysuria, haematuria, myalgia, conjunctivitis, pharyngitis, sneezing, tinitus, sweating, oily skin, pruritus, rash, acne, photosensitivity, flushing, hypotension

**Dose**

- ADULT over 18 years 125 mg 1 hour before chemotherapy, then 80 mg daily as a single dose for the next 2 days; consult product literature for dose of concomitant corticosteroid and 5HT antagonist

### Emend® (MSD)

- Capsules, aprepitant 80 mg (white), net price 2-cap pack = £31.61; 125 mg (white/pink), 5-cap pack = £79.03; 3-day pack of one 125-mg capsule and two 80-mg capsules = £47.42

### Fosaprepitant

**Note** Fosaprepitant is a prodrug of aprepitant

**Indications** adjunct to dexamethasone and a 5HT antagonist in preventing nausea and vomiting associated with moderately and highly emetogenic chemotherapy

**Caution** hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (aprepitant)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** anorexia, constipation, diarrhoea, dyspepsia, hiccups; asthenia, dizziness, headache; less commonly weight changes, abdominal pain, colitis, dry mouth, duodenal ulcer, flatulence, gastro-oesophageal reflux, stomatitis, taste disturbances, bradycardia, oedema, cough, abnormal dreams, anxiety, disorientation, confusion, euphoria, thirst, hyperglycaemia, dysuria, polyuria, flushing, neutropenia, anaemia, haematuria, hyponatraemia, myalgia, conjunctivitis, pharyngitis, sneezing, tinitus, flushing, oily skin, pruritus, rash, acne, photosensitivity, flushing, pruritus, oily skin, sweating

**Dose**

- By intravenous infusion, over 15 minutes, ADULT over 18 years, 115 mg 30 minutes before chemotherapy on day 1 of cycle (followed by aprepitant on days 2 and 3 of cycle); consult product literature for...
dose of concomitant corticosteroid and SHT antagonist

Ivemend® (MSD) ▼ (MSD)
Injection, powder for reconstitution, fosaprepitant (as dimeglumine), net price 115-mg vial = £20.55
The Scottish Medicines Consortium (p. 3) has advised (September 2008) that fosaprepitant (Ivemend®) is accepted for restricted use for the prevention of acute and delayed nausea and vomiting associated with highly emetogenic cisplatin-based chemotherapy

Cannabinoid

NABILONE

Indications nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics (under close observation, preferably in hospital setting)

Cautions history of psychiatric disorder; elderly; hypertension; heart disease; adverse effects on mental state can persist for 48–72 hours after stopping; pregnancy (Appendix 4); interactions: Appendix 1 (nabilone)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications severe hepatic impairment; breast-feeding (Appendix 5)

Side-effects drowsiness, vertigo, euphoria, dry mouth, ataxia, visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension, headache and nausea; also confusion, disorientation, hallucinations, psychosis, depression, decreased coordination, tremors, tachycardia, decreased appetite, and abdominal pain

Behavioural effects Patients should be made aware of possible changes of mood and other adverse behavioural effects

Dose

• Initially 1 mg twice daily, increased if necessary to 2 mg twice daily, throughout each cycle of cytotoxic therapy and, if necessary, for 48 hours after the last dose of each cycle; max. 6 mg daily given in 3 divided doses. The first dose should be taken the night before initiation of cytotoxic treatment and the second dose 1–3 hours before the first dose of cytotoxic drug; ADOLESCENT and CHILD under 18 years consult local treatment protocol [unlicensed use]

Nabilone (Valeant) (MSD)
Capsules, blue/white, nabilone 1 mg. Net price 20-cap pack = £125.84. Label: 2, counselling, behavioural effects

Hyoscine

HYOSCINE HYDROBROMIDE
(Scopolamine Hydrobromide)

Indications motion sickness; hypersalivation associated with clozapine therapy; premedication (section 15.1.3); excessive respiratory secretions (see Precautions in Palliative Care, p. 16)

Cautions 15.1.3); excessive respiratory secretions (see Precautions in Palliative Care, p. 16)

Contra-indications section 1.2

Side-effects section 1.2

Dose

• Motion sickness, by mouth, ADULT and CHILD over 10 years, 150–300 micrograms up to 30 minutes before start of journey repeated every 6 hours if required; max. 900 micrograms daily; CHILD 3–4 years 75 micrograms up to 30 minutes before start of journey repeated after 6 hours if required, max. 150 micrograms daily; 4–10 years 75–150 micrograms up to 30 minutes before start of journey repeated every 6 hours if required; max. 450 micrograms daily

• Hypersalivation associated with clozapine therapy [unlicensed indication], by mouth, ADULT over 16 years, 300 micrograms up to 3 times daily; max. 900 micrograms daily

Joy Rides® (GSK Consumer Healthcare)
Chewable tablets, raspberry-flavoured, hyoscine hydrobromide 150 micrograms, net price 12-tab pack = £1.49. Label: 2, 24

Kwells® (Bayer Consumer Care)
Chewable tablets, scored, hyoscine hydrobromide 150 micrograms (Kwells® Kids) (white), net price 12-tab pack = £1.52; 300 micrograms (pink), 12-tab pack = £1.52. Label: 2, 24

Patches

Scopoderm TTS® (Novartis Consumer Health) Patch, self-adhesive, pink, releasing hyoscine approx. 1 mg/72 hours when in contact with skin. Net price 2 = £4.30. Label: 19, counselling, see below

Dose motion sickness prevention, apply 1 patch to hairless area of skin behind ear 5–6 hours before journey; replace if necessary after 72 hours, siting replacement patch behind other ear, CHILD under 10 years not recommended

Counselling Explain accompanying instructions to patient and in particular emphasise advice to wash hands after handling and to wash application site after removing, and to use one patch at a time

Parenteral preparations
Section 15.1.3

Other drugs for Ménière’s disease

Betalistine has been promoted as a specific treatment for Ménière’s disease.

BETAHISTINE DIHYDROCHLORIDE

Indications vertigo, tinnitus and hearing loss associated with Ménière’s disease

Cautions asthma, history of peptic ulcer; pregnancy and breast-feeding; interactions: Appendix 1 (betahistine)

Contra-indications phaeochromocytoma

Side-effects gastro-intestinal disturbances; headache, rashes and pruritus reported

Dose

• Initially 16 mg 3 times daily, preferably with food; maintenance 24–48 mg daily; CHILD not recommended

Betalistine Dihydrochloride (Non-proprietary) Tablets, betahistine dihydrochloride 8 mg, net price 84-tab pack = £2.85, 120-tab pack = £1.56; 16 mg, 84-tab pack = £2.38. Label: 21
4.7 Analgesics

4.7.1 Non-opioid analgesics

The non-opioid drugs (section 4.7.1), paracetamol and aspirin (and other NSAIDs), are particularly suitable for pain in musculoskeletal conditions, whereas the opioid analgesics (section 4.7.2) are more suitable for moderate to severe pain, particularly of visceral origin.

Pain in palliative care For advice on pain relief in palliative care, see p. 15.

Pain in sickle-cell disease The pain of mild sickle-cell crises is managed with paracetamol, a NSAID, codeine, or dihydrocodeine. Severe crises may require the use of morphine or diamorphine; concomitant use of a NSAID may potentiate analgesia and allow lower doses of the opioid to be used. Pethidine should be avoided if possible because accumulation of a neurotoxic metabolite can precipitate seizures; the relatively short half-life of pethidine necessitates frequent injections.

Dental and orofacial pain Analgesics should be used judiciously in dental care as a temporary measure until the cause of the pain has been dealt with.

Dental pain of inflammatory origin, such as that associated with pulpsitis, apical infection, localized osteitis (dry socket) or pericoronitis is usually best managed by treating the infection, providing drainage, restorative procedures, and other local measures. Analgesics provide temporary relief of pain (usually for about 1 to 7 days) until the causative factors have been brought under control. In the case of pulpsitis, intra-osseous treatment with another NSAID which may be helpful but it should only be prescribed on a short-term basis during the acute phase. Analgesics such as aspirin (section 4.7.1) or ibuprofen (section 10.1.1) may also be required.

For the management of neuropathic pain, persistent idiopathic facial pain, and trigeminal neuralgia, see section 4.7.3.

Dysmenorrhoea Use of an oral contraceptive prevents the pain of dysmenorrhoea which is generally associated with ovulatory cycles. If treatment is necessary paracetamol or a NSAID (section 10.1.1) will generally provide adequate relief of pain. The vomiting and severe pain associated with dysmenorrhoea in women with endometriosis may call for an antiemetic (in addition to an analgesic). Antispasmodics (such as alverine citrate, section 1.2) have been advocated for dysmenorrhoea but the antispasmodic action does not generally provide significant relief.

4.7.1 Non-opioid analgesics

Aspirin is indicated for headache, transient musculoskeletal pain, dysmenorrhoea and pyrexia. In inflammatory conditions, most physicians prefer anti-inflammatory treatment with another NSAID which may be better tolerated and more convenient for the patient. Aspirin is used increasingly for its antiplatelet properties (section 2.9). Aspirin tablets or dispersible aspirin tablets are adequate for most purposes as they act rapidly. Gastric irritation may be a problem; it is minimised by taking the dose after food. Enteric-coated preparations are available, but have a slow onset of action and are therefore unsuitable for single-dose analgesic use (though their prolonged action may be useful for night pain).
Aspirin interacts significantly with a number of other drugs and its interaction with warfarin is a special hazard, see interactions: Appendix 1 (aspirin).

Paracetamol is similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irri-
tant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly. Over-
dosage with paracetamol is particularly dangerous as it may cause hepatic damage which is sometimes not
apparent for 4 to 6 days (see Emergency Treatment of
Poisoning, p. 29).

Nefopam may have a place in the relief of persistent
pain unresponsive to other non-opioid analgesics. It
causes little or no respiratory depression, but sympatho-
mimetic and antimuscarnic side-effects may be trou-lesome.

Non-steroidal anti-inflammatory analgesics
( NSAIDs, section 10.1.1) are particularly useful for
the treatment of patients with chronic disease accompanied
by pain and inflammation. Some of them are also used
in the short-term treatment of mild to moderate pain
including transient musculoskeletal pain but paracetam-
ol is now often preferred, particularly in the elderly
(see also p. 20). They are also suitable for the relief of
pain in dysmenorrhoea and to treat pain caused by
secondary bone tumours, many of which produce lysis
of bone and release prostaglandins (see Prescribing in
Palliative Care, p. 15). Selective inhibitors of cyclo-oxy-
genase-2 may be used in preference to non-selective
NSAIDs for patients at high risk of developing serious
gastro-intestinal side-effects. NSAIDs including ketoro-
lac are also used for peri-operative analgesia (section
15.1.4.2).

A non-opioid analgesic administered by intrathecal infu-
sion (ziconotide (Prialt® ▼), available from Eisai) is
licensed for the treatment of chronic severe pain;
ziconotide can be used by a hospital specialist as an
adjunct to opioid analgesics.

Dental and orofacial pain Most dental pain is
relieved effectively by NSAIDs (section 10.1.1). Aspirin
(below) is effective against mild to moderate dental
pain; dispersible tablets provide a rapidly absorbed
form of aspirin suitable for most purposes.

The analgesic effect of paracetamol in mild to moder-
ate dental pain is probably less than that of aspirin, but
it does not affect bleeding time or interact significantly
with warfarin. Moreover, it is less irritant to the stomach.
Paracetamol is a suitable analgesic for children; sugar-
free versions can be requested by specifying ‘sugar-free’
on the prescription.

For further information on the management of dental
and orofacial pain, see p. 229.

Compound analgesic preparations
Compound analgesic preparations that contain a simple
analgesic (such as aspirin or paracetamol) with an
opioid component reduce the scope for effective titra-
tion of the individual components in the management of
pain of varying intensity.

Compound analgesic preparations containing paraceta-
mol or aspirin with a low dose of an opioid analgesic (e.g.
8 mg of codeine phosphate per compound tablet) are
commonly used, but the advantages have not been
substantiated. The low dose of the opioid may be
enough to cause opioid side-effects (in particular, con-
stipation) and can complicate the treatment of over-
dosage (see p. 51) yet may not provide significant
additional relief of pain.

A full dose of the opioid component (e.g. 60 mg codeine
phosphate) in compound analgesic preparations effec-
tively augments the analgesic activity but is associated
with the full range of opioid side-effects (including
nausea, vomiting, severe constipation, drowsiness, respi-
atory depression, and risk of dependence on long-term
administration). For details of the side-effects of opioid
analgesics, see p. 233 (important: the elderly are par-
cularly susceptible to opioid side-effects and should
receive lower doses).

In general, when assessing pain, it is necessary to weigh
up carefully whether there is a need for a non-opioid and
an opioid analgesic to be taken simultaneously.

For information on the use of combination analgesic
preparations in dental and orofacial pain, see p. 229.

Caffeine is a weak stimulant that is often included, in
small doses, in analgesic preparations. It is claimed that
the addition of caffeine may enhance the analgesic
effect, but the alerting effect, mild habit-forming effect
and possible provocation of headache may not always
be desirable. Moreover, in excessive dosage or on with-
drawal caffeine may itself induce headache.

Co-proxamol tablets (dextropropoxyphene in combina-
tion with paracetamol) are no longer licensed because
doctor safety concerns, particularly toxicity in overdose. Co-
proxamol tablets [unlicensed] may still be prescribed for
patients who find it difficult to change, because, for
example, alternatives are not effective or suitable.

A8.5.1 Non-opioid analgesics

Indications mild to moderate pain, pyrexia; anti-
platelet (section 2.9)

Cautions asthma, allergic disease, hepatic impairment
(Appendix 2), renal impairment (Appendix 3), dehy-
dration; preferably avoid during fever or viral infection
in children (risk of Reye’s syndrome, see below);
pregnancy (Appendix 4); elderly; G6PD-deficiency
(section 9.1.5); concomitant use of drugs that increase
risk of bleeding; interactions: Appendix 1 (aspirin)

Contra-indications children under 16 years and in
breast-feeding (Reye’s syndrome, see below; Appen-
dix 5), previous or active peptic ulceration, haemoph-
ilia; not for treatment of gout

Hypersensitivity Aspirin and other NSAIDs are contra-
indicated in patients with a history of hypersensitivity to
aspirin or any other NSAID—can be used in whom
attacks of asthma, angioedema, urticaria or rhinitis have
been precipitated by aspirin or any other NSAID

Reye’s syndrome Owing to an association with Reye’s
syndrome, the CSM has advised that aspirin-containing
preparations should not be given to children under 16 years,
unless specifically indicated, e.g. for Kawasaki syndrome

Side-effects generally mild and infrequent but high
incidence of gastro-intestinal irritation with slight
asymptomatic blood loss, increased bleeding time,
bronchospasm and skin reactions in hypersensitive
patients. Prolonged administration, see section 10.1.1.

Overdosage: see Emergency Treatment of Poisoning,
p. 29

ASPIRIN
(Acetylsalicylic Acid)

4.7.1 Non-opioid analgesics BNF 57

Central nervous system
infusion; important: liver damage (and less frequently renal damage) following overdose, see Emergency Treatment of Poisoning, p. 29

Dose

- By mouth, 0.5–1 g every 4–6 hours to a max. of 4 g daily; CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD under 50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily

- By rectum, ADULT and CHILD over 12 years 0.5–1 g every 4–6 hours to a max. 4 g daily; CHILD under 3 months, see BNF for Children, 3 months–1 year 60–125 mg, 1–5 years 125–250 mg, 5–12 years 250–500 mg; these doses may be repeated every 4–6 hours as necessary (max. 4 doses in 24 hours)

- By intravenous infusion over 15 minutes, ADULT and CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD 10–50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily

- By rectum, ADULT and CHILD under 16 years not recommended (see Reye’s Syndrome, above)

- By intravenous infusion over 15 minutes, ADULT and CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD 10–50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily

- By rectum, ADULT and CHILD over 12 years 0.5–1 g every 4–6 hours to a max. of 4 g daily; CHILD under 3 months, see BNF for Children, 3 months–1 year 60–125 mg, 1–5 years 125–250 mg, 5–12 years 250–500 mg; these doses may be repeated every 4–6 hours as necessary (max. 4 doses in 24 hours)

- By intravenous infusion over 15 minutes, ADULT and CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD 10–50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily

- By rectum, ADULT and CHILD under 16 years not recommended (see Reye’s Syndrome, above)

- By intravenous infusion over 15 minutes, ADULT and CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD 10–50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily

- By rectum, ADULT and CHILD over 12 years 0.5–1 g every 4–6 hours to a max. of 4 g daily; CHILD under 3 months, see BNF for Children, 3 months–1 year 60–125 mg, 1–5 years 125–250 mg, 5–12 years 250–500 mg; these doses may be repeated every 4–6 hours as necessary (max. 4 doses in 24 hours)

- By intravenous infusion over 15 minutes, ADULT and CHILD over 50 kg, 1 g every 4–6 hours, max. 4 g daily; ADULT and CHILD 10–50 kg, 15 mg/kg every 4–6 hours, max. 60 mg/kg daily; NEONATE and CHILD less than 10 kg, 7.5 mg/kg every 4–6 hours, max. 30 mg/kg daily

- By rectum, ADULT and CHILD under 16 years not recommended (see Reye’s Syndrome, above)
Central nervous system

4.7.1 Non-opioid analgesics

1. Can be sold to the public in certain circumstances; for exemptions see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available)

Perfadgan® (Bristol-Myers Squibb) ▼ (NF)

**Intravenous infusion**, paracetamol 10 mg/mL, net price 50-mL vial = £1.80, 100-mL vial = £1.98

**Co-codamol 8/500**

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate 8 mg and paracetamol 500 mg should be dispensed.

**Co-codamol 8/500 (Non-proprietary)** (NF) ▼

**Tablets**, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg), net price 30-tab pack = £1.05. Label: 29, 30

**Brands include Panadeine**

**Dose**

1–2 tablets every 4–6 hours; max. 8 tablets daily; **CHILD** 6–12 years ½–1 tablet, max. 4 tablets daily

**Effervescent or dispersible tablets**, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg). Net price 100-tab pack = £4.62. Label: 13, 29, 30

**Brands include Paracodol**

**Note** The Drug Tariff allows tablets of co-codamol labelled ‘dispersive’ to be dispensed against an order for ‘effervescent’ and vice versa

**Dose**

1–2 tablets in water every 4–6 hours; max. 8 tablets daily; **CHILD** 6–12 years ½–1 tablet, max. 4 tablets daily

**Capsules**, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol 500 mg). Net price 10-cap pack = £1.10, 20-cap pack = £1.66. Label: 29, 30

**Brands include Paracodol**

**Dose**

1–2 capsules every 4 hours; max. 8 capsules daily

**Co-codamol 15/500**

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate 8 mg and paracetamol 500 mg should be dispensed (see preparations above).

See warnings and notes on p. 230 (**important**: special care in elderly—reduce dose)

Codipar® (Goldshield) (NF) ▼

**Caplets** (= tablets), co-codamol 15/500 (codeine phosphate 15 mg, paracetamol 500 mg). Net price 100-tab pack = £8.25. Label: 2, 29, 30

**Dose**

1–2 caplets every 4 hours; max. 8 caplets daily; **CHILD** not recommended

**Co-codamol 30/500**

When co-codamol tablets, dispersible (or effervescent) tablets, or capsules are prescribed and **no strength is stated**, tablets, dispersible (or effervescent) tablets, or capsules, respectively, containing codeine phosphate 8 mg and on paracetamol 500 mg should be dispensed (see preparations above).

See warnings and notes on p. 230 (**important**: special care in elderly—reduce dose)

Co-codamol 30/500 (Non-proprietary) (NF) ▼

**Tablets (and caplets)**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £3.97. Label: 2, 29, 30

**Dose**

1–2 tablets every 4 hours; max. 8 tablets daily; **CHILD** not recommended

**Capsules**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £5.32. Label: 2, 29, 30

**Brands include Medocodene, Zapain**

**Dose**

1–2 capsules every 4 hours; max. 8 capsules daily; **CHILD** not recommended

**Effervescent tablets**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-tab pack = £9.89. Label: 2, 13, 29, 30

**Brands include Medocodene Effervescent** (contains Na+ 13.6 mmol/tablet)

**Dose**

1–2 tablets in water every 4 hours; max. 8 tablets daily; **CHILD** not recommended

Kapake® (Galen) (NF) ▼

**Tablets**, scored, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 30-tab pack = £2.26 (hosp. only), 100-tab pack = £7.10. Label: 2, 29, 30

**Dose**

1–2 tablets every 4 hours; max. 8 tablets daily; **CHILD** not recommended

**Capsules**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg), net price 100-cap pack = £7.10. Label: 2, 29, 30

**Dose**

1–2 capsules every 4 hours; max. 8 capsules daily; **CHILD** not recommended

**Effervescent tablets**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg). Contains Na+ 16.9 mmol/tablet; avoid in renal impairment, net price 100-tab pack = £8.30. Label: 2, 13, 29, 30

**Dose**

2 tablets in water every 4 hours; max. 8 tablets daily; **CHILD** not recommended

Solpadol® (Sanofi-Synthelabo) (NF) ▼

**Caplets** (= tablets), co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg). Net price 100-cap pack = £7.54. Label: 2, 29, 30

**Dose**

2 caplets every 4 hours; max. 8 caplets daily; **CHILD** not recommended

**Capsules**, grey/purple, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg). Net price 100-cap pack = £7.54. Label: 2, 29, 30

**Dose**

1–2 capsules every 4 hours; max. 8 capsules daily; **CHILD** not recommended

**Effervescent tablets**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg). Contains Na+ 16.9 mmol/tablet; avoid in renal impairment. Net price 32-tab pack = £2.69, 100-tab pack = £9.05. Label: 2, 13, 29, 30

**Dose**

2 tablets in water every 4 hours; max. 8 tablets daily; **CHILD** not recommended

Tylex® (UCB Pharma) (NF) ▼

**Capsules**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg). Net price 100-cap pack = £8.01. Label: 2, 29, 30

**Dose**

1–2 capsules every 4 hours; max. 8 capsules daily; **CHILD** not recommended

**Effervescent tablets**, co-codamol 30/500 (codeine phosphate 30 mg, paracetamol 500 mg). Contains Na+ 13.6 mmol/tablet; avoid in renal impairment. Net price 100-tab pack = £8.80. Label: 2, 13, 29, 30

**Excipients** include aspartame 25 mg/tablet (section 9.4.1)

**Dose**

1–2 tablets in water every 4 hours; max. 8 tablets daily; **CHILD** not recommended
### Opioid analgesics

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause dependence and tolerance, but this is no deterrent in the control of pain in terminal illness, for guidelines see Prescribing in Palliative Care, p. 15. Regular use of a potent opioid may be appropriate for certain cases of chronic non-malignant pain; treatment should be supervised by a specialist and the patient should be assessed at regular intervals.

**Cautions**

Opioids should be used with caution in patients with impaired respiratory function (avoid in chronic obstructive pulmonary disease) and asthma (avoid during an acute attack), hypotension, shock, myasthenia gravis, prostatic hypertrophy, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders. A reduced dose is recommended in elderly or debilitated patients, in hepatic impairment (avoid if severe; Appendix 2) and renal impairment (avoid if severe; Appendix 3), in hypothyroidism, and in adrenocortical insufficiency. Repeated use of opioid analgesics is associated with the development of psychological and physical dependence; although this is rarely a problem with therapeutic use, caution is advised if prescribing for patients with a history of drug dependence. Avoid abrupt withdrawal after long-term treatment. Transdermal preparations (fentanyl or buprenorphine patches) are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. For prescribing in pregnancy and breast-feeding, see Appendix 4 and Appendix 5, respectively. Interactions: Appendix 1 (opioid analgesics; important: special hazard with pethidine and possibly other opioids and MAOIs).

**Palliative Care**

In the control of pain in terminal illness, the cautions listed above should not necessarily be a deterrent to the use of opioid analgesics.

### Contra-indications

Opioid analgesics should be avoided in patients with acute respiratory depression and when there is a risk of paralytic ileus. They are also contra-indicated in conditions associated with raised intracranial pressure and in head injury (opioid analgesics interfere with pupillary responses vital for neurological assessment). Comatose patients should not be treated with opioid analgesics.

### Side-effects

Opioid analgesics share many side-effects, although qualitative and quantitative differences exist. The most common side-effects include nausea and vomiting (particularly in initial stages), constipation, dry mouth, and biliary spasm; larger doses produce muscle rigidity, hypotension, and respiratory depression (for reversal of opioid-induced respiratory depression, see section 15.1.7). Other common side-effects of opioid
analgesics include bradycardia, tachycardia, palpitation, oedema, postural hypotension, hallucinations, vertigo, euphoria, dysphoria, mood changes, dependence, dizziness, confusion, drowsiness, sleep disturbances, headache, sexual dysfunction, difficulty with micturition, urinary retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus. Overdose: see Emergency Treatment of Poisoning, p. 31.

Driving  Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced.

Choice  Morphine remains the most valuable opioid analgesic for severe pain although it frequently causes nausea and vomiting. It is the standard against which other opioid analgesics are compared. In addition to relief of pain, morphine also confers a state of euphoria and mental detachment.

Morphine is the opioid of choice for the oral treatment of severe pain in palliative care. It is given regularly every 4 hours (or every 12 or 24 hours as modified-release preparations). For guidelines on dosage adjustment in palliative care, see p. 15.

Buprenorphine has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in patients dependent on other opioids. It has abuse potential and may itself cause dependence. It has a much longer duration of action than morphine and sublingually is an effective analgesic for 6 to 8 hours. Unlike most opioid analgesics, the effects of buprenorphine are only partially reversed by naloxone.

Codeine is effective for the relief of mild to moderate pain but is too constipating for long-term use.

Diphenoxylate (in combination with atropine, as co-phenotrope) is used in acute diarrhoea (section 1.4.2). (in combination with atropine, as co-phenotrope) is used in acute diarrhoea (section 1.4.2). Dipipanone used alone is less sedating than morphine but the only preparation available contains an antieptic and is therefore not suitable for regular regimens in palliative care.

Diamorphine (heroin) is a powerful opioid analgesic. It is used most widely. Methadone is less sedating than morphine and acts for longer periods. In prolonged use, methadone should not be administered more often than twice daily to avoid the risk of accumulation and opioid overdosage. Methadone may be used instead of morphine in the occasional patient who experiences excitation (or exacerbation of pain) with morphine.

Oxycodone has an efficacy and side-effect profile similar to that of morphine. It is used primarily for control of pain in palliative care.

Papaveretum is rarely used; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pentazocine has both agonist and antagonist properties and precipitates withdrawal symptoms, including pain in patients dependent on other opioids. By injection it is more potent than dihydrocodeine or codeine, but hallucinations and thought disturbances may occur. It is not recommended and, in particular, should be avoided after myocardial infarction as it may increase pulmonary and aortic blood pressure as well as cardiac work.

Pethidine produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. It is not suitable for severe continuing pain. It is used for analgesia in labour; however, other opioids, such as morphine or diamorphine, are often preferred for obstetric pain.

Tramadol produces analgesia by two mechanisms: an opioid effect and an enhancement of serotonergic and adrenergic pathways. It has fewer of the typical opioid side-effects (notably, less respiratory depression, less constipation and less addiction potential); psychiatric reactions have been reported.

Dose  The dose of opioids in the BNF may need to be adjusted individually according to the degree of analgesia and side-effects; patients’ response to opioids varies widely.

Postoperative analgesia  The use of intra-operative opioids affects the prescribing of postoperative analgesics and in many cases delays the need for a post-operative analgesic. A postoperative opioid analgesic should be given with care since it may potentiate any residual respiratory depression (for the treatment of opioid-induced respiratory depression, see section 15.1.7). Non-opioid analgesics are also used for post-operative pain (section 15.1.4.2).

Morphine is used most widely. Tramadol is not as effective in severe pain as other opioid analgesics. Buprenorphine may antagonise the analgesic effect of previously administered opioids and is generally not recommended. Pethidine is metabolised to norpethidine which may accumulate, particularly in renal impairment; norpethidine stimulates the central nervous system and may cause convulsions.

Opioids are also given epidurally [unlicensed route] in the postoperative period but are associated with side-effects such as pruritus, urinary retention, nausea and vomiting; respiratory depression can be delayed, particularly with morphine.

For details of patient-controlled analgesia (PCA) to relieve postoperative pain, consult hospital protocols. Formulations specifically designed for PCA are available (Pharma-Ject® Morphine Sulphate).

Dental and orofacial pain  Opioid analgesics are relatively ineffective in dental pain. Like other opioids, dihydrocodeine often causes nausea and vomiting which limits its value in dental pain; if taken for more than a few doses it is also liable to cause constipation. Dihydrocodeine is not very effective in postoperative dental pain.
Pethidine can be taken by mouth, but for optimal effect, it needs to be given by injection. Its efficacy in post-operative dental pain is not proven and its use in dentistry is likely to be minimal. The side-effects of pethidine are similar to those of dihydrocodeine and, apart from constipation, pethidine is also more likely to cause them. Dependence is unlikely if very few tablets are prescribed on very few occasions; nevertheless, dental surgeons need to be aware of the possibility that addicts may seek to acquire supplies.

For the management of dental and orofacial pain, see p. 229.

Addicts Although caution is necessary, addicts (and ex-addicts) may be treated with analgesics in the same way as other people when there is a real clinical need. Doctors do not require a special licence to prescribe opioid analgesics for addicts for relief of pain due to organic disease or injury.

**BUPRENORPHINE**

**Indications** see under Dose and under Patches; opioid dependence (section 4.10)

**Cautions** see notes above; also impaired consciousness; effects only partially reversed by naloxone

**Fever or external heat** Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat (may also increase absorption)

**Contra-indications** see notes above

**Side-effects** see notes above; can induce mild withdrawal symptoms in patients dependent on opioids; also diarrhoea, abdominal pain, anorexia, dyspepsia; vasodilatation; dyspnoea; paraesthesia, asthenia, fatigue, agitation, anxiety, less commonly fluctuence, taste disturbance, angina, hypertension, syncope, hypoxia, wheezing, cough, restlessness, depersonalisation, dysoria, impaired memory, hypoesthesia, tremor, influenza-like symptoms, pyrexia, rhinitis, rigors, muscle cramp, myalgia, tinnitus, dry eye, and dry skin; rarely paralytic ileus, dysphagia, impaired concentration, and psychosis; very rarely retching, hyperventilation, hiccup, and muscle fasciculation

**Dose**

- Moderate to severe pain, by sublingual administration, 200–400 micrograms every 6–8 hours; CHILD over 6 years, 16–25 kg, 100 micrograms every 6–8 hours; 25–37.5 kg, 100–200 micrograms every 6–8 hours; 37.5–50 kg, 200–300 micrograms every 6–8 hours
- By intramuscular or slow intravenous injection, 300–600 micrograms every 6–8 hours; CHILD over 6 months 3–6 micrograms/kg every 6–8 hours (max. 9 micrograms/kg)
- Premedication, by sublingual administration, 400 micrograms
- By intramuscular injection, 300 micrograms
- Intra-operative analgesia, by slow intravenous injection, 300–450 micrograms

**Temgesic®** (Scherling-Plough) Tablets (sublingual), buprenorphine (as hydrochloride), 200 micrograms, net price 50-tab pack = £5.33; 400 micrograms, 50-tab pack = £10.66. Label: 2, 26

**Injection**, buprenorphine (as hydrochloride) 300 micrograms/mL, net price 1-ML amp = 49p

**Patches**

**BuTrans®** (Napp) Patches, self-adhesive, beige, buprenorphine, ‘5’ patch (releasing 5 micrograms/hour for 96 hours), net price 4 = £16.69; ‘52.5’ patch (releasing 52.5 micrograms/hour for 96 hours), 4 = £25.04; ‘70’ patch (releasing 70 micrograms/hour for 96 hours), 4 = £33.37. Label: 2

- **Dose** severe chronic pain unresponsive to non-opioid analgesics, ADULT over 18 years, initially one ‘5 micrograms/hour’ patch; apply to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 7 days and siting replacement patch on a different area (avoid same area for at least 3 weeks)
- **Dose adjustment** When starting, analgesic effect should not be evaluated until the system has been worn for 72 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at 3-day intervals using a patch of the next strength or 2 patches of the same strength (applied at same time to avoid confusion). Max. 2 patches can be used at any one time

**Transtec®** (Napp) Patches, self-adhesive, skin-coloured, buprenorphine, ‘35’ patch (releasing 35 micrograms/hour for 96 hours), net price 4 = £16.69; ‘52.5’ patch (releasing 52.5 micrograms/hour for 96 hours), 4 = £25.04; ‘70’ patch (releasing 70 micrograms/hour for 96 hours), 4 = £33.37. Label: 2

- **Dose** moderate to severe chronic cancer pain and severe pain unresponsive to non-opioid analgesics, ADULT over 18 years, apply to dry, non-irritated, non-hairy skin on upper torso, removing after no longer than 96 hours and siting replacement patch on a different area (avoid same area for at least 6 days). Patients who have not previously received strong opioid analgesic, initially, one ‘35 micrograms/hour’ patch replaced after no longer than 96 hours, patients who have received strong opioid analgesic, initial dose based on previous 24-hour opioid requirement, consult product literature
- **Dose adjustment** When starting, analgesic effect should not be evaluated until the system has been worn for 24 hours (to allow for gradual increase in plasma-buprenorphine concentration)—if necessary, dose should be adjusted at intervals of no longer than 96 hours using a patch of the next strength or using 2 patches of the same strength (applied at same time to avoid confusion). Max. 2 patches can be used at any one time. For breakthrough pain, consider 200–400 micrograms buprenorphine sublingually

**Important:** it may take approx. 30 hours for the plasma-buprenorphine concentration to decrease by 50% after patch is removed

**Long duration of action** In view of the long duration of action, patients who have severe side-effects should be monitored for up to 30 hours after removing patch

**CODEINE PHOSPHATE**

**Indications** mild to moderate pain; diarrhoea (section 1.4.2); cough suppression (section 3.9.1)

**Cautions** see notes above; also cardiac arrhythmias; acute abdomen; gallstones

**Variation in metabolism** The capacity to metabolise codeine can vary considerably and lead to either reduced therapeutic effect or marked increase in side-effects

**Contra-indications** see notes above

**Side-effects** see notes above; also abdominal pain, anorexia, seizures, malaise, hypothermia, and muscle fasciculation; pancreatitis also reported

**Dose**

- **By mouth**, 30–60 mg every 4 hours when necessary, to a max. of 240 mg daily; CHILD 1–12 years, 3 mg/kg daily in divided doses
- **By intramuscular injection**, 30–60 mg every 4 hours when necessary
4 Central nervous system

**Dihydrocodeine (Non-proprietary)**

**Tablets** *(DF)*, dihydrocodeine tartrate 30 mg. Net price 28 = £1.34. Label: 2, 21

**Dental prescribing on NHS** Dihydrocodeine Tablets 30 mg may be prescribed

**Oral solution** *(DF)*, dihydrocodeine tartrate 10 mg/5 mL. Net price 150 mL = £3.08. Label: 2, 21

**Injection** *(DF)*, dihydrocodeine tartrate 50 mg/mL. Net price 1 mL amp = £2.29

**DF 118 Forte** *(Mirtindal)* *(DF)*

**Tablets**, dihydrocodeine tartrate 40 mg. Net price 100-tab pack = £11.51. Label: 2, 21

**Dose** ADULT and CHILD over 12 years, severe pain, 40–80 mg 3 times daily; max. 240 mg daily

**Modified release**

**DHC Continus** *(Napp)* *(DF)*

**Tablets**, m/r, dihydrocodeine tartrate 60 mg. Net price 56-tab pack = £5.50; 90 mg, 56-tab pack = £8.66; 120 mg, 56-tab pack = £11.57. Label: 2, 25

**Dose** ADULT and CHILD over 12 years, chronic severe pain, 60–120 mg every 12 hours

**Note** Dihydrocodeine is an ingredient of some compound analgesic preparations, section 4.7.1

**DIOPANONE HYDROCHLORIDE**

**(Heroin Hydrochloride)**

**Indications** see under Dose; acute pulmonary oedema

**Cautions** see notes above; also severe diarrhoea; toxic psychosis, CNS depression; severe cor pulmonale

**Contra-indications** see notes above; also pancreatitis; severe cor pulmonale

**Side-effects** see notes above; also anorexia, taste disturbance; syncope; asthenia, raised intracranial pressure; myocardial infarction also reported

**Dose**

- Acute pain, by subcutaneous or intramuscular injection, 5 mg repeated every 4 hours if necessary (up to 10 mg for heavier well-muscled patients); by slow intravenous injection, quarter to half corresponding intramuscular dose
- Myocardial infarction, by slow intravenous injection (1 mg/minute), 5 mg followed by a further 2.5–5 mg if necessary; elderly or frail patients, reduce dose by half
- Acute pulmonary oedema, by slow intravenous injection (1 mg/minute) 2.5–5 mg
- Chronic pain, by mouth or by subcutaneous or intramuscular injection, 5–10 mg regularly every 4 hours; dose may be increased according to needs; intramuscular dose should be approx. half corresponding oral dose, and approx. one third corresponding oral morphine dose—see also Prescribing in Palliative Care, p. 15; by subcutaneous infusion (using syringe driver), see Prescribing in Palliative Care, p. 18

**Diamorphine (Non-proprietary)** *(DF)*

**Tablets**, diamorphine hydrochloride 10 mg. Net price 100-tab pack = £12.92. Label: 2

**Injection**, powder for reconstitution, diamorphine hydrochloride. Net price 5-mg amp = £2.69, 10-mg amp = £3.37, 30-mg amp = £3.60, 100-mg amp = £9.92, 500-mg amp = £43.44

**DIHYDROCODEINE TARTRATE**

**Indications** moderate to severe pain

**Cautions** see notes above; also diabetes mellitus; phaeochromocytoma

**Contra-indications** see notes above

**Side-effects** see notes above; also psychositis, restlessness, raised intracranial pressure

**Dose**

- See preparation below

**Diconal** *(Amdipharm)* *(DF)*

**Tablets**, pink, scored, dipipanone hydrochloride 10 mg, cyclazine hydrochloride 30 mg. Net price 50-tab pack = £8.70. Label: 2

**Dose** acute pain, 1 tablet gradually increased to 3 tablets every 6 hours; CHILD not recommended

**Caution** Not recommended in palliative care, see Nausea and Vomiting, p. 18

**FENTANYL**

**Indications** see under preparations; parenteral indications (section 15.1.4.3)

**Cautions** see notes above; also diabetes mellitus, impaired consciousness, cerebral tumour; iontophoretic transdermal system, impaired hearing, chest or abdominal surgery, remove before magnetic resonance imaging (MRI), cardioversion or diathermy

**Fever or external heat** Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat (may also increase absorption)

**Transdermal fentanyl** Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic; manufacturer recommends use only in opioid tolerant patients

**Contra-indications** see notes above

**Side-effects** see notes above; also abdominal pain, anorexia, dyspepsia, dysphagia, mouth ulceration, taste disturbance, dry mouth; vasodilatation; apnoea; anxiety; myoclonus; less commonly flatulence, diarrhoea, laryngospasm, dysphonia, hypoventilation, depersonalisation, dysarthria, amnesia, incoordin-
Fentanyl

Dose

- See under preparations
- Conversion (from oral morphine to transdermal fentanyl) see Prescribing in Palliative Care, p. 16

Tablets

Abstral® (ProStrakan) ▼ TC

Fentanyl (as citrate) 100 micrograms, net price 3 = £18.85; 30 micrograms/hour for 72 hours), 5 = £50.32; ‘75’ patch (releasing approx. 75 micrograms/hour for 72 hours), 5 = £70.15; ‘100’ patch (releasing approx. 100 micrograms/hour for 72 hours), 5 = £88.32. Label: 2

Dose

- breakthrough dose for each pain episode); adjust dose according to
- chronic cancer pain, initially 200 micrograms (over 15 minutes)
- ADULT over 18 years, initially 100 micrograms repeated if necessary after 15–30 minutes; adjust dose according to
- dose units for each pain episode); adjust dose according to
- seizures; shock, astyole, pyrexia, ataxia, and muscle
- fentanyl (as citrate) 100 micrograms, net price 4.7.2 Opioid analgesics 237

Actiq
Abstral

£49.99, 30-tab pack = £149.70; 400 micrograms, 10-tab pack = £49.99, 30-tab pack = £149.70: 300 micrograms, 10-tab pack = £49.99, 30-tab pack = £149.70: 600 micrograms, 30-tab pack = £149.70. Label: 2, 26

Note

- may take up to 25 hours for the plasma-fentanyl concentration to decrease by 50%—replacement opioid therapy should be initiated at a low dose and increased gradually.

Long duration of action

- in view of the long duration of action, patients who have had severe side-effects should be monitored for up to 24 hours after patch removal

Durogesic DTrans® (Janssen-Cilag) ▼ TC

Patches, self-adhesive, transparent, fentanyl, ‘12’ patch (releasing approx. 12 micrograms/hour for 72 hours), net price 5 = £18.85; ‘25’ patch (releasing approx. 25 micrograms/hour for 72 hours), 5 = £26.94; ‘50’ patch (releasing approx. 50 micrograms/hour for 72 hours), 5 = £50.32; ‘75’ patch (releasing approx. 75 micrograms/hour for 72 hours), 5 = £70.15; ‘100’ patch (releasing approx. 100 micrograms/hour for 72 hours), 5 = £88.32. Label: 2

Dose

- chronic intractable pain, apply to dry, non-irritated, non-
- rash, erythema, and itching reported
- dermatitis, and itching reported

Patches

Prescriptions

- to avoid confusion)—consider additional or alternative

Fentanyl

Dose

- severe chronic pain, apply to dry, non-irritated, non-
- and itching reported

Dose adjustment

- in view of the long duration of action, patients who have had severe side-effects should be monitored for up to 24 hours after patch removal

Iontophoretic transdermal system

IONSYS® is a needle-free patient-controlled device that consists of an electronic controller and 2 hydrogel reservoirs, one of which contains fentanyl.

IONSYS® (Janssen-Cilag) ▼ TC

Iontophoretic transdermal system, self-adhesive, fentanyl 40 micrograms/dose, net price 1 unit (80 doses) = £62.00 (hosp. only). Label: 2

Dose

- acute moderate to severe post-

Note

- Titrate analgesic requirement before starting treatment with IONSYS®. Patient and healthcare professional should be familiar with IONSYS® operating system (consult product literature)
**4 Central nervous system**

**Indications**
- Severe pain in cancer

**Cautions**
- See notes above; also paralytic ileus, seizures, asthena, agitation, and myoclonus

**Contra-indications**
- See notes above; also myocardial infarction, severe cor pulmonale

**Side-effects**
- See notes above; also pancreatitis, cardiac arrhythmias, severe cor pulmonale

**Dose**
- By mouth
  - See under preparations below
- **Palladone® (Napp)**
  - **Capsules**
    - Hydromorphone hydrochloride 1.3 mg (orange/clear), net price 56-cap pack = £8.82; 2.6 mg (red/clear), 56-cap pack = £17.64. Label: 2, counselling, see below
    - **Dose**
      - 1.3 mg every 4 hours, increased if necessary according to severity of pain; **CHILD** under 12 years not recommended
      - **Counselling**
        - Swallow whole or open capsule and sprinkle contents on soft food
- **Modified release**
  - **Palladone® SR (Napp)**
    - **Capsules**, m/s, hydromorphone hydrochloride 2 mg (yellow/clear), net price 56-cap pack = £20.98; 4 mg (pale blue/clear), 56-cap pack = £28.75; 8 mg (pink/clear), 56-cap pack = £56.08; 16 mg (brown/clear), 56-cap pack = £106.53; 24 mg (dark blue/clear), 56-cap pack = £159.82. Label: 2, counselling, see below
    - **Dose**
      - 4 mg every 12 hours, increased if necessary according to severity of pain; **CHILD** under 12 years not recommended
      - **Counselling**
        - Swallow whole or open capsule and sprinkle contents on soft food

**MEPTAZINOL**

**Indications**
- Moderate to severe pain, including post-operative and obstetric pain and renal colic; peri-operative analgesia, section 15.4.3

**Cautions**
- See notes above; effects only partially reversed by naloxone

**Contra-indications**
- See notes above; also myocardial infarction, phaeochromocytoma

**Side-effects**
- See notes above; can induce withdrawal symptoms in patients dependent on opioids; also diarrhoea, abdominal pain, dyspepsia, and hypothermia

**Dose**
- **By mouth**
  - 200 mg every 3–6 hours as required; **CHILD** not recommended
- **By intramuscular injection**
  - 75–100 mg every 2–4 hours if necessary; obstetric analgesia, 100–150 mg according to patient’s weight (2 mg/kg); **CHILD** not recommended
- **By slow intravenous injection**
  - 50–100 mg every 2–4 hours if necessary; **CHILD** not recommended

**Meptid® (Shire)**

- **Tablets**
  - Orange, f/c, meptazinol 200 mg, net price 112-tab pack = £22.11. Label: 2
  - **Injection**
    - Meptazinol 100 mg (as hydrochloride)/mL, net price 1-mL amp = £19.98; 2-mL amp = £31.81; 3.5-mL amp = £51.76; 5-mL amp = £82.89; 10-mL amp = £165.78. Label: 2

**METHADONE HYDROCHLORIDE**

**Indications**
- Severe pain, see notes above; cough in terminal disease (section 3.9.1); adjunct in treatment of opioid dependence (section 4.10)

**Cautions**
- See notes above; also history of cardiac conduction abnormalities, family history of sudden death (ECG monitoring recommended; see also QT Interval Prolongation, below)

**Contra-indications**
- See notes above; also phaeochromocytoma

**Side-effects**
- See notes above; also QT interval prolongation, torsade de pointes, hypothermia, restlessness, raised intracranial pressure, dysmenorrhoea, dry eyes, and hyperprolactinaemia

**Dose**
- **By mouth or by subcutaneous or intramuscular injection**
  - 5–10 mg every 6–8 hours, adjusted according to response; on prolonged use not to be given more frequently than every 12 hours; **CHILD** not recommended

**Methadone (Non-proprietary)**

- **Tablets**
  - Methadone hydrochloride 5 mg. Net price 50 = £2.97. Label: 2

- **Injection**
  - Methadone hydrochloride, 10 mg/mL, net price 1-mL amp = 93p; 2-mL amp = £1.61; 3.5-mL amp = £1.98; 5-mL amp = £2.14

**Linclus**

- Section 3.9.1

**Oral solution and oral concentrate**

- Section 4.10

**MORPHINE SALTS**

**Indications**
- See notes above and under Dose; acute diarrhoea (section 1.4.2); cough in terminal care (section 3.9.1)

**Cautions**
- See notes above; also pancreatitis, cardiac arrhythmias, severe cor pulmonale

**Contra-indications**
- See notes above; also delayed gastric emptying, acute abdomen; heart failure secondary to chronic lung disease; phaeochromocytoma

**Side-effects**
- See notes above; also paralytic ileus, abdominal pain, anorexia, dyspepsia, exacerbation of pancreatitis, taste disturbance, hypertension, hypothermia, syncope, bronchospasm, inhibition of cough reflex, restlessness, seizures, paraesthesia, asthenia, malaise, disorientation, excitation, agitation, delirium, raised intracranial pressure, amenorrhoea, myoclonus, muscle fasciculation, and rhabdomyolysis

**Dose**
- The patient should be closely monitored for pain relief as well as for side-effects especially respiratory depression. See also notes above.

- **Acute pain, by subcutaneous injection (not suitable for oedematous patients) or by intramuscular injection**, initially 10 mg (ELDERLY or frail 5 mg) every 4 hours (or more frequently during titration), adjusted according to response; **NEONATE** initially 100 micrograms/kg every 6 hours, adjusted according to response; **CHILD** 1–6 months initially 100–200 micrograms/kg every 6 hours, adjusted according to response; **CHILD** 6 months–2 years
initially 100–200 micrograms/kg every 4 hours, adjusted according to response; CHILD 2–12 years initially 200 micrograms/kg every 4 hours, adjusted according to response; CHILD 12–18 years initially 2.5–10 mg every 4 hours, adjusted according to response

By slow intravenous injection, initially 2.5 mg (reduce dose in ELDERLY or frail) every 4 hours (or more frequently during titration), adjusted according to response; NEONATE initially 40–100 micrograms/kg every 6 hours, adjusted according to response; CHILD 1–6 months initially 100–200 micrograms/kg every 6 hours, adjusted according to response; CHILD 6 months–12 years initially 100–200 micrograms/kg every 4 hours, adjusted according to response

• Premedication, by subcutaneous or intramuscular injection, up to 10 mg 60–90 minutes before operation; CHILD, by intramuscular injection, 150 micrograms/kg

• Patient controlled analgesia (PCA), consult hospital protocols

• Myocardial infarction, by slow intravenous injection (2 mg/minute), 10 mg followed by a further 5–10 mg if necessary; ELDERLY or frail patients, reduce dose by half

• Acute pulmonary oedema, by slow intravenous injection (2 mg/minute) 5–10 mg; ELDERLY or frail patients, reduce dose by half

• Chronic pain, by mouth or by subcutaneous injection (not suitable for oedematous patients) or by intramuscular injection, initially 5–20 mg every 4 hours, adjusted according to response; see also Prescribing in Palliative Care, p. 15

By rectum, initially 15–30 mg every 4 hours, adjusted according to response

Note The doses stated above refer equally to morphine hydrochloride and sulphate

Oral solutions

Note For advice on transfer from oral solutions of morphine to modified-release preparations of morphine, see Prescribing in Palliative Care, p. 15

Morphine Oral Solutions

Oral solutions of morphine can be prescribed by writing the formula: Morphine hydrochloride 5 mg Chloroform water to 5 mL

Note The proportion of morphine hydrochloride may be altered when specified by the prescriber; if above 15 mg per 5 mL, the solution becomes a controlled drug. For example prescribing see Controlled Drugs and Drug Dependence, p. 7. It is usual to adjust the strength so that the dose volume is 5 or 10 mL.

Oramorph® (Boehringer Ingelheim) Oramorph® oral solution (PML), morphine sulphate 10 mg/5 mL. Net price 100-mL pack = £1.87; 300-mL pack = £5.21; 500-mL pack = £7.86. Label: 2

Oramorph® concentrated oral solution (BM), sugar-free, morphine sulphate 100 mg/5 mL. Net price 30-mL pack = £5.24; 120-mL pack = £19.57 (both with calibrated dropper). Label: 2

Tablets

Sevedrol® (Napp) Tablets, f/c, scored, morphine sulphate 10 mg (blue), net price 56-tab pack = £5.61; 20 mg (pink), 56-tab pack = £11.21; 50 mg (pale green), 56-tab pack = £28.02. Label: 2

Modiﬁed-release 12-hourly oral preparations

Morphgesic® SR (Amdipharm) Tablets, m/r, f/c, morphine sulphate 10 mg (buff), net price 60-tab pack = £4.09; 30 mg (violet), 60-tab pack = £9.81; 60 mg (orange), 60-tab pack = £19.15; 100 mg (grey), 60-tab pack = £30.30. Label: 2, 25

Dose every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 15; dosage requirements should be reviewed if the brand is altered

Note Prescriptions must also specify ‘tablets’ (i.e. Morphgesic SR tablets)

MST Continus® (Napp) Tablets, m/r, f/c, morphine sulphate 5 mg (white), net price 60-tab pack = £3.29; 10 mg (brown), 60-tab pack = £5.48; 15 mg (green), 60-tab pack = £9.61; 30 mg (purple), 60-tab pack = £13.17; 60 mg (orange), 60-tab pack = £25.69; 100 mg (grey), 60-tab pack = £40.66; 200 mg (green), 60-tab pack = £81.34. Label: 2, 25

Suspension (= sachet of granules to mix with water), m/r, pink, morphine sulphate 20 mg/sachet, net price 30-sachet pack = £24.58; 30 mg/sachet, 30-sachet pack = £25.54; 60 mg/sachet, 30-sachet pack = £51.09; 100 mg/sachet, 30-sachet pack = £85.15; 200 mg/sachet pack, 30-sachet pack = £170.30. Label: 2, 13

Dose every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 15; dosage requirements should be reviewed if the brand is altered

Note Prescriptions must also specify ‘tablets’ or ‘suspension’ (i.e. ‘MST Continus tablets’ or ‘MST Continus suspension’)

Zomorph® (Link) Capsules, m/r, morphine sulphate 10 mg (yellow/clear enclosing pale yellow pellets), net price 60-cap pack = £4.08; 30 mg (pink/clear enclosing pale yellow pellets), 60-cap pack = £9.77; 60 mg (orange/clear enclosing pale yellow pellets), 60-cap pack = £19.06; 100 mg (white/clear enclosing pale yellow pellets), 60-cap pack = £30.18; 200 mg (clear enclosing pale yellow pellets), 60-cap pack = £60.35. Label: 2, counselling, see below

Dose every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining doses, see Prescribing in Palliative Care, p. 15; dosage requirements should be reviewed if the brand is altered

Counselling Swallow whole or open capsule and sprinkle contents on soft food

Note Prescriptions must also specify ‘capsules’ (i.e. ‘Zomorph capsules’)

Modiﬁed-release 24-hourly oral preparations

MXL® (Napp) Capsules, m/r, morphine sulphate 30 mg (light blue), net price 28-cap pack = £10.91; 60 mg (brown), 28-cap pack = £14.95; 90 mg (pink), 28-cap pack = £22.04; 120 mg (green), 28-cap pack = £29.15; 150 mg (blue), 28-cap pack = £36.43; 200 mg (red/brown), 28-cap pack = £46.15. Label: 2, counselling, see below

Dose every 24 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 15; dosage requirements should be reviewed if the brand is altered

Counselling Swallow whole or open capsule and sprinkle contents on soft food

Note Prescriptions must also specify ‘capsules’ (i.e. ‘MXL capsules’)
4 Central nervous system

---

**Suppositories**

**Morphine** (Non-proprietary)

Suppositories, morphine hydrochloride or sulphate

10 mg, net price 12 = £8.69; 15 mg, 12 = £7.50; 20 mg, 12 = £33.22; 30 mg, 12 = £10.90. Label: 2

Available from Aurum, Martindale

Note Both the strength of the suppositories and the morphine salt contained in them must be specified by the prescriber

---

**Injections**

**Morphine Sulphate** (Non-proprietary)

Injection, morphine sulphate 10, 15, 20, and 30 mg/mL, net price 1- and 2-mL amp (all) = £72p–£1.40; 10 mg/mL, 1-mL prefilled syringe = £5.00

Intravenous infusion, morphine sulphate 1 mg/mL, net price 50 mL vial = £5.00; 2 mg/mL, 50-mL vial = £5.89

Minijet® Morphine Sulphate (UCB Pharma)

Injection, morphine sulphate 1 mg/mL, net price 10-mL disposable syringe = £7.58

---

**Injection with antiemetic**

Caution In myocardial infarction cyclizine may aggravate severe heart failure and counteract the haemodynamic benefits of opioids, section 4.6. Not recommended in palliative care, see Nausea and Vomiting, p. 17

---

**Cyclimorph®** (Amidpharm)

Cyclimorph-10® Injection, morphine tartrate 10 mg, cyclazine tartrate 50 mg/mL. Net price 1-mL amp = £1.34

Dose ADULT and CHILD over 12 years, moderate to severe pain (short-term use only) by subcutaneous, intramuscular, or intravenous injection, 1 mL, repeated not more often than every 4 hours; max. 3 doses in any 24-hour period

Cyclimorph-15® Injection, morphine tartrate 15 mg, cyclazine tartrate 50 mg/mL. Net price 1-mL amp = £1.39

Dose ADULT and CHILD over 12 years, moderate to severe pain (short-term use only) by subcutaneous, intramuscular, or intravenous injection, 1 mL, repeated not more often than every 4 hours; max. 3 doses in any 24-hour period

---

**OXYCODONE HYDROCHLORIDE**

**Indications** moderate to severe pain in patients with cancer; postoperative pain; severe pain

**Caution** see notes above; also toxic psychosis; pancreatitis

**Contra-indications** see notes above; also acute abdomen; delayed gastric emptying; chronic constipation; cor pulmonale; acute porphyria (section 9.8.2)

**Side-effects** see notes above; also diarrhoea, abdominal pain, anorexia, dyspepsia; bronchospasm, dysphonia, impaired cough reflex; asthma, anxiety, chills; muscle fasciculation; less commonly paralytic ileus, gastritis, flatulence, dyspepsia, taste disturbance, belching, hiccups, vasodilatation, supraventricular tachycardia, syncope, amenoria, hypoesthesia, restlessless, seizures, pyrexia, amenorrhoea, hypotonia, paraesthesia, disorders of taste, agitation, speech disorder, tremor, and dry skin

**Dose**

- By mouth, initially 5 mg every 4–6 hours, increased if necessary according to severity of pain, usual max. 400 mg daily, but some patients may require higher doses; CHILD under 18 years, see BNF for Children

- By slow intravenous injection, 1–10 mg every 4 hours when necessary; CHILD under 18 years, not recommended

- By intravenous infusion, initially 2 mg/hour, adjusted according to response; CHILD under 18 years not recommended

- By subcutaneous injection, initially 5 mg every 4 hours when necessary; CHILD under 18 years, not recommended

- By subcutaneous infusion, initially 7.5 mg/24 hours adjusted according to response; CHILD under 18 years, not recommended

- Patient controlled analgesia (PCA), consult hospital protocols

**Note** 2 mg oral oxycodone is approximately equivalent to 1 mg parenteral oxycodone

**OxyNorm®** (Napp)

**Capsules**, oxycodone hydrochloride 5 mg (orange/beige), net price 56-cap pack = £12.07; 10 mg (white/beige), 56-cap pack = £24.14; 20 mg (pink/beige), 56-cap pack = £48.27. Label: 2

**Liquid** (oral solution), sugar-free, oxycodone hydrochloride 5 mg/5 mL, net price 250 mL = £10.26. Label: 2

**Concentrate** (concentrated oral solution), sugar-free, oxycodone hydrochloride 10 mg/mL, net price 120 mL = £49.25. Label: 2

**Injection**, oxycodone hydrochloride 10 mg/mL, net price 1-mL amp = £1.60, 2-mL amp = £3.20

**Note** The Scottish Medicines Consortium has advised (October 2004) that OxyNorm injection is used only in patients with cancer who have difficulty in tolerating morphine or diamorphine

**Modified release**

**OxyContin®** (Napp)

**Tablets**, f/c, m/r, oxycodone hydrochloride 5 mg (blue), net price 28-tab pack = £13.23; 10 mg (white), 56-tab pack = £26.45; 20 mg (pink), 56-tab pack = £52.89; 40 mg (yellow), 56-tab pack = £105.80; 80 mg (green), 56-tab pack = £211.61. Label: 2

**Dose** initially 10 mg every 12 hours, increased if necessary according to severity of pain, usual max. 200 mg every 12 hours, but some patients may require higher doses; CHILD under 18 years, see BNF for Children

**PAPAVERETUM**

**Important** Do not confuse with papaverine (section 7.4.5)

A mixture of 253 parts of morphine hydrochloride, 23 parts of papaverine hydrochloride and 20 parts of codeine hydrochloride

The CSM has advised that to avoid confusion the figures of 7.7 mg/mL or 15.4 mg/mL should be used for prescribing purposes

**Indications** premedication; enhancement of anaesthesia (but see section 15.1.4.3); postoperative analgesia; severe chronic pain

**Caution** see notes above; supraventricular tachycardia

**Contra-indications** see notes above; heart failure secondary to chronic lung disease; phaeochromocytoma

**Side-effects** see notes above; also hypothermia

**Dose**

- By subcutaneous, intramuscular, or intravenous injection, 7.7–15.4 mg repeated every 4 hours if necessary (ELDERLY initially 7.7 mg); CHILD up to 1 month 115 micrograms/kg, 1–12 months 154 micro-
PENTAZOCINE

Indications moderate to severe pain, but see notes above

Cautions see notes above; also pancreatitis, arterial or pulmonary hypertension, cardiac arrhythmias, myocardial infarction, pheochromocytoma; effects only partially reversed by naloxone

Contra-indications see notes above; patients dependent on opioids (can precipitate withdrawal); heart failure secondary to chronic lung disease; acute porphyria (section 9.8.2)

Side-effects see notes above; also abdominal pain, hypertension, syncope, seizures, paraesthesia, tremor, raised intracranial pressure, disorientation, hypothermia, chills, blood disorders, myalgia, and toxic epidermal necrolysis

Dose
• By mouth, pentazocine hydrochloride 50 mg every 3–4 hours preferably after food (range 25–100 mg); max. 600 mg daily; CHILD 6–12 years 25 mg
• By subcutaneous, intramuscular, or intravenous injection, moderate pain, pentazocine 30 mg, severe pain 45–60 mg every 3–4 hours when necessary; CHILD over 1 year, by subcutaneous or intramuscular injection, up to 1 mg/kg, by intravenous injection up to 500 micrograms/kg
• By rectum in suppositories, pentazocine 50 mg up to 4 times daily; CHILD not recommended

Pentazocine (Non-proprietary) Capsules, pentazocine hydrochloride 50 mg. Net price 28-cap pack = £1.57. Label: 2, 21
Brands include Fortral

Tablets, pentazocine hydrochloride 25 mg. Net price 28-tab pack = £0.83. Label: 2, 21
Brands include Fortral

Injection, pentazocine 30 mg (as lactate)/mL. Net price 1-mL amp = £1.67; 2-mL amp = £3.21
Brands include Fortral

PETRIDINE HYDROCHLORIDE

Indications moderate to severe pain, obstetric analgesia; peri-operative analgesia

Cautions see notes above; not suitable for severe continuing pain; accumulation of metabolites may result in neurotoxicity; cardiac arrhythmias, severe cor pulmonale

Contra-indications see notes above; pheochromocytoma

Side-effects see notes above; also restlessness and hypothermia; convulsions reported in overdosage

Dose
• Acute pain, by mouth, 50–150 mg every 4 hours; CHILD 0.5–2 mg/kg
• By subcutaneous or intramuscular injection, 25–100 mg, repeated after 4 hours; CHILD, by intramuscular injection, 0.5–2 mg/kg
• By slow intravenous injection, 25–50 mg, repeated after 4 hours
• Obstetric analgesia, by subcutaneous or intramuscular injection, 50–100 mg, repeated 1–3 hours later if necessary; max. 400 mg in 24 hours
• Premedication, by intramuscular injection, 25–100 mg 1 hour before operation; CHILD 0.5–2 mg/kg
• Postoperative pain, by subcutaneous or intramuscular injection, 25–100 mg, every 2–3 hours if necessary; CHILD, by intramuscular injection, 0.5–2 mg/kg

Note In the postoperative period, the patient should be closely monitored for pain relief as well as for side-effects especially respiratory depression

Pethidine (Non-proprietary) Tablets, pethidine hydrochloride 50 mg, net price 20 = £2.07. Label: 2

Injection, pethidine hydrochloride 50 mg/mL, net price 1-mL amp = 53p, 2-mL amp = 56p; 10 mg/mL, 5-mL amp = £3.17, 10-mL amp = £2.18

Pamergan P100® (Martindale) Injection, pethidine hydrochloride 50 mg, promethazine hydrochloride 25 mg/mL. Net price 2-mL amp = £1.44

Dose by intramuscular injection, premedication, 2 mL 60–90 minutes before operation; CHILD 6–12 years 0.75 mL, 13–16 years 1 mL

Obstetric analgesia, 1–2 mL every 4 hours if necessary

Severe pain, 1–2 mL every 4–6 hours if necessary

Note Although usually given intramuscularly, may be given intravenously after dilution to at least 10 mL with water for injections

TRAMADOL HYDROCHLORIDE

Indications moderate to severe pain

Cautions see notes above; impaired consciousness; excessive bronchial secretions; not suitable as a substitute in opioid-dependent patients

General anaesthesia Not recommended for anaesthesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported)

Contra-indications see notes above; uncontrolled epilepsy; acute porphyria (section 9.8.2)

Side-effects see notes above; also diarrhoea; fatigue; less commonly retching, gastritis, and flatulence; rarely anorexia, syncope, hypertension, bronchospasm, dysphoria, wheezing, seizures, paraesthesia, and muscle weakness; blood disorders also reported

Dose
• ADULT and CHILD over 12 years, by mouth, 50–100 mg not more often than every 4 hours; total of more than 400 mg daily not usually required
• ADULT and CHILD over 12 years, by intramuscular injection or by intravenous injection (over 2–3
4.7.3 Neuropathic pain

Neuropathic pain, which occurs as a result of damage to neural tissue, includes postherpetic neuralgia (see below), phantom limb pain, complex regional pain syndrome (reflex sympathetic dystrophy, causalgia) compression neuropathies, peripheral neuropathies (e.g. due to diabetes, haematological malignancies, rheumatoid arthritis, alcoholism, drug misuse), trauma, central pain (e.g. pain

---

**Tramadol Hydrochloride**

- **Capsules**, tramadol hydrochloride 50 mg, net price 30-cap pack = £1.15; 100-cap pack = £2.21. Label: 2
- **Brands** include **Tramake**
- **Injection**, tramadol hydrochloride 50 mg/mL. Net price 2-mL amp = £1.15

**Tramadol (Meda)**

- **Capsules**, tramadol hydrochloride 50 mg, net price 100-cap pack = £8.00. Label: 2
- **Orodispersible tablets** (**Zamadol Melt®**), tramadol hydrochloride 50 mg, net price 60-tab pack = £7.12. Label: 2, counselling, administration
- **Excipients** include aspartame (section 9.4.1)
- **Counselling** **Zamadol Melt** should be sucked and then swallowed. May also be dispersed in water
- **Injection**, tramadol hydrochloride 50 mg/mL. Net price 2-mL amp = £1.10

**Modified release**

**Dromadol SR** (**IVAX**)**

- **Tablets**, m/r, tramadol hydrochloride 100 mg (white), net price 60-tab pack = £12.78; 150 mg (beige), 60-tab pack = £19.17; 200 mg (orange), 60-tab pack = £25.56. Label: 2, 25
- **Dose** _ADULT and CHILD_ over 12 years, initially 100 mg twice daily increased if necessary; usual max. 200 mg twice daily

**Larapam SR** (**Sandoz**)**

- **Tablets**, m/r, tramadol hydrochloride 100 mg, net price 60-tab pack = £18.25; 150 mg, 60-tab pack = £27.35; 200 mg, 60-tab pack = £36.50. Label: 2, 25
- **Dose** _ADULT and CHILD_ over 12 years, initially 100 mg twice daily increased if necessary; usual max. 200 mg twice daily

**Mabron®** (**Morningside**)**

- **Tablets**, m/r, tramadol hydrochloride 100 mg, net price 60-tab pack = £18.26; 150 mg, 60-tab pack = £27.39; 200 mg, 60-tab pack = £36.52. Label: 2, 25
- **Dose** _ADULT and CHILD_ over 12 years, 100 mg twice daily increased if necessary; max. 200 mg twice daily

**Maxitram SR®** (**Trinity-Chiesi**)**

- **Capsules**, m/r, tramadol hydrochloride 50 mg (white), net price 60-cap pack = £6.48; 100 mg (yellow), 60-cap pack = £12.14; 150 mg (yellow), 60-cap pack = £18.21; 200 mg (yellow), 60-cap pack = £24.28. Label: 2, 25
- **Dose** _ADULT and CHILD_ over 12 years, 100–200 mg twice daily, total of more than 400 mg daily not usually required
following stroke, spinal cord injury and syringomyelia) and idiopathic neuropathy. The pain occurs in an area of sensory deficit and may be described as burning, shooting or scalding and is often accompanied by pain that is evoked by a non-noxious stimulus (allodynia).

Trigeminal neuralgia is also caused by dysfunction of neural tissue, but its management (see below) is distinct from other forms of neuropathic pain.

Neuropathic pain is generally managed with a tricyclic antidepressant and certain antiepileptic drugs. Neuropathic pain may respond only partially to opioid analgesics. Of the opioids, methadone, tramadol, and oxycodeone are probably the most effective for neuropathic pain and they may be considered when other measures fail. Nerve blocks, transcutaneous electrical nerve stimulation (TENS) and, in selected cases, central electrical stimulation may help. Many patients with chronic neuropathic pain require multidisciplinary management, including physiotherapy and psychological support.

Gabapentin (p. 252) and pregabalin (p. 253) are effective for the treatment of neuropathic pain. Amitriptyline (p. 208) is also prescribed frequently (unlicensed indication); nortriptyline (unlicensed indication) (p. 210) may be better tolerated than amitriptyline.

Capsaicin (section 10.3.2) is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use). Ketamine (section 15.1.1), an NMDA antagonist, or lidocaine (lignocaine) by intravenous infusion may also be useful in some forms of neuropathic pain (both unlicensed indication; specialist use only).

A corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain. The management of trigeminal neuralgia and postherpetic neuralgia are outlined below; for the management of neuropathic pain in palliative care see p. 16; for the management of diabetic neuropathy, see section 6.1.5.

**Trigeminal neuralgia**

Surgery may be the treatment of choice in many patients; a neurological assessment will identify those who stand to benefit. Carbamazepine (section 4.8.1) taken during the acute stages of trigeminal neuralgia, reduces the frequency and severity of attacks. It is very effective for the severe pain associated with trigeminal neuralgia and (less commonly) glossopharyngeal neuralgia. Blood counts and electrolytes should be monitored when high doses are given. Small doses should be used initially to reduce the incidence of side-effects e.g. dizziness. Oxcarbazepine [unlicensed indication] is an alternative to carbamazepine. Lamotrigine [unlicensed indication] and gabapentin are also used in trigeminal neuralgia. Some cases respond to phenytoin (section 4.8.1); the drug may be given by intravenous infusion (possibly as fosphenytoin) in a crisis (specialist use only).

**Postherpetic neuralgia**

Postherpetic neuralgia can follow acute herpes zoster infection (shingles), particularly in the elderly. If amitriptyline [unlicensed indication] fails to manage the pain adequately, gabapentin may improve control. A topical analgesic preparation containing capsaicin 0.075% (section 10.3.2) is licensed for use in postherpetic neuralgia. Application of topical local anaesthetic preparations such as lidocaine medicated plasters (section 15.2) may be helpful in some patients.

**Chronic facial pain**

Chronic oral and facial pain including persistent idiopathic facial pain (also termed ‘atypical facial pain’) and temporomandibular dysfunction (previously termed temporomandibular joint pain dysfunction syndrome) may call for prolonged use of analgesics or for other drugs. Tricyclic antidepressants (section 4.3.1) may be useful for facial pain [unlicensed indication], but are not on the Dental Practitioners’ List. Disorders of this type require specialist referral and psychological support to accompany drug treatment. Patients on long-term therapy need to be monitored both for progress and for side-effects.

**Central nervous system**

**4.7.4 Antimigraine drugs**

**4.7.4.1 Treatment of acute migraine**

**4.7.4.2 Prophylaxis of migraine**

**4.7.4.3 Cluster headache**

Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A simple analgesic such as aspirin, paracetamol (preferably in a soluble or dispersible form) or a NSAID is often effective; concomitant antimetoc treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as a 5HT agonist (‘trip-tan’). Ergot alkaloids are rarely required now, oral and rectal preparations are associated with many side-effects and they should be avoided in cerebrovascular or cardiovascular disease.

Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs careful management.

**Analgesics**

Most migraine headaches respond to analgesics such as aspirin or paracetamol (section 4.7.1) but because peristalsis is often reduced during migraine attacks the medication may not be sufficiently well absorbed to be effective; dispersible or effervescent preparations are therefore preferred.

The NSAID tolfenamic acid is licensed specifically for the treatment of an acute attack of migraine; diclofenac potassium, flurbiprofen, ibuprofen, and naproxen sodium (section 10.1.1) are also licensed for use in migraine.
4.7.4 Antimigraine drugs

**ANALGESICS**

- **Aspirin**
  Section 4.7.1
- **Paracetamol**
  Section 4.7.1
- **Non-steroidal anti-inflammatory drugs (NSAIDs)**
  Section 10.1.1

**With antiemetics**

- **Migraleve** (McNeil)
  Tablets, all 1/2 c, pink tablets, buclizine hydrochloride 6.25 mg, paracetamol 500 mg, codeine phosphate 8 mg; yellow tablets, paracetamol 500 mg, codeine phosphate 8 mg. Yellow price 48-tab Migraleve (32 pink + 16 yellow) = £5.10; 48 pink (Migraleve Pink) = £5.56; 48 yellow (Migraleve Yellow) = £4.70. Label: 2, (Migraleve Pink), 17, 30

- **MigraMax** (Zeneus)
  Tablets, 12.5 mg, net price 3-tab pack = £9.07; 6-tab pack = £18.14; 9-tab pack = £27.20. Label: 3

- **Paramax** (Sanofi-Synthelabo)
  Tablets, scored, paracetamol 500 mg, metoclopramide hydrochloride 5 mg. Net price 42-tab pack = £8.03. Label: 17, 30

**TOLFENAMIC ACID**

**Indications** treatment of acute migraine

**Cautions** see NSAIDs, section 10.1.1

**Contra-indications** see NSAIDs, section 10.1.1

**Side-effects** see NSAIDs, section 10.1.1; also dysuria

**Dose**

- **ADULT** over 18 years, 200 mg at onset repeated once after 1–2 hours if necessary

- **Clotam Rapid** (Galen)
  Tablets, tolafenamic acid 200 mg. Net price 10-tab pack = £15.00. Label: 21

**5HT1 agonists**

A 5HT agonist is of considerable value in the treatment of an acute migraine attack. The 5HT agonists (‘triptans’) act on the 5HT (serotonin) 1B/1D receptors and they are therefore sometimes referred to as 5HT receptor agonists. A 5HT agonist may be used during the established headache phase of an attack and is the preferred treatment in those who fail to respond to conventional analgesics.

The 5HT agonists available for treating migraine are almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. Sumatriptan is also of value in cluster headache (section 4.7.4.3).

**Cautions** 5HT agonists should be used with caution in conditions which predispose to coronary artery disease (pre-existing cardiac disease, see Contra-indications below); hepatic impairment (see Appendix 2); pregnancy (see Appendix 4) and breast-feeding (see Appendix 5). 5HT agonists are recommended as mono-therapy and should not be taken concurrently with other therapies for acute migraine; see also interactions: Appendix 1 (5HT agonists). Little information is available on the use of these drugs in the elderly (over 65 years).

**Contra-indications** 5HT agonists are contra-indicated in ischaemic heart disease, previous myocardial infarction, coronary vasospasm (including Prinzmetal’s angina), and uncontrolled or severe hypertension.

**Side-effects** Side-effects of the 5HT agonists include sensations of tingling, heat, heaviness, pressure, or tightness of any part of the body (including throat and chest—discontinue if intense, may be due to coronary vasoconstriction or to anaphylaxis; see also CSM advice under Sumatriptan); flushing, dizziness, feeling of weakness; fatigue; nausea and vomiting also reported.

**ALMOTRIPTAN**

**Indications** treatment of acute migraine

**Cautions** see under 5HT agonists above; sensitivity to sulphonamides; hepatic impairment (avoid if severe—Appendix 2); renal impairment (Appendix 3); inter- actions: Appendix 1 (5HT agonists)

**Contra-indications** see under 5HT agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease

**Side-effects** see under 5HT agonists above; also transient increase in blood pressure, drowsiness; less commonly diarrhoea, dyspepsia, dry mouth, chest pain, palpitation, paraesthesia, headache, myalgia, bone pain, tinnitus; very rarely myocardial infarction, and tachycardia

**Dose**

- 12.5 mg as soon as possible after onset repeated after 2 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 25 mg in 24 hours; CHILD and ADOLESCENT under 18 years not recommended

- **Almogran** (Organon)
  Tablets, 1/2 c, almogran (as hydrogen maleate) 12.5 mg, net price 3-tab pack = £9.07; 6-tab pack = £18.14; 9-tab pack = £27.20. Label: 3
**ELETRIPTAN**

**Indications** treatment of acute migraine

**Cautions** see under 5HT agonists above; renal impairment (avoid if severe—Appendix 3); interactions: Appendix 1 (5HT agonists)

**Contra-indications** see under 5HT agonists above; previous cerebrovascular accident or transient ischaemic attack; arrhythmias; heart failure; peripheral vascular disease; severe hepatic impairment

**Side-effects** see under 5HT agonists above; also abdominal pain, dry mouth, dyspepsia; tachycardia, palpitation; drowsiness, headache; pharyngitis, rhinitis, chills; myasthenia, myalgia; sweating; less commonly diarrhoea, glossitis, thirst, anorexia, taste disturbance; dyspnoea, yawning, oedema, agitation, confusion, euphoria, depression, insomnia, depersonalisation, tremor, dysarthria, stupor, movement disorders, hypertonia, urinary frequency, arthralgia, photophobia, visual disturbances, tinnitus, rash, and pruritus; rarely constipation, oesophagitis, bradyarrhythmias, asthma, syncope, lymphadenopathy, and menorrhagia; ischaemic colitis and hypertension also reported

**Dose**

- **ADULT** over 18 years, 40 mg repeated after 2 hours if migraine recurs (patient not responding to initial dose should not take second dose for same attack); increase to 80 mg for subsequent attacks if 40-mg dose inadequate; max. 80 mg in 24 hours

*Relpax* (Pfizer) ▼

Tablets, f/c, orange, eletriptan (as hydrobromide)

20 mg, net price 6-tab pack = £22.50; 40 mg, 6-tab pack = £22.50. Label: 3

**NARATRIPTAN**

**Indications** treatment of acute migraine

**Cautions** see under 5HT agonists above; sensitivity to sulphonamides; renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3); interactions: Appendix 1 (5HT agonists)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving)

**Contra-indications** see under 5HT agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease

**Side-effects** see under 5HT agonists above; also less commonly bradyarrhythmias, tachycardia, palpitation, and visual disturbance; rarely ischaemic colitis

**Dose**

- 2.5 mg, repeated after at least 4 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 5 mg in 24 hours; **CHILD** and **ADOLESCENT** under 18 years not recommended

*Naramig*® (GSK)

Tablets, f/c, green, naratriptan (as hydrochloride)

2.5 mg, net price 6-tab pack = £24.55, 12-tab pack = £49.10. Label: 3

**RIZATRIPTAN**

**Indications** treatment of acute migraine

**Cautions** see under 5HT agonists above; renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); interactions: Appendix 1 (5HT agonists)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving)

**Contra-indications** see under 5HT agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease

**Side-effects** see under 5HT agonists above; drowsiness, palpitation, tachycardia, dry mouth, diarrhoea, dyspepsia, thirst, pharyngeal discomfort, dyspnoea, headache, paraesthesia, decreased alertness, insomnia, tremor, ataxia, nervousness, vertigo, confusion, myalgia and muscle weakness, sweating, urticaria, pruritus, blurred vision; rarely syncope, hypertension; hypersensitivity reactions (including rash, angioedema, and toxic epidermal necrolysis) and taste disturbance reported

**Dose**

- 10 mg as soon as possible after onset repeated after 2 hours if migraine recurs (patient not responding should not take second dose for same attack); max. 20 mg in 24 hours; **CHILD** and **ADOLESCENT** under 18 years not recommended

*Maxalt*® (MSD)

Tablets, pink, rizatriptan (as benzoate) 5 mg, net price 6-tab pack = £26.74; 10 mg, 3-tab pack = £13.37, 6-tab pack = £26.74. Label: 3

Oral lyophilisate (*Maxalt*® Melt Wafers), rizatriptan (as benzoate) 10 mg, net price 3-wafer pack = £13.37.
4 Central nervous system

6-wafer pack = £26.74. Label: 3, counselling, administration. Counselling Melt wafers should be placed on the tongue and allowed to dissolve. Excipients include aspartame equivalent to phenylalanine 2.1 mg (section 9.4.1).

SUMATRIPTAN

Indications treatment of acute migraine; cluster headache (subcutaneous injection only)

Cautions see under 5HT agonists above; history of seizures; renal impairment; sensitivity to sulphonamides; interactions: Appendix 1 (5HT agonists)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications see under 5HT agonists above; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease; moderate and severe hypertension

Side-effects see under 5HT agonists above; also drowsiness, transient increase in blood pressure; very rarely ischaemic colitis, hypotension, bradycardia or tachycardia, palpitation, arrhythmias, myocardial infarction, Raynaud's syndrome, seizures, tremor, dystonia, nystagmus, and visual disturbances; erythema at injection site; nasal irritation and epistaxis with nasal spray

CSM advice Following reports of chest pain and tightness (coronary vasospastic/vasoconstrictive) CSM has emphasised that sumatriptan should not be used in ischaemic heart disease or Prinzmetal's angina, and that use with ergotamine should be avoided (see also Cautions).

Dose

- By mouth, 50 mg (some patients may require 100 mg); dose may be repeated after at least 2 hours if migraine recurs; max. 300 mg in 24 hours; CHILD and ADOLESCENT under 18 years, see BNF for Children

- By subcutaneous injection using auto-injector, 6 mg; dose may be repeated once after at least 1 hour if migraine recurs; max. 12 mg in 24 hours; CHILD and ADOLESCENT under 18 years not recommended

Important Not for intravenous injection which may cause coronary vasospasm and angina

- Intranasally, 10–20 mg (ADOLESCENT 12–17 years) into one nostril; dose may be repeated once after at least 2 hours if migraine recurs; max. 40 mg (ADOLESCENT 12–17 years 20 mg) in 24 hours

Note Patient not responding to initial dose should not take second dose for same attack

1 Sumatriptan (Non-proprietary) (Astrazeneca)

Tablets, sumatriptan (as succinate) 50 mg, net price 6-tab pack = £9.09; 100 mg, 6-tab pack = £13.77. Label: 3, 10, patient information leaflet

1 Sumatriptan 50 mg tablets can be sold to the public to treat previously diagnosed migraine; max. daily dose 100 mg

Imigran® (GSK) (Astrazeneca)

Tablets, sumatriptan (as succinate) 50 mg, net price 6-tab pack = £27.62, 12-tab pack = £52.48; 100 mg, 6-tab pack = £44.64, 12-tab pack = £89.28. Label: 3, 10, patient information leaflet

Injection, sumatriptan (as succinate) 12 mg/mL (= 6/0.5 mL syringe), net price, treatment pack (2 x 0.5 mL prefilled syringes and auto-injector) = £44.19; refill pack 2 x 0.5 mL prefilled cartridges = £42.05. Label: 3, 10, patient information leaflet

Nasal spray, sumatriptan 10 mg/0.1 mL actuation, net price 2 unit-dose spray device = £12.28; 20 mg/0.1 mL actuation, 2 unit-dose spray device = £12.28, 6 unit-dose spray device = £36.83. Label: 3, 10, patient information leaflet

Imigran® Radis (GSK)

Tablets, f/c, sumatriptan (as succinate) 50 mg (pink), net price 6-tab pack = £24.87, 12-tab pack = £49.77; 100 mg (white), 6-tab pack = £44.64, 12-tab pack = £89.28. Label: 3, 10, patient information leaflet

ZOLMITRIPTAN

Indications treatment of acute migraine

Cautions see under 5HT agonists above; should not be taken within 12 hours of any other 5HT agonist; interactions: Appendix 1 (5HT agonists)

Contra-indications see under 5HT agonists above; Wolff-Parkinson-White syndrome or arrhythmias associated with accessory cardiac conduction pathways; previous cerebrovascular accident or transient ischaemic attack

Side-effects see under 5HT agonists above; also dry mouth, drowsiness, paraesthesia, myalgia, muscle weakness; rarely palpitation, tachycardia, angioedema, headache, urticaria; very rarely abdominal pain, gastro-intestinal and splenic infarction, ischaemic colitis, angina, myocardial infarction, polyuria, transient increase in blood pressure; with nasal spray, taste disturbance and nasal discomfort

Dose

- By mouth, ADOLESCENT over 18 years, 2.5 mg repeated after not less than 2 hours if migraine persists or recurs (increase to 5 mg for subsequent attacks in patients not achieving satisfactory relief with 2.5-mg dose); max. 10 mg in 24 hours

- Intranasally, ADOLESCENT over 18 years, 5 mg (1 spray) into one nostril as soon as possible after onset repeated after not less than 2 hours if migraine persists or recurs; max. 10 mg in 24 hours

Zomig® (AstraZeneca)

Tablets, f/c, yellow, zolmitriptan 2.5 mg, net price 6-tab pack = £24.00, 12-tab pack = £48.00

Ordispersible tablets (Zomig Rapimelt®), zolmitriptan 2.5 mg, net price 6-tab pack = £24.00; 5 mg, 6-tab pack = £26.16 Counselling, administration

Counselling Zomig Rapimelt should be placed on the tongue, allowed to disperse and swallowed. Excipients include aspartame equivalent to phenylalanine 2.81 mg/tablet (section 9.4.1)

Nasal spray, zolmitriptan 5 mg/0.1 mL unit-dose spray device, net price 6 unit-dose sprays = £40.50

Ergotalkaloids

The value of ergotamine for migraine is limited by difficulties in absorption and by its side-effects, particularly nausea, vomiting, abdominal pain, and muscular cramps; it is best avoided. The recommended doses of ergotamine preparations should not be exceeded and treatment should not be repeated at intervals of less than 4 days.

To avoid habituation the frequency of administration of ergotamine should be limited to no more than twice a month. It should never be prescribed prophylactically but in the management of cluster headache a low dose (e.g. ergotamine 1 mg at night for 6 nights in 7) is
Antiemetics (section 4.6), such as metoclopramide or domperidone, or phenothiazine and antihistamine antiemetics, relieve the nausea associated with migraine attacks. Antiemetics may be given by intramuscular injection or rectally if vomiting is a problem. Metoclopramide and domperidone have added the advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms. Oral analgesic preparations containing metoclopramide are a convenient alternative (important: for warnings relating to extrapyramidal effects of metoclopramide particularly in children and young adults, see p. 222).

### ERGOTAMINE TARTRATE

**Indications** treatment of acute migraine and migraine variants unresponsive to analgesics

**Cautions** risk of peripheral vasospasm (see below); elderly; dependence (see Ergot Alkaloids above); cardiac disease; anaemia; interaction: Appendix 1 (ergot alkaloids)

**Peripheral vasospasm** Warn patient to stop treatment immediately if numbness or tingling of extremities develops and to contact doctor.

**Contra-indications** peripheral vascular disease, coronary heart disease, obliterator vascular disease and Raynaud’s syndrome, temporal arteritis, hepatic impairment (Appendix 2), renal impairment (Appendix 3), sepsis, severe or inadequately controlled hypertension, hyperthyroidism, pregnancy (Appendix 4), breast-feeding (Appendix 3), acute porphyria (section 9.8.2)

**Side-effects** abdominal pain, nausea, vomiting; dizzeness; less commonly diarrhoea, pain and weakness in extremities, cyanosis, peripheral vasoconstriction, paraesthesia, and hypoesthesia; rarely intestinal ischaemia, arrhythmias, increased blood pressure, dyspnoea, ergotism (including absence of pulse and numbness in extremities), myalgia, rash, and urticaria; very rarely myocardial ischaemia, myocardial infarction, heart-valve fibrosis, and gangrene; constipation, dry mouth, cerebral ischaemia, thrombosis, drowsiness, sleep disturbances, tremor, seizures, extrapyramidal effects, anxiety, depression, confusion, hallucinations, renal artery spasm, urinary retention, blood disorders, blurred vision, and arthralgia also reported; with suppositories rectal and anal ulcers on prolonged use

**Dose**

- See under preparations below

**Cafergot® (Alliance)**

<table>
<thead>
<tr>
<th>Tablets, s/c, ergotamine tartrate 1 mg, caffeine 100 mg. Net price 30-tab pack = £5.02. Label: 18, counselling, dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose: ADULT and CHILD over 12 years, 1–2 tablets at onset; max. 4 tablets in 24 hours; not to be repeated at intervals of less than 4 days; max. 8 tablets in one week (but see also notes above)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suppositories, ergotamine tartrate 2 mg, caffeine 100 mg. Net price 30 = £10.13. Label: 18, counselling, dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose: ADULT and CHILD over 12 years, 1 suppository at onset; max. 2 in 24 hours; max. 4 suppositories in one week (but see also notes above)</td>
</tr>
</tbody>
</table>

**Migril® (CP)**

<table>
<thead>
<tr>
<th>Tablets, scored, ergotamine tartrate 2 mg, cyclizine hydrochloride 50 mg, caffeine hydroxy 100 mg. Net price 20 = £10.20. Label: 2, 18, counselling, dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose: 1 tablet at onset, followed after 30 minutes by ½–1 tablet, repeated every 30 minutes if necessary; max. 3 tablets in 24 hours, 4 tablets per attack, 6 tablets in one week (but see also notes above), CHILD not recommended</td>
</tr>
</tbody>
</table>

**ANTIEMETICS**

**Indications** prevention of vascular headache including classical migraine, common migraine, and cluster headache

**PIZOTIFEN**

**Indications** prevention of vascular headache including classical migraine, common migraine, and cluster headache

**4.7.4 Prophylaxis of migraine**

Where migraine attacks are frequent, possible provoking factors such as stress, irregular life-style (e.g. lack of sleep), or chemical triggers (e.g. alcohol and nitrates) should be sought; combined oral contraceptives may also provoke migraine, see section 7.3.1 for advice.

Preventive treatment for migraine should be considered for patients who:

- suffer at least two attacks a month;
- suffer an increasing frequency of headaches;
- suffer significant disability despite suitable treatment for migraine attacks;
- cannot take suitable treatment for migraine attacks.

Prophylaxis is also necessary in some rare migraine subtypes and those at risk of migraineous infarction.

The beta-blockers propranolol, metoprolol, nadolol, and timolol (section 2.4) are all effective. Propranolol is the most commonly used.

Pizotifen is an antihistamine and serotonin antagonist structurally related to the tricyclic antidepressants. It affords good prophylaxis but may cause weight gain. To avoid undue drowsiness treatment may be started at a low dose and gradually increased.

**Sodium valproate** (section 4.8.1) may be effective for migraine prophylaxis [unlicensed indication] in a starting dose of 300 mg twice daily, increased if necessary to 1.2 g daily in divided doses. **Valproic acid** (as semisodium valproate) (section 4.2.3) is similarly effective [unlicensed indication] in a starting dose of 250 mg twice daily, increased if necessary to 1 g daily in divided doses.

**Topiramate** (section 4.8.1) is effective for migraine prophylaxis. Treatment should be supervised by a specialist.

Tricyclic antidepressants (section 4.3.1) (e.g. amitriptyline) are also used for preventing migraine [unlicensed indication].

Cyproheptadine (section 3.4.1), an antihistamine with serotonin-antagonist and calcium channel-blocking properties, may also be tried in refractory cases.

Clonidine (Dixari®) is not recommended and may aggravate depression or produce insomnia. Methysergide, a semi-synthetic ergot alkaloid, has dangerous side-effects (retroperitoneal fibrosis and fibrosis of the heart valves and pleura); important: it should only be administered under hospital supervision.
Central nervous system

Cautions urinary retention; susceptibility to angle-closure glaucoma; renal impairment; pregnancy; breast-feeding (Appendix 5); interactions: Appendix 1 (pizotifen)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Side-effects antimuscarinic effects (very rarely angle-closure glaucoma), drowsiness, increased appetite and weight gain; occasionally nausea, dizziness, rarely anxiety, aggression, and depression; CNS stimulation may occur in children

Dose

- Initially 500 micrograms at night increased gradually to usual dose of 1.5 mg at night or in 3 divided doses; may be further increased up to max. daily dose 4.5 mg (but rarely necessary), max. single dose 3 mg; CHILD over 2 years, up to 1.5 mg daily in divided doses; max. single dose at night 1 mg

Pizotifen (Non-proprietary) [AU]
Tablets, pizotifen (as hydrogen maleate), 500 micrograms, net price 28-tab pack = £1.37; 1.5 mg, 28-tab pack = £2.75. Label: 2

Sanomigran® (Novartis) [AU]
Tablets, both ivory-yellow, s/c, pizotifen (as hydrogen maleate), 500 micrograms, net price 60-tab pack = £2.57; 1.5 mg, 28-tab pack = £4.28. Label: 2

Elixir, pizotifen (as hydrogen maleate) 250 micrograms/5 mL, net price 300 mL = £4.51. Label: 2

Contra-indications renal, hepatic, pulmonary, and cardiovascular disease, severe hypertension, collagen disease, cellulitis, urinary-tract disorders, cachectic or septic conditions, pregnancy, breast-feeding

Side-effects nausea, vomiting, heartburn, abdominal discomfort, drowsiness, and dizziness occur frequently in initial treatment; mental and behavioural disturbances, insomnia, oedema, weight gain, rashes, loss of scalp hair, cramps, arterial spasm (including coronary artery spasm with angina and possible myocardial infarction), paraesthesias of extremities, postural hypotension, and tachycardia also occur; retroperitoneal and other abnormal fibrotic reactions may occur on prolonged administration, requiring immediate withdrawal of treatment

Dose

- Initially 1 mg at bedtime, increased gradually over about 2 weeks to 1–2 mg 3 times daily with food (see notes above); CHILD not recommended

- Diarrhoea associated with carcinoid syndrome, usual range, 12–20 mg daily (hospital supervision); CHILD not recommended

Deseril® (Alliance) [AU]
Tablets, s/c, methysergide (as maleate) 1 mg, net price 60-tab pack = £13.46. Label: 2, 21

4.8 Antiepileptic drugs

4.8.1 Control of epilepsy

4.8.2 Drugs used in status epilepticus

4.8.3 Febrile convulsions

4.7.4.3 Cluster headache

Cluster headache rarely responds to standard analgesics. Sumatriptan given by subcutaneous injection is the drug of choice for the treatment of cluster headache. Alternatively, 100% oxygen at a rate of 7–12 litres/minute is useful in aborting an attack.

Prophylaxis of cluster headache is considered if the attacks are frequent, or last over 3 weeks, or if the attacks cannot be treated effectively. Verapamil or lithium [both unlicensed use] are used for prophylaxis. Ergotamine, used on an intermittent basis is an alternative for patients with short bouts, but it should not be used for prolonged periods. Methysergide is effective but must be used with extreme caution (section 4.7.4.2) and only if other drugs cannot be used or if they are not effective.

4.8 Antiepileptic drugs

The object of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Careful adjustment of doses is necessary, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.

When choosing an antiepileptic drug, the seizure type, concomitant medication, co-morbidity, age, and sex should be taken into account. For women of child-bearing age, see Pregnancy and Breast-feeding, p. 250.
The dose frequency is often determined by the plasma-drug half-life, and should be kept as low as possible to encourage adherence with the prescribed regimen. Most antiepileptics, when used in the usual dosage, may be given twice daily. Lamotrigine, phenobarbital, and phenytoin, which have long half-lives, can be given once daily at bedtime. However, with large doses, some antiepileptics may need to be given more frequently to avoid adverse effects associated with high peak plasma-drug concentration. Young children metabolise antiepileptics more rapidly than adults and therefore require more frequent doses and a higher dose in proportion to their body-weight.

Interaction	Interactions	Interactions between antiepileptic drugs

Phenobarbital or Primidone

Often lowers plasma concentration of phenytoin

Oxcarbazepine

Sometimes lowers plasma concentration of carbamazepine (but may raise concentration of an active metabolite of carbamazepine)

Phenytoin

Often lowers plasma concentration of clonazepam, carbamazepine, lamotrigine, and of phenytoin (but may also raise phenytoin concentration), tiagabine, valproate, and zonisamide

Levetiracetam

No interactions with levetiracetam reported

Valproate

Sometimes raises plasma concentration of an active metabolite of oxcarbazepine

Pregabalin

No interactions with pregabalin reported

Somewhat raises plasma concentration of phenytoin

Topiramate

Sometimes raises plasma concentration of phenytoin

Somewhat raises plasma concentration of an active metabolite of oxcarbazepine

Rufinamide

Sometimes raises plasma concentration of phenytoin

Sometimes lowers plasma concentration of phenobarbital

Vigabatrin

Often lowers plasma concentration of phenytoin

Sometimes lowers plasma concentration of phenobarbital, and primidone

For other important interactions see Appendix 1; for advice on hormonal contraception and enzyme-inducing drugs (including antiepileptics), see section 7.3.1 and section 7.3.2.

Withdrawal

Antiepileptic drugs should be withdrawn under specialist supervision. Abrupt withdrawal, particularly of the barbiturates and benzodiazepines, should be avoided because this may precipitate severe rebound seizures. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months.

The decision to withdraw antiepileptic drugs from a seizure-free patient, and its timing, is often difficult and depends on individual circumstances. Even in patients who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal.

In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.
Central nervous system

**Driving**  Patients suffering from epilepsy may drive a motor vehicle (but not a heavy goods or public service vehicle) provided that they have had a seizure-free period of one year or, if subject to attacks only while asleep, have established a 3-year period of asleep attacks without awake attacks. Patients affected by drowsiness should not drive or operate machinery.

Guidance issued by the Drivers Medical Unit of the Driver and Vehicle Licensing Agency (DVLA) recommends that patients should be advised not to drive during withdrawal of antiepileptic drugs, or for 6 months afterwards (see also Drugs and Driving under General Guidance, p. 3).

**Pregnancy and breast-feeding** There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (reduced if treatment is limited to a single drug). In view of the increased risk of neural tube and other defects associated, in particular, with carbamazepine, lamotrigine, oxcarbazepine, phenytoin, and valproate, women taking antiepileptic drugs who may become pregnant should be informed of the possible consequences. Those who wish to become pregnant should be referred to an appropriate specialist for advice. Women who become pregnant should be counselled and offered antenatal screening (alpha-fetoprotein measurement and a second trimester ultrasound scan).

To counteract the risk of neural tube defects, adequate folate supplements are advised for women before and during pregnancy (section 9.1.2).

The concentration of antiepileptic drugs in the blood can change during pregnancy, particularly in the later stages. The dose of antiepileptic drugs should be monitored carefully during pregnancy and after birth, and adjustments made on a clinical basis.

Routine injection of vitamin K (section 9.6.6) at birth effectively counteracts any antiepileptic-associated risk of neonatal haemorrhage.

Breast-feeding is acceptable with all antiepileptic drugs, taken in normal doses, with the possible exception of the barbiturates, and also some of the more recently introduced ones, see Appendix 5.

**Partial seizures with or without secondary generalisation**

Carbamazepine, lamotrigine, oxcarbazepine, and sodium valproate are the drugs of choice for partial (focal) seizures; second-line drugs include clobazam, gabapentin, levetiracetam, pregabalin, tiagabine, topiramate, and zonisamide.

**Generalised seizures**

**Tonic-clonic seizures (grand mal)** The drugs of choice for tonic-clonic seizures are carbamazepine, lamotrigine, and sodium valproate. Clobazam, levetiracetam, oxcarbazepine, and topiramate are second-line drugs.

**Absence seizures (petit mal)** Ethosuximide and sodium valproate are the drugs of choice in typical absence seizures; alternatives include clonazepam and lamotrigine. Sodium valproate is also highly effective in treating the generalised tonic-clonic seizures which can co-exist with absence seizures in idiopathic primary generalised epilepsy.

**Myoclonic seizures** Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably. Sodium valproate is the drug of choice; clonazepam and levetiracetam can also be used. Alternatives include lamotrigine and topiramate, but lamotrigine may occasionally exacerbate myoclonic seizures. For reference to the adjunctive use of piracetam, see section 4.9.3.

Sodium valproate and levetiracetam are effective in treating the generalised tonic-clonic seizures that co-exist with myoclonic seizures in idiopathic generalised epilepsy.

**Atypical absence, tonic, and tonic seizures** Atypical absence, tonic, and tonic seizures are usually seen in childhood, in specific epilepsy syndromes, or associated with cerebral damage or mental retardation. They may respond poorly to the traditional drugs. Sodium valproate, lamotrigine, and clonazepam can be tried. Second-line drugs that are occasionally helpful include clobazam, ethosuximide, levetiracetam, and topiramate.

**Carbamazepine and oxcarbazepine**

Carbamazepine is a drug of choice for simple and complex partial seizures and for tonic-clonic seizures secondary to a focal discharge. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly with increments of 100–200 mg every two weeks. Reversible blurring of vision, dizziness, and unsteadiness are dose-related, and may be dose-limiting. These side-effects may be reduced by altering the timing of medication; use of modified-release tablets also significantly lessens the incidence of dose-related side-effects.

Oxcarbazepine is licensed for the treatment of partial seizures with or without secondarily generalised tonic-clonic seizures. Oxcarbazepine induces hepatic enzymes to a lesser extent than carbamazepine.

---

**CARBAMAZEPINE**

**Indications** partial and secondary generalised tonic-clonic seizures; primary generalised tonic-clonic seizures; trigeminal neuralgia; prophylaxis of bipolar disorder unresponsive to lithium

**Cautions** hepatic impairment (Appendix 2) or renal impairment; cardiac disease (see also Contra-indications); skin reactions (see also Blood, hepatic or skin disorders below and under Side-effects); test for HLA-B*1502 allele in individuals of Han Chinese or Thai origin—risk of Stevens-Johnson syndrome in presence of HLA-B*1502 allele; history of haematological reactions to other drugs; manufacturer recommends blood counts and hepatic and renal function tests (but evidence of practical value unsatisfactory); may exacerbate absence and myoclonic seizures; susceptibility to angle-closure glaucoma; pregnancy (important: see above and Appendix 4 (neural tube...
Carbamazepine (Non-proprietary) Tablets, carbamazepine 100 mg, net price 45-tab pack = £2.43; 200 mg, 45-tab pack = £4.50; 400 mg, 56-tab pack = £5.90. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Chewtabs, orange, carbamazepine 100 mg, net price 56-tab pack = £3.72; 200 mg, 56-tab pack = £6.92. Label: 3, 8, 21, 24, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Suppositories, carbamazepine 125 mg, net price 5 = £9.45; 250 mg, 5 = £12.60. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Dose epilepsy, for short-term use (max. 7 days) when oral therapy temporarily not possible, consider equivalent in therapeutic effect to tablets of 100 mg but final adjustment should always depend on clinical response (plasma concentration monitoring recommended); max. rectum 1 g daily in 4 divided doses

Modified release

Carbagene SR (Generics) Tablets, m/r, f/c, both scored, carbamazepine 200 mg, net price 56-tab pack = £4.88; 400 mg, 56-tab pack = £9.63. Label: 3, 8, 25, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Dose epilepsy (ADULT and CHILD over 5 years), as above, trigeminal neuralgia, as above; total daily dose given in 1–2 divided doses; bipolar disorder, as above

Tegretol® Retard (Novartis) Tablets, both scored, carbamazepine 200 mg (beige-orange), net price 56-tab pack = £5.52; 400 mg (brown-orange), 56-tab pack = £10.86. Label: 3, 8, 25, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Dose epilepsy (ADULT and CHILD over 5 years), as above; trigeminal neuralgia, as above; total daily dose given in 2 divided doses

OXCARBAZEPINE

Indications monotherapy and adjunctive treatment of partial seizures with or without secondarily generalised tonic-clonic seizures; trigeminal neuralgia [unlicenced indication] (section 4.7.3)

Cautions hypersensitivity to carbamazepine; avoid abrupt withdrawal; hyponatraemia (monitor plasma-sodium concentration in patients at risk), heart failure (monitor body-weight), cardiac conduction disorders; avoid in acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (see p. 250 and Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1

Blood, hepatic or skin disorders Patients or their carers should be told to recognise signs of blood, liver, or skin disorders, and advised to seek immediate medical attention if symptoms such as lethargy, confusion, muscular twitching, fever, sore throat, rash, blistering, mouth ulcers, bruising, or bleeding develop

Side-effects nausea, vomiting, constipation, diarrhoea, abdominal pain; dizziness, headache, drowsiness, agitation, amnesia, astaxia, ataxia, confusion,
impaired concentration, depression, tremor; hypo-
natraemia; acne, alopecia, rash,ystagmus, visual
disorders including diplopia; less commonly urticaria,
leucopenia; very rarely hepatitis, pancreatitis, arrhyth-
thmias, hypersensitivity reactions, thrombocytopenia,
systemic lupus erythematosus, Stevens-Johnson
syndrome, and toxic epidermal necrolysis

**Dose**

- Initially 300 mg twice daily increased according to
  response in steps of up to 600 mg daily at weekly
  intervals; usual dose range 0.6–2.4 g daily in divided
doses; CHILD 6–18 years, 8–10 mg/kg daily in 2
  divided doses increased according to response in
  steps of up to 10 mg/kg daily at weekly intervals (in
  adjunctive therapy, maintenance dose approx. 30 mg/
  kg daily); max. 46 mg/kg daily in divided doses

**Note** In adjunctive therapy, the dose of concomitant anti-
epileptics may need to be reduced when using high doses of
oxcarbazepine

**Oxcarbazepine (Non-proprietary)**

**Tablets**

- oxcarbazepine 150 mg, net price 50-tab pack
  = £10.00; 300 mg, 50-tab pack = £19.93; 600 mg 50-
tab pack = £39.48. Label: 3, 8, counselling, blood,
  hepatic, or skin disorders (see above), driving (see
  notes above)

**Oral suspension**, sugar-free, oxcarbazepine 300 mg/
5 mL, net price 250 mL (with oral syringe) = £40.00.
Label: 3, 8, counselling, blood, hepatic or skin dis-
orders (see above), driving (see notes above)

**Excipients** include propylene glycol (see Excipients, p. 2)

**ETHOSUXIMIDE**

**Ethosuximide** is used in typical absence seizures; it
may also be used in atypical absence seizures. Ethosux-
imide is rarely used for myoclonic or tonic seizures.

**ETHOSUXIMIDE**

**Indications** see notes above

**Cautions** avoid abrupt withdrawal; hepatic impair-
ment; renal impairment; pregnancy (see p. 250 and
Appendix 4); breast-feeding (Appendix 5); avoid in
acute porphyria (section 9.8.2); interactions: Appen-
dix 1 (ethosuximide)

**Blood disorders** Patients or their carers should be told how
to recognise signs of blood disorders, and advised to seek
immediate medical attention if symptoms such as fever, sore
throat, mouth ulcers, bruising, or bleeding develop

**Side-effects** gastrointestinal disturbances (including
nausea, vomiting, diarrhoea, abdominal pain, ano-
exia, weight loss); less frequently headache, fatigue,
drowsiness, dizziness, hiccups, ataxia, mild euphoria,
irritability, aggression, impaired concentration; rarely
tongue swelling, sleep disturbances, night terrors,
depression, psychosis, photophobia, dyskinesia,
increased libido, vaginal bleeding, myopia, gingival
hypertrophy, and rash; also reported, hyperactivity,
increase in seizure frequency, blood disorders such as
leucopenia, agranulocytosis, pancytopenia, and
 aplastic anaemia (blood counts required if features of
infection), systemic lupus erythematosus, and Stev-
ens-Johnson syndrome

**Dose**

- **ADULT** and **CHILD** over 6 years, initially 500 mg daily,
increased by 250 mg at intervals of 4–7 days to usual
dose of 1–1.5 g daily; occasionally up to 2 g daily may
be needed; **CHILD** up to 6 years initially 250 mg daily,
increased gradually to usual dose of 20 mg/kg daily;
max. 1 g daily

**Ethosuximide (Non-proprietary)**

**Capsules**

- ethosuximide 250 mg, net price 56-cap
  pack = £38.23. Label: 8, counselling, blood disorders (see
  above), driving (see notes above)

**Emeside® (Chemidex)**

**Syrup**

- black currant, ethosuximide 250 mg/5 mL, net
  price 200-mL pack = £6.60. Label: 8, counselling,
  blood disorders (see above), driving (see notes above)

**Zarontin® (Pfizer)**

**Syrup**

- yellow, ethosuximide 250 mg/5 mL, net price
  200-mL pack = £4.48. Label: 8, counselling, blood
  disorders (see above), driving (see notes above)

**Gabapentin and pregabalin**

Gabapentin and pregabalin are used for the treatment of
partial seizures with or without secondary general-
isation. They are also licensed for the treatment of
neuropathic pain (p. 242). Pregabalin is licensed for the
treatment of generalised anxiety disorder (p. 207).

**GABAPENTIN**

**Indications** monotherapy and adjunctive treatment of
partial seizures with or without secondary general-
isation; peripheral neuropathic pain (section 4.7.3)

**Cautions** avoid abrupt withdrawal (may cause anxiety,
insomnia, nausea, pain, and sweating—taper off over
at least 1 week); elderly; renal impairment (Appendix
3); diabetes mellitus; false positive readings with some
urinary protein tests; pregnancy (see p. 250 and
Appendix 4); breast-feeding (see p. 250 and Appendix
5); interactions: Appendix 1 (gabapentin)

**Side-effects** diarrhoea, dry mouth, dyspepsia, nausea,
vomiting, constipation, abdominal pain, flatulence,
appetite changes, gingivitis, weight gain; hyper-
tension, vasodilation, oedema; dyspnoea, cough,
rhinitis; confusion, depression, hostility, sleep distur-
bances, headache, dizziness, anxiety, amnesia, ataxia,
dysarthria, ataxia, tinnitus, acute renal failure, Stevens-
Johnson syndrome, and toxic epidermal necrolysis

**Dose**

- **Epilepsy.** 300 mg on day 1, then 300 mg twice daily on
day 2, then 300 mg 3 times daily on day 3 or initially
300 mg 3 times daily on day 1; then increased
according to response in steps of 300 mg daily (in 3
divided doses) every 2–3 days; usual dose 0.9–3.6 g
daily in 3 divided doses; **CHILD** 2–6 years see **BNF for
Children**; **CHILD** 6–12 years (adjunctive therapy only)
10–15 mg/kg daily initially, then increased according
to response over 3 days to usual maintenance dose
25–35 mg/kg daily in 3 divided doses; max. 50 mg/kg
daily in 3 divided doses
- Neuropathic pain, ADULT over 18 years, 300 mg on
day 1, then 300 mg twice daily on day 2, then 300 mg 3
times daily (approx. every 8 hours) on day 3 or initially
300 mg 3 times daily on day 1, then increased
according to response in steps of 300 mg daily (in 3
divided doses) every 2–3 days to max. 3.6 g daily

**Gabapentin** (Non-proprietary)

**Capsules**, gabapentin 100 mg, net price 100-cap pack = £5.78; 300 mg, 100-cap pack = £8.96; 400 mg, 100-
cap pack = £9.24. Label: 3, 5, 8, counselling, driving
(see notes above)

**Tablets**, gabapentin 600 mg, net price 100-tab pack =
£106.00; 800 mg, 100-tab pack = £83.38. Label: 3, 5, 8,
counselling, driving (see notes above)

**Neurontin** (Pfizer)

**Capsules**, gabapentin 100 mg (white), net price 100-
cap pack = £22.86; 300 mg (yellow), 100-cap pack =
£53.00; 400 mg (orange), 100-cap pack = £61.33.
Label: 3, 5, 8, counselling, driving (see notes above)

**Tablets**, f/c, gabapentin 600 mg, net price 100-tab
pack = £106.00; 800 mg, 100-tab pack = £122.66.
Label: 3, 5, 8, counselling, driving (see notes above)

**PREGABALIN**

**Indications** peripheral and central neuropathic pain;
adjunctive therapy for partial seizures with or without
secondary generalisation; generalised anxiety disor-
der

**Cautions** avoid abrupt withdrawal (taper over at least
1 week); severe congestive heart failure; renal
impairment (Appendix 3); pregnancy (Appendix 4)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** dry mouth, constipation, nausea, vomit-
ing, flatulence; oedema; dizziness, drowsiness, irrit-
ability, attention disturbance, disturbances in muscle
control and movement, memory impairment,
paraesthesia, euphoria, confusion, fatigue, appetite
changes, weight gain; changes in sexual function;
visual disturbances and ocular disorders (including
blurred vision, diplopia, eye strain and eye irritation);
less commonly abdominal distension, increased sali-
vation, gastro-oesophageal reflux disease, taste dis-
turbance, thirst, hot flushes, tachycardia, syncope,
dysphonia, chest tightness, nasal dryness, stupor,
depersonalisation, depression, insomnia, abnormal
dreams, hallucinations, agitation, mood swings, panic
attacks, asthenia, speech disorder; dysuria, urinary
incontinence, thrombocytopenia, joint swelling,
muscle cramp, myalgia, arthralgia, sweating, and rash;
rarely ascites, dysphagia, pancreatitis, hypotension,
hypertension, cold extremities, first-degree AV block,
arrrhythmia, bradycardia, nasopharyngitis, cough,
epistaxis, rhinitis, parosmia, pyrexia, rashes, disinhibi-
tion, weight loss, hypoglycaemia or hyperglycaemia,
renal failure, menstrual disturbances, breast pain,
breast discharge, breast hypertrophy, neutropenia,
rhabdomyolysis, hyperacusis, hypokalaemia, and leu-
cytosis; diarrhoea, congestive heart failure, angio-
edema, loss of consciousness, headache, Stevens-
Johnson syndrome, and pruritus also reported

**Dose**

- Neuropathic pain, ADULT over 18 years, initially 150 mg
daily in 2–3 divided doses, increased if necessary after
3–7 days to 300 mg daily in 2–3 divided doses, increased
further if necessary after 7 days to max. 600 mg daily in 2–3
divided doses
- Epilepsy, ADULT over 18 years, initially 25 mg twice
daily, increased at 7-day intervals in steps of 50 mg
daily to 300 mg daily in 2–3 divided doses, increased
further if necessary after 7 days to max. 600 mg daily
in 2–3 divided doses
- Generalised anxiety disorder, ADULT over 18 years,
initially 150 mg daily in 2–3 divided doses, increased if
necessary at 7-day intervals in steps of 150 mg daily;
max. 600 mg daily in 2–3 divided doses

**Note** Pregabalin doses in BNF may differ from those in product
literature

**Lyrica** (Pfizer)

**Capsules**, pregabalin 25 mg (white), net price 56-cap
pack = £64.40, 84-cap pack = £96.60; 50 mg (white),
84-cap pack = £96.60; 75 mg (white/orange), 56-cap
pack = £64.40; 100 mg (orange), 84-cap pack =
£96.60; 150 mg (white), 56-cap pack = £64.40; 200 mg
(oranger), 84-cap pack = £96.60; 225 mg (white/or-
gange), 56-cap pack = £64.40; 300 mg (white/or-
gange), 56-cap pack = £64.40. Label: 3, 8, counsel-
lng, driving (see notes above)

**Note** The Scottish Medicines Consortium has advised (July
2007) that Lyrica is not recommended for the treatment of
central neuropathic pain

**Lacosamide**

Lacosamide is licensed for adjunctive treatment of
partial seizures with or without secondary generalisation.

**Vimpat** (UCB Pharma)

**Tablets**, f/c, lacosamide 50 mg (pink), net price 14-tab
pack = £9.01; 100 mg (yellow), 14-tab pack = £18.02,
56-tab pack = £72.08; 150 mg (pink), 14-tab pack =
£27.03, 56-tab pack = £108.12; 200 mg (blue), 56-tab
pack = £96.60; 225 mg (white/orange), 56-tab pack =
£144.16. Label: 8, counselling, driving (see notes above)

**Note** Pregabalin doses in BNF may differ from those in product
literature

**Indications** see notes above

**Cautions** conduction problems, severe cardiac disease
(increased risk of PR-interval prolongation), elderly,
hepatic impairment (Appendix 2), renal impairment
(Appendix 3); pregnancy (p. 250 and Appendix 4);
breast-feeding (see p. 250 and Appendix 5); interac-
tions: Appendix 1 (lacosamide)

**Side-effects** nausea, vomiting, flatulence, constipa-
tion; dizziness, headache, depression, diplopia, nys-
tagmus, impaired coordination, impaired memory,
cognitive disorder, drowsiness, tremor, asthenia, fati-
gue; pruritus; less commonly PR-interval prolongation

**Dose**

- By intravenous infusion over 15–60 minutes (for up
to 5 days) or by mouth, ADULT and CHILD over 16
years, initially 50 mg twice daily, increased weekly by
50 mg twice daily to max. 200 mg twice daily

**Vimpat** (UCB Pharma)

**Tablets**, f/c, lacosamide 50 mg (pink), net price 14-tab
pack = £9.01; 100 mg (yellow), 14-tab pack = £18.02,
56-tab pack = £72.08; 150 mg (pink), 14-tab pack =
£27.03, 56-tab pack = £108.12; 200 mg (blue), 56-tab
pack = £96.60. Label: 8, counselling, driving (see notes above)

**Syrup**, lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Electrolytes** Na 0.4 mmol/5 mL

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)

**Excipients** include aspartame (section 9.4.1)

**Syrup** lacosamide 15 mg/mL, net price 200 mL =
£38.61. Label: 8, counselling, driving (see notes above)
Lamotrigine

Lamotrigine is an antiepileptic for partial seizures and primary and secondarily generalised tonic-clonic seizures. Lamotrigine may cause serious skin rash especially in children; dose recommendations should be adhered to closely.

Lamotrigine is used either as sole treatment or as an adjunct to treatment with other antiepileptic drugs. Valproate increases plasma-lamotrigine concentration whereas the enzyme inducing antiepileptics reduce it; care is therefore required in choosing the appropriate initial dose and subsequent titration. Where the potential for interaction is not known, treatment should be initiated with lower doses such as those used with valproate.

LAMOTRIGINE

**Indications** monotherapy and adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures; seizures associated with Lennox-Gastaut syndrome; trigeminal neuralgia (unlicensed indication) (section 4.7.3)

**Cautions** closely monitor and consider withdrawal if rash, fever, or other signs of hypersensitivity syndrome develop; avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (see p. 250 and Appendix 4); breast-feeding (Appendix 5); interactions: see p. 249 and Appendix 1 (lamotrigine)

**Blood disorders** The CSM has advised prescribers to be alert for symptoms and signs suggestive of bone-marrow failure such as anaemia, bruising, or infection. Aplastic anaemia, bone-marrow depression and pancytopenia have been associated rarely with lamotrigine.

**Side-effects** rash (see Skin Reactions, below); hypersensitivity syndrome (possibly including rash, fever, lymphadenopathy, hepatic dysfunction, blood disorders, disseminated intravascular coagulation and multi-organ dysfunction); nausea, vomiting, diarrhoea, hepatic dysfunction; headache, fatigue, dizziness, sleep disturbances, tremor, movement disorders, agitation, confusion, hallucinations, occasional increase in seizure frequency; blood disorders (including leucopenia, thrombocytopenia, pancytopenia—see Blood Disorders, above); arthralgia; lupus erythematosus-like effect; photosensitivity; rash (erythema multiforme, toxic epidermal necrolysis); Stevens-Johnson syndrome and toxic epidermal necrolysis (rarely with fatalities) have developed especially in children; most rashes occur in the first 8 weeks. Rash is sometimes associated with hypersensitivity syndrome (see Side-effects, above) and is more common in patients with history of allergy or rash from other antiepileptic drugs. Consider withdrawal if rash or signs of hypersensitivity syndrome develop. The CSM has advised that factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.

**Counselling** Warn patients to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop

**Dose** Important Do not confuse the different combinations; see also notes below

**Note** Dose titration should be repeated if restarting after an interval of more than 5 days

- Monotherapy, **ADULT** and **CHILD** over 12 years, initially 25 mg once daily for 14 days, increased to 50 mg once daily for further 14 days, then increased by max. 50–100 mg daily every 7–14 days; usual maintenance 100–200 mg daily in 1–2 divided doses (up to 500 mg daily has been required)

- Adjunctive therapy with valproate, initially 25 mg on alternate days for 14 days then 25 mg once daily for further 14 days, thereafter increased by max. 25–50 mg daily every 7–14 days; usual maintenance, 100–200 mg daily in 1–2 divided doses; **CHILD** 2–12 years initially 150 micrograms/kg once daily for 14 days (those weighing under 13 kg may receive 2 mg on alternate days for first 14 days) then 300 micrograms/kg once daily for further 14 days, thereafter increased by max. 300 micrograms/kg daily every 7–14 days; usual maintenance 1–5 mg/kg daily in 1–2 divided doses (max. single dose 100 mg)

- Adjunctive therapy (with enzyme inducing drugs) **without valproate**, initially 50 mg once daily for 14 days then 50 mg twice daily for further 14 days, thereafter increased by max. 100 mg daily every 7–14 days; usual maintenance 200–400 mg daily in 2 divided doses (up to 700 mg daily has been required); **CHILD** 2–12 years initially 600 micrograms/kg daily in 2 divided doses for 14 days then 1.2 mg/kg daily in 2 divided doses for further 14 days, thereafter increased by max. 1.2 mg/kg daily every 7–14 days; usual maintenance 5–15 mg/kg daily in 2 divided doses (max. single dose 200 mg)

- Adjunctive therapy with oxcarbazepine, initially 25 mg once daily for 14 days, increased to 50 mg once daily for further 14 days, then increased by max. 50–100 mg daily every 7–14 days; usual maintenance 100–200 mg daily in 1–2 divided doses; **CHILD** 2–12 years initially 300 micrograms/kg daily in 1–2 divided doses for 14 days then 600 micrograms/kg daily in 1–2 divided doses for further 14 days, thereafter increased by max. 600 micrograms/kg daily every 7–14 days; usual maintenance 1–10 mg/kg daily in 1–2 divided doses; max. 200 mg daily

**Lamotrigine** (Non-proprietary)  
**Tablets**, lamotrigine 25 mg, net price 56-tab pack = £3.45; 50 mg, 56-tab pack = £4.13; 100 mg, 56-tab pack = £5.45; 200 mg, 30-tab pack = £27.53, 56-tab pack = £9.36. Label: 8, counselling, driving (see notes above), skin reactions (see above)

**Dispersible tablets**, lamotrigine 5 mg, net price 28-tab pack = £2.87; 25 mg, 56-tab pack = £3.87; 100 mg, 56-tab pack = £7.70. Label: 8, 13, counselling, driving (see notes above), skin reactions (see above)

**Lamictal®** (GSK)  
**Tablets**, yellow, lamotrigine 25 mg, net price 21-tab pack (Valproate Add-on therapy ’Starter Pack’ = £7.65, 42-tab pack (’Monotherapy’ Starter Pack) = £15.30, 56-tab pack = £20.41; 50 mg, 42-tab pack (’Non-valproate Add-on therapy’ Starter Pack) = £26.02, 56-tab pack = £34.70; 100 mg, 56-tab pack = £59.86; 200 mg, 56-tab pack = £101.76. Label: 8, counselling, driving (see notes above), skin reactions (above)

**Dispersible tablets**, chewable, lamotrigine 2 mg, net price 30-tab pack = £8.71; 5 mg, 28-tab pack = £8.14; 25 mg, 56-tab pack = £20.41; 100 mg, 56-tab pack = £59.86. Label: 8, 13, counselling, driving (see notes above), skin reactions (above)
Levetiracetam

Levetiracetam is licensed for monotherapy and adjunctive treatment of partial seizures with or without secondary generalisation, and for adjunctive therapy of myoclonic seizures and primarily generalised tonic-clonic seizures.

**LEVETIRACETAM**

**Indications** see notes above

**Cautions** avoid abrupt withdrawal; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (see p. 250 and Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (levetiracetam)

**Side-effects** nausea, vomiting, dyspepsia, diarrhoea, abdominal pain, anorexia, weight changes; cough; drowsiness, asthenia, anemia, ataxia, seizures, dizziness, headache, tremor, hyperkinesia, depression, emotional lability, insomnia, anxiety, impaired attention, aggression, irritability; thrombocytopenia; myalgia; visual disturbances; pruritus, rash; also reported pancreatitis, hepatic dysfunction, confusion, psychosis, hallucinations, suicidal ideation, paraesthesia, leucopenia, pancytopenia, and alopecia

**Dose**

- Monotherapy of partial seizures with or without secondary generalisation, by mouth or by intravenous infusion, **ADULT** and **CHILD** over 16 years, initially 250 mg twice daily increased according to response in steps of 250 mg twice daily every 2 weeks; max. 1.5 g twice daily
- Adjunctive therapy of partial seizures with or without secondary generalisation, myoclonic seizures, and primarily generalised tonic-clonic seizures, by mouth or by intravenous infusion, **ADULT** and **CHILD** over 12 years, body-weight over 50 kg, initially 500 mg twice daily, adjusted in steps of 500 mg twice daily every 2 to 4 weeks; max. 1.5 g twice daily; **CHILD** 4–18 years (12–18 years for myoclonic and tonic-clonic seizures), body-weight under 50 kg, initially 10 mg/kg twice daily, adjusted in steps not exceeding 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily

**Keppra** (UCB Pharma) (R)

- **Tablets**, f/c, levetiracetam 250 mg (blue), net price 60-tab pack = £29.70; 500 mg (yellow), 60-tab pack = £52.30; 750 mg (orange) 60-tab pack = £89.10; 1 g (white), 60-tab pack = £101.10. **Label**: 8
- **Oral solution**, sugar-free, levetiracetam 100 mg/mL, net price 300 mL = £71.00. **Label**: 8
- **Concentrate for intravenous infusion**, levetiracetam 100 mg/mL. For dilution before use. **Net price** 5-mL vial = £13.50
- **Electrolytes**: Na < 0.5 mmol/vial

Phenobarbital and other barbiturates

Phenobarbital (phenobarbitone) is effective for tonic-clonic and partial seizures but may be sedative in adults and cause behavioural disturbances and hyperkinesia in children. It may be tried for atypical absence, atonic, and tonic seizures. Rebound seizures may be a problem on withdrawal. Monitoring plasma concentrations is less useful than with other drugs because tolerance occurs.

Primidone is largely converted to phenobarbital and this is probably responsible for its antiepileptic action. A small starting dose of primidone (125 mg) is essential, and the drug should be introduced over several weeks.

**PHENOBARBITAL**

(Phenobarbitone)

**Indications** all forms of epilepsy except absence seizures; status epilepticus (section 4.8.2)

**Cautions** see notes above; elderly; debilitated; children; respiratory depression (avoid if severe); avoid abrupt withdrawal (dependence with prolonged use); history of drug or alcohol abuse; avoid in acute porphyria (section 9.8.2); hepatic impairment (avoid if severe—Appendix 2); renal impairment; pregnancy (see p. 250 and Appendix 4); breast-feeding (see p. 250 and Appendix 5); **interactions**: see p. 249 and Appendix 1 (barbiturates)

**Side-effects** hepatatitis, cholestasis; hypotension; respiratory depression; behavioural disturbances, nystagmus, irritability, drowsiness, lethargy, depression, ataxia, paradoxical excitement, hallucinations, impaired memory and cognition, hyperactivity particularly in the elderly and in children; osteomalacia; megaloblastic anaemia (may be treated with folic acid); agranulocytosis, thrombocytopenia; allergic skin reactions; very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis; **overdosage**: see Emergency Treatment of Poisoning. p. 28

**Dose**

- By mouth, 60–180 mg at night; **CHILD** 5–8 mg/kg daily

**Note** For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect. Plasma-phenobarbital concentration for optimum response 15–40 mg/litre (60–180 micromol/litre)

**Phenobarbital** (Non-proprietary) (C)

- **Tablets**, phenobarbital 15 mg, net price 28-tab pack = 88p; 30 mg, 28-tab pack = 59p; 60 mg, 28-tab pack = 69p. **Label**: 2, 8, counselling, driving (see notes above)
- **Elixir**, phenobarbital 15 mg/5 mL in a suitable flavoured vehicle, containing alcohol 38%, net price 100 mL = 77p. **Label**: 2, 8, counselling, driving (see notes above)

**Note** Some hospitals supply alcohol-free formulations of varying phenobarbital strengths

**Injection**

Section 4.8.2

**PRIMIDONE**

**Indications** all forms of epilepsy except absence seizures; essential tremor (also section 4.9.3)

**Cautions** see under Phenobarbital; **interactions**: see p. 249 and Appendix 1 (primidone)

**Side-effects** see under Phenobarbital; also nausea and visual disturbances; less commonly vomiting, headache, and dizziness; rarely arthralgia

**Dose**

- Epilepsy, **ADULT** and **CHILD** over 9 years, initially 125 mg daily at bedtime, increased by 125 mg every 3 days to 500 mg daily in 2 divided doses, then increased according to response by 250 mg every 3 days to usual maintenance 0.75–1.5 g daily in 2 divided doses; **CHILD** under 9 years, initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to
response; usual maintenance, CHILD under 2 years, 250–500 mg daily in 2 divided doses; 2–5 years, 500–750 mg daily in 2 divided doses; 5–9 years 0.75–1 g daily in 2 divided doses

• Essential tremor, initially 62.5 mg daily increased gradually over 2–3 weeks according to response; max. 750 mg daily

Note Monitor plasma concentrations of derived phenobarbital; optimum range as for phenobarbital. Primidone doses in BNF may differ from those in product literature

Mysoline® (Acornus) Tablets, scored, primidone 250 mg, net price 100-tab pack = £12.60. Label: 2, 8, counselling, driving (see notes above)

Phenytoin

Phenytoin is effective in tonic-clonic and partial seizures. It has a narrow therapeutic index and the relationship between dose and plasma concentration is non-linear; small dosage increases in some patients may produce large rises in plasma concentrations with acute toxic side-effects. Monitoring of plasma concentration greatly assists dosage adjustment. A few missed doses or a small change in drug absorption may result in a marked change in plasma concentration. Phenytoin may cause coarse facies, acne, hirsutism, and gingival hyperplasia and so may be particularly undesirable in adolescent patients.

When only parenteral administration is possible, fosphenytoin (section 4.8.2), a pro-drug of phenytoin, may be convenient to give. Whereas phenytoin can be given intravenously only, fosphenytoin may also be given by intramuscular injection.

PHENYTOIN

Indications all forms of epilepsy except absence seizures; status epilepticus (section 4.8.2); trigeminal neuralgia if carbamazepine inappropriate (see also section 4.7.3)

Caution avoid abrupt withdrawal; manufacturer recommends blood counts (but evidence of practical value unsatisfactory); avoid in acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); pregnancy (important: see notes above and Appendix 4); breast-feeding (see notes above and Appendix 5); interactions: see p. 249 and Appendix 1 (phenytoin)

Blood or skin disorders Patients or their carers should be told how to recognise signs of blood or skin disorders, and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, bruising, or bleeding develop. Leucopenia which is severe, progressive, or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative)

Side-effects nausea, vomiting, constipation, insomnia, transient nervousness, tremor, paraesthesia, diarrhoea, headache, anorexia; gingival hypertrophy and tenderness; rash (discontinue; if mild re-introduce cautiously but discontinue immediately if recurrence), acne, hirsutism, coarse facies; rarely hepatotoxicity, peripheral neuropathy, dyskinesia, lymphadenopathy, osteomalacia, blood disorders (including megaloblastic anaemia (may be treated with folic acid), leucopenia, thrombocytopenia, and aplastic anaemia), polyarteritis nodosa, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis; also reported pneumonitis and interstitial nephritis; with excessive dosage nyctagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia

Dose

• By mouth, initially 3–4 mg/kg daily or 150–300 mg daily (as a single dose or in 2 divided doses) increased gradually as necessary (with plasma-phenytoin concentration monitoring); usual dose 200–500 mg daily (exceptionally, higher doses may be used); CHILD initially 5 mg/kg daily in 2 divided doses, usual dose range 4–8 mg/kg daily (max. 300 mg daily)

Note Plasma concentration for optimum response 10–20 mg/litre (40–80 micromol/litre)

Counselling Take preferably with or after food

Phenytoin (Non-proprietary) Tablets, coated, phenytoin sodium 100 mg, net price 28-tab pack = £30.00. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note On the basis of single dose tests there are no clinically relevant differences in bioavailability between available phenytoin sodium tablets and capsules but there may be a pharmacokinetic basis for maintaining the same brand of phenytoin in some patients

Epanutin® (Pfizer) Capsules, phenytoin sodium 25 mg (white/purple), net price 28-cap pack = 66p; 50 mg (white/pink), 28-cap pack = 67p; 100 mg (white/orange), 84-cap pack = £2.83; 300 mg (white/green), 28-cap pack = £2.83. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Infatabs® (= chewable tablets), yellow, scored, phenytoin 50 mg, net price 112 = £7.38. Label: 8, 24, counselling, blood or skin disorder symptoms (see above), driving (see notes above)

Note Contain phenytoin 50 mg (as against phenytoin sodium) therefore care is needed on changing to capsules or tablets containing phenytoin sodium

Suspension, red, phenytoin 30 mg/5 mL, net price 500 mL = £4.27. Label: 8, counselling, administration, blood or skin disorder symptoms (see above), driving (see notes above)

Note Suspension of phenytoin 90 mg in 15 mL may be considered to be approximately equivalent in therapeutic effect to capsules or tablets containing phenytoin sodium 100 mg, but nevertheless care is needed in making changes

Rufinamide

Rufinamide is licenced for the adjunctive treatment of seizures in Lennox-Gastaut syndrome.

The Scottish Medicines Consortium (p. 3) has advised (October 2008) that rufinamide (Inovelon) is accepted for restricted use within NHS Scotland as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients four years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.

RUFINAMIDE

Indications adjunctive treatment of seizures in Lennox-Gastaut syndrome

Caution closely monitor and consider withdrawal if rash, fever, or other signs of hypersensitivity syndrome develop; avoid abrupt withdrawal; hepatic
Topiramate

**Topiramate** can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or partial seizures with or without secondary generalisation. It can be used as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome. Topiramate is also licensed for prophylaxis of migraine (section 4.7.4.2).

### Tiagabine

Tiagabine is used as adjunctive treatment for partial seizures, with or without secondary generalisation.

#### Tiagabine

**Indications**

- adjunctive treatment for partial seizures with or without secondary generalisation not satisfactorily controlled with other antiepileptics

**Cautions**

- avoid in acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); renal impairment; pregnancy (see notes above and Appendix 4); interactions: see p. 249 and Appendix 1 (tiagabine)

**Driving**

- May impair performance of skilled tasks (e.g. driving)

**Side-effects**

- diaphoresis; dizziness, tiredness, nervousness, tremor, impaired concentration, emotional lability, speech impairment; rarely confusion, depression, drowsiness, psychosis, non-convulsive status epilepticus, bruising, and visual disturbances; leucopenia also reported

**Dose**

- Adjunctive therapy, **ADULT** and **CHILD** over 12 years, with enzyme-inducing drugs, 5 mg twice daily for 1 week, then increased at weekly intervals in steps of 5–10 mg daily; usual maintenance dose 30–45 mg daily (doses above 30 mg given in 3 divided doses); in patients receiving non-enzyme-inducing drugs, initial maintenance dose 15–30 mg daily

### Gabitril® (Cephalon) [tbr]

**Tablets, 1/c, tiagabine (as hydrochloride) 5 mg, net price 100-tab pack = £43.37; 10 mg, 100-tab pack = £86.74; 15 mg, 100-tab pack = £130.11. Label: 21**

---

**TOPIRAMATE**

**Indications**

- monotherapy and adjunctive treatment of generalised tonic-clonic seizures or partial seizures with or without secondary generalisation; adjunctive treatment of seizures in Lennox-Gastaut syndrome; migraine prophylaxis (under specialist supervision)

**Cautions**

- avoid abrupt withdrawal; ensure adequate hydration (especially if predisposition to nephrolithiasis or in strenuous activity or warm environment); avoid in acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (see notes above and Appendix 4); interactions: see p. 249 and Appendix 1 (topiramate)

**CSM advice**

- Topiramate has been associated with acute myopia with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Choroidal effusions resulting in anterior displacement of the lens and iris have also been reported. The CSM advises that if raised intra-ocular pressure occurs:
  - seek specialist ophthalmological advice;
  - use appropriate measures to reduce intra-ocular pressure;
  - stop topiramate as rapidly as feasible

**Contra-indications**

- breast-feeding (Appendix 5)

**Side-effects**

- nausea, vomiting, constipation, diarrhoea, abdominal pain, weight loss, anorexia; rhinitis, epistaxis; dizziness, headache, drowsiness, insomnia, anxiety, fatigue, increase in seizure frequency, impaired coordination, hyperactivity, tremor, gait disturbances; influenza-like symptoms; oligomenorrhea; back pain; nystagmus, diplopia, blurred vision; rash and acne; hypersensitivity syndrome (possibly including rash, fever, lymphadenopathy, hepatic dysfunction, haematuria, and multiorgan dysfunction) also reported

**Hypersensitivity syndrome**

- Serious hypersensitivity syndrome (see Side-effects) has developed, especially in children and upon initiation of therapy; consider withdrawal if rash or signs of hypersensitivity syndrome develop

**Counselling**

- Warn patients to seek immediate medical attention if signs or symptoms of hypersensitivity develop

**Dose**

- **ADULT** and **CHILD** over 4 years body-weight over 30 kg, initially 200 mg twice daily increased according to response in steps of 200 mg twice daily at intervals of not less than 2 days; body-weight 30–50 kg max. 900 mg twice daily; body-weight 50–70 kg max. 1.2 g twice daily; body-weight over 70 kg max. 1.6 g twice daily; **CHILD** over 4 years body-weight less than 30 kg, initially 100 mg twice daily increased according to response in steps of 100 mg twice daily at intervals of not less than 2 days; max. 500 mg twice daily (max. 300 mg twice daily if adjunctive therapy with valproate)

**Inovelon®** (Eisai) ▼ [tbr]

**Tablets, pink, 1/c, scored, rufinamide 100 mg, net price 10-tab pack = £8.58; 200 mg, 60-tab pack = £51.48; 400 mg, 60-tab pack = £85.80. Label: 21, counselling, driving (see notes above), hypersensitivity syndrome (see above)

**Intra-ocular pressure occurs:**

- iris have also been reported. The CSM advises that if raised intra-ocular pressure occurs:
  - seek specialist ophthalmological advice;
  - use appropriate measures to reduce intra-ocular pressure;
  - stop topiramate as rapidly as feasible

---

**4.8.1 Control of epilepsy**

**257**

---

**Central nervous system**
intervals of 1–2 weeks taken in 2 divided doses; recommended dose range 5–9 mg/kg daily in 2 divided doses; max. 15 mg/kg daily

- Migraine prophylaxis ADULT and CHILD over 16 years, initially 25 mg daily at night for 1 week then increased in steps of 25 mg daily at intervals of 1 week; usual dose 50–100 mg daily in 2 divided doses

Note If patient cannot tolerate titration regimens recommended above then smaller steps or longer interval between steps may be used

**Topamax** (Janssen-Cilag) ▼ (NM)

**Tablets**, e/c, topiramate 25 mg, net price 60-tab pack = £20.48; 50 mg (light yellow), 60-tab pack = £33.64; 100 mg (yellow), 60-tab pack = £60.26; 200 mg (salmon), 60-tab pack = £117.02. Label: 3, 8, counselling, driving (see notes above)

**Sprinkle capsules**, topiramate 15 mg, net price 60-cap pack = £15.70; 25 mg, 60-cap pack = £23.55; 50 mg, 60-cap pack = £38.69. Label: 3, 8, counselling, administration, driving (see notes above)

**Counselling** Swallow whole or open capsule and sprinkle contents on soft food

**Valproate**

**Sodium valproate** is effective in controlling tonic-clonic seizures, particularly in primary generalised epilepsy. It is a drug of choice in primary generalised epilepsy, generalised absences and myoclonic seizures, and can be tried in atypical absence, atonic, and tonic seizures. It is a drug of choice in primary generalised epilepsy, generalised absences and myoclonic seizures, and can be tried in atypical absence, atonic, and tonic seizures.

Valproate concentrations are not a useful index of efficacy, therefore routine monitoring is unhelpful.

Liver toxicity Liver dysfunction (including fatal hepatic failure) has occurred in association with valproate (especially in children under 3 years and in those with metabolic or degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation) usually in first 6 months and usually involving multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormality prolonged prothrombin time (particular in association with other relevant abnormalities).

**Blood or hepatic disorders** Patients or their carers should be told how to recognise signs and symptoms of blood or liver disorders and advised to seek immediate medical attention if symptoms develop

Pancreatitis Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea and vomiting develop; discontinue if pancreatitis is diagnosed

**Contra-indications** active liver disease, family history of severe hepatic dysfunction; acute porphyria (section 9.8.2)

**Side-effects** nausea, gastric irritation, diarrhoea; weight gain; hyperammonaemia, thrombocytopenia; transient hair loss (regrowth may be curvy); less frequently increased alertness, aggression, hyperactivity, behavioural disturbances, ataxia, tremor, and vasculitis; rarely hepatic dysfunction (see under Cautions); withdrawal treatment immediately if persistent vomiting and abdominal pain, anorexia, jaundice, oedema, malaise, drowsiness, or loss of seizure control; lethargy, drowsiness, confusion, stupor, hallucinations, menstrual disturbances, anaemia, leucopenia, pancytopenia, hearing loss, and rash; very rarely pancreatitis (see under Cautions), peripheral oedema, increase in bleeding time, extrapyramidal symptoms, dementia, encephalopathy, coma, gynaecomastia, Fanconi’s syndrome, hirsutism, acne, enuresis, hypnornatremia, toxic epidermal necrolysis, and Stevens-Johnson syndrome

**Dose**

- By mouth, initially 600 mg daily in 2 divided doses, preferably after food, increased by 200 mg daily every 3 days to max. 2.5 g daily, usual maintenance dose 1–2 g daily (20–30 mg/kg daily); CHILD body-weight up to 20 kg, initially 20 mg/kg daily in divided doses, may be increased provided plasma concentration monitored (dose above 40 mg/kg daily also monitor clinical chemistry and haematological parameters); CHILD under 12 years body-weight up to 20 kg, initially 400 mg daily in divided doses increased according to response (usual range 20–30 mg/kg daily); max. 35 mg/kg daily

- By intravenous injection (over 3–5 minutes) or by intravenous infusion, continuation of valproate treatment, same as current dose by oral route Initiation of valproate therapy, by intravenous injection (over 3–5 minutes), 400–800 mg (up to 10 mg/kg) followed by intravenous infusion up to max. 2.5 g daily; CHILD under 12 years, usually 20–30 mg/kg daily, may be increased provided plasma concentration monitored (dose above 40 mg/kg daily also monitor clinical chemistry and haematological parameters)

**Oral**

**Sodium Valproate** (Non proprietary) ▼

**Tablets** (crushable), scored, sodium valproate 100 mg, net price 100-tab pack = £4.67. Label: 8, counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Tablets**, e/c, sodium valproate 200 mg, net price 100-tab pack = £5.71; 500 mg, 100-tab pack = £12.15. Label: 5, 8, 25, counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Brands include** Orlept

**Oral solution**, sodium valproate 200 mg/5 mL, net price 300 mL = £8.20. Label: 8, counselling, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Brands include** Orlept sugar-free

**Epilim** (Sanofi-Synthelabo) ▼

**Tablets** (crushable), scored, sodium valproate 100 mg, net price 100 = £4.67. Label: 8, counselling,
blood or hepatic disorder symptoms (see above),
driving (see notes above)

Tablets, both e/c, lilac, sodium valproate 200 mg, net
price 100 = £7.70; 500 mg, 100 = £19.25. Label: 5, 8,
25, counselling, blood or hepatic disorder symptoms
(see above), driving (see notes above)

Liquid, red, sugar-free, sodium valproate 200 mg/5
mL, net price 300-mL pack = £7.78. Label: 8,
counselling, blood or hepatic disorder symptoms (see
above), driving (see notes above)

Syrup, red, sodium valproate 200 mg/5 mL, net price
300-mL pack = £7.78. Label: 8, counselling, blood
or hepatic disorder symptoms (see above), driving (see
notes above)

### Modified release

**Epilim Chrono** (Sanofi-Synthelabo) (£)

Tablets, m/r, lilac, sodium valproate 200 mg (as sodium
valproate and valproic acid), net price 100-tab pack
= £9.71; 300 mg, 100-tab pack = £14.56; 500 mg,
100-tab pack = £24.25. Label: 8, 25, counselling, blood
or hepatic disorder symptoms (see above), driving
(see notes above)

Dose ADULT and CHILD over 20 kg, as above, total daily dose
given in 1–2 divided doses

**Epilim Chronosphere** (Sanofi-Aventis) (£)

Granules, m/r, sodium valproate 50 mg (as sodium
valproate, and valproic acid), net price 30-sachet pack
= £30.00; 100 mg, 30-sachet pack = £30.00; 250 mg,
30-sachet pack = £30.00; 500 mg, 30-sachet pack =
£30.00; 750 mg, 30-sachet pack = £30.00. Label: 8,
counselling, administration, blood or hepatic disorder
symptoms (see above), driving (see notes above)

Dose ADULT and CHILD, as above, total daily dose given in 1–2
divided doses

Counselling Granules may be mixed with cold food or drink and
swallowed immediately without chewing

**Episenta** (Beacon) (£)

Capsules, m/r, sodium valproate 150 mg, net price
100-cap pack = £5.70; 300 mg, 100-cap pack = £10.90.
Label: 8, 25, counselling, administration, blood or
hepatic disorder symptoms (see above), driving (see
notes above)

Dose ADULT and CHILD, as above, total daily dose given in 1–2
divided doses

Counselling Contents of capsule may be mixed with cold food or
drink and swallowed immediately without chewing

Granules, m/r, sodium valproate 500 mg, net price
100-sachet pack = £18.00; 1 g, 100-sachet pack =
£35.50. Label: 8, 25, counselling, administration,
blood or hepatic disorder symptoms (see above),
driving (see notes above)

Dose ADULT and CHILD, as above, total daily dose given in 1–2
divided doses

Counselling Granules may be mixed with cold food or drink and
swallowed immediately without chewing

### Parenteral

**Epilim** Intravenous (Sanofi-Synthelabo) (£)

Injection, powder for reconstitution, sodium val-
proate, net price 400-mg vial (with 4-mL amp water
for injections) = £11.58

**Episenta** (Beacon) (£)

Injection, sodium valproate 100 mg/mL, net price 3-
ml amp = £7.00, 10-mL amp = £23.33

### Valproic acid

**Convulex** (Pharmacia) (£)

Capsules, e/c, valproic acid 150 mg, net price 100-
cap pack = £3.68; 300 mg, 100-cap pack = £7.35;
500 mg, 100-cap pack = £12.25. Label: 8, 25, coun-
selling, blood or hepatic disorder symptoms (see
above), driving (see notes above)

Dose ADULT and CHILD as for sodium valproate, total daily dose
given in 2–4 divided doses

Equivalence to sodium valproate Manufacturer advises that Con-
vulex has a 1:1 dose relationship with products containing sodium
valproate, but nevertheless care is needed in making changes.

**Depakote** (Sanofi-Synthelabo) (£)

Section 4.2.3 (bipolar disorder)

---

### Vigabatrin

**Indications** initiated and supervised by appropriate
specialist, adjunctive treatment of partial seizures
with or without secondary generalisation not satis-
factory controlled with other antiepileptics; mono-
therapy for management of infantile spasms (West's
syndrome)

About one-third of patients treated with vigabatril have
suffered visual field defects; counselling and careful
monitoring for this side-effect are required (see also
Visual Field Defects under Cautions below). Vigabatrin
has prominent behavioural side-effects in some patients.

### Vigabatrin

**Indications** initiated and supervised by appropriate
specialist, adjunctive treatment of partial seizures
with or without secondary generalisation not satis-
factory controlled with other antiepileptics; mono-
therapy for management of infantile spasms (West's
syndrome)

**Cautions** renal impairment (Appendix 3); elderly;
clo-
sely monitor neurological function; avoid sudden
withdrawal (taper off over 2–4 weeks); history of
psychosis, depression or behavioural problems;
pregnancy (see p. 250 and Appendix 4) and breast-
feeding (Appendix 5); absence seizures (may be exa-
cerated); interactions: see p. 249 and Appendix 1
(vigabatrin)

**Visual field defects** Vigabatrin is associated with visual
field defects. The CSM has advised that onset of symptoms
varies from 1 month to several years after starting. In most
cases, visual field defects have persisted despite discontin-
uation. Product literature advises visual field testing before
treatment and at 6-month intervals; a procedure for testing
visual fields in those with a developmental age of less than 9
years is available from the manufacturers. Patients should be
warned to report any new visual symptoms that develop and
those with symptoms should be referred for an urgent
ophthalmological opinion. Gradual withdrawal of vigabatrin
should be considered.

**Contra-indications** visual field defects

**Side-effects** nausea, abdominal pain; oedema; drow-
siness (rarely encephalopathic symptoms including
marked sedation, stupor, and confusion with non-
specific slow wave EEG—reduce dose or withdraw),
fatigue, excitement, and agitation (especially in chil-
dren), dizziness, headache, nervousness, depression,
agression, paranoia, impaired concentration, mem-
ory disturbances, tremor, paraesthesia, weight gain;
visual field defects (see also under Cautions), blurred
vision, nystagmus, diplopia; less commonly ataxia,
sychosis, mania, and rash; occasional increase in
seizure frequency (especially if myoclonic); rarely suicidal ideation and retinal disorders (including peripheral retinal neuropathy); very rarely hepatitis, optic neuritis and optic atrophy; also reported, decrease in liver enzymes and speech disorder

Dose

- With current antiepileptic therapy, initially 1 g daily in single or 2 divided doses then increased according to response in steps of 500 mg at weekly intervals; usual range 2–3 g daily (max. 3 g daily); CHILD initially 40 mg/kg daily in single or 2 divided doses then adjusted according to body-weight 10–15 kg, 0.5–1 g daily; body-weight 15–30 kg, 1–1.5 g daily; body-weight 30–50 kg, 1.5–3 g daily; body-weight over 50 kg, 2–3 g daily
- Infantile spasms (West's syndrome), monotherapy, 50 mg/kg daily, adjusted according to response over 7 days; up to 150 mg/kg daily used with good tolerability

Sabril® (Aventis Pharma)

Tablets, 1/2, scored, vigabatrin 500 mg, net price 100-tab pack = £30.84. Label: 3, 8, counselling, driving (see notes above)

Powder, sugar-free, vigabatrin 500 mg/sachet. Net price 50-sachet pack = £17.08. Label: 3, 8, 15, counselling, driving (see notes above)

Note The contents of a sachet should be dissolved in water or a soft drink immediately before taking

Zonisamide

Zonisamide can be used as adjunctive treatment for refractory partial seizures with or without secondary generalisation.

ZONISAMIDE

Indications adjunctive therapy for refractory partial seizures with or without secondary generalisation

Cautions elderly; ensure adequate hydration (especially if predisposition to nephrolithiasis or in strenuous activity or warm environment); concomitant use of drugs that increase risk of hyperthermia or nephrolithiasis; avoid abrupt withdrawal; hepatic impairment (avoid if severe—Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: see p. 249 and Appendix 1 (zonisamide)

Contra-indications hypersensitivity to sulphonamides; breast-feeding (Appendix 5)

Side-effects nausea, diarrhoea, abdominal pain, anorexia, weight loss; drowsiness, dizziness, confusion, agitation, irritability, depression, ataxia, speech disorder, impaired memory and attention, pyrexia; diplopia; rash (consider withdrawal); less commonly vomiting, cholelithiasis, cholecytitis, aggression, suicidal ideation, convulsions, psychosis, urinary calcilus, hypokalaemia; very rarely hepatitis, pancreatitis, dysphonia, hallucinations, insomnia, amnesia, coma, myasthenic syndrome, neuroleptic malignant syndrome, heat stroke, hydrenephrosis, renal impairment, metabolic acidosis, blood disorders, rhabdomyolysis, impaired sweating, pruritus, and Stevens-Johnson syndrome

Dose

- ADULT over 18 years, initially 50 mg daily in 2 divided doses, increased after 7 days to 100 mg daily in 2 divided doses; then increase if necessary by 100 mg every 7 days; usual maintenance 300–500 mg daily in 1–2 divided doses

Zonegran® (Eisai)

Capsules, zonisamide 25 mg (white), net price 14-cap pack = £8.82; 50 mg (white/grey), 56-cap pack = £47.04; 100 mg (white/red), 56-cap pack = £62.72. Label: 3

Benzodiazepines

Clonazepam is occasionally used in tonic-clonic or partial seizures, but its sedative side-effects may be prominent. Clobazam may be used as adjunctive therapy in the treatment of epilepsy (section 4.1.2), but the effectiveness of these and other benzodiazepines may wane considerably after weeks or months of continuous therapy.

CLOBAZAM

Indications adjunct in epilepsy; anxiety (short-term use)

Cautions see under Diazepam (section 4.1.2)

Contra-indications see under Diazepam (section 4.1.2)

Side-effects see under Diazepam (section 4.1.2)

Dose

- Epilepsy, 20–30 mg daily; max. 60 mg daily; CHILD over 3 years, not more than half adult dose
- Anxiety, 20–30 mg daily in divided doses or as a single dose at bedtime, increased in severe anxiety (in hospital patients) to a max. of 60 mg daily in divided doses; ELDERLY (or debilitated) 10–20 mg daily

Clobazam (Non-proprietary)

Tablets, clobazam 10 mg. Net price 30-tab pack = £9.74. Label: 2 or 19, 8, counselling, driving (see notes above)

Brands include Frisium

1. except for epilepsy and endorsed ‘SLS’

CLONAZEPAM

Indications all forms of epilepsy; myoclonus; status epilepticus (section 4.8.2)

Cautions see notes above; elderly and debilitated, respiratory disease, spinal or cerebellar ataxia; history of alcohol or drug abuse, depression or suicidal ideation; avoid sudden withdrawal; myasthenia gravis (avoid if unstable); acute porphyria (section 9.8.2); hepatic impairment (avoid if severe; Appendix 2); renal impairment; pregnancy (see notes above and Appendix 4); breast-feeding (see notes above and Appendix 5); interactions: Appendix 1 (anxiolytics and hypnotics)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome; marked neuromuscular respiratory weakness including unstable myasthenia gravis

Side-effects drowsiness, fatigue, dizziness, muscle hypotonia, co-ordination disturbances; also poor concentration, restlessness, confusion, amnesia, dependence, and withdrawal; salivary or bronchial hypersecretion in infants and small children; rarely gastro-intestinal symptoms, respiratory depression,
headache, paradoxical effects including aggression, anxiety, sexual dysfunction, urinary incontinence, urticaria, pruritus, reversible hair loss, skin pigmentation changes; dysarthria, and visual disturbances on long-term treatment; blood disorders reported; over-dosage: see Emergency Treatment of Poisoning, p. 32

Dose

- 1 mg (ELDERLY 500 micrograms) initially at night for 4 nights, increased according to response over 2–4 weeks to usual maintenance dose of 4–8 mg usually at night (may be given in 3–4 divided doses if necessary); CHILD up to 1 year, initially 250 micrograms increased as above to usual maintenance dose of 0.5–1 mg, 1–5 years, initially 250 micrograms increased as above to 1–3 mg, 5–12 years, initially 500 micrograms increased as above to 3–6 mg

Note Clonazepam doses in BNF may differ from those in product literature

Rivotril® (Roche) (NH)

Tablets, both scored, clonazepam 500 micrograms (beige), net price 100 = £3.92; 2 mg (white), 100 = £5.23. Label: 2, 8, counselling, driving (see notes above)

Injection, section 4.8.2

Other drugs

Acetazolamide (section 11.6), a carbonic anhydrase inhibitor, has a specific role in treating epilepsy associated with menstruation. It can also be used with other antiepileptics for tonic-clonic and partial seizures. It is occasionally helpful in atypical absence, atomic, and tonic seizures.

Piracetam (section 4.9.3) is used as adjunctive treatment for cortical myoclonus.

4.8.2 Drugs used in status epilepticus

Immediate measures to manage status epilepticus include positioning the patient to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Parenteral thiamine should be considered if alcohol abuse is suspected; pyridoxine (section 9.6.2) should be given if the status epilepticus is caused by pyridoxine deficiency.

Major status epilepticus should be treated urgently with intravenous lorazepam, repeated once after 10 minutes if seizures recur. Intravenous diazepam is effective but it is associated with a high risk of thrombophlebitis (reduced by using an emulsion formulation). Absorption of diazepam from intramuscular injection or from suppositories is too slow for treatment of status epilepticus. Clonazepam can also be used as an alternative.

Where facilities for resuscitation are not immediately available, diazepam can be administered as a rectal solution or midazolam [unlicensed use] can be given into the buccal cavity.

Phenytoin sodium may be given by slow intravenous injection, with ECG monitoring, followed by the maintenance dosage. Intramuscular use of phenytoin is not recommended (absorption is slow and erratic).

Alternatively, fosphenytoin, a pro-drug of phenytoin, can be given more rapidly and when given intravenously causes fewer injection-site reactions than phenytoin. Intravenous administration requires ECG monitoring. Although it can also be given intramuscularly, absorption is too slow by this route for treatment of status epilepticus. Doses of fosphenytoin should be expressed in terms of phenytoin sodium.

Paraldehyde also remains a valuable drug. Given rectally it causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

For advice on the management of epileptic seizures in dental practice, see p. 22.

Non-convulsive status epilepticus

The urgency to treat non-convulsive status epilepticus depends upon the severity of the patient’s condition. If there is incomplete loss of awareness, usual oral antiepileptic therapy should be continued or restarted. Patients who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as for convulsive status epilepticus, although anaesthesia is rarely needed.

CLONAZEPAM

Indications status epilepticus; other forms of epilepsy, and myoclonus (section 4.8.1)

Cautions see section 4.8.1; facilities for reversing respiratory depression with mechanical ventilation must be at hand (but see also notes above)

Intravenous infusion Intravenous infusion of clonazepam is potentially hazardous (especially if prolonged), calling for close and constant observation and best carried out in specialist centres with intensive care facilities. Prolonged infusion may lead to accumulation and delay recovery

Contra-indications see section 4.8.1; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Side-effects see section 4.8.1; hypotension and apnoea

Dose

- By intravenous injection into a large vein (over at least 2 minutes) or by intravenous infusion, 1 mg, repeated if necessary; CHILD all ages, 500 micrograms

Rivotril® (Roche) (NH)

Injection, clonazepam 1 mg/mL in solvent, for dilution with 1 mL water for injections immediately before
4 Central nervous system

4.8.2 Drugs used in status epilepticus

**FOSPHENYTOIN SODIUM**

**Note** Fosphenytoin is a pro-drug of phenytoin.

**Indications** status epilepticus; seizures associated with neurosurgery or head injury; when phenytoin by mouth not possible

**Cautions** see Phenytoin Sodium; liver impairment

**Contra-indications** see section 4.1.2

**Side-effects** see section 4.1.2; hypotension and apnoea

**Dose**

- Status epilepticus, by intravenous infusion (at a rate of 100–150 mg(PE)/minute), initially 20 mg(PE)/kg then by intravenous infusion (at a rate of 50–100 mg(PE)/minute), 4–5 mg(PE)/kg daily in 1–2 divided doses, dose adjusted according to response and trough plasma-phenytoin concentration
- CHILD 5 years and over, by intravenous infusion (at a rate of 2–3 mg(PE)/kg/minute), initially 20 mg(PE)/kg then by intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute), 4–5 mg(PE)/kg daily in 1–4 divided doses, dose adjusted according to response and trough plasma-phenytoin concentration
- Prophylaxis or treatment of seizures associated with neurosurgery or head injury, by intramuscular injection or by intravenous infusion (at a rate of 50–100 mg(PE)/minute), initially 10–15 mg(PE)/kg then by intramuscular injection or by intravenous infusion (at a rate of 50–100 mg(PE)/minute), 4–5 mg(PE)/kg daily (in 1–2 divided doses), dose adjusted according to response and trough plasma-phenytoin concentration
- CHILD 5 years and over, by intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute), initially 10–15 mg(PE)/kg then 4–5 mg(PE)/kg daily in 1–4 divided doses, dose adjusted according to response and trough plasma-phenytoin concentration
- Temporary substitution for oral phenytoin, by intramuscular injection or by intravenous infusion (at a rate of 50–100 mg(PE)/minute), same dose and dosing frequency as oral phenytoin therapy; CHILD 5 years and over, by intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute), same dose and dosing frequency as oral phenytoin therapy

**Note** ELDERLY consider 10–25% reduction in dose or infusion rate

**Note** Fosphenytoin sodium doses in BNF may differ from those in product literature

**Pro-Epanutin® (Pfizer)**

**Injection**, fosphenytoin sodium 75 mg/mL (equivalent to phenytoin sodium 50 mg/mL), net price 10-mL vial = £40.00

Electrolytes phosphate 3.7 micromol/mg fosphenytoin sodium (phosphate 5.6 micromol/mg phenytoin sodium)

**LORAZEPAM**

**Indications** status epilepticus; other indications (section 4.1.2)

**Cautions** see section 4.1.2

**Contra-indications** see under Diazepam (section 4.1.2)

**Side-effects** see under Diazepam (section 4.1.2)

**Dose**

- By slow intravenous injection (into large vein), 4 mg repeated once after 10 minutes if necessary; CHILD under 12 years 100 micrograms/kg (max. 4 mg) repeated once after 10 minutes if necessary

**Preparations**

Section 4.1.2
**MIDAZOLAM**

**Indications** status epilepticus [unlicensed indication]; other indications (section 15.1.4)

**Cautions** section 15.1.4

**Contra-indications** section 15.1.4

**Side-effects** section 15.1.4

**Dose**

- By buccal administration, *ADULT* and *CHILD* over 10 years, 10 mg repeated once if necessary; *CHILD* up to 6 months, 300 micrograms/kg (max. 2.5 mg); 6 months–1 year, 2.5 mg; 1–5 years, 5 mg; 5–10 years, 7.5 mg

**Note** Midazolam injection solution may be given by buccal administration

**Midazolam** (Non-proprietary) [EB]

Buccal liquid, midazolam 10 mg/mL

'Special order' [unlicensed] product; brands include Epistatus

**Injection**

Section 15.1.4

---

**PARALDEHYDE**

**Indications** status epilepticus

**Cautions** bronchopulmonary disease, hepatic impairment; pregnancy (Appendix 4) and breast-feeding (Appendix 5); *interactions:* Appendix 1 (paraldehyde)

**Contra-indications** gastric disorders; rectal administration in colitis

**Side-effects** rashes; rectal irritation after enema

**Dose**

- By rectum, *ADULT* and *CHILD* over 12 years, 20 mL; *CHILD* up to 3 months 0.5 mL, 3–6 months 1 mL, 6–12 months 1.5 mL, 1–2 years 2 mL, 2–5 years 3–4 mL, 6–12 years 5–10 mL

**Administration** Administer as an enema containing 1 part paraldehyde diluted with 9 parts physiological saline (some centres mix paraldehyde with an equal volume of arachis (peanut) oil instead)

**Note** Do not use paraldehyde if it has a brownish colour or an odour of acetic acid. Avoid contact with rubber and plastics.

**Paraldehyde** (Non-proprietary) [P]

**Injection**, sterile paraldehyde, net price 5-mL amp = £9.49

---

**PHENOBARBITAL SODIUM**

(Phenobarbitone sodium)

**Indications** status epilepticus; other forms of epilepsy except absence seizures (section 4.8.1)

**Cautions** see under Phenobarbital (section 4.8.1)

**Side-effects** see under Phenobarbital (section 4.8.1)

**Dose**

- Status epilepticus, by intravenous injection (dilute injection 1 in 10 with water for injections), 10 mg/kg at a rate of not more than 100 mg/minute; max. 1 g

**Note** For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect

**Phenobarbital** (Non-proprietary) [P]

**Injection**, phenobarbital sodium 200 mg/mL, net price 1-mL amp = £2.00

**Excipients** include propylene glycol 90% (see Excipients, p. 2)

**Note** Must be diluted before intravenous administration (see under Dose)

**Oral preparations**

Section 4.8.1

---

**PHENYTOIN SODIUM**

**Indications** status epilepticus; seizures in neurosurgery; arrhythmias, but now obsolete (section 2.3.2)

**Cautions** hypotension and heart failure; resuscitation facilities must be available; injection solutions alkaline (irritant to tissues); see also p. 256; *interactions:* see p. 249 and Appendix 1 (phenytoin)

**Contra-indications** sinus bradycardia, sino-atrial block, and second- and third-degree heart block; Stokes-Adams syndrome; acute porphyria (section 9.8.2)

**Side-effects** intravenous injection may cause cardiovascular and CNS depression (particularly if injection too rapid) with arrhythmias, hypotension, and cardiovascular collapse; alterations in respiratory function (including respiratory arrest); injection site reactions; see also p. 256

**Dose**

- By slow intravenous injection or infusion (with blood pressure and ECG monitoring), status epilepticus, 18 mg/kg at a rate not exceeding 50 mg per minute, as a loading dose (see also notes above); maintenance doses of about 100 mg should be given thereafter at intervals of every 6–8 hours, monitored by measurement of plasma concentrations; rate and dose reduced according to weight; *CHILD* 18 mg/kg as a loading dose (NEONATE 15–20 mg/kg at rate of 1–3 mg/kg/minute)

**Side-effects**

- Ventricular arrhythmias (but use now obsolete), by intravenous injection via caval catheter, 3.5–5 mg/kg at a rate not exceeding 50 mg/minute, with blood pressure and ECG monitoring; repeated once if necessary

**Note** To avoid local venous irritation each injection or infusion should be preceded and followed by an injection of sterile physiological saline through the same needle or catheter

- By intramuscular injection, not recommended (see notes above)

**Note** Phenytoin sodium doses in BNF may differ from those in product literature

**Phenytoin** (Non-proprietary) [PM]

**Injection**, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections, net price 5-mL amp = £3.40

**Epanutin® Ready-Mixed Parenteral** (Pfizer) [PM]

**Injection**, phenytoin sodium 50 mg/mL with propylene glycol 40% and alcohol 10% in water for injections, net price 5-mL amp = £4.88

**Electrolytes** 1.1 mmol Na per 5 mL ampoule

**Oral preparations**

Section 4.8.1

---

**4.8.3 Febrile convulsions**

Brief febrile convulsions need no specific treatment; antipyretic medication, e.g., *paracetamol* (section 4.7.1) is commonly used to reduce fever and prevent further convulsions but evidence to support this practice is lacking. *Prolonged febrile convulsions* (those lasting 15 minutes or longer), *recurrent convulsions,* or those occurring in a child at known risk must be treated more actively, as there is the possibility of resulting brain damage. *Diazepam* is the drug of choice given either by slow intravenous injection or preferably rectally in solution (section 4.8.2). The rectal route is preferred as
In idiopathic Parkinson’s disease, the progressive degeneration of pigmented neurones in the substantia nigra leads to a deficiency of the neurotransmitter dopamine. The resulting neurochemical imbalance in the basal ganglia causes the characteristic signs and symptoms of the illness. Drug therapy does not prevent disease progression, but it improves most patients’ quality of life.

Patients with suspected Parkinson’s disease should be referred to a specialist to confirm the diagnosis; the diagnosis should be reviewed every 6–12 months.

Features resembling those of Parkinson’s disease can occur in diseases such as progressive supranuclear palsy and multiple system atrophy, but they do not normally show a sustained response to the drugs used in the treatment of idiopathic Parkinson’s disease.

When initiating treatment, patients should be advised about its limitations and possible side-effects. About 5–10% of patients with Parkinson’s disease respond poorly to treatment.

Treatment is usually not started until symptoms cause significant disruption of daily activities. Therapy with two or more antiparkinsonian drugs may be necessary as the disease progresses. Most patients eventually require levodopa and subsequently develop motor complications.

Antiparkinsonian drug therapy should never be stopped abruptly as this carries a small risk of neuroleptic malignant syndrome.

Elderly Antiparkinsonian drugs can cause confusion in the elderly. It is particularly important to initiate treatment with low doses and to increase the dose gradually.

4.9 Drugs used in parkinsonism and related disorders

4.9.1 Dopaminergic drugs used in parkinsonism

Dopamine receptor agonists

The dopamine receptor agonists, bromocriptine, cabergoline, pergolide, pramipexole, ropinirole, and rotigotine have a direct action on dopamine receptors. The treatment of new patients is often started with dopamine receptor agonists. They are also used with levodopa in more advanced disease. Rotigotine is licensed for use as monotherapy in early-stage Parkinson’s disease.

When used alone, dopamine receptor agonists cause fewer motor complications in long-term treatment compared with levodopa treatment but the overall motor performance improves slightly less. The dopamine receptor agonists are associated with more neuropsychiatric side-effects than levodopa. The ergot-derived dopamine receptor agonists, bromocriptine, cabergoline, and pergolide, have been associated with fibrotic reactions (see notes below). Patients should be monitored for signs of cardiac fibrosis, using ECG before and at regular intervals during treatment with cabergoline or pergolide. In most cases, non-ergot-derived dopamine agonists are preferred over ergot-derived dopamine agonists.

Dopamine receptor agonists can cause excessive daytime sleepiness and sudden onset of sleep, see Sudden Onset of Sleep, p. 268.

Hypotensive reactions can occur in some patients taking dopamine agonists; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

Doses of dopamine receptor agonists should be increased slowly according to response and tolerability. Treatment with dopamine receptor agonists should not be withdrawn abruptly.

Fibrotic reactions

The CSM (updated by MHRA/CHM July and October 2008) has advised that ergot-derived dopamine receptor agonists, bromocriptine, cabergoline, lisuride [discontinued], and pergolide, have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for Parkinson’s disease or chronic endocrine disorders (excludes suppression of lactation); it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline or pergolide should be regularly monitored for cardiac fibrosis by echocardiography (within 3–6 months of initiating treatment and subsequently at 6–12 month intervals).

Apomorphine is a potent dopamine agonist that is sometimes helpful in advanced disease for patients due to lack of satisfactory absorption is achieved within minutes and administration is much easier. Suppositories are not suitable because absorption is too slow.

Intermittent prophylaxis (i.e. the anticonvulsant administered at the onset of fever) is possible in only a small proportion of children. Again diazepam is the treatment of choice, orally or rectally.

Long-term anticonvulsant prophylaxis for febrile convulsions is rarely indicated. Anticonvulsant treatment needs to be considered only for children at risk from prolonged or complex febrile convulsions, including those whose first seizure occurred at under 14 months or who have neurological abnormalities or who have had previous prolonged or focal convulsions.

4.9.2 Antimuscarinic drugs used in parkinsonism

4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders
experiencing unpredictable ‘off’ periods with levodopa treatment. Apomorphine is highly emetogenic; patients must receive domperidone for at least 2 days before starting treatment. Specialist supervision is advisable throughout apomorphine treatment.

**APOMORPHINE HYDROCHLORIDE**

**Indications** refractory motor fluctuations in Parkinson’s disease (“off” episodes) inadequately controlled by levodopa with dopa-decarboxylase inhibitor or other dopaminergics (for capable and motivated patients under specialist supervision)

**Cautions** see notes above; pulmonary or cardiovascular disease, history of postural hypotension (special care on initiation); neuropsychiatric problems or dementia; hepatic, haemopoietic, renal, and cardiovascular monitoring; on administration with levodopa test initially and every 6 months for haemolytic anaemia (development calls for specialist haematological care with dose reduction and possible discontinuation); renal impairment; pregnancy; interactions: Appendix 1 (apomorphine)

**Contra-indications** respiratory depression, hypersensitivity to opioids; not suitable if ‘on’ response to levodopa marred by severe dyskinesia, hypotonia or psychiatric effects; hepatic impairment; breast-feeding; not for intravenous administration

**Side-effects** nausea, vomiting (see below under Dose); drowsiness (including sudden onset of sleep), confusion, hallucinations, injection-site reactions (including nodule formation and ulceration)—change injection sites in rotation; less commonly postural hypotension, breathing difficulties, dykinesias during ‘on’ periods (may require discontinuation), haemolytic anaemia with levodopa (see Cautions), and rash; rarely eosinophilia; pathological gambling, increased libido, and hypersexuality also reported

**Dose**

- **By subcutaneous injection**, usual range (after initiation as below) 3–30 mg daily in divided doses; subcutaneous infusion may be preferable in those requiring division of injections into more than 10 doses daily; max. single dose 10 mg; CHILD and ADOLESCENT under 18 years not recommended

- **By continuous subcutaneous infusion** (those requiring division into more than 10 injections daily) initially 1 mg/hour daily increased according to response (not more often than every 4 hours) in max. steps of 500 micrograms/hour, to usual rate of 1–4 mg/hour (14–60 micrograms/kg/hour); change infusion site every 12 hours and give during waking hours only (24-hour infusions not advised unless severe night-time symptoms)—intermittent bolus boosts also usually needed; CHILD and ADOLESCENT under 18 years not recommended

**Note** Total daily dose by either route (or combined routes) max. 100 mg

**Requirements for initiation** Hospital admission and at least 2 days of pretreatment with domperidone for nausea and vomiting, after at least 3 days withhold existing antiparkinsonian medication overnight to provoke ‘off’ episode, determine threshold dose, re-establish other antiparkinsonian drugs, determine effective apomorphine regimen, teach to administer by subcutaneous injection into lower abdomen or outer thigh at first sign of ‘off’ episode, discharge from hospital, monitor frequently and adjust dosage regimen as appropriate (domperidone may normally be withdrawn over several weeks or longer)—for full details of initiation requirements, consult product literature

**Injection** apomorphine hydrochloride 10 mg/mL, net price 2-mL amp = £7.59, 5-mL amp = £14.62

**Excipients** include sulphites

**Injection (APO-go® Pen)**, apomorphine hydrochloride 10 mg/mL, net price 3-mL pen injector = £24.78

**Excipients** include sulphites

**Injection (APO-go® PFS)**, apomorphine hydrochloride 5 mg/mL, net price 10-mL prefilled syringe = £14.62

**Excipients** include sulphites

**BROMOCRIPTINE**

**Indications** parkinsonism (but not drug-induced extrapyramidal symptoms); endocrine disorders (section 6.7.1)

**Cautions** see section 6.7.1 and notes above

**Contra-indications** section 6.7.1

**Side-effects** section 6.7.1

**Dose**

- **First week** 1–1.25 mg at night, second week 2–2.5 mg at night, third week 2.5 mg twice daily, fourth week 2.5 mg 3 times daily then increasing by 2.5 mg every 3–4 days according to response to a usual range of 10–30 mg daily; taken with food

**Preparations** Section 6.7.1

**CABERGOLINE**

**Indications** alone or as adjunct to levodopa with dopa-decarboxylase inhibitor in Parkinson’s disease where dopamine receptor agonists other than ergot derivative not appropriate; endocrine disorders (section 6.7.1)

**Cautions** see section 6.7.1 and notes above

**Contra-indications** section 6.7.1

**Side-effects** section 6.7.1

**Dose**

- **Initially** 1 mg daily, increased by increments of 0.5–1 mg at 7 or 14 day intervals; usual range 2–3 mg daily

**Note** Concurrent dose of levodopa may be decreased gradually while dose of cabergoline is increased

**Cabergoline** (Non-proprietary) Tablets, scored, cabergoline 1 mg, net price 20-tab pack = £52.97; 2 mg, 20-tab pack = £63.78. Label: 21, counselling, hypotensive reactions, driving, see notes above

**Note** Dispense in original container (contains desiccant)

**Cabaser®** (Pharmacia) Tablets, scored, cabergoline 1 mg, net price 20-tab pack = £83.00; 2 mg, 20-tab pack = £83.00. Label: 21, counselling, hypotensive reactions, driving, see notes above

**Note** Dispense in original container (contains desiccant)

**PERGOLIDE**

**Indications** alone or as adjunct to levodopa with dopa-decarboxylase inhibitor in Parkinson’s disease where dopamine receptor agonists other than ergot derivative not appropriate

**Cautions** see notes above; arrhythmias or underlying cardiac disease; history of confusion, psychosis, or...
hallucinations, dyskinesia (may exacerbate); acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (pergolide)

Contra-indications
history of fibrotic disorders; cardiac valvulopathy (exclude before treatment, see Fibrotic Reactions, p. 264)

Side-effects
see notes above; also nausea, vomiting, dyspepsia, abdominal pain; dysphonia, rhinitis; hallucinations, dyskinesia, drowsiness (including sudden onset of sleep); diplopia; also reported constipation, diarrhoea, tachycardia, atrial premature contractions, palpitation, hypotension, syncope, Raynaud's phenomenon, cardiac valvulopathy, pericarditis, pericardial effusion, pleuritis, pleural effusion, pleural fibrosis, insomnia, confusion, dizziness, pathological gambling, neuroleptic malignant syndrome, fever, increased libido, hypersexuality, and rash

Dose
- Monotherapy, 50 micrograms at night on day 1, then 50 micrograms twice daily on days 2–4, then increased by 100–250 micrograms daily every 3–4 days to 1.5 mg daily in 3 divided doses at day 28; after day 30, further increases every 3–4 days of up to 250 micrograms daily; usual maintenance dose 2.1–2.5 mg daily; max. 3 mg daily
- Adjunctive therapy with levodopa, 50 micrograms daily for 2 days, increased gradually by 100–150 micrograms every 3 days over next 12 days, usually given in 3 divided doses; further increases of 250 micrograms every 3 days; max. 3 mg daily; during pergolide titration levodopa dose may be reduced cautiously

Pergolide (Non-proprietary)
Tablets, pergolide (as mesilate) 50 micrograms, net price 100-tab pack = £13.80; 250 micrograms, 100-tab pack = £11.27; 1 mg, 100-tab pack = £28.96. Counselling, hypotensive reactions, driving, see notes above

Celance® (Lilly)
Tablets, all scored, pergolide (as mesilate) 50 micrograms (ivory), net price 100-tab pack = £32.44; 250 micrograms (green), 100-tab pack = £48.92; 1 mg (pink), 100-tab pack = £176.58. Counselling, hypotensive reactions, driving, see notes above

Pramipexole
Indications Parkinson's disease, used alone or as an adjunct to levodopa with a dopa-decarboxylase inhibitor; moderate to severe restless legs syndrome
Caution see notes above; psychotic disorders; ophthalmological testing recommended (risk of visual disorders); severe cardiovascular disease; renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (pramipexole)

Contra-indications
breast-feeding (Appendix 5)

Side-effects
see notes above; also nausea, constipation; postural hypotension, hypotension, headache, confusion, drowsiness (including sudden onset of sleep), fatigue, insomnia, dizziness, hallucinations (mostly visual), dyskinesia, peripheral oedema; hyperkinesia, delusions, abnormal dreams, paradoxical worsening of restless legs syndrome, and behavioural changes including pathological gambling, binge eating, hypersexuality, and changes in libido also reported

Dose
Important Doses and strengths are stated in terms of pramipexole (base); equivalent strengths in terms of pramipexole dihydrochloride monohydrate (salt) are as follows: 88 micrograms base = 125 micrograms salt; 180 micrograms base = 250 micrograms salt; 350 micrograms base = 500 micrograms salt; 700 micrograms base = 1 mg salt
- Parkinson's disease, initially 88 micrograms 3 times daily, dose doubled every 5–7 days if tolerated to 350 micrograms 3 times daily; further increased if necessary by 180 micrograms 3 times daily at weekly intervals; max. 3.3 mg daily in 3 divided doses
Note During pramipexole dose titration and maintenance, levodopa dose may be reduced
- Restless legs syndrome, initially 88 micrograms once daily 2–3 hours before bedtime, dose doubled every 4–7 days if necessary to 350 micrograms daily; max. 540 micrograms daily; CHILD under 18 years not recommended

Mirapexin® (Boehringer Ingelheim)
Tablets, pramipexole (as hydrochloride) 88 micrograms, net price 100-tab pack = £9.55; 180 micrograms (scored), 30-tab pack = £19.10, 100-tab pack = £63.67; 350 micrograms (scored), 30-tab pack = £38.20, 100-tab pack = £127.34; 700 micrograms (scored), 30-tab pack = £76.40, 100-tab pack = £254.69. Counselling, hypotensive reactions, driving, see notes above

Ropinirole
Indications Parkinson's disease, either used alone or as an adjunct to levodopa with a dopa-decarboxylase inhibitor; moderate to severe restless legs syndrome
Caution see notes above; severe cardiovascular disease, major psychotic disorders; hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (ropinirole)

Contra-indications pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects
see notes above; also nausea, vomiting, abdominal pain, dyspepsia, constipation; syncope, peripheral oedema; drowsiness (including sudden onset of sleep, see p. 268), dizziness, nervousness, fatigue, dyskinesia, hallucinations, confusion; less commonly psychosis, pathological gambling, hypersexuality, and increased libido; very rarely hepatic disorders; also reported paradoxical worsening of restless legs syndrome

Dose
- See under preparations

Adartrel® (GSK)
Tablets, 1.5 mg, ropinirole (as hydrochloride) 250 micrograms (white), net price 12-tab pack = £3.94; 500 micrograms (yellow), 28-tab pack = £15.75, 84-tab pack = £47.26; 2 mg (pink), 28-tab pack = £31.51, 84-tab pack = £94.53. Label: 21, counselling, driving, see notes above

Dose restless legs syndrome, initially 250 micrograms at night for 2 days, increased if tolerated to 500 micrograms at night for 3 days and then to 1 mg at night for 7 days; further increased at weekly intervals in steps of 250 micrograms daily according to response; usual dose 2 mg once at night; max. 4 mg once daily; CHILD under 18 years not recommended
Note Repeat dose titration if restarting after interval of more than a few days

The Scottish Medicines Consortium has advised (June 2006) that Adartrel should be restricted for use in patients with a baseline score of 24 points or more on the International Restless Legs Scale
Requip® (GSK) 

Tablets, f/c, ropinirole (as hydrochloride) 1 mg (green), net price 84-tab pack = £47.26; 2 mg (pink), 84-tab pack = £94.53; 5 mg (blue), 84-tab pack = £163.27; 28-day starter pack of 42 × 250-microgram (white) tablets, 42 × 500-microgram (yellow) tablets, and 21 × 1-mg (green) tablets = £40.10; 28-day follow-on pack of 42 × 500-microgram (yellow) tablets, 42 × 1-mg (green) tablets, and 63 × 2-mg (pink) tablets = £74.40. Label: 21, counselling, driving, see notes above

Dose Parkinson’s disease, initially 750 micrograms daily in 3 divided doses, increased by increments of 750 micrograms at weekly intervals to 3 mg daily; further increased by increments of up to 3 mg at weekly intervals according to response, usual range 9–16 mg daily (but higher doses may be required if used with levodopa); max. 24 mg daily

Note When administered as adjunct to levodopa, concurrent dose of levodopa may be reduced by approx. 20%, ropinirole doses in the BNF may differ from those in product literature

Modified release

Requip® XL (GSK) ▼ (FW)

Tablets, m/f, f/c, ropinirole (as hydrochloride) 2 mg (pink), net price 28-tab pack = £31.36; 4 mg (brown), 28-tab pack = £62.72; 8 mg (red), 28-tab pack = £105.28. Label: 25, counselling, driving, see notes above

Dose stable Parkinson’s disease in patients transferring from ropinirole immediate-release tablets, initially Requip XL once daily substituted for total daily dose equivalent of ropinirole immediate-release tablets; if control not maintained after switching, in patients receiving less than 8 mg once daily, increase in steps of 2 mg at intervals of at least 1 week to 8 mg once daily according to response, in patients receiving 8 mg once daily or more, increase in steps of 2 mg at intervals of at least 2 weeks according to response; max. 24 mg once daily

Note When administered as adjunct to levodopa, concurrent dose of levodopa may be reduced

ROTIGOTINE

Indications Parkinson’s disease, either used alone or as an adjunct to levodopa with dopa-decarboxylase inhibitor

Cautions see notes above; ophthalmic testing recommended; avoid exposure of patch to heat; hepatic impairment (Appendix 2); interactions: Appendix 1 (rotigotine)

Contra-indications pregnancy (Appendix 4); breast-feeding (Appendix 5); remove patch (aluminium-containing) before magnetic resonance imaging or cardioversion

Side-effects nausea, vomiting, constipation, dry mouth, diarrhoea, dyspepsia, weight changes; postural hypotension, peripheral oedema; confusion, drowsiness (including sudden onset of sleep), sleep disorders, dizziness, headache, dyskinesia, asthenia, hallucinations; hyperhidrosis, rash (including local reactions to patch), and pruritus; less commonly abdominal pain, anorexia, taste disturbance, palpitation, tachycardia, hypotension, hypertension, atrial fibrillation, syncope, dyspnoea, cough, hiccup, tremor, psychosis, pathological gambling, anxiety, impaired attention, dystonia, paraesthesia, impaired memory, erectile dysfunction, increased libido, arthralgia, and visual disturbances; rarely convulsions and loss of consciousness

Dose

• Monotherapy, apply ‘2 mg/24 hours’ patch to dry, non-irritated skin on torso, thigh, or upper arm, removing after 24 hours and siting replacement patch on a different area (avoid using the same area for 14 days); increased in steps of 2 mg/24 hours at weekly intervals if required; max. 8 mg/24 hours

• Adjunctive therapy with levodopa, apply ‘4 mg/24 hours’ patch to dry, non-irritated skin on torso, thigh, or upper arm, removing after 24 hours and siting replacement patch on a different area (avoid using the same site for 14 days); increased in steps of 2 mg/24 hours at weekly intervals if required; max. 16 mg/24 hours

Neupro® (UCB Pharma) ▼ (FW)

Tablets, self-adhesive, beige, rotigotine 2 mg/24 hours, net price 28 = £77.24; 4 mg/24 hours, 28 = £117.71; 6 mg/24 hours, 28 = £142.79; 8 mg/24 hours, 28 = £142.79; 28-day starter pack of 7 × 2 mg/24 hours, 7 × 4 mg/24 hours, 7 × 6 mg/24 hours, and 7 × 8 mg/24 hours patches = £142.79. Counselling, hypotensive reactions, driving, see notes above

Note The Scottish Medicines Consortium has advised that Neupro is accepted as monotherapy for the treatment of early-stage idiopathic Parkinson’s disease (June 2007) and for restricted use for the treatment of advanced Parkinson’s disease in combination with levodopa where the transdermal route would facilitate treatment (July 2007)

Lеводопа

Lеводопа, the amino-acid precursor of dopamine, acts by replenishing depleted striatal dopamine; it is given with an extracerebral dopa-decarboxylase inhibitor that reduces the peripheral conversion of levodopa to dopamine, thereby limiting side-effects such as nausea, vomiting and cardiovascular effects. Additionally, effective brain-dopamine concentrations can be achieved with lower doses of levodopa. The extracerebral dopa-decarboxylase inhibitors used with levodopa are benzserazide (in co-beneldopa) and carbidopa (in co-careldopa). Levodopa, in combination with a dopa-decarboxylase inhibitor, is useful in the elderly or frail, in patients with other significant illnesses, and in those with more severe symptoms. It is effective and well tolerated in the majority of patients. Levodopa therapy should be initiated at a low dose and increased in small steps; the final dose should be as low as possible. Intervals between doses should be chosen to suit the needs of the individual patient. Note When co-careldopa is used, the total daily dose of carbidopa should be at least 70 mg. A lower dose may not achieve full inhibition of extracerebral dopa-decarboxylase, with a resultant increase in side-effects.

Nausea and vomiting with co-beneldopa or co-careldopa are rarely dose-limiting but domperidone (section 4.6) may be useful in controlling these effects. Levodopa treatment is associated with the development of potentially troublesome motor complications including response fluctuations and dyskinasias. Response fluctuations are characterised by large variations in motor performance, with normal function during the ‘on’ period, and weakness and restricted mobility during the ‘off’ period. ‘End-of-dose’ deterioration also occurs, where the duration of benefit after each dose becomes progressively shorter. Modified-release preparations
may help with ‘end-of-dose’ deterioration or nocturnal immobility and rigidity. Motor complications are particularly problematic in young patients treated with levodopa.

**Cautions** Levodopa should be used with caution in severe cardiovascular or pulmonary disease, psychiatric illness (avoid if severe), endocrine disorders (including hyperthyroidism, Cushing’s syndrome, diabetes mellitus, osteomalacia, and pheochromocytoma), and in those with a history of convulsions, malignant melanoma, or peptic ulcer. Levodopa should be used with caution in open-angle glaucoma and patients susceptible to angle-closure glaucoma, and in hepatic or renal impairment. Patients should be advised to avoid abrupt withdrawal (risk of neuroleptic malignant syndrome and rhabdomyolysis), and to be aware of the potential for excessive drowsiness and sudden onset of sleep (see Sudden Onset of Sleep, below). Levodopa should be used with caution in pregnancy (Appendix 4); **interactions:** Appendix 1 (levodopa).

**Contra-indications** Levodopa should be avoided in breast-feeding (Appendix 5).

**Side-effects** Side-effects of levodopa include nausea, vomiting, taste disturbances, dry mouth, anorexia, arrhythmias, postural hypotension, syncope, drowsiness (including sudden onset of sleep), fatigue, dementia, psychoses, hallucinations, confusion, euphoria, abnormal dreams, insomnia, depression (very rarely with suicidal ideation), anxiety, dizziness, dystonia, dyskinesia, and chorea.

Less commonly weight loss or gain, constipation, diarrhoea, hypersalivation, dysphagia, flatulence, hypertension, chest pain, oedema, hoarseness, ataxia, increased hand tremor, malaise, muscle cramps, and reddish discoloration of the urine and other body fluids may occur. Rare side-effects include abdominal pain, gastro-intestinal bleeding, dyspepsia, phlebitis, dyspnkea, agitation, paraesthesia, bruxism, trismus, hiccup, neuroleptic malignant syndrome (associated with abrupt withdrawal), convulsions, reduced mental acuity, disorientation, headache, urinary retention, urinary incontinence, priapism, activation of malignant melanoma, leucopenia, haemolytic and non-haemolytic anaemia, thrombocytopenia, agranulocytosis, blurred vision, blepharospasm, diplopia, activation of Horner’s syndrome, pupil dilatation, oculogyric crisis, angioedema, rash, urticaria, pruritus, flushing, alopecia, exanthema, Henoch-Schönlein purpura, and increased sweating. Very rarely angle-closure glaucoma may occur; pathological gambling, increased libido, hypersexuality, and false positive tests for urinary ketones have also been reported.

**CO-BENELDOPA**

A mixture of benserazide hydrochloride and levodopa in mass proportions corresponding to 1 part of benserazide and 4 parts of levodopa

**Indications** parkinsonism (but not drug-induced extrapyramidal symptoms), see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- See preparations

**Madopar** (Roche) (pH)

Capsules 62.5, blue/pink, co-beneldopa 12.5/50 (benserazide 12.5 mg (as hydrochloride), levodopa 50 mg). Net price 100-cap pack = £6.20. Label: 14, counselling, driving, see notes above

Capsules 125, blue/pink, co-beneldopa 25/100 (benserazide 25 mg (as hydrochloride), levodopa 100 mg). Net price 100-cap pack = £8.64. Label: 14, counselling, driving, see notes above

Capsules 250, blue/caramel, co-beneldopa 50/200 (benserazide 50 mg (as hydrochloride), levodopa 200 mg). Net price 100-cap pack = £14.73. Label: 14, counselling, driving, see notes above

**Dispersible tablets** 62.5, scored, co-beneldopa 12.5/50 (benserazide 12.5 mg (as hydrochloride), levodopa 50 mg). Net price 100-tab pack = £7.37. Label: 14, counselling, administration, see below, driving, see notes above

**Dispersible tablets** 125, scored, co-beneldopa 25/100 (benserazide 25 mg (as hydrochloride) levodopa 100 mg). Net price 100-tab pack = £13.06. Label: 14, counselling, administration, see below, driving, see notes above

**Note** The tablets can be dispersed in water or orange squash (not orange juice) or swallowed whole

**Dose** expressed as levodopa, initially 50 mg 3–4 times daily (100 mg 3 times daily in advanced disease), increased by 100 mg daily once or twice weekly according to response; usual maintenance dose 400–600 mg daily in divided doses; **ELDERLY** initially 50 mg once or twice daily; increased by 50 mg daily every 3–4 days according to response

**Note** When transferring from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued 12 hours before (although interval can be shorter)

**Modified release**

**Madopar CR** (Roche) (pH)

Capsules 125, m/r, dark green/light blue, co-beneldopa 25/100 (benserazide 25 mg (as hydrochloride), levodopa 100 mg). Net price 100-cap pack = £15.96. Label: 5, 14, 25, counselling, driving, see notes above

**Dose** Patients not taking levodopa/dopa-decarboxylase inhibitor therapy, initially 1 capsule 3 times daily (max. initial dose 6 capsules daily)

Patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations, initially 1 capsule substituted for every 100 mg of levodopa and given at same dosage frequency, increased every 2–3 days according to response; average increase of 50% needed over previous levodopa dose and titration may take up to 4 weeks

Supplementary dose of immediate-release Madopar may be needed with first morning dose; if response still poor to total daily dose of Madopar CR plus Madopar corresponding to 1.2 g levodopa, consider alternative therapy

---

**Sudden onset of sleep**

Excessive daytime sleepiness and sudden onset of sleep can occur with co-careldopa, co-beneldopa, and dopamine receptor agonists.

Patients starting treatment with these drugs should be warned of the possibility of these effects and of the need to exercise caution when driving or operating machinery.

Patients who have suffered excessive sedation or sudden onset of sleep, should refrain from driving or operating machines until those effects have stopped recurring.
CO-CARELDOPA
A mixture of carbidopa and levodopa; the proportions are expressed in the form $x/y$ where $x$ and $y$ are the strengths in milligrams of carbidopa and levodopa respectively.

**Indications** parkinsonism (but not drug-induced extrapyramidal symptoms), see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Expressed as levodopa, initially 100 mg (with carbidopa 25 mg) 3 times daily, increased by 50–100 mg (with carbidopa 12.5–25 mg) daily or on alternate days according to response, up to 800 mg (with carbidopa 200 mg) daily in divided doses
- Alternatively, initially 50–100 mg (with carbidopa 10–12.5 mg) 3–4 times daily, increased by 50–100 mg daily or on alternate days according to response, up to 800 mg (with carbidopa 80–100 mg) daily in divided doses
- Alternatively, initially 125 mg (with carbidopa 12.5 mg, as ½ tablet of co-careldopa 25/250) 1–2 times daily, increased by 125 mg (with carbidopa 12.5 mg) daily or on alternate days according to response

**Note** At least 70 mg carbidopa daily is necessary to achieve full inhibition of peripheral dopa-decarboxylase. When transferring patients from another levodopa/dopa-decarboxylase inhibitor preparation, the previous preparation should be discontinued at least 12 hours before

**Co-careldopa** (Non-proprietary)

**Tablets**
- co-careldopa 10/100 (carbidopa 10 mg (anhydrous), levodopa 100 mg), net price 100-tab pack = £23.07. Label: 14, counselling, driving, see notes above
- co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 100-tab pack = £20.97. Label: 14, counselling, driving, see notes above
- co-careldopa 25/250 (carbidopa 25 mg (anhydrous), levodopa 250 mg), net price 100-tab pack = £32.23. Label: 14, counselling, driving, see notes above

**Sinemet®** (Bristol-Myers Squibb)

**Sinemet-62.5 tablets**
- yellow, scored, co-careldopa 12.5/50 (carbidopa 12.5 mg (anhydrous), levodopa 50 mg), net price 90-tab pack = £6.54. Label: 14, counselling, driving, see notes above

**Sinemet-110 tablets**
- blue, scored, co-careldopa 10/100 (carbidopa 10 mg (anhydrous), levodopa 100 mg), net price 90-tab pack = £6.84. Label: 14, counselling, driving, see notes above

**Sinemet-Plus tablets**
- yellow, scored, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 90-tab pack = £10.05. Label: 14, counselling, driving, see notes above

**Sinemet-275 tablets**
- blue, scored, co-careldopa 25/250 (carbidopa 25 mg (anhydrous), levodopa 250 mg), net price 90-tab pack = £14.28. Label: 14, counselling, driving, see notes above

**For use with enteral tube**

**Duodopa®** (Solvay)

Intestinal gel, co-careldopa 5/20 (carbidopa 5mg as monohydrate, levodopa 20mg/mL, net price 100 mL cassette (for use with Duodopa® portable pump) = £77.00. Label: 14, counselling, driving, see notes above

**Dose** Severe Parkinson’s disease inadequately controlled by other preparations, consult product literature

**Modified release**

**Caramet® CR** (Teva)

**Tablets**
- m/r, orange-brown, co-careldopa 25/100 (carbidopa 25 mg (as monohydrate), levodopa 100 mg), net price 60-tab pack = £11.47; co-careldopa 50/200 (carbidopa 50 mg (as monohydrate), levodopa 200 mg), 60-tab pack = £11.47. Label: 14, 25, counselling, driving, see notes above

**Dose** Patients not receiving levodopa/dopa-decarboxylase inhibitor preparations, expressed as levodopa, initially 100–200 mg twice daily (at least 6 hours between doses); dose adjusted according to response at intervals of at least 2 days

Patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations, 1 tablet twice daily at least 12 hours before first dose of Caramet CR, substitute Caramet CR to provide a similar amount of levodopa daily and extend dosing interval by 30–50%; dose then adjusted according to response at intervals of at least 2 days

**Half Sinemet® CR** (Bristol-Myers Squibb)

**Tablets**
- m/r, pink, co-careldopa 25/100 (carbidopa 25 mg (anhydrous), levodopa 100 mg), net price 60-tab pack = £12.07. Label: 14, 25, counselling, driving, see notes above

**Dose** For fine adjustment of Sinemet CR dose (see below)

**Sinemet® CR** (Bristol-Myers Squibb)

**Tablets**
- m/r, peach, scored, co-careldopa 50/200 (carbidopa 50 mg (anhydrous), levodopa 200 mg), net price 60-tab pack = £12.07. Label: 14, 25, counselling, driving, see notes above

**Dose** Patients not receiving levodopa/dopa-decarboxylase inhibitor therapy, initially, 1 Sinemet CR tablet twice daily; both dose and interval then adjusted according to response at intervals of not less than 3 days

Patients transferring from immediate-release levodopa/dopa-decarboxylase inhibitor preparations, 1 Sinemet CR tablet twice daily can be substituted for a daily dose of levodopa 300–400 mg in immediate-release Sinemet tablets (substitute Sinemet CR to provide approx. 10% more levodopa per day and extend dosing interval by 30–50%), dose and interval then adjusted according to response at intervals of not less than 3 days

**With entacapone**

**Note** For Parkinson’s disease and end-of-dose motor fluctuations not adequately controlled with levodopa and dopa-decarboxylase inhibitor treatment

**Stalevo®** (Orion)

**Stalevo 50 mg/12.5 mg/200 mg tablets**
- f/c, brown, levodopa 50 mg, carbidopa 12.5 mg, entacapone 200 mg, net price 30-tab pack = £21.72, 100-tab pack = £72.40. Label: 14 (urine reddish-brown), 25, counselling, driving, see notes above, avoid iron-containing preparations at the same time of day

**Stalevo 100 mg/25 mg/200 mg tablets**
- f/c, brown, levodopa 100 mg, carbidopa 25 mg, entacapone 200 mg, net price 30-tab pack = £21.72, 100-tab pack = £72.40. Label: 14 (urine reddish-brown), 25, counselling, driving, see notes above, avoid iron-containing preparations at the same time of day

**Stalevo 150 mg/37.5 mg/200 mg tablets**
- f/c, brown, levodopa 150 mg, carbidopa 37.5 mg, entacapone 200 mg, net price 30-tab pack = £21.72, 100-tab
Monoamine-oxidase-B inhibitors

Rasagiline, a monoamine-oxidase-B inhibitor, is licensed for the management of Parkinson’s disease used alone or as an adjunct to levodopa for ‘end-of-dose’ fluctuations.

Selegiline is a monoamine-oxidase-B inhibitor used in conjunction with levodopa to reduce ‘end-of-dose’ deterioration in advanced Parkinson’s disease. Early treatment with selegiline alone can delay the need for levodopa therapy. When combined with levodopa, selegiline should be avoided or used with great caution in postural hypotension.

**RASAGILINE**

**Indications** Parkinson’s disease, used alone or as an adjunct to levodopa with dopa-decarboxylase inhibitor

**Cautions** avoid abrupt withdrawal; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (rasagiline)

**Side-effects** dry mouth, dyspepsia, constipation; angina; headache, depression, anorexia, weight loss, abdominal dreams, vertigo, hallucinations; influenza-like symptoms; urinary urgency; leucopenia; arthralgia; conjunctivitis; rash; less commonly myocardial infarction, and cerebrovascular accident

**Dose**
- 1 mg daily

Azilect® (Teva)

Tablets, rasagiline (as mesilate) 1 mg, net price 28-tab pack = £70.72

**SELEGILINE HYDROCHLORIDE**

**Indications** Parkinson’s disease, used alone or as an adjunct to levodopa with dopa-decarboxylase inhibitor

**Cautions** avoid abrupt withdrawal; gastric and duodenal ulceration (avoid in active ulceration), uncontrolled hypertension, arrhythmias, angina, psychosis, side-effects of levodopa may be increased, concurrent levodopa dosage can be reduced by 10–20%; interactions: Appendix 1 (selegiline)

**Contra-indications** pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Side-effects** nausea, constipation, diarrhoea, dry mouth; postural hypotension; dyskinesia, vertigo, sleeping disorders, confusion, hallucinations; arthralgia, myalgia; mouth ulcers with oral lyophilisate; rarely arrhythmias, agitation, headache, micturition difficulties, skin reactions; also reported chest pain

**Dose**
- 10 mg in the morning, or 5 mg at breakfast and midday; ELDERLY see below

**Elderly** To avoid initial confusion and agitation, it may be appropriate to start treatment with a dose of 2.5 mg daily, particularly in the elderly

Selegiline Hydrochloride (Non-proprietary)

Tablets, selegiline hydrochloride 5 mg, net price 56-tab pack = £4.99; 10 mg, 30-tab pack = £8.21

**Elderyl®** (Orion)

Tablets, both scored, selegiline hydrochloride 5 mg, net price 60-tab pack = £10.35; 10 mg, 30-tab pack = £10.10

**Oral liquid** selegiline hydrochloride 10 mg/5 mL, net price 200 mL = £18.72

**Oral lyophilisate**

Zelapar® (Cephalon)

Oral lyophilisates (= freeze-dried tablets), yellow, selegiline hydrochloride 1.25 mg, net price 30-tab pack = £59.95. Counselling, administration Excerpts include apartame (section 9.4.1)

**Dose** initially 1.25 mg daily before breakfast

Counselling Tablets should be placed on the tongue and allowed to dissolve. Advise patient not to drink, rinse, or wash mouth out for 5 minutes after taking the tablet

**Note** Patients receiving 10 mg conventional selegiline hydrochloride tablets can be switched to Zelapar 1.25 mg

Catechol-O-methyltransferase inhibitors

Entacapone and tolcapone prevent the peripheral breakdown of levodopa, by inhibiting catechol-O-methyltransferase, allowing more levodopa to reach the brain. They are licensed for use as an adjunct to co-beneldopa or co-careldopa for patients with Parkinson’s disease who experience ‘end-of-dose’ deterioration and cannot be stabilised on these combinations. Due to the risk of hepatotoxicity, tolcapone should be prescribed under specialist supervision only, when other catechol-O-methyltransferase inhibitors combined with co-beneldopa or co-careldopa are ineffective.

**ENTACAPONE**

**Indications** adjunct to levodopa with dopa-decarboxylase inhibitor in Parkinson’s disease and ‘end-of-dose’ motor fluctuations

**Cautions** avoid abrupt withdrawal; concurrent levodopa dose may need to be reduced by about 10–30%; interactions: Appendix 1 (entacapone)

**Contra-indications** pregnancy (Appendix 4); breastfeeding (Appendix 5); hepatic impairment; phaeochromocytoma; history of neuroleptic malignant syndrome or non-traumatic rhabdomyolysis

**Side-effects** nausea, vomiting, abdominal pain, constipation, diarrhoea, urine may be coloured reddish-brown, dry mouth; confusion, dizziness, abnormal dreams, fatigue, insomnia, dystonia, dyskinesia, hallucinations; increased sweating; rarely hepatic dysfunction and rash; very rarely anorexia, weight loss, agitation, and urticaria; also reported colitis, neuroleptic malignant syndrome, rhabdomyolysis, and skin, hair, and nail discoloration
Dose
- 200 mg with each dose of levodopa with dopa-decarboxylase inhibitor; max. 2 g daily

Comtess® (Orion) (cf)
Tablets, f/c, brown/orange, entacapone 200 mg, net price 30-tab pack = £18.00. 100-tab pack = £60.00. Label: 14, (urine reddish-brown), counselling, driving, see notes above, avoid iron-containing products at the same time of day

TOLCAPONE

Indications  adjunct to levodopa with dopa-decarboxylase inhibitor in Parkinson’s disease and ‘end-of-dose’ motor fluctuations if another inhibitor of peripheral catechol-O-methyltransferase inappropriate (under specialist supervision)

Cautions  avoid abrupt withdrawal; most patients receiving more than 600 mg levodopa daily require reduction of levodopa dose by about 30%; renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (tolcapone)

Hepatotoxicity  Potentially life-threatening hepatotoxicity including fulminating hepatitis reported rarely, usually in females and during the first 6 months, but late-onset liver injury has also been reported; test liver function before treatment, and monitor every 2 weeks for first year, every 4 weeks for next 6 months and every 8 weeks thereafter (restart monitoring schedule if dose increased); discontinue if abnormal liver function tests or symptoms of liver disorder (counselling, see below); do not re-introduce tolcapone once discontinued

Counselling  Patients should be told how to recognise signs of liver disorder and advised to seek immediate medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop

Contra-indications  hepatic impairment or raised liver enzymes (see Hepatotoxicity above), severe neuroleptic malignant syndrome, rhabdomyolysis, or hyperthermia; breast-feeding (Appendix 5)

Side-effects  diarrhoea, constipation, dyspepsia, abdominal pain, nausea, vomiting, anorexia, xerostomia, hepatotoxicity (see above); chest pain; confusion, dystonia, dyskinesia, drowsiness, headache, dizziness, sleep disturbances, excessive dreaming, hallucinations; syncope; urine discoloration, sweating; neuroleptic malignant syndrome and rhabdomyolysis reported on dose reduction or withdrawal

Dose
- 100 mg 3 times daily, leave 6 hours between each dose; max. 200 mg 3 times daily in exceptional circumstances; first daily dose should be taken at the same time as levodopa with dopa-decarboxylase inhibitor

Note  Continue beyond 3 weeks only if substantial improvement

Tasmar® (Valeant) (cf)
Tablets, f/c, yellow, tolcapone 100 mg, net price 100-tab pack = £95.20. Label: 14, 25

Amantadine

Amantadine  is a weak dopamine agonist with modest antiparkinsonian effects. It improves mild bradykinetic disabilities as well as tremor and rigidity. It may also be useful for dyskinesias in more advanced disease. Tolerance to its effects may develop and confusion and hallucinations may occasionally occur. Withdrawal of amantadine should be gradual irrespective of the patient’s response to treatment.

AMANTADINE HYDROCHLORIDE

Indications  Parkinson’s disease (but not drug-induced extrapyramidal symptoms); antiviral (section 5.3.4)

Cautions  hepatic impairment; renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3), congestive heart disease (may exacerbate oedema), confused or hallucinatory states, elderly; avoid abrupt withdrawal in Parkinson’s disease; interactions: Appendix 1 (amantadine)

Driving  May affect performance of skilled tasks (e.g. driving)

Contra-indications  epilepsy; history of gastric ulceration; pregnancy (Appendix 4), breast-feeding (Appendix 5)

Side-effects  anorexia, nausea, nervousness, inability to concentrate, insomnia, dizziness, convulsions, hallucinations or feelings of detachment, blurred vision, gastrointestinal disturbances, livedo reticularis and peripheral oedema; rarely leucopenia, rashes

Dose
- Parkinson’s disease, 100 mg daily increased after one week to 100 mg twice daily, usually in conjunction with other treatment; some patients may require higher doses, max. 400 mg daily; elderly 65 years and over, 100 mg daily adjusted according to response
- Post-herpetic neuralgia, 100 mg twice daily for 14 days, continued for a further 14 days if necessary

Symmetrel® (Alliance) (cf)
Capsules, red-brown, amantadine hydrochloride 100 mg. Net price 56-cap pack = £16.88. Counselling, driving

Syrup, amantadine hydrochloride 50 mg/5 mL. Net price 150-mL pack = £5.55. Counselling, driving

Lysovir® (Alliance) (cf)
See p. 350

4.9.2 Antimuscarinic drugs used in parkinsonism

Antimuscarinic drugs exert their antiparkinsonian action by reducing the effects of the relative central cholinergic excess that occurs as a result of dopamine deficiency. Antimuscarinic drugs can be useful in drug-induced parkinsonism, but they are generally not used in idiopathic Parkinson’s disease because they are less effective than dopaminergic drugs and they are associated with cognitive impairment.

The antimuscarinic drugs orphenadrine, procyclidine, and trihexyphenidyl (benzhexol), reduce the symptoms of parkinsonism induced by antipsychotic drugs, but there is no justification for giving them routinely in the absence of parkinsonian side-effects. Tardive dyskinesia is not improved by antimuscarinic drugs and may be made worse.

In idiopathic Parkinson’s disease, antimuscarinic drugs reduce tremor and rigidity but they have little effect on bradykinesia. They may be useful in reducing sialorrhoea.
No important differences exist between the antimuscarinic drugs, but some patients tolerate one better than another.

Procyclidine may be given parenterally and it is effective emergency treatment for acute drug-induced dystonic reactions.

**Cautions**
Antimuscarinics should be used with caution in cardiovascular disease, hypertension, psychotic disorders, prostatic hypertrophy, pyrexia, in those susceptible to angle-closure glaucoma, and in the elderly. Antimuscarinics should not be withdrawn abruptly in patients receiving long-term treatment. Antimuscarinics are liable to abuse. They should also be used with caution in hepatic impairment, renal impairment, pregnancy (Appendix 4), and breast-feeding (Appendix 5).

**Interactions:** Appendix 1 (Antimuscarinics)

**Driving**
May affect performance of skilled tasks (e.g. driving)

**Contra-indications**
Antimuscarinics should be avoided in gastro-intestinal obstruction and myasthenia gravis.

**Side-effects**
Side-effects of antimuscarinics include constipation, dry mouth, nausea, vomiting, tachycardia, dizziness, confusion, euphoria, hallucinations, impaired memory, anxiety, restlessness, urinary retention, blurred vision, and rash. Angle-closure glaucoma may occur very rarely.

**ORPHENADRINE HYDROCHLORIDE**

**Indications**
parkinsonism; drug-induced extrapyramidal symptoms (but not tardive dyskinesia, see notes above)

**Cautions**
see notes above

**Contra-indications**
see notes above; also acute porphyria (section 9.8.2)

**Side-effects**
see notes above; less commonly: insomnia and impaired coordination

**Dose**
- Initially 150 mg daily in divided doses, increased gradually in steps of 50 mg every 2–3 days according to response; usual dose range 150–300 mg daily in divided doses; max. 400 mg daily; ELDERLY preferably lower end of range

**Orphenadrine Hydrochloride (Non-proprietary)**

Tablets, orphenadrine hydrochloride 50 mg, net price 20 = £11.13. Counselling, driving

Oral solution, orphenadrine hydrochloride 50 mg/5 mL, net price 200 mL = £9.47. Counselling, driving

**Biorphen®** (Alliance)

Liquid, sugar-free, orphenadrine hydrochloride 25 mg/5 mL, net price 200 mL = £7.07. Counselling, driving

**Disipal®** (Astellas)

Tablets, yellow, s/c, orphenadrine hydrochloride 50 mg, net price 20 = 69p. Counselling, driving

Excipients include tartarazine

**TRIHEXYPHENIDYL HYDROCHLORIDE**

(Benzhexol hydrochloride)

**Indications**
parkinsonism; drug-induced extrapyramidal symptoms (but not tardive dyskinesia, see notes above)

**Cautions**
see notes above

**Contra-indications**
see notes above

**Side-effects**
see notes above

**Dose**
- 1 mg daily, increased gradually; usual maintenance dose 5–15 mg daily in 3–4 divided doses (max. 20 mg daily); ELDERLY preferably lower end of range

**Trihexyphenidyl (Non-proprietary)**

Tablets, trihexyphenidyl hydrochloride 2 mg, net price 84-tab pack = £24.63; 5 mg, 100-tab pack = £14.36. Counselling, with or after food, driving

**Broflex®** (Alliance)

Syrup, pink, black currant, trihexyphenidyl hydrochloride 5 mg/5 mL, net price 200 mL = £6.20. Counselling, driving
4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

Tetrabenazine is mainly used to control movement disorders in Huntington’s chorea and related disorders. It may act by depleting nerve endings of dopamine. It has useful action in only a proportion of patients and its use may be limited by the development of depression.

Haloperidol may be useful in improving motor tics and symptoms of Tourette syndrome and related choreas.

Piracetam is used as an adjunctive treatment for myoclonus. Propranolol is given in a dosage of 40 mg 2 or 3 times daily, increased if necessary; 80 to 160 mg daily is usually required for maintenance.

Piracetam is used as an adjunctive treatment for myoclonus of cortical origin.

Riluzole is used to extend life in patients with motor neurone disease who have amyotrophic lateral sclerosis.

Riluzole for motor neurone disease (January 2001)

Riluzole is recommended for treating the amyotrophic lateral sclerosis (ALS) form of motor neurone disease (MND). Treatment should be initiated by a specialist in MND but it can then be supervised under a shared-care arrangement involving the general practitioner.

HALOPERIDOL

Indications motor tics, adjunctive treatment in choreas and Tourette syndrome; other indications, section 4.2.1

Cautions section 4.2.1

Contra-indications section 4.2.1

Side-effects section 4.2.1

Dose

- By mouth, 0.5–1.5 mg 3 times daily adjusted according to the response; 10 mg daily or more may occasionally be necessary in Tourette syndrome; CHILD 5–12 years, Tourette syndrome, 12.5–25 microgram/kg twice daily, adjusted according to response up to max. 10 mg daily

Preparations

Section 4.2.1

PIRACETAM

Indications adjunctive treatment of cortical myoclonus

Cautions avoid abrupt withdrawal; elderly; haemostasis, major surgery, or severe haemorrhage; renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3)

Contra-indications cerebral haemorrhage; hepatic impairment; pregnancy; breast-feeding

Side-effects weight gain, nervousness, hyperkinesia; less commonly drowsiness, depression, asthma; also reported abdominal pain, nausea, vomiting, diarrhoea, headache, anxiety, confusion, hallucination, vertigo, ataxia, insomnia, and rash

Dose

- Initially 7.2 g daily in 2–3 divided doses, increased according to response by 4.8 g daily every 3–4 days to max. 20 g daily (subsequently, attempts should be made to reduce dose of concurrent therapy); CHILD under 16 years not recommended

Oral solution Follow the oral solution with a glass of water (or soft drink) to reduce bitter taste.

Nootropil® (UCB Pharma) Tablets, f/c, scored, piracetam 800 mg, net price 90-tab pack = £14.69; 1.2 g, 60-tab pack = £13.71. Label: 3

Oral solution, piracetam, 333.3 mg/mL, net price 300-mL pack = £20.39. Label: 3

RILUZOLE

Indications to extend life in patients with amyotrophic lateral sclerosis, initiated by specialists experienced in the management of motor neurone disease

Cautions history of abnormal hepatic function (consult product literature for details)

Blood disorders Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever occur; white blood cell counts should be determined in febrile illness; neutropenia requires discontinuation of riluzole

Driving Dizziness or vertigo may affect performance of skilled tasks (e.g. driving)

Contra-indications hepatic impairment; renal impairment (Appendix 3); pregnancy (Appendix 4); breastfeeding (Appendix 5)

Side-effects nausea, vomiting, diarrhoea, abdominal pain; tachycardia; asthenia, headache, dizziness, drowsiness, oral paraesthesia; less commonly pan-creatitis and anaemia; rarely neutropenia; very rarely hepatitis

Dose

- 50 mg twice daily; CHILD not recommended

Rilutek® (Aventis Pharma) Tablets, f/c, riluzole 50 mg. Net price 56-tab pack = £242.39. Counselling, blood disorders, driving

TETRABENAZINE

Indications see under Dose

Cautions pregnancy (Appendix 4); avoid in breast-feeding; interactions: Appendix 1 (tetrabenazine)

Driving May affect performance of skilled tasks (e.g. driving)

Side-effects drowsiness, gastro-intestinal disturbances, depression, extrapyramidal dysfunction,
 hypotension; rarely parkinsonism; neuroleptic malignant syndrome reported

**Dose**

- Movement disorders due to Huntington’s chorea, hemiballismus, senile chorea, and related neurological conditions, initially 12.5 mg twice daily (elderly 12.5 mg daily) gradually increased to 12.5–25 mg 3 times daily; max. 200 mg daily
- Moderate to severe tardive dyskinesia, initially 12.5 mg daily, gradually increased according to response

**Side-effects**

- Increased electrophysiologic jitter in history of dysphagia or aspiration; neuroleptic malignant syndrome reported

**Cautions**

- Supervision.

**Botulinum toxin type A** should be used under specialist supervision. Botox® and Dysport® are licensed for the treatment of focal spasticity (including arm symptoms in conjunction with physiotherapy, dynamic equinus foot deformity caused by spasticity in ambulant paediatric cerebral palsy patients over 2 years of age, hand and wrist disability associated with stroke), blepharospasm, hemifacial spasm, and spasmodic torticollis. Botox® is also licensed for severe hyperhidrosis of the axillae.

Vistabel® is licensed for the temporary improvement of moderate to severe wrinkles between the eyebrows. Xeomin® is licensed for the treatment of blepharospasm and spasmodic torticollis.

**BOTULINUM TOXIN TYPE A**

**Indications** see notes above; preparations are not interchangeable and should be used under specialist supervision

**Cautions** history of dysphagia or aspiration; neurological disorders (can lead to increased sensitivity and exaggerated muscle weakness); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Specific cautions for blepharospasm or hemifacial spasm** Caution if risk of angle-closure glaucoma; reduced blinking can lead to corneal exposure, persistent epithelial defect and corneal ulceration (especially those with VIIth nerve disorders)—careful testing of corneal sensation in previously operated eyes, avoidance of injection in lower lid area to avoid ectropion, and vigorous treatment of epithelial defect needed

**Contra-indications** generalised disorders of muscle activity (e.g. myasthenia gravis)

**Side-effects** increased electrophysiologic jitter in some distant muscles; misplaced injections may paralyse nearby muscle groups and excessive doses may paralyse distant muscles; influenza-like symptoms; rarely arrhythmias, myocardial infarction, seizures, hypersensitivity reactions including rash, pruritus and anaphylaxis, antibody formation (substantial deterioration in response), and injection-site reactions; very rarely exaggerated muscle weakness, dysphagia, and aspiration (seek medical attention if swallowing, speech, or respiratory disorders)

**Specific side-effects for blepharospasm or hemifacial spasm** Ptosis; keratitis, lagophthalmos, dry eye, irritation, photophobia, lacrimation; facial oedema; less commonly dry mouth, facial weakness (including drooping), dizziness, tiredness, ectropion, entropion, diplopia, visual disturbances, conjunctivitis; rarely eyelid bruising and swelling (minimised by applying gentle pressure at injection site immediately after injection); very rarely angle-closure glaucoma, corneal ulceration

**Specific side-effects in paediatric cerebral palsy** Drowsiness, paraesthesia, urinary incontinence, myalgia

**Specific side-effects for temporary improvement of moderate to severe wrinkles between the eyebrows** Headache; ptosis; less commonly nausea, dry mouth, facial oedema, dizziness, asthenia, anxiety, paraesthesia, visual disturbances, blepharitis, photosensitivity reactions, and dry skin

**Specific side-effects in spasmodic torticollis** Dysphagia and pooling of saliva (occurs most frequently after injection into sternomastoid muscle), nausea, dry mouth, rhinitis, drowsiness, headache, dizziness, hypertonia, stiffness; less commonly dyspnoea, voice alteration, diaphoresis, and ptosis

**Specific side-effects in axillary hyperhidrosis** Non-axillary sweating; hot flushes; less commonly myalgia and joint pain

**Specific side-effects in focal upper-limb spasticity associated with stroke** Dysphagia; hypertonia; less commonly arthralgia and bursitis

**Dose**

- Consult product literature (important: specific to each individual preparation and not interchangeable)

**Botox® (Allergan)**

**Injection**, powder for reconstitution, botulinum toxin type A complex, net price 50-unit vial = £72.30, 100-unit vial = £128.93

**Dysport® (Ipsen)**

**Injection**, powder for reconstitution, botulinum toxin-haemagglutinin complex type A, net price 500-unit vial = £164.50

**Vistabel® (Allergan)**

**Injection**, powder for reconstitution, botulinum toxin type A, net price 50-unit vial = £85.00

**Xeomin® (Merz)**

**Injection**, powder for reconstitution, botulinum toxin type A, net price 100-unit vial = £119.90

**BOTULINUM TOXIN TYPE B**

**Indications** spasmodic torticollis (cervical dystonia)—specialist use only

**Cautions** history of dysphagia or aspiration; inadvertent injection into a blood vessel; tolerance may occur

**Contra-indications** neuromuscular or neuromuscular junctional disorders; pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** increased electrophysiologic jitter in some distant muscles; dry mouth, dyspnea, worsening torticollis, neck pain, myasthenia, voice changes, taste disturbances; very rarely exaggerated muscle weakness, dysphagia, and aspiration (seek medical attention if swallowing, speech, or respiratory disorders)

**Dose**

- By intramuscular injection, initially 5000–10 000 units divided between 2–4 most affected muscles; adjust dose and frequency according to response; important: not interchangeable with other botulinum toxin preparations

**NeuroBloc® (Eisai)**

**Injection**, botulinum toxin type B 5000 units/mL, net price 0.5-mL vial = £111.20; 1-mL vial = £148.27; 2-mL vial = £197.69

**Note** May be diluted with sodium chloride 0.9%
This section includes drugs used in alcohol dependence, cigarette smoking, and opioid dependence.

The health departments of the UK have produced a report, *Drug Misuse and Dependence* which contains guidelines on clinical management.

*Drug Misuse and Dependence*. London, The Stationery Office, 1999 can be obtained from:
The Publications Centre
PO Box 276
London, SW8 5DT
Tel: (087) 0600 5522
Fax: (087) 0600 5533

or from The Stationery Office bookshops and through all good book sellers.

It is important to be aware that people who misuse drugs may be at risk not only from the intrinsic toxicity of the drug itself but also from the practice of injecting preparations intended for administration by mouth. Excipients used in the production of oral dose forms are usually insoluble and may lead to *obscure formation at the site of injection*, or even to *necrosis and gangrene*, moreover, deposits in the heart or lungs may lead to *cardiac or pulmonary toxicity*. Additional hazards include *infection* following the use of a dirty needle or an unsterilised diluent.

### Alcohol dependence

**Disulfiram** is used as an adjunct to the treatment of alcohol dependence. It gives rise to extremely unpleasant systemic reactions after the ingestion of even a small amount of alcohol because it leads to accumulation of acetaldehyde in the body. Reactions include flushing of the face, throbbing headache, palpitation, tachycardia, nausea, vomiting, and, with large doses of alcohol, arrhythmias, hypotension, and collapse. Small amounts of alcohol included in many oral medicines may be sufficient to precipitate a reaction (even toiletries and mouthwashes that contain alcohol should be avoided). It may be advisable for patients to carry a card warning of the danger of administration of alcohol.

Long-acting *benzodiazepines* (section 4.1) are used to attenuate withdrawal symptoms but they also have a dependence potential. To minimise the risk of dependence, administration should be for a limited period only (e.g. *chloridiazepoxide* 10–50 mg 4 times daily, gradually reducing over 7–14 days). Benzodiazepines should not be prescribed if the patient is likely to continue drinking alcohol.

**Clomethiazole** (*clormethiazole*) (section 4.1.1) should be used for the management of withdrawal in an *inpatient setting only*. It is associated with a risk of dependence and should not be prescribed if the patient is likely to continue drinking alcohol.

**Acamprosate**, in combination with counselling, may be helpful in maintaining abstinence in alcohol-dependent patients. It should be initiated as soon as possible after abstinence has been achieved and should be maintained if the patient relapses. Continued alcohol abuse, however, negates the therapeutic benefit of acamprosate.

### Acamprosate Calcium

**Indications** maintenance of abstinence in alcohol dependence

**Cautions** continued alcohol abuse (risk of treatment failure)

**Contra-indications** severe hepatic impairment; renal impairment (avoid if serum creatinine greater than 120 micromol/litre; Appendix 3); pregnancy; breast-feeding

**Side-effects** diarrhoea, nausea, vomiting, abdominal pain; fluctuation in libido; pruritus, maculopapular rash; rarely bullous skin reactions

**Dose**

- **ADULT** 18–65 years, body-weight 60 kg and over, 666 mg 3 times daily; body-weight less than 60 kg, 666 mg at breakfast, 333 mg at midday and 333 mg at night

**Treatment course** Treatment should be initiated as soon as possible after alcohol withdrawal period and maintained if patient relapses; recommended treatment period 1 year

**Campral EC®** (Merck) $\xrightarrow{\text{c}}$

Tablet, 625 mg, acamprosate calcium 333 mg. net price 168-tab pack = £28.92. Label: 21, 25

| Electrolytes | Ca 0.8 mmol/tablet |

**DISULFIRAM**

**Indications** adjunct in the treatment of chronic alcohol dependence (under specialist supervision)

**Cautions** ensure that alcohol not consumed for at least 24 hours before initiating treatment; see also notes above; alcohol challenge not recommended on routine basis (if considered essential—specialist units only with resuscitation facilities); hepatic or renal impairment, respiratory disease, diabetes mellitus, epilepsy; interactions: Appendix 1 (disulfiram)

**Alcohol reaction** Patients should be warned of unpredictable and occasionally severe nature of disulfiram-alcohol interactions. Reactions can occur within 10 minutes and last several hours (may require intensive supportive therapy—oxygen should be available). Patients should not ingest alcohol at all and should be warned of possible presence of alcohol in liquid medicines, remedies, tonics, foods and even in toiletries (alcohol should also be avoided for at least 1 week after stopping)

**Contra-indications** cardiac failure, coronary artery disease, history of cerebrovascular accident, hypertension, psychosis, severe personality disorder, suicide risk, pregnancy (Appendix 4), breast-feeding (Appendix 5)

**Side-effects** initially drowsiness and fatigue; nausea, vomiting, halitosis, reduced libido; rarely psychotic reactions (depression, paranoia, schizophrenia, mania), allergic dermatitis, peripheral neuritis, hepatic cell damage

**Dose**

- 800 mg as a single dose on first day, reducing over 5 days to 100–200 mg daily; should not be continued for longer than 6 months without review; **CHILD** not recommended

**Antabuse®** (Actavis) $\xrightarrow{\text{c}}$

Cigarette smoking

Smoking cessation interventions are a cost-effective way of reducing ill health and prolonging life. Smokers should be advised to stop and offered help if interested in doing so, with follow-up when appropriate.

When possible, smokers should have access to a smoking cessation clinic for behavioural support. Nicotine replacement therapy and bupropion are effective aids to smoking cessation for those smoking more than 10 cigarettes a day. Bupropion has been used as an antidepressant but its mode of action in smoking cessation is not clear and may involve an effect on noradrenaline and dopamine neurotransmission. Varenicline is a selective nicotine receptor partial agonist used as an aid for smoking cessation. Nicotine replacement therapy is regarded as the pharmacological treatment of choice in the management of smoking cessation.

Cigarette smoking should stop completely before starting nicotine replacement therapy. If complete smoking cessation is not possible some nicotine preparations are licensed for use as part of a programme to reduce smoking before stopping completely; the smoking cessation regimen can be followed during a quit attempt.

BSM advice (bupropion)
The BSM has issued a reminder that bupropion is contra-indicated in patients with a history of seizures or of eating disorders, a CNS tumour, or who are experiencing acute symptoms of alcohol or benzodiazepine withdrawal. Bupropion should not be prescribed to patients with other risk factors for seizures unless the potential benefit of smoking cessation clearly outweighs the risk. Factors that increase the risk of seizures include concomitant administration of drugs that can lower the seizure threshold (e.g. antidepresants, antimalarials [such as mefloquine and chloroquine], antipsychotics, quinolones, sedating antihistamines, systemic corticosteroids, theophylline, tramadol), alcohol abuse, history of head trauma, diabetes, and use of stimulants and anorectics.

**BUPROPION HYDROCHLORIDE**

**(Amfebutamone hydrochloride)**

**Indications** see notes above

**Cautions** elderly; predisposition to seizures (see BSM advice above); measure blood pressure before and during treatment (monitor weekly if used with nicotine products); hepatic impairment (Appendix 2), renal impairment (Appendix 3); interactions: Appendix 1 (bupropion)

**Driving** May impair performance of skilled tasks (e.g. driving)

**Contra-indications** see BSM advice above; history of bipolar disorder; pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Side-effects** dry mouth, gastrointestinal disturbances, taste disturbance, insomnia (reduced by avoiding dose at bedtime), tremor, impaired concentration, headache, dizziness, depression, agitation, anxiety; fever; rash, pruritus, sweating; less commonly chest pain, tachycardia, hypertension, flushing, confusion, tinnitus, asthma, and visual disturbances; rarely jaundice, hepatitis, palpitation, postural hypotension, hallucinations, depersonalisation, seizures, dystonia, ataxia, abnormal dreams, memory impairment, paraesthesia, blood-glucose disturbances, urinary retention, urinary frequency, Stevens-Johnson syndrome, and exacerbation of psoriasis; very rarely delusions, and aggression

**Dose**

- **ADULT** over 18 years, start 1–2 weeks before target stop date, initially 150 mg daily for 6 days then 150 mg twice daily (max. single dose 150 mg, max. daily dose 300 mg; minimum 8 hours between doses); period of treatment 7–9 weeks; discontinue if abstinence not achieved at 7 weeks; consider max. 150 mg daily in patients with risk factors for seizures (see BSM advice above); **ELDERLY** max. 150 mg daily

**Zyban®** (GSK) Tablets, m/r, f/c, bupropion hydrochloride 150 mg, net price 60-tab pack = £39.85. Label: 25, counselling, driving, see above

**NICOTINE**

**Indications** see notes above

**Cautions** severe or unstable cardiovascular disease (including hospitalisation for severe arrhythmias, recent myocardial infarction, or recent cerebrovasc-
ular accident)—initiate under medical supervision; uncontrolled hyperthyroidism; diabetes mellitus (monitor blood-glucose concentration closely when initiating treatment); phaeochromocytoma; oral preparations, oesophagitis, gastritis, peptic ulcers; patches, skin disorders (patches should not be placed on broken skin); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Note Most warnings under Cautions also apply to continuation of cigarette smoking

**Side-effects** gastro-intestinal disturbances (including nausea, vomiting, dyspepsia); headache, dizziness; influenza-like symptoms; dry mouth; rash; less frequently palpitation; rarely atrial fibrillation; with nasal spray, sneezing, epistaxis, watering eyes, ear sensations; with lozenges, thirst, paraesthesia of mouth, taste disturbances; with patches, skin reactions (discontinue if severe)—vasculitis also reported, blood pressure disturbances; with spray, palpitation; less frequently sweating, sneezing, epistaxis, watering eyes, ear sensations; with nicotine inhalator, hiccups, throat irritation

**Dose**
- See under preparations, below

**Nicopass** (Fabre)

**Lozenges**, sugar-free, fresh mint- or liquorice mint-flavoured, nicotine (as resinate complex) 1.5 mg, net price pack of 12 = £1.68; pack of 36 = £4.18, pack of 96 = £8.94. Label: 24

Excipients include aspartame (section 9.4.1)

**Dose** smoking cessation, **ADULT** over 18 years (not heavily dependent on nicotine), initially suck 1 lozenge when urge to smoke occurs (max. 20 lozenges daily), withdraw gradually after 3 months, max. period of treatment should not exceed 6 months; review treatment if abstinence not achieved within 3 months; **CHILD** 12–18 years, treatment continued for up to 8 weeks followed by gradual reduction over 4 weeks; review treatment if abstinence not achieved within 9 months; **CHILD** 12–18 years, treatment continued for up to 8 weeks followed by gradual reduction over 4 weeks; review treatment if abstinence not achieved within 3 months

**Note** Children under 18 years should consult a healthcare professional before starting smoking-reduction regimen

**Patches**, self-adhesive, beige, nicotine, ‘5 mg’ patch (releasing approx. 5 mg/16 hours), net price 7 = £9.07; ‘10 mg’ patch (releasing approx. 10 mg/16 hours), 7 = £9.07; ‘15 mg’ patch (releasing approx. 15 mg/16 hours), 2 = £2.85, 7 = £9.07

**Dose** smoking cessation, **ADULT** and **CHILD** over 12 years, apply in waking hours on non-hairy skin on hip, chest or upper arm, removing after approx. 16 hours, usually when retiring to bed, site next patch on different area (avoid using same area on consecutive days); initially ‘15-mg’ patch for 16 hours daily for 8 weeks then if abstinence achieved ‘10-mg’ patch for 16 hours daily for 2 weeks then ‘5-mg’ patch for 16 hours daily for 6 weeks, stop altogether at end of next 2 weeks; review treatment if abstinence not achieved within 3 months—further courses may be given if considered beneficial

**Nicopatch** (Fabre)

**Patches**, self-adhesive, nicotine ‘7 mg’ patch (releasing approx. 7 mg/24 hours), net price 7 = £8.95; ‘14 mg’ patch (releasing approx. 14 mg/24 hours), 7 = £8.95; ‘21 mg’ patch (releasing approx. 21 mg/24 hours), 7 = £8.95

**Dose** smoking cessation, **ADULT** over 18 years, apply to dry, non-hairy skin site, removing after 24 hours and site replacement patch on a different area (avoid using same area for 24 hours); individuals smoking less than 20 cigarettes daily, initially ‘14-mg’ or ‘21-mg’ patch daily (depending on severity of withdrawal symptoms); individuals smoking 20 or more cigarettes daily, initially ‘21-mg’ patch daily, reducing dose every 3–4 weeks. review treatment if abstinence not achieved within 3 months; max. period of treatment should not exceed 6 months

**Note** Children under 18 years should consult a healthcare professional before starting a smoking-reduction regimen

**Nicorette** (Pharmacia)

**Microtab** (sublingual), nicotine (as a cyclodextrin complex) 2 mg, net price starter pack of 2 x 15-tablet discs with dispenser = £9.99; refill pack of 7 x 15-tablet discs = £11.12. Label: 26

**Dose** smoking cessation, individuals smoking 20 cigarettes or less daily, sublingually, 2 mg each hour; for patients who fail to stop smoking or have significant withdrawal symptoms, consider increasing to 4 mg each hour; individuals smoking more than 20 cigarettes daily, sublingually, 4 mg each hour, max. 80 mg daily. treatment continued for at least 3 months followed by a gradual reduction in dose, review treatment if abstinence not achieved within 9 months; **CHILD** 12–18 years, treatment continued for up to 8 weeks followed by gradual reduction over 4 weeks; review treatment if abstinence not achieved within 3 months

**Chewing gum**, sugar-free, nicotine (as resin) 2 mg, net price pack of 15 = £1.71, pack of 30 = £3.25, pack of 105 = £8.89; 4 mg, net price pack of 15 = £2.11, pack of 30 = £3.99, pack of 105 = £10.83

**Note** Also available in mint, freshfruit, and freshmint flavours

**Dose** smoking cessation, individuals smoking 20 cigarettes or less daily, initially chew one 2-mg piece slowly (chew gum until taste becomes strong, then rest gum between cheek and gum, when taste fades start chewing again) for approx. 30 minutes when urge to smoke occurs; individuals smoking more than 20 cigarettes daily or needing more than 15 pieces of 2-mg gum daily should use the 4-mg strength gum (releasing approx. 15 pieces of 4-mg strength gum daily, withdraw gradually after 3 months; review treatment if abstinence not achieved within 9 months; **CHILD** 12–18 years, treatment continued for up to 8 weeks followed by gradual reduction over 4 weeks; review treatment if abstinence not achieved within 3 months

Smoking reduction, chew 1 piece when urge to smoke occurs between smoking episodes; reduce smoking within 6 weeks and attempt smoking cessation within 6 months, review treatment if abstinence not achieved within 9 months

**Note** Children under 18 years should consult a healthcare professional before starting smoking-reduction regimen

**Patches** (Novartis Consumer Health)

**Chewing gum**, sugar-free, nicotine (as polacrilm complex) 2 mg, net price pack of 12 = £1.71, pack of 24 = £3.01, pack of 96 = £8.26, pack of 204 = £14.23; 4 mg, net price pack of 12 = £1.70, pack of 24 = £3.30, pack of 96 = £10.26

**Note** Also available in fruit, liquorice and mint flavours

**Dose** smoking cessation, individuals smoking 20 cigarettes or less daily, initially chew one 2-mg piece slowly (chew gum until taste becomes strong, then rest gum between cheek and gum, when taste fades start chewing again) for approx. 30 minutes, when urge to smoke occurs; individuals smoking more than 20 cigarettes daily should use the 4-mg strength, max. 60 mg daily; withdraw gradually after 3 months, max. period of treatment should not exceed 6 months; **CHILD** 12–18 years, withdraw gradually and review treatment if abstinence not achieved within 3 months

**Mint lozenge**, sugar-free, nicotine (as bitartrate) 1 mg, net price pack of 12 = £1.71, pack of 36 = £4.27, pack...
of 96 = £9.12; 2 mg, net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 36 = £5.12, pack of 72 = £9.97. Contains 0.65 mmol Na+/lozenge. Label: 24

**NiQuitin®** (GSK Consumer Healthcare)

**Chewing gum**, sugar-free, mint-flavoured, nicotine 2 mg (white), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55; 4 mg (yellow), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55

**Dose** smoking cessation, initial use: smoking cessation, individuals smoking 30 cigarettes or less daily, initially suck one 1-mg lozenge every 1–2 hours, when urge to smoke occurs; individuals smoking more than 30 cigarettes daily should use the 2-mg strength; max. 30 mg/day, withdraw gradually after 3 months; max. period of treatment should not usually exceed 6 months; CHILD 12–18 years, withdraw gradually and review treatment if abstinence not achieved within 3 months

**Lozenges**, sugar-free, nicotine (as polacrilex) 2 mg, net price pack of 36 = £5.12, pack of 72 = £9.97; 4 mg, pack of 36 = £5.12, pack of 72 = £9.97. Contains 0.65 mmol Na+/lozenge. Label: 24

**Excipients** include aspartame (section 9.4.1)

**Dose** smoking cessation, initial use: smoking cessation, individuals smoking 30 cigarettes or less daily, initially suck one 1-mg lozenge every 1–2 hours, when urge to smoke occurs; individuals smoking more than 30 cigarettes daily should use the 2-mg strength; max. 30 mg/day, withdraw gradually after 3 months; max. period of treatment should not usually exceed 6 months; CHILD 12–18 years, withdraw gradually and review treatment if abstinence not achieved within 3 months

**TTS Patches**, self-adhesive, all yellowish-ochre, nicotine, '10' patch (releasing approx. 7 mg/24 hours), net price 7 = £9.12, '20' patch (releasing approx. 14 mg/24 hours), net price 2 = £2.57, 7 = £9.40; '30' patch (releasing approx. 21 mg/24 hours), net price 2 = £2.85, 7 = £9.97, 21 = £24.51

**Dose** smoking cessation, ADULT and CHILD over 12 years, apply to dry, non-hairy skin on trunk or upper arm, removing after 24 hours and siting replacement patch on a different area (avoid using the same area for several days); individuals smoking less than 20 cigarettes daily, initially '20' patch daily, individuals smoking 20 or more cigarettes daily, initially '30' patch daily, withdraw gradually, reducing dose every 3–4 weeks; review treatment if abstinence not achieved within 3 months

**NiQuitin®** (GSK Consumer Healthcare)

Chewing gum, sugar-free, mint-flavoured, nicotine 2 mg (white), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55; 4 mg (yellow), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55

**Dose** smoking cessation, initial use: smoking cessation, individuals smoking 30 cigarettes or less daily, initially suck one 1-mg lozenge every 30 minutes, when urge to smoke occurs; max. 15 pieces daily; withdraw gradually after 3 months; review treatment if abstinence not achieved within 9 months; CHILD 12–18 years, withdraw gradually and review treatment if abstinence not achieved within 3 months

Smoking reduction, chew 1 piece when urge to smoke occurs between smoking episodes (max. 15 pieces daily); reduce smoking within 6 weeks and attempt cessation within 6 months; review treatment if abstinence not achieved within 3 months

**Note** Children under 18 years should consult a healthcare professional before starting smoking-reduction regimen

Temporary abstinence, chew 1 piece when urge to smoke occurs between smoking episodes (max. 15 pieces daily); review treatment if abstinence not achieved after 6 months; review treatment if abstinence not achieved within 3 months

Smoking reduction, chew 1 piece when urge to smoke occurs between smoking episodes (max. 15 pieces daily); reduce smoking within 6 weeks and attempt cessation within 6 months; review treatment if abstinence not achieved within 3 months

Temporary abstinence, chew 1 piece when urge to smoke occurs between smoking episodes (max. 15 pieces daily); review treatment if abstinence not achieved after 6 months; review treatment if abstinence not achieved within 3 months

VARENCLINE

**Indications** see notes above

**Cautions** risk of relapse, irritability, depression, and insomnia on discontinuation (consider dose tapering on completion of 12-week course); history of psychiatric illness (may exacerbate underlying illness including depression); renal impairment (Appendix 3); breast-feeding (Appendix 5)

**MHRA/CHM advice**

**Suicidal behaviour and varencline**

Suicidal thoughts and behaviour have been reported in patients taking varencline. Patients should be advised to discontinue treatment and seek prompt medical advice if they develop depression or suicidal thoughts.

Patients with a history of psychiatric illness should be monitored closely while taking varencline.

**Contra-indications** pregnancy (Appendix 4)

**Side-effects** gastro-intestinal disturbances, appetite changes, dry mouth, taste disturbance; headache, drowsiness, dizziness, sleep disorders, abnormal dreams; less common, thirst, weight gain, apthous stomatitis, gingival pain, chest pain, hypertension, tachycardia, atrial fibrillation, palpitation, panic attack, abnormal thinking, mood swings, dysarthria, asthenia, tremor, inco-ordination, hypertonia, restlessness, hypoesthesia, impaired temperature regulation, menorrhagia, vaginal discharge, sexual dysfunction, dysuria, arthralgia, muscle spasm, visual disturbances, eye pain, lacrimation, tinnitus, acne, sweating, rash, and pruritus; myocardiad infarction, depression, and suicidal ideation (see MHRA/CHM advice above) also reported

**Dose**

- ADULT over 18 years, start 1–2 weeks before target stop date, initially 500 micrograms once daily for 3 days, increased to 500 micrograms twice daily for 4 days, then 1 mg twice daily for 11 weeks (reduce to 500 micrograms twice daily if not tolerated); 12-week course can be repeated in abstinent individuals to reduce risk of relapse

**Champix®** (Pfizer) ▼

**Tablets**, 1/2, varencline (as tartrate) 500 micrograms (white), net price 56-tab pack = £54.60; 1 mg (blue) 28-tab pack = £27.30, 56-tab pack = £54.60; starter pack of 11 × 500-microgram tabs with 14 × 1-mg tabs = £27.30. Label: 3

**Opioid dependence**

The management of opioid dependence requires medical, social, and psychological treatment; access to a multidisciplinary team is valuable. Treatment with opioid substitutes or with naltrexone is best initiated under the supervision of an appropriately qualified physician.
Methadone, an opioid agonist, can be substituted for opioids such as diamorphine, preventing the onset of withdrawal symptoms; it is itself addictive and should only be prescribed for those who are physically dependent on opioids. It is administered in a single daily dose usually as methadone oral solution 1 mg/mL. The dose is adjusted according to the degree of dependence.

**Buprenorphine** is an opioid partial agonist. Because of its abuse and dependence potential it should be prescribed only for those who are already physically dependent on opioids. It can be used as substitution therapy for patients with moderate opioid dependence. In patients dependent on high doses of opioids, buprenorphine may precipitate withdrawal due to its partial antagonist properties; in these patients, the daily opioid dose should be reduced gradually before initiating therapy with buprenorphine.

**Naltrexone**, an opioid antagonist, blocks the action of opioids and precipitates withdrawal symptoms in opioid-dependent subjects. Because the euphoric action of opioid agonists is blocked by naltrexone it is given to former addicts as an aid to prevent relapse.

Lofoxdine is used for the alleviation of symptoms in individuals whose opioid use is well controlled and are undergoing opioid withdrawal. Like clonidine it is an alpha-adrenergic agonist and appears to act centrally to produce a reduction in sympathetic tone, but reduction in blood pressure is less marked.

### Methadone and buprenorphine for the management of opioid dependence (January 2007)

Oral methadone and buprenorphine are recommended for maintenance therapy in the management of opioid dependence. Patients should be committed to a supportive care programme including a flexible dosing regimen administered under supervision for at least 3 months, until compliance is assured. Selection of methadone or buprenorphine should be made on a case-by-case basis, but methadone should be prescribed if both drugs are equally suitable.

### Naltrexone for the management of opioid dependence (January 2007)

Naltrexone is recommended for the prevention of relapse in detoxified formerly opioid-dependent patients who are motivated to remain in a supportive care abstention programme. Naltrexone should be administered under supervision and its effectiveness in preventing opioid misuse reviewed regularly.

### Dose

- **By sublingual administration**, initially, 0.8–4 mg as a single daily dose, adjusted according to response; max. 32 mg daily; withdraw gradually; **CHILD** under 16 years not recommended

**Note** In patients who have not undergone opioid withdrawal, buprenorphine should be given at least 6 hours after last use of opioid or when signs of withdrawal appear.

In patients receiving methadone, dose of methadone should be reduced to max. 30 mg daily before starting buprenorphine.

**Buprenorphine** (Non-proprietary)

- **Tablets** (sublingual), buprenorphine (as hydrochloride) 400 micrograms, net price 7-tab pack = £1.57; 2 mg, 7-tab pack = £6.59; 8 mg, 7-tab pack = £19.76. Label: 2, 26

**Subutex** (Scherer-Plough)

- **Tablets** (sublingual), buprenorphine (as hydrochloride) 400 micrograms, net price 7-tab pack = £1.60; 2 mg, 7-tab pack = £6.72; 8 mg, 7-tab pack = £20.16. Label: 2, 26

**With naloxone**

**Suboxone** (Scherer-Plough) ▼

- **Suboxone 2 mg/500 micrograms tablets** (sublingual), buprenorphine (as hydrochloride) 2 mg, naloxone (as hydrochloride) 500 micrograms, net price 28-tab pack = £26.88. Label: 2, 26

- **Suboxone 8mg/2mg tablets** (sublingual), buprenorphine (as hydrochloride) 8 mg, naloxone (as hydrochloride) 2 mg, net price 28-tab pack = £80.64. Label: 2, 26

**Note** In patients who have not undergone opioid withdrawal, **Suboxone** should be given when signs of withdrawal appear, at least 6 hours after last use of opioid. In patients receiving methadone, dose of methadone should be reduced to max. 30 mg daily before starting **Suboxone**; first dose of **Suboxone** should be given when signs of withdrawal appear, at least 24 hours after last dose of methadone.

**Note** The Scottish Medicines Consortium has advised (February 2007) that **Suboxone** should be restricted for use in patients in whom methadone is not suitable.

### LOFOXIDINE HYDROCHLORIDE

**Indications** management of symptoms of opioid withdrawal

**Cautions** severe coronary insufficiency, recent myocardial infarction, cerebrovascular disease, marked bradycardia (monitor pulse rate); history of QT prolongation, concomitant administration of drugs that prolong QT interval; withdraw gradually over 2–4 days (or longer) to minimise risk of rebound hypertension and associated symptoms; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (lofoxdine)

**Side-effects** dry mucus membranes, hypotension, bradycardia, rebound hypertension on withdrawal, drowsiness

**Dose**

- Initially, 800 micrograms daily in divided doses, increased as necessary in steps of 400–800 micrograms daily to max. 2.4 mg daily in divided doses; max. single dose 800 micrograms; recommended duration of treatment 7–10 days if no opioid use (but

### BUPRENORPHINE

**Indications** adjunct in the treatment of opioid dependence; premedication, peri-operative analgesia, analgesia in other situations (section 4.7.2)

**Cautions** see section 4.7.2 and notes above; effects only partially reversed by naloxone

**Contra-indications** see section 4.7.2; breast-feeding (Appendix 5)

**Side-effects** see section 4.7.2
4.11 Drugs for dementia

Acetylcholinesterase inhibiting drugs are used in the treatment of Alzheimer’s disease, specifically for mild to moderate disease. Rivastigmine is also licensed for mild to moderate dementia associated with Parkinson’s disease. The evidence to support the use of these drugs relates to their cognitive enhancement.

Treatment with drugs for dementia should be initiated and supervised only by a specialist experienced in the management of dementia.

Benefit is assessed by repeating the cognitive assessment at around 3 months. Such assessment cannot demonstrate how the disease may have progressed in the absence of treatment but it can give a good guide to response. Up to half the patients given these drugs will show a slower rate of cognitive decline. Drugs for dementia should be discontinued in those thought not to be responding. Many specialists repeat the cognitive assessment 4 to 6 weeks after discontinuation to assess deterioration; if significant deterioration occurs during this short period, consideration should be given to restarting therapy.

Donepezil is a reversible inhibitor of acetylcholinesterase. Galantamine is a reversible inhibitor of acetylcholinesterase and it also has nicotinic receptor agonist properties. Rivastigmine is a reversible non-competitive inhibitor of acetylcholinesterases; it is also licensed...
for treating mild to moderate dementia in Parkinson’s disease.

Acetylcholinesterase inhibitors can cause unwanted dose-related cholinergic effects and should be started at a low dose and the dose increased according to response and tolerability.

**Memantine** is a NMDA-receptor antagonist that affects glutamate transmission; it is licensed for treating moderate to severe Alzheimer’s disease.

### NICE guidance

**Donepezil, galantamine, rivastigmine, and memantine for Alzheimer’s disease** (September 2007)

Donepezil, galantamine, and rivastigmine are recommended for the adjunctive treatment of moderate Alzheimer's disease in those whose mini mental-state examination (MMSE) score is 10–20 points under the following conditions:

- Alzheimer’s disease must be diagnosed in a specialist clinic; the clinic should also assess cognitive, global, and behavioural functioning, activities of daily living, and the likelihood of compliance with treatment;
- treatment should be initiated by specialists but can be continued by general practitioners under a shared-care protocol;
- the carers’ views of the condition should be sought before and during drug treatment;
- the patient should be assessed every 6 months and drug treatment should normally continue only if the MMSE score remains at or above 10 points and if treatment is considered to have a worthwhile effect on the global, functional, and behavioural condition.

Patients receiving acetylcholinesterase inhibitors for mild Alzheimer’s disease can continue treatment until they, their carers, or their specialist consider it appropriate to stop.

Healthcare professionals should not rely solely on the MMSE score to assess the severity of Alzheimer’s disease when the patient has learning or other disabilities, or other communication difficulties.

NICE does not recommend memantine for moderately severe to severe Alzheimer’s disease except as part of well designed clinical studies; patients already receiving memantine can continue treatment until they, their carers, or their specialist consider it appropriate to stop.

### Donepezil Hydrochloride

**Indications** mild to moderate dementia in Alzheimer’s disease

**Cautions** sick sinus syndrome or other supraventricular conduction abnormalities; hepatic impairment (Appendix 2); pregnancy (Appendix 4); **interactions:** Appendix 1 (parasympathomimetics)

**Contra-indications** renal impairment (avoid if creatinine clearance less than 9 mL/minute; Appendix 3); breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain, dyspepsia; syncope; rinitis; sleep disturbances, dizziness, confusion, depression, headache, fatique, anorexia, tremor; fever; weight loss; less commonly arrhythmias, palpitation, myocardial infarction, cerebrovascular disease, paraesthesia, tinnitus, and leg cramps; rarely bradycardia, seizures, hallucinations, agitation, aggression, dehydration, hypokalaemia, and rash; very rarely gastrointestinal bleeding, dysphagia, hypotension, exacerbation of Parkinson’s disease, and sweating

**Dose**

- Initially 4 mg twice daily for 4 weeks increased to 8 mg twice daily for 4 weeks; maintenance 8–12 mg twice daily

**Reminyl®** (Shire)

**Tablets**

- all f/c, galantamine (as hydrobromide) 8 mg (pink), net price 56-tab pack = £68.32; 12 mg (orange-brown), 56-tab pack = £84.00. Label: 3, 21

**Oral solution**

- galantamine (as hydrobromide) 4 mg/mL, net price 100 mL with pipette = £120.00. Label: 3, 21

**Modified release**

**Reminyl® XL** (Shire)

**Capsules**

- m/r, galantamine (as hydrobromide) 8 mg (white), net price 28-cap pack = £54.60; 16 mg (pink), 28-cap pack = £68.32; 24 mg (beige), 28-cap pack = £84.00. Label: 3, 21, 25

**Dose** initially 8 mg once daily for 4 weeks increased to 16 mg once daily for 4 weeks; maintenance 16–24 mg daily

GALANTAMINE

**Indications** mild to moderate dementia in Alzheimer’s disease

**Cautions** cardiac disease (including sick sinus syndrome or other supraventricular conduction abnormalities, unstable angina, congestive heart failure); electrolyte disturbances; susceptibility to peptic ulcers; asthma, chronic obstructive pulmonary disease, pulmonary infection; avoid in urinary retention and gastro-intestinal obstruction; hepatic impairment (Appendix 2)—avoid if severe; pregnancy (Appendix 4); **interactions:** Appendix 1 (parasympathomimetics)

**Contra-indications** renal impairment (avoid if creatinine clearance less than 9 mL/minute; Appendix 3); breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain, dyspepsia; syncope; rinitis; sleep disturbances, dizziness, confusion, depression, headache, fatigue, anorexia, tremor; fever; weight loss; less commonly arrhythmias, palpitation, myocardial infarction, cerebrovascular disease, paraesthesia, tinnitus, and leg cramps; rarely bradycardia, seizures, hallucinations, agitation, aggression, dehydration, hypokalaemia, and rash; very rarely gastrointestinal bleeding, dysphagia, hypotension, exacerbation of Parkinson’s disease, and sweating

**Dose**

- Initially 5 mg once daily at bedtime, increased if necessary after one month to max. 10 mg daily

**Aricept®** (Pfizer, Eisai)

**Tablets**

- donepezil hydrochloride 5 mg (white), net price 28-tab pack = £63.54; 10 mg (yellow), 28-tab pack = £89.06.

**Aricept Evess®** (Pfizer, Eisai)

**Orodispersible tablets**

- donepezil hydrochloride 5 mg (white), net price 28-tab pack = £63.54; 10 mg (yellow), 28-tab pack = £89.06. Counselling, administration

**Counselling** Aricept Evess should be placed on the tongue, allowed to disperse, and swallowed
MEMANTINE HYDROCHLORIDE

**Indications**  moderate to severe dementia in Alzheimer's disease

**Cautions**  history of convulsions; renal impairment (avoid if creatinine clearance less than 5 mL/minute; Appendix 3); pregnancy (Appendix 4); Interactions: Appendix 1 (memantine)

**Contra-indications**  breast-feeding

**Side-effects**  constipation; hypertension; headache, dizziness, drowsiness; less commonly vomiting, thrombosis, confusion, fatigue, hallucinations, and abnormal gait; very rarely seizures; pancreatitis, psychosis, depression, and suicidal ideation also reported

**Dose**
- Initially 5 mg once daily, increased in steps of 5 mg at weekly intervals; max. 20 mg daily

**Ebixa**<sup>®</sup> (Lundbeck)

**Tablets**, f/c, scored, memantine hydrochloride 10 mg, net price 28-tab pack = £34.50, 56-tab pack = £69.01, 112-tab pack = £138.01; 20 mg, 28-tab pack = £69.01; treatment initiation pack, 7 <sup>5/10</sup> <sup>mg</sup>, 7 <sup>10</sup> <sup>mg</sup>, 7 <sup>15</sup> <sup>mg</sup>, and 7 <sup>20</sup> <sup>mg</sup> = £43.13

**Oral drops**, memantine hydrochloride 10 mg/g, net price 50 g = £61.61, 100 g = £123.23

Note 5 mg = 10 drops of memantine hydrochloride oral drops

Note The Scottish Medicines Consortium has advised (January 2004) that Ebixa is not recommended for the treatment of Alzheimer’s disease

RIVASTIGMINE

**Indications**  mild to moderate dementia in Alzheimer's disease or in Parkinson’s disease

**Cautions**  gastric or duodenal ulcers (or susceptibility to ulcers); monitor body-weight; sick sinus syndrome, conduction abnormalities; history of asthma or chronic obstructive pulmonary disease; history of seizures; bladder outflow obstruction; hepatic impairment (avoid if severe—Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); Interactions: Appendix 1 (parasympathomimetics)

**Contra-indications**  breast-feeding (Appendix 5)

**Side-effects**  nausea, vomiting, diarrhoea, dyspepsia, anorexia, abdominal pain; dizziness, headache, drowsiness, tremor, asthma, malaise, agitation, confusion; sweating; weight loss; less commonly gastric or duodenal ulceration, bradycardia, syncope, depression, insomnia, rarely angina pectoris, seizures; very rarely gastro-intestinal haemorrhage, pancreatitis, cardiac arrhythmias, hypertension, hallucinations, extrapyramidal symptoms (including worsening of Parkinson's disease), and rash; with patches application-site reactions

Note Gastro-intestinal side-effects more common in women

**Dose**
- See under preparations below

**Exelon**<sup>®</sup> (Novartis)

**Capsules**, rivastigmine (as hydrogen tartrate) 1.5 mg (yellow), net price 28-cap pack = £39.12, 56-cap pack = £78.25; 3 mg (orange), 28-cap pack = £39.12, 56-cap pack = £78.25; 4.5 mg (red), 28-cap pack = £39.12, 56-cap pack = £78.25; 6 mg (red/orange), 28-cap pack = £39.12, 56-cap pack = £78.25. Label: 21, 25

Oral solution, rivastigmine (as hydrogen tartrate) 2 mg/mL, net price 120 mL (with oral syringe) = £116.64. Label: 21

**Dose**  initially 1.5 mg twice daily, increased in steps of 1.5 mg twice daily at intervals of at least 2 weeks according to response and tolerance; usual range 3–6 mg twice daily; max. 6 mg twice daily

**Patches**, self-adhesive, beige, rivastigmine 4.6 mg/24 hours, net price 30 = £83.84; 9.5 mg/24 hours, 30 = £83.84

**Dose**  initially apply 4.6 mg/24 hours patch to clean, dry, non-hairy, non-irritated skin on back, upper arm, or chest, removing after 24 hours and siting a replacement patch on a different area (avoid using the same area for 14 days); if well tolerated increase to 9.5 mg/24 hours patch daily after no less than 4 weeks; if patch not applied for more than several days, treatment should be restarted with 4.6 mg/24 hours patch

Note When switching a patient from oral to transdermal therapy, patients taking 3-6 mg daily should be prescribed the 4.6 mg/24 hours patch; patients taking 9 mg daily who do not tolerate the dose well should be prescribed the 4.6 mg/24 hours patch, while those taking 9 mg daily who tolerate the dose well should be prescribed the 9.5 mg/24 hours patch; patients taking 12 mg daily should be prescribed the 9.5 mg/24 hours patch. The first patch should be applied on the day following the last oral dose

Note The Scottish Medicines Consortium has advised (October 2007) that Exelon patches should be restricted for use in patients with moderately severe Alzheimer’s disease under the conditions of the NICE guidance (September 2007) and when a transdermal patch is an appropriate choice of formulation
5 Infections

5.1 Antibacterial drugs

5.1.1 Penicillins

5.1.1.1 Benzylpenicillin and phenoxy-methylpenicillin

5.1.1.2 Penicillinase-resistant penicillins

5.1.1.3 Broad-spectrum penicillins

5.1.1.4 Antipseudomonal penicillins

5.1.1.5 Mecillinams

5.1.2 Cephalosporins, carbapenems, and other beta-lactams

5.1.2.1 Cephalosporins

5.1.2.2 Carbapenems

5.1.2.3 Other beta-lactam antibiotics

5.1.3 Tetracyclines

5.1.4 Aminoglycosides

5.1.5 Macrolides

5.1.6 Clindamycin

5.1.7 Some other antibacterials

5.1.8 Sulphonamides and trimethoprim

5.1.9 Antituberculosis drugs

5.1.10 Antileprotic drugs

5.1.11 Metronidazole and tinidazole

5.1.12 Quinolones

5.1.13 Urinary-tract infections

5.2 Antifungal drugs

5.3 Antiviral drugs

5.3.1 HIV infection

5.3.2 Herpesvirus infections

5.3.2.1 Herpes simplex and varicella-zoster infection

5.3.2.2 Cytomegalovirus infection

5.3.3 Viral hepatitis

5.3.4 Influenza

5.3.5 Respiratory syncytial virus

5.4 Antiprotozoal drugs

5.4.1 Antimalarials

5.4.2 Amoebicides

5.4.3 Trichomonacides

5.4.4 Antigiardial drugs

5.4.5 Leishmaniacides

5.4.6 Trypanocides

5.4.7 Drugs for toxoplasmosis

5.4.8 Drugs for pneumocystis pneumonia

5.5 Anthelmintics

5.5.1 Drugs for threadworms

5.5.2 Ascaricides

5.5.3 Drugs for tapeworm infections

5.5.4 Drugs for hookworms

5.5.5 Schistosomicides

5.5.6 Filaricides

5.5.7 Drugs for cutaneous larva migrans

5.5.8 Drugs for strongyloidiasis

This chapter also includes advice on the drug management of the following:
- anthrax, p. 323
- Clostridium difficile infection, p. 285
- Lyme disease, p. 293
- MRSA infections, p. 292
- oral infections, p. 284, p. 287, p. 327

5 Notifiable diseases

Doctors must notify the Proper Officer of the local authority (usually the consultant in communicable disease control) when attending a patient suspected of suffering from any of the diseases listed below; a form is available from the Proper Officer.

- Anthrax
- Ophthalmia neonatorum
- Cholera
- Paratyphoid fever
- Diphtheria
- Plague
- Dysentery (amoebic or bacillary)
- Poliomyelitis, acute
- Encephalitis, acute
- Rabies
- Food poisoning
- Relapsing fever
- Haemorrhagic fever (viral)
- Rubella
- Hepatitis, viral
- Scarlet fever
- Leptospirosis
- Smallpox
- Leprosy
- Tetanus
- Malaria
- Tuberculosis
- Measles
- Typhoid fever
- Meningitis
- Typhus
- Meningococcal septicaemia (without meningitis)
- Yellow fever
- Whooping cough
- Measles
- Mumps

Note: It is good practice for doctors to also inform the consultant in communicable disease control of instances of other infections (e.g. psittacosis) where there could be a public health risk.


5.1 Antibacterial drugs

Choice of a suitable drug  Before selecting an antibacterial the clinician must first consider two factors—the patient and the known or likely causative organism. Factors related to the patient which must be considered include history of allergy, renal and hepatic function, susceptibility to infection (i.e. whether immunocompromised), ability to tolerate drugs by mouth, severity of illness, ethnic origin, age, whether taking other medication and, if female, whether pregnant, breast-feeding or taking an oral contraceptive.

The known or likely organism and its antibacterial sensitivity in association with the above factors, will suggest one or more antibacterials, the final choice depending on the microbiological, pharmacological, and toxicological properties.

An example of a rational approach to the selection of an antibacterial is treatment of a urinary-tract infection in a patient complaining of nausea and symptoms of a urinary-tract infection in early pregnancy. The organism is reported as being resistant to ampicillin but sensitive to nitrofurantoin (can cause nausea), gentamicin (can be given only by injection and best avoided in pregnancy), tetracycline (causes dental discoloration) and trimethoprim (folic acid antagonist therefore theoretical teratogenic risk), and cefalexin. The safest antibiotics in pregnancy are the penicillins and cephalosporins; therefore, cefalexin is reported as being resistant to ampicillin but sensitive to these antibiotics that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

Antibacterial policies  Local policies often limit the antibacterials that may be used to achieve reasonable economy consistent with adequate cover, and to reduce the development of resistant organisms. A policy may indicate a range of drugs for general use, and permit other drugs only on the advice of the microbiologist or physician responsible for the control of infectious diseases.

Before starting therapy  The following precepts should be considered before starting:

- Viral infections should not be treated with antibacterials. However, antibacterials are occasionally helpful in controlling secondary bacterial infection (e.g. acute necrotising ulcerative gingivitis secondary to herpes simplex infection);
- Samples should be taken for culture and sensitivity testing; ‘blind’ antibacterial prescribing for unexplained pyrexia usually leads to further difficulty in establishing the diagnosis;
- Knowledge of prevalent organisms and their current sensitivity is of great help in choosing an antibacterial before bacteriological confirmation is available. Generally, narrow-spectrum antibacterials are preferred to broad-spectrum antibacterials unless there is a clear clinical indication (e.g. life-threatening sepsis);
- The dose of an antibacterial varies according to a number of factors including age, weight, hepatic function, renal function, and severity of infection.

The prescribing of the so-called ‘standard’ dose in serious infections may result in failure of treatment or even death of the patient; therefore it is important to prescribe a dose appropriate to the condition. An inadequate dose may also increase the likelihood of antibacterial resistance. On the other hand, for an antibacterial with a narrow margin between the toxic and therapeutic dose (e.g. an aminoglycoside) it is also important to avoid an excessive dose and the concentration of the drug in the plasma may need to be monitored;

- The route of administration of an antibacterial often depends on the severity of the infection. Life-threatening infections require intravenous therapy. Antibacterials that are well absorbed may be given by mouth even for some serious infections. Parenteral administration is also appropriate when the oral route cannot be used (e.g. because of vomiting) or if absorption is inadequate. Whenever possible, painful intramuscular injections should be avoided in children;

- Duration of therapy depends on the nature of the infection and the response to treatment. Courses should not be unduly prolonged because they encourage resistance, they may lead to side-effects and they are costly. However, in certain infections such as tuberculosis or chronic osteomyelitis it is necessary to treat for prolonged periods. Conversely, a single dose of an antibacterial may cure uncomplicated urinary-tract infections.

Oral bacterial infections  Antibacterial drugs should only be prescribed for the treatment of oral infections on the basis of defined need. They may be used in conjunction with (but not as an alternative to) other appropriate measures, such as providing drainage or extracting a tooth.

The ‘blind’ prescribing of an antibacterial for unexplained pyrexia, cervical lymphadenopathy, or facial swelling can lead to difficulty in establishing the diagnosis. In severe oral infections, a sample should always be taken for bacteriology.

Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acute sinusitis, severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destruactive forms of chronic periodontal disease. Most of these infections are readily resolved by the early establishment of drainage and removal of the cause (typically an infected necrotic pulp). Antibacterials may be indicated if treatment has to be delayed and they are essential in immunocompromised patients or in those with conditions such as diabetes or Paget’s disease.

 Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving faccial spaces such as Ludwig’s angina, require antibiotics and specialist hospital care.

Antibacterial drugs may also be useful after dental surgery in some cases of spreading infection. Infection may spread to involve local lymph nodes, to fascial spaces (where it can cause airway obstruction), or into the bloodstream (where it can lead to cavernous sinus thrombosis and other serious complications). Extension of an infection can also lead to maxillary sinusitis; osteomyelitis is a complication, which usually arises when host resistance is reduced.

If the oral infection fails to respond to antibacterial treatment within 48 hours the antibacterial should be...
changed, preferably on the basis of bacteriological investigation. Failure to respond may also suggest an incorrect diagnosis, lack of essential additional measures (such as drainage), poor host resistance, or poor patient compliance.

Combination of a penicillin (or erythromycin) with metronidazole may sometimes be helpful for the treatment of severe oral infections or oral infections that have not responded to initial antibacterial treatment.

See also Penicillins (section 5.1.1), Cephalosporins (section 5.1.2), Tetracyclines (section 5.1.3), Macrolides (section 5.1.5), Clindamycin (section 5.1.6), Metronidazole (section 5.1.11), Fusidic acid (section 13.10.1.2).

Superinfection In general, broad-spectrum antibacterial drugs such as the cephalosporins are more likely to be associated with adverse reactions related to the selection of resistant organisms e.g. fungal infections or antibiotic-associated colitis (pseudomembranous colitis); other problems associated with superinfection include vaginitis and pruritus ani.

Therapy Suggested treatment is shown in table 1. When the pathogen has been isolated treatment may be changed to a more appropriate antibacterial if necessary. If no bacterium is cultured the antibacterial can be continued or stopped on clinical grounds. Infections for which prophylaxis is useful are listed in table 2.

### Table 1. Summary of antibacterial therapy

<table>
<thead>
<tr>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>If treating a patient suspected of suffering from a notifiable disease, the consultant in communicable disease control should be informed (see p. 283)</td>
</tr>
</tbody>
</table>

### Gastro-intestinal system

**Gastro-enteritis**
- Antibacterial not usually indicated
  - Frequently self-limiting and may not be bacterial

**Campylobacter enteritis**
- Ciprofloxacin or erythromycin
  - Frequently self-limiting; treat severe infection

**Invasive salmonellosis**
- Ciprofloxacin or cefotaxime
  - Includes severe infections which may be invasive

**Shigellosis**
- Ciprofloxacin or azithromycin (unlicensed indication)
  - Amoxicillin or trimethoprim can be used if organism sensitive.
  - Antibacterial not indicated for mild cases

**Typhoid fever**
- Ciprofloxacin or cefotaxime
  - Infections from Indian subcontinent, Middle-East, and South-East Asia may be multiple-antibacterial-resistant and sensitivity should be tested; azithromycin (unlicensed indication) may be an option in mild or moderate disease caused by multiple antibiotic-resistant organisms

**Clostridium difficile infection**
- Oral metronidazole or oral vancomycin
  - Treat for 7–10 days. Use vancomycin for severe infection or in patients intolerant of metronidazole. Give metronidazole by intravenous infusion if oral treatment inappropriate

**Biliary-tract infection**
- Ciprofloxacin or gentamicin or a cephalosporin

**Peritonitis**
- A cephalosporin (or gentamicin) + metronidazole (or clindamycin)

**Peritoneal dialysis-associated peritonitis**
- Either vancomycin<sup>1</sup> + cefazidine added to dialysis fluid or vancomycin added to dialysis fluid + ciprofloxacin by mouth
  - Treat for 14 days or longer

### Cardiovascular system

**Endocarditis: initial ‘blind’ therapy**
- Fluvoxacinil (or benzylpenicillin if symptoms less severe) + gentamicin
  - Substitute fluvoxacinil (or benzylpenicillin) with vancomycin + rifampicin if cardiac prostheses present, or if penicillin-allergic, or if meticillin-resistant *Staphylococcus aureus* suspected

**Endocarditis caused by staphylococci**
- Fluvoxacinil (or vancomycin + rifampicin if penicillin-allergic or if meticillin-resistant *Staphylococcus aureus*)
  - Treat for at least 4 weeks; treat prosthetic valve endocarditis for at least 6 weeks and if using fluvoxacinil add rifampicin for at least 2 weeks

**Endocarditis caused by streptococci**
- Benzylpenicillin (or vancomycin<sup>1</sup> if penicillin-allergic or highly penicillin-resistant) + gentamicin
  - Treat endocarditis caused by fully sensitive streptococci with benzylpenicillin or vancomycin alone for 4 weeks or (if no intracardial abscess or infected emboli) with benzylpenicillin + gentamicin for 2 weeks. Treat more resistant organisms for 4–6 weeks (stopping gentamicin after 2 weeks for organisms moderately sensitive to penicillin); if aminoglycoside cannot be used and if streptococci moderately sensitive to penicillin, treat with benzylpenicillin alone for 4 weeks. Treat prosthetic valve endocarditis for at least 6 weeks (stopping gentamicin after 2 weeks if organisms fully sensitive to penicillin)

**Endocarditis caused by enterococci**
- (e.g. *Enterococcus faecalis*)
  - Amoxicillin<sup>2</sup> (or vancomycin<sup>1</sup> if penicillin-allergic or penicillin-resistant) + gentamicin
    - Treat for at least 4 weeks (at least 6 weeks for prosthetic valve endocarditis); if gentamicin-resistant, substitute gentamicin with streptomycin

**Endocarditis caused by haemophilus, actinobacillus, cardiobacterium, eikenella, and kingella species (‘HACEK’ organisms)**
- Amoxicillin<sup>2</sup> (or ceftriaxone if amoxicillin-resistant) + low-dose gentamicin
  - Treat for 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

### Respiratory system

**Haemophilus influenzae epiglotitis**
- Cefotaxime or chloramphenicol
  - Give intravenously

**Exacerbations of chronic bronchitis**
- Amoxicillin<sup>2</sup> or tetracycline (or erythromycin<sup>3</sup>)
  - Some pneumococci and *Haemophilus influenzae* strains tetracycline-resistant; approx. 20% *H. influenzae* strains amoxicillin-resistant

**Uncomplicated community-acquired pneumonia**
- Amoxicillin<sup>2</sup> (or benzylpenicillin if previously healthy chest or erythromycin<sup>1</sup> if penicillin-allergic)
  - Add fluvoxacinil if staphylococci suspected, e.g. in influenza or measles (or vancomycin<sup>1</sup> if meticillin-resistant *Staphylococcus aureus*) suspected; treat for 7 days (14–21 days for infections caused by staphylococci); pneumococci with decreased penicillin sensitivity being isolated but not yet common in UK; add erythromycin<sup>1</sup> if atypical pathogens suspected

---

<sup>1</sup> Where vancomycin is suggested teicoplanin may be used.

<sup>2</sup> Where amoxicillin is suggested ampicillin may be used.

<sup>3</sup> Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.
Severe community-acquired pneumonia of unknown aetiology
Cefuroxime (or cefotaxime) + erythromycin
Add flucloxacillin if staphylococci suspected (or vancomycin if meticillin-resistant Staphylococcus aureus suspected); treat for 10 days (14–21 days if staphylococci, legionella, or Gram-negative enteric bacilli suspected)

Pneumonia possibly caused by atypical pathogens
Erythromycin
Severe Legionella infections may require addition of rifampicin; tetracycline is an alternative for chlamydial and mycoplasma infections; treat for at least 14 days (14–21 days for legionella)

Hospital-acquired pneumonia
A broad-spectrum cephalosporin (e.g. cefotaxime or ceftazidime) or an antipseudomonal penicillin or another antipseudomonal beta-lactam or a quinolone (e.g. ciprofloxacin)
An aminoglycoside may be added in severe illness

Central nervous system
Meningitis: initial empirical therapy
- Transfer patient urgently to hospital
- If bacterial meningitis and especially if meningococcal disease suspected, general practitioners should give benzylpenicillin (see p. 291 for dose) before urgent transfer to hospital; cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol (section 5.1.7) may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins
- Consider adjunctive treatment with dexamethasone (particularly if pneumococcal meningitis suspected in adults; section 6.3.2) starting before or with first dose of antibacterial; avoid dexamethasone in septic shock, meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery

Meningitis caused by meningococci
Benzylenicillin or cefotaxime
Treat for at least 5 days; substitute chloramphenicol if history of immediate hypersensitivity reaction to penicillin or to cephalosporins. To eliminate nasopharyngeal carriage give rifampicin for 2 days (see Table 2, section 5.1)

Meningitis caused by pneumococci
Cefotaxime
Treat for 10–14 days; substitute benzylpenicillin if organism penicillin-sensitive; if organism highly penicillin- and cephalosporin-resistant, add vancomycin and if necessary rifampicin. Consider adjunctive treatment with dexamethasone (section 6.3.2) starting before or with first dose of antibacterial (but may reduce penetration of vancomycin into cerebrospinal fluid)

Meningitis caused by *Haemophilus influenzae*
Cefotaxime
Treat for at least 10 days; substitute chloramphenicol if history of immediate hypersensitivity reaction to penicillin or to cephalosporins, or if organism resistant to cefotaxime. Consider adjunctive treatment with dexamethasone (section 6.3.2) starting before or with first dose of antibacterial. For *H. influenzae* type b give rifampicin for 4 days before hospital discharge (see Table 2, section 5.1)

Meningitis caused by *Listeria*
Amoxicillin + gentamicin
Treat for 10–14 days

Urinary tract
Acute pyelonephritis
A broad-spectrum cephalosporin or a quinolone
Treat for 10–14 days; longer treatment may be necessary in complicated pyelonephritis

1. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.
2. Where vancomycin is suggested teicoplanin may be used.
3. Where amoxicillin is suggested ampicillin may be used.

Acute prostatitis
A quinolone or trimethoprim
Treat for 28 days; in severe infection, start treatment with a high dose broad-spectrum cephalosporin (e.g. cefuroxime or cefotaxime) + gentamicin
‘Lower’ urinary-tract infection
Trimethoprim or nitrofurantoin or amoxicillin or oral cephalosporin
Treat for 7 days but a short course (e.g. 3 days) is usually adequate for uncomplicated urinary-tract infections in women. See also section 5.1.13

Genital system
Syphilis
Benzathine benzylpenicillin [unlicensed] or doxycycline or erythromycin
Treat early syphilis (infection of less than 2 years) with benzathine benzylpenicillin as a single dose (repeat dose after 7 days for women in the third trimester of pregnancy) or with doxycycline or erythromycin for 14 days. Treat late latent syphilis (asymptomatic infection of more than 2 years) with doxycycline for 28 days or with benzathine benzylpenicillin once weekly for 2 weeks. Treat asymptomatic contacts of patients with infectious syphilis with doxycycline for 14 days. Contact tracing recommended.

Uncomplicated gonorrhoea
Cefixime [unlicensed indication] or ciprofloxacin
Single-dose treatment in uncomplicated infection. Choice depends on locality where infection acquired. Pharyngeal infection requires treatment with ceftriaxone. Use ciprofloxacin only if organism sensitive. Contact-tracing recommended; remember chlamydia

Uncomplicated genital chlamydial infection, non-gonococcal urethritis and non-specific genital infection
Doxycycline or azithromycin
Treat with doxycycline for 7 days or with azithromycin as a single dose; alternatively, treat with erythromycin for 14 days. Contact tracing recommended

Pelvic inflammatory disease
Doxycycline + metronidazole + i/m ceftriaxone or ofloxacin + metronidazole
Treat for at least 14 days (use i/m ceftriaxone as a single dose). In severely ill patients initial treatment with doxycycline + i/v ceftriaxone (as a single dose) + i/v metronidazole, then switch to oral treatment with doxycycline + metronidazole to complete 14 days’ treatment. Contact tracing recommended

Bacterial vaginosis
Oral or topical metronidazole or topical clindamycin
Oral treatment for 5–7 days (or with high-dose metronidazole as a single dose); topical treatment for 5 days (7 days with clindamycin)

Blood
Community-acquired septicaemia
A broad-spectrum antipseudomonal penicillin (e.g. *Tazocin®, Timentin®*) or a broad-spectrum cephalosporin (e.g. cefazidime, cefotaxime)
Add aminoglycoside if pseudomonas suspected, or if severe sepsis, or if patient recently discharged from hospital. Add vancomycin if meticillin-resistant *Staphylococcus aureus* suspected. Add metronidazole to broad-spectrum cephalosporin if anaerobic infection suspected

Hospital-acquired septicaemia
A broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. *Tazocin®, Timentin®, cefazidime, imipenem (with cilastatin as Primaxin®) or meropenem)
Add aminoglycoside if pseudomonas suspected, or if multiple-resistant organisms suspected, or if severe sepsis. Add vancomycin if meticillin-resistant *Staphylococcus aureus* suspected. Add metronidazole to broad-spectrum cephalosporin if anaerobic infection suspected
Septicaemia related to vascular catheter
Vancomycin
Add an aminoglycoside + a broad-spectrum antipseudo-
monal beta-lactam if Gram-negative sepsis suspected, especially in the immunocompromised. Consider removing vascular catheter, particularly if infection caused by *Staphy-
lococcus aureus*, pseudomonas, or candida

Meningococcal septicaemia
Benzylenicillin or cefotaxime
If meningococcal disease suspected, general practitioners advised to give a single dose of benzylenicillin (see p. 291 for dose) before urgent transfer to hospital; cefotaxime (sees 1.2) may be an alternative in penicillin allergy; chloramphenicol may be used if history of immediate hypersensitivity reaction to penicillin or to cephalosporins. To eliminate nasopharyngeal carriage give rifampicin for 2 days (see Table 2, section 5.1)

Musculoskeletal system
Osteomyelitis
Flucloxacillin or clindamycin if penicillin-allergic (or vancomycin if resistant *Staphylococcus epidermidis* or meticillin-resistant *Staph. aureus*). Treat acute infection for 4–6 weeks and chronic infection for at least 12 weeks. Combine vancomycin with either fusidic acid or rifampicin if protheses present or if life-threatening condition

Septic arthritis
Flucloxacillin or clindamycin if penicillin-allergic (or vancomycin if resistant *Staphylococcus epidermidis* or meticillin-resistant *Staph. aureus*) (of cefotaxime if gono-
coccal arthritis or Gram-negative infection) Treat usually for 6 weeks (longer if infection complicated or if prothesis present; treat for 2 weeks if gonococcal infection). Combine vancomycin with either fusidic acid or rifampicin if protheses present or if life-threatening condition

Skin
Impetigo
Topical fusidic acid (or mupirocin if meticillin-resistant *Staphylococcus aureus*); oral flucloxacillin or erythromycin if widespread Traditional treatment for 7 days usually adequate; max. duration of topical treatment 10 days; seek local microbiology advice before using topical treatment in hospital; oral treatment for 7 days; add phosphomycillin to flucloxacillin if streptococcal infection suspected

Erysipelas
Phenoxymethylpenicillin (or erythromycin if penicillin-allergic) Treat for at least 7 days; add flucloxacillin to phenox-
ymethylpenicillin if staphylococcus suspected; substitute benzylpenicillin for phenoxymethylpenicillin if parenteral treatment required

Cellulitis
Benzylenicillin + flucloxacillin (or erythromycin alone if penicillin-allergic) Substitute phenoxymethylpenicillin for benzylpenicillin if oral treatment appropriate. Discontinue flucloxacillin if streptococcal infection confirmed. Substitute treatment with broad-spectrum antibacterials if Gram-negative bacteria or anaerobes suspected

Animal and human bites
Co-amoxiclav alone (or doxycycline + metronidazole if penicillin-allergic)

Acne
See section 13.6

---

5.1 Antibacterial drugs

**Sinusitis**

*Amoxicillin* or *doxycycline* or *erythromycin*

Antibacterial should usually be used only for persistent symptoms and purulent discharge lasting at least 7 days or if severe symptoms. Also, consider antibacterial for those at high risk of serious complications (e.g. in immunosuppres-
sion, cystic fibrosis). Treat for 7 days

**Otitis externa**

Flucloxacillin (or erythromycin if penicillin-allergic) Consider systemic antibacterial if spreading cellulitis or patient systemically unwell. Use ciprofloxacin (or an ami-
oglycoside) if pseudomonas suspected. For topical pre-
parations see section 12.1.1

**Otitis media**

*Amoxicillin* (or *erythromycin* if penicillin-allergic)

Many infections caused by viruses. Most uncomplicated cases resolve without antibacterial treatment. In children without systemic features, antibacterial treatment may be started after 72 hours if no improvement. Consider earlier treatment if deterioration, if systemically unwell, if at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis). If mastoiditis present, or in children under 2 years of age with bilateral otitis media. Treat for 5 days (longer if severely ill); initial parenteral therapy in severe infections; consider co-amoxiclav or ceftriaxone if no improvement after 24–48 hours

---

1. Where vancomycin is suggested teicoplanin may be used.
2. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.
3. Where amoxicillin is suggested ampicillin may be used.
### Table 2. Summary of antibacterial prophylaxis

#### Prevention of recurrence of rheumatic fever

Phenoxyemethylenicillin 250 mg twice daily or sulfadiazine 1 g daily (500 mg daily for patients under 30 kg)

#### Prevention of secondary case of invasive group A streptococcal infection

Phenoxyemethylenicillin 250–500 mg every 6 hours for 10 days; CHILD under 1 year 62.5 mg every 6 hours, 1–5 years 125 mg every 6 hours, 6–12 years 250 mg every 6 hours

Patients who are penicillin allergic, either erythromycin ADULT and CHILD over 8 years, 250–500 mg every 6 hours for 10 days; CHILD under 2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours or azithromycin [unlicensed indication] 500 mg once daily for 5 days; CHILD over 6 months, 12 mg/kg (max. 500 mg) once daily

#### Prevention of secondary case of meningococcal meningitis

Rifampicin 600 mg every 12 hours for 2 days; CHILD 10 mg/kg (under 1 year, 5 mg/kg) every 12 hours for 2 days

or ciprofloxacin [unlicensed indication] 500 mg as a single dose; CHILD 2–5 years 125 mg; 5–12 years 250 mg

or i/m ceftriaxone [unlicensed indication] 250 mg as a single dose; CHILD under 12 years 125 mg

#### Prevention of secondary case of Haemophilus influenzae type b disease

Rifampicin 600 mg once daily for 4 days (regimen of choice for adults); CHILD 1–3 months 10 mg/kg once daily for 4 days, over 3 months 20 mg/kg once daily for 4 days (max. 600 mg daily)

#### Prevention of secondary case of diphtheria in non-immune patient

Erythromycin 500 mg every 6 hours for 7 days; CHILD up to 2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours

Treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment

---

1. For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Health Protection Agency Laboratory).

2. For details of those who should receive chemoprophylaxis contact a consultant in communicable disease control (or a consultant in infectious diseases or the local Health Protection Agency Laboratory). Unless there has been direct exposure of the mouth or nose to infectious droplets from a patient with meningococcal disease who has received less than 24 hours of antibacterial treatment, healthcare workers do not generally require chemoprophylaxis.

3. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.

4. For details of those who should receive chemoprophylaxis contact the lead clinician for local tuberculosis services (or a consultant in communicable disease control). See also section 5.1.9, for advice on immunocompromised patients and on prevention of tuberculosis.

5. Additional intra-operative or postoperative doses of antibiotic may be given for prolonged procedures or if there is major blood loss.

6. Metronidazole may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.
Resections of colon and rectum for carcinoma, and resections in inflammatory bowel disease, and appendectomy

Single dose$^1$ of i/v gentamicin + i/v metronidazole$^2$ or i/v cefuroxime + i/v metronidazole$^2$ or i/v co-amoxiclav alone

Endoscopic retrograde cholangiopancreatography

Single dose of i/v gentamicin or oral or i/v ciprofloxacin

Prophylaxis particularly recommended if bile stasis, pancreatic pseudocyst, previous cholangitis or neutropenia

Prevention of infection in orthopaedic surgery

Joint replacement including hip and knee and management of fractures

Single dose$^1$ of i/v cefuroxime or i/v fluocxacillin

Substitute i/v vancomycin if history of allergy to penicillins or to cephalosporins or if high risk of meticillin-resistant Staphylococcus aureus; use cefuroxime + metronidazole for complex open fractures with extensive soft-tissue damage; prophylaxis continued for 24 hours in open fractures (longer if complex open fractures)

Prevention of infection in urological procedures

Transrectal prostate biopsy

Single dose$^1$ of oral ciprofloxacin + oral metronidazole or i/v gentamicin + i/v metronidazole$^2$

Transurethral resection of prostate

Single dose$^1$ of oral ciprofloxacin or i/v gentamicin or i/v cefuroxime

Prevention of infection in obstetric and gynaecological surgery

Caesarean section

Single dose$^1$ of i/v cefuroxime

Administer immediately after umbilical cord is clamped; substitute i/v clindamycin if history of allergy to penicillins or cephalosporins

Hysterectomy

Single dose$^1$ of i/v cefuroxime + i/v metronidazole$^2$ or i/v gentamicin + i/v metronidazole$^2$ or i/v co-amoxiclav alone

Termination of pregnancy

Single dose$^1$ of oral metronidazole

If genital chlamydial infection cannot be ruled out, give doxycycline (section 5.1.3) postoperatively

Prevention of infection in vascular surgery

Reconstructive arterial surgery of abdomen, pelvis or legs

Single dose$^1$ of i/v cefuroxime or i/v ciprofloxacin

Add i/v metronidazole for patients at risk from anaerobic infections including those with diabetes, gangrene, or undergoing amputation; add i/v vancomycin if high risk of meticillin-resistant Staphylococcus aureus

NICE guidance

Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures (March 2008)

Antibacterial prophylaxis and chlorhexidine mouthwash are not recommended for the prevention of endocarditis in patients undergoing dental procedures.

Antibacterial prophylaxis is not recommended for the prevention of endocarditis in patients undergoing procedures of the:

- upper and lower respiratory tract (including ear, nose, and throat procedures and bronchoscopy);
- genito-urinary tract (including urological, gynaecological, and obstetric procedures);
- upper and lower gastro-intestinal tract.

Whilst these procedures can cause bacteraemia, there is no clear association with the development of infective endocarditis. Prophylaxis may expose patients to the adverse effects of antimicrobials when the evidence of benefit has not been proven.

Any infection in patients at risk of endocarditis should be investigated promptly and treated appropriately to reduce the risk of endocarditis.

If patients at risk of endocarditis are undergoing a gastro-intestinal or genito-urinary tract procedure at a site where infection is suspected, they should receive appropriate antibacterial therapy that includes cover against organisms that cause endocarditis.

Patients at risk of endocarditis should be:

- advised to maintain good oral hygiene;
- told how to recognise signs of infective endocarditis, and advised when to seek expert advice.

Dermatological procedures

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who undergo dermatological procedures do not require antibacterial prophylaxis against endocarditis.

1. Additional intra-operative or postoperative doses of antibacterial may be given for prolonged procedures or if there is major blood loss.
2. Metronidazole may alternatively be given by suppository but to allow adequate absorption, it should be given 2 hours before surgery.
3. Patients at risk of endocarditis include those with valve replacement, acquired valvular heart disease with stenosis or regurgitation, structural congenital heart disease (including surgically corrected or palliated structural conditions, but excluding isolated atrial septal defect, fully repaired ventricular septal defect, fully repaired patent ductus arteriosus, and closure devices considered to be endothelialised), hypertrophic cardiomyopathy, or a previous episode of infective endocarditis.
4. The British Association of Dermatologists Therapy Guidelines and Audit Subcommittee advise that such dermatological procedures include skin biopsies and excision of moles or of malignant lesions.
Joint protheses and dental treatment

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients with prosthetic joint implants (including total hip replacements) do not require antibiotic prophylaxis for dental treatment. The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibiotics when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibiotics to which the infecting organisms are sensitive. The Working Party has commented that joint infections have rarely been shown to follow dental procedures and are even more rarely caused by oral streptococci.

Immunosuppression and indwelling intraperitoneal catheters

Advice of a Working Party of the British Society for Antimicrobial Chemotherapy is that patients who are immunosuppressed (including transplant patients) and patients with indwelling intraperitoneal catheters do not require antibiotic prophylaxis for dental treatment provided there is no other indication for prophylaxis. The Working Party has commented that there is little evidence that dental treatment is followed by infection in immunosuppressed and immunodeficient patients nor is there evidence that dental treatment is followed by infection in patients with indwelling intraperitoneal catheters.

Penicillins

The penicillins are bactericidal and act by interfering with bacterial cell wall synthesis. They diffuse well into body tissues and fluids, but penetration into the cerebrospinal fluid is poor except when the meninges are inflamed. They are excreted in the urine in therapeutic concentrations.

Hypersensitivity reactions

The most important side-effect of the penicillins is hypersensitivity which causes rashes and anaphylaxis and can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals; anaphylactic reactions occur in fewer than 0.05% of treated patients. Patients with a history of atopic allergy (e.g. asthma, eczema, hay fever) are at a higher risk of anaphylactic reactions to penicillins. Individuals with a history of anaphylaxis, urticaria, or rash immediately after penicillin administration are at risk of immediate hypersensitivity to a penicillin; these individuals should not receive a penicillin. Patients who are allergic to one penicillin will be allergic to all because the hypersensitivity is related to the basic penicillin structure. As patients with a history of immediate hypersensitivity to penicillins may also react to the cephalosporins and other beta-lactam antibiotics, they should not receive these antibiotics; aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients and can be used with caution. If a penicillin (or another beta-lactam antibiotic) is essential in an individual with immediate hypersensitivity to penicillin then specialist advice should be sought on hypersensitivity testing or using a beta-lactam antibiotic with a different structure to the penicillin that caused the hypersensitivity (see also p. 297).

Individuals with a history of a minor rash (i.e. non-confluent, non-pruritic rash restricted to a small area of the body) or a rash that occurs more than 72 hours after penicillin administration are probably not allergic to penicillin and in these individuals a penicillin should not be withheld unnecessarily for serious infections; the possibility of an allergic reaction should, however, be borne in mind. Other beta-lactam antibiotics (including cephalosporins) can be used in these patients.

A rare but serious toxic effect of the penicillins is encephalopathy due to cerebral irritation. This may result from excessively high doses or in patients with severe renal failure. The penicillins should not be given by intrathecal injection because they can cause encephalopathy which may be fatal.

Another problem relating to high doses of penicillin, or normal doses given to patients with renal failure, is the accumulation of electrolyte since most injectable penicillins contain either sodium or potassium.

Diarrhoea frequently occurs during oral penicillin therapy. It is most common with broad-spectrum penicillins, which can also cause antibiotic-associated colitis.

Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin sodium (Penicillin G) remains an important and useful antibiotic but is inactivated by bacterial beta-lactamases. It is effective for many streptococcal (including pneumococcal), gonococcal, and meningococcal infections and also for anthrax (section 5.1.12), diphtheria, gas-gangrene, leptospirosis, and treatment of Lyme disease (section 5.1.1.3). Pneumococci, meningococci, and gonococci which have decreased sensitivity to penicillin have been isolated; benzylpenicillin is no longer the drug of first choice for pneumococcal meningitis. Although benzylpenicillin is effective in the treatment of tetanus, metronidazole (section 5.1.11) is preferred. Benzylpenicillin is inactivated by gastric acid and absorption from the gut is low; therefore it is best given by injection.

Benzathine benzylpenicillin (available on a named-patient basis from specialist importing companies, see p. 939) is used for the treatment of early syphilis and late latent syphilis; it is given by intramuscular injection.

Phenoxymethylpenicillin (Penicillin V) has a similar antibacterial spectrum to benzylpenicillin, but is less active. It is gastric acid-stable, so is suitable for oral administration. It should not be used for serious infec-
tions because absorption can be unpredictable and plasma concentrations variable. It is indicated principally for respiratory-tract infections in children, for streptococcal tonsillitis, and for continuing treatment after one or more injections of benzylpenicillin when clinical response has begun. It should not be used for meningococcal or gonococcal infections. Phenoxymethylpenicillin is used for prophylaxis against streptococcal infections following rheumatic fever and against pneumococcal infections following splenectomy or in sickle-cell disease.

**Oral infections**  Phenoxymethylpenicillin is effective for dental alveolar abscess.

---

### BENZYLPCNILLIN SODIUM
(Penicillin G)

**Indications**  throat infections, otitis media, endocarditis, meningococcal disease, pneumonia, cellulitis (Table 1, section 5.1); anthrax; prophylaxis in limb amputation (Table 2, section 5.1); see also notes above

**Cautions**  history of allergy; false-positive urinary glucose (if tested for reducing substances); renal impairment (Appendix 3); **interactions:** Appendix 1 (penicillins)

**Contra-indications**  penicillin hypersensitivity

**Side-effects**  hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reaction; rarely CNS toxicity including convulsions (especially with high doses or in severe renal impairment), interstitial nephritis, haemolytic anaemia, leucopenia, thrombocytopenia, and coagulation disorders; also reported diarrhoea (including antibiotic-associated colitis)

**Dose**
- **By intramuscular or by slow intravenous injection** or by infusion, 2.4–4.8 g daily in 4 divided doses, increased if necessary in more serious infections (single doses over 1.2 g intravenous route only; see also below); **PRETERM NEONATE** and **NEONATE** under 1 week, 50 mg/kg daily in 2 divided doses; **NEONATE** 1–4 weeks, 75 mg/kg daily in 3 divided doses; **CHILD** 1 month–12 years, 100 mg/kg daily in 4 divided doses; **INFANT** A 1–9 years, 150 mg/kg daily in 4 divided doses; **INFANT** B 1–9 years, 250 mg every 6 hours, increased up to 12.5 mg/kg every 6 hours in severe infections; 6–12 years, 250 mg every 6 hours, increased up to 12.5 mg/kg every 6 hours in severe infections; 6–12 years, 250 mg every 6 hours, increased up to 12.5 mg/kg every 6 hours in severe infections

**Note**  Phenoxymethylpenicillin doses in the BNF may differ from those in product literature

---

### PHENOXYMETHYLPENICILLIN
(Penicillin V)

**Indications**  oral infections (see notes above); tonsillitis, otitis media, erysipelas, cellulitis; group A streptococcal infection, rheumatic fever and pneumococcal infection prophylaxis (Table 2, section 5.1)

**Cautions**  see under Benzylpenicillin

**Contra-indications**  see under Benzylpenicillin

**Side-effects**  see under Benzylpenicillin

**Dose**
- **By intrathecal injection, not recommended**

**Note**  Benzylpenicillin doses in BNF may differ from those in product literature

---

### 5.1.1.2 Penicillinase-resistant penicillins

Most staphylococci are now resistant to benzylpenicillin because they produce penicillinases. **Flucloxacillin**, however, is not inactivated by these enzymes and is thus effective in infections caused by penicillin-resistant staphylococci, which is the sole indication for its use. Flucloxacillin is acid-stable and can, therefore, be given by mouth as well as by injection. Flucloxacillin is well absorbed from the gut. For CSM warning on hepatic disorders see under Flucloxacillin.

**Temocillin** is active against Gram-negative bacteria and is stable against a wide range of beta-lactamases. It should be reserved for the treatment of infections caused by beta-lactamase-producing strains of Gram-negative bacteria, including those resistant to third-generation cephalosporins. Temocillin is not active against *Pseudomonas aeruginosa* or *Acinetobacter spp.*
MRSA  Infection from *Staphylococcus aureus* strains resistant to meticillin [now discontinued] (meticillin-resistant *Staph. aureus*, MRSA) and to flucloxacillin can be difficult to manage. Treatment is guided by the sensitivity of the infecting strain.

Rifampicin (section 5.1.9) or sodium fusidate (section 5.1.7) should not be used alone because resistance may develop rapidly. A tetracycline alone or a combination of rifampicin and sodium fusidate can be used for skin and soft-tissue infections caused by MRSA; clindamycin alone is an alternative. A glycopeptide (e.g. vancomycin, section 5.1.7) can be used for severe skin and soft-tissue infections involving Gram-negative organisms, it can be used for mixed skin and soft-tissue infections only when other treatments are not available; linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. A combination of a glycopeptide and sodium fusidate or a glycopeptide and rifampicin can be considered for skin and soft-tissue infections that have failed to respond to a single antibacterial.

The combination of the streptogramin antibiotics quinupristin and dalfopristin (section 5.1.7) should be reserved for skin and soft-tissue infections that have not responded to other antibacterials or for patients who cannot tolerate other antibacterials. Tigecycline (section 5.1.3) and daptomycin (section 5.1.7) are licensed for the treatment of complicated skin and soft-tissue infections involving MRSA.

A tetracycline or clindamycin can be used for bronchiectasis caused by MRSA. A glycopeptide can be used for pneumonia associated with MRSA; if a glycopeptide is unsuitable, linezolid (section 5.1.7) can be used on expert advice. Linezolid must be given with other antibacterials if the infection also involves Gram-negative organisms. Quinupristin and dalfopristin should be reserved for hospital-acquired pneumonia that has not responded to other antibacterials or for patients who cannot tolerate other antibacterials.

A tetracycline can be used for urinary-tract infections caused by MRSA; trimethoprim or nitrofurantoin are alternatives. A glycopeptide can be used for urinary-tract infections that are severe or resistant to other antibacterials.

A glycopeptide can be used for septicaemia associated with MRSA.

For the management of endocarditis, osteomyelitis, or septic arthritis associated with MRSA, see Table 1, section 5.1.

Prophylaxis with vancomycin or teicoplanin (alone or in combination with another antibacterial active against other pathogens) is appropriate for patients undergoing surgery if:

- there is a history of MRSA colonisation or infection without documented eradication;
- there is a risk that the patient’s MRSA carriage has recurred;
- the patient comes from an area with a high prevalence of MRSA.

For eradication of nasal carriage of MRSA, see section 12.2.3.

---

**FLUCLOXACILLIN**

**Indications** infections due to beta-lactamase-producing *Staphylococi* including *Staphylococcus aureus*; acute and chronic osteomyelitis, including *Staphylococcus aureus* osteomyelitis; and acute and chronic skin and soft-tissue infections due to beta-lactamase-producing *Staphylococci*.

**Contra-indications** see under Benzylpenicillin (section 5.1.1.1)

**Side-effects** see under Benzylpenicillin (section 5.1.1.1): also gastrointestinal disturbances; very rarely hepatitis and cholestatic jaundice (see also CSM advice above)

**Dose**

- **By mouth**, 250–500 mg every 6 hours, at least 30 minutes before food; **CHILD** under 2 years quarter adult dose; 2–10 years half adult dose
- **By intramuscular injection**, 250–500 mg every 6 hours; **CHILD** under 2 years quarter adult dose; 2–10 years half adult dose
- **By slow intravenous injection or by intravenous infusion**, 0.25–2 g every 6 hours; **CHILD** under 2 years quarter adult dose; 2–10 years half adult dose
- Endocarditis (in combination with another antibacterial, see Table 1, section 5.1), body-weight under 85 kg, 8 g daily in 4 divided doses; body-weight over 85 kg, 12 g daily in 6 divided doses
- Osteomyelitis (see Table 1, section 5.1), up to 8 g daily in 3–4 divided doses
- Surgical prophylaxis, by slow intravenous injection or by intravenous infusion, 1–2 g at induction; up to 4 further doses of 500 mg may be given every 6 hours by mouth, or by intramuscular injection, or by slow intravenous injection or by intravenous infusion for high risk procedures

**Note** Flucloxacillin doses in BNF may differ from those in product literature

**Flucloxacillin** (Non-proprietary) [Flucloxacillin]

**Capsules**, flucloxacillin (as sodium salt) 250 mg, net price £2.38; 500 mg, net price £4.30. Label: 9, 23

Brands include *Fluclox*, *Fluclox*, *Ladroxin*, *Ladroxin*

**Oral solution** (= elixir or syrup), flucloxacillin (as sodium salt) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £2.97; 250 mg/5 mL, 100 mL = £8.84. Label: 9, 23

Brands include *Ladroxin*, *Ladroxin*

**Injection**, powder for reconstitution, flucloxacillin (as sodium salt). Net price 250-mg vial = £1.23; 500-mg vial = £2.45; 1-g vial = £4.90

**CSM advice (hepatic disorders)**

CSM has advised that very rarely cholestatic jaundice and hepatitis may occur up to several weeks after treatment with flucloxacillin has been stopped. Administration for more than 2 weeks and increasing age are risk factors. CSM has reminded that:

- flucloxacillin should not be used in patients with a history of hepatic dysfunction associated with flucloxacillin;
- flucloxacillin should be used with caution in patients with hepatic impairment;
- careful enquiry should be made about hypersensitivity reactions to beta-lactam antibacterials.
Fluxapen® (GSK) Furn.
Suspension (= syrup), flucoxacin (as magnesium salt) for reconstitution with water, 125 mg/5 mL. net price 100 mL = £3.25; 250 mg/5 mL, 100 mL = £6.48. Label: 9, 23

TEMOCILLIN

Indications septicaemia, urinary-tract infections, lower respiratory-tract infections caused by susceptible Gram-negative bacteria

Cautions see under Benzylpenicillin (section 5.1.1.1); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Contra-indications see under Benzylpenicillin (section 5.1.1.1)

Side-effects see under Benzylpenicillin (section 5.1.1.1)

Dose

- By intramuscular injection or by intravenous infusion over 3–4 minutes, or by intravenous infusion
- ADULT and CHILD over 12 years (body-weight over 45 kg), 1–2 g every 12 hours
- Uncomplicated urinary-tract infections, ADULT and CHILD over 12 years (body-weight over 45 kg), 1 g daily as a single daily dose or in divided doses

Negaban® (Euromedica) Furn.
Injection, powder for reconstitution, temocillin (as sodium salt), net price 1-g vial = £25.45
Electrolytes Na 4.35 mmol/g

5.1.1.3 Broad-spectrum penicillins

Ampicillin is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinas inclu

ing those produced by Staphylococcus aureus and by common Gram-negative bacilli such as Escherichia coli. Almost all staphylococci, approx. 60% of E. coli strains and approx. 20% of Haemophilus influenzae strains are now resistant. The likelihood of resistance should therefore be considered before using ampicillin for the ‘blind’ treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

Ampicillin is well excreted in the bile and urine. It is principally indicated for the treatment of exacerbations of chronic bronchitis and middle ear infections, both of which may be due to Streptococcus pneumoniae and H. influenzae, and for urinary-tract infections (section 5.1.13).

Ampicillin can be given by mouth but less than half the dose is absorbed, and absorption is further decreased by the presence of food in the stomach. Amoxicillin may also be used for the treatment of Lyme disease [not licensed], see below.

Co-amoxiclav consists of amoxicillin with the beta-lactamase inhibitor clavulanic acid. Clavulanic acid itself has no significant antibacterial activity but, by inactivating beta-lactamases, it makes the combination active against beta-lactamase-producing bacteria that are resistant to amoxicillin. These include resistant strains of Staph. aureus, E. coli, and H. influenzae, as well as many Bacteroides and Klebsiella spp. Co-amoxiclav should be reserved for infections likely, or known, to be caused by amoxicillin-resistant beta-lactamase-producing strains; for CSM warning on cholestatic jaundice see under Co-amoxiclav.

A combination of ampicillin with flucoxacin (as co-fluampicil) is available to treat infections involving either streptococci or staphylococci (e.g. cellulitis).

Lyme disease Lyme disease should generally be treated by those experienced in its management. Doxycycline (p. 304), amoxicillin [unlicensed indication] or cefuroxime axetil are the antibacterials of choice for early Lyme disease or Lyme arthritis. If these antibacterials are contra-indicated, a macrolide (e.g. erythromycin) can be used for early Lyme disease. Intravenous administration of ceftriaxone, cefotaxime (p. 297), or benzylpenicillin (p. 291) is recommended for Lyme disease associated with cardiac or neurological complications. The duration of treatment is usually 2–4 weeks; Lyme arthritis may require further treatment.

Oral infections Amoxicillin or ampicillin are as effective as phenoxymethylpenicillin (section 5.1.1.1) but they are better absorbed; however, they may encourage emergence of resistant organisms. Like phenoxymethylpenicillin, amoxicillin and ampicillin are ineffective against bacteria that produce beta-lactamases. Amoxicillin may be useful for short-course oral regimens. Co-amoxiclav is active against beta-lactamase-producing bacteria that are resistant to amoxicillin. Co-amoxiclav may be used for severe dental infection with spreading cellulitis or dental infection not responding to first-line antibacterial treatment.

AMOXICILLIN

(Amoxyccillin)

Indications see under Ampicillin; oral infections (see notes above); also endocarditis treatment (Table 1, section 5.1); anthrax (section 5.1.12); adjunct in listerial meningitis (Table 1, section 5.1); Helicobacter pylori eradication (section 1.3)

Cautions see under Ampicillin; maintain adequate hydration with high doses (particularly during parenteral therapy)

Contra-indications see under Ampicillin

Side-effects see under Ampicillin

Dose

- By mouth, 250 mg every 8 hours, doubled in severe infections; CHILD up to 10 years, 125 mg every 8 hours, doubled in severe infections
- Otitis media, 1 g every 8 hours; CHILD 40 mg/kg daily in 3 divided doses (max. 3 g daily)
- Pneumonia, 0.5–1 g every 8 hours
- Anthrax (treatment and post-exposure prophylaxis—see also section 5.1.12), 500 mg every 8 hours; CHILD body-weight under 20 kg, 80 mg/kg daily in 3 divided doses, body-weight over 20 kg, adult dose
5.1.1 Penicillins

- **Short-course oral therapy**
  Dental abscess, 3 g repeated after 8 hours
  Urinary-tract infections, 3 g repeated after 10–12 hours

- **By intramuscular injection**
  500 mg every 8 hours; **CHILD**, 50–100 mg/kg daily in divided doses

- **By intravenous injection or infusion**
  500 mg every 8 hours increased to 1 g every 6 hours in severe infections; **CHILD**, 50–100 mg/kg daily in divided doses

- Listerial meningitis (in combination with another antibiotic if necessary, see Table 1, section 5.1), **by intravenous infusion**, 2 g every 4 hours for 10–14 days

- Endocarditis (in combination with another antibiotic if necessary, see Table 1, section 5.1), **by intravenous infusion**, 2 g every 6 hours, increased to 2 g every 4 hours e.g. in enterococcal endocarditis or if amoxicillin used alone

**Note** Amoxicillin doses in BNF may differ from those in product literature

### Amoxicillin (Non-proprietary)

**Capsules**
- amoxicillin (as trihydrate) 250 mg, net price 21 = £1.14; 500 mg, 21 = £1.56. Label: 9
- Brands include Amix, Amoram, Amoxident, Galenamox, Rimoxallin

**Oral suspension**
- amoxicillin (as trihydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.37; 250 mg/5 mL, 100 mL = £1.54. Label: 9
- **Note** Sugar-free versions are available and can be ordered by specifying ‘sugar-free’ on the prescription
- Brands include Amoram, Galenamox, Rimoxallin

**Sachets**
- sugar-free, amoxicillin (as trihydrate) 3 g/sachet, net price 2-sachet pack = £5.56, 14-sachet pack = £31.94. Label: 9, 13

**Injection**
- powder for reconstitution, amoxicillin (as sodium salt), net price 250-mg vial = 32p; 500-mg vial = 66p; 1-g vial = £1.16

**Dental prescribing on NHS**
- Amoxicillin Sachets may be prescribed. Amoxicillin Sachets may be prescribed as Amoxicillin Oral Powder

### Amoxicillin Capsules and Oral Suspension

**Brands include**
- Amix, Amoram, Amoxident, Galenamox, Rimoxallin

**Note** Amoxicillin doses in BNF may differ from those in product literature

### Amoxicillin (Non-proprietary)

**Capsules**
- amoxicillin 250 mg, net price 28 = £3.88; 500 mg, 28 = £19.68. Label: 9, 23
- Brands include Rimoxallin

**Oral suspension**
- amoxicillin 125 mg/5 mL when reconstituted with water, net price 100 mL = £3.38; 250 mg/5 mL, 100 mL = £6.61. Label: 9, 23
- Brands include Rimoxallin

**Injection**
- powder for reconstitution, amoxicillin (as sodium salt), net price 500-mg vial = £7.83

**Dental prescribing on NHS**
- Amoxicillin Capsules and Oral Suspension may be prescribed

### Penbritin® (Chemidex)

**Capsules**
- grey/red, ampicillin (as trihydrate) 250 mg, net price 28-cap pack = £2.10; 500 mg, 28-cap pack = £5.28. Label: 9, 23

**Syrup**
- apricot-caramel- and peppermint-flavoured, ampicillin (as trihydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £3.78; 250 mg/5 mL, 100 mL = £7.39. Label: 9, 23

**Exciptients**
- include sucrose 6 g/5 mL

**With fluocxacillin**
- See Co-fluampicil

### CO-AMOXICLAV

A mixture of amoxicillin (as the trihydrate or as the sodium salt) and clavulanic acid (as potassium clavulanate); the proportions are expressed in the form x/y where x and y are the strengths in milligrams of amoxicillin and clavulanic acid respectively

### Indications
- infections due to beta-lactamase-producing strains (where amoxicillin alone not appropriate) including respiratory-tract infections, genito-urinary and abdominal infections, cellulitis, animal bites,
severe dental infection with spreading cellulitis or dental infection not responding to first-line anti-
bacterial

**Cautions** see under Ampicillin and notes above; also caution in hepatic impairment (monitor hepatic function), pregnancy; maintain adequate hydration with high doses (particularly during parenteral ther-

**Cholestatic jaundice** CSM has advised that cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-

**Contra-indications** penicillin hypersensitivity, history of co-amoxiclav-associated or penicillin-associated jaundice or hepatic dysfunction

**Side-effects** see under Ampicillin; hepatitis, chole-

**Dose**

- **By mouth**, expressed as amoxicillin, 250 mg every 8 hours, dose doubled in severe infections; CHILD see under preparations below (under 6 years **Augmentin** ‘125/31 SF’ suspension; 6–12 years **Augmentin** ‘250/62 SF’ suspension or for short-
term treatment with twice daily dosage in CHILD 2 months–12 years **Augmentin-Duo** 400/57 suspend-

Severe dental infections (but not generally first-line, see notes above), expressed as amoxicillin, 250 mg every 8 hours for 5 days

- **By intravenous injection** over 3–4 minutes or by intravenous infusion, expressed as amoxicillin, 1 g every 8 hours increased to 1 g every 6 hours in more serious infections; INFANTS up to 3 months 25 mg/kg every 8 hours (every 12 hours in the perinatal period and in premature infants); CHILD 3 months–12 years, 25 mg/kg every 8 hours increased to 25 mg/kg every 6 hours in more serious infections Surgical prophylaxis, expressed as amoxicillin, 1 g at induction; for high risk procedures (e.g. colorectal surgery) up to 2–3 further doses of 1 g may be given every 8 hours

**Co-amoxiclav** (Non-proprietary) Tablets, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £3.04. Label: 9 Dental prescribing on NHS Co-amoxiclav 250/125 Tablets may be prescribed Tablets, co-amoxiclav 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £6.32. Label: 9 Oral suspension, co-amoxiclav 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31.25 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL = £3.07. Label: 9 Oral suspension, co-amoxiclav 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62.5 mg as potassium salt)/5 mL when reconstituted with water, net price 100 mL = £3.87. Label: 9 **Injection 500/100**, powder for reconstitution, co-

**Augmentin** (GSK) Tablets 375 mg, f/c, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt), net price 21-tab pack = £4.45. Label: 9 Tablets 625 mg, f/c, co-amoxiclav 500/125 (amoxicillin 500 mg as trihydrate, clavulanic acid 125 mg as potassium salt). Net price 21-tab pack = £8.49. Label: 9 **Dispersible tablets**, sugar-free, co-amoxiclav 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt). Net price 21-tab pack = £10.22. Label: 9, 13 **Suspension ‘125/31 SF’**, sugar-free, co-amoxiclav 125/31 (amoxicillin 125 mg as trihydrate, clavulanic acid 31 mg as potassium salt)/5 mL when reconstituted with water. Net price 100 mL (raspberry-and orange-flavoured) = £4.25. Label: 9 Excipients include aspartame 12.5 mg/5 mL (section 9.4.1) **Dose** CHILD 1–6 years (10–18 kg) 5 mL every 8 hours or INFANT and CHILD up to 6 years 0.8 mL/kg daily in 3 divided doses; in severe infections dose increased to 1.6 mL/kg daily in 3 divided doses **Suspension ‘250/62 SF’**, sugar-free, co-amoxiclav 250/62 (amoxicillin 250 mg as trihydrate, clavulanic acid 62 mg as potassium salt)/5 mL when reconstituted with water. Net price 100 mL (raspberry-and orange-flavoured) = £5.97. Label: 9 Excipients include aspartame 12.5 mg/5 mL (section 9.4.1) **Dose** CHILD 6–12 years (18–40 kg) 5 mL every 8 hours or 0.6 mL/kg/day in 3 divided doses; in severe infections dose increased to 0.8 mL/kg/day in 3 divided doses **Injection 600 mg**, powder for reconstitution, co-

**Augmentin-Duo** (GSK) Tablets 400/57, sugar-free, strawberry-flavoured, co-amoxiclav 400/57 (amoxicillin 400 mg as trihydrate, clavulanic acid 57 mg as potassium salt)/ 5/mL when reconstituted with water. Net price 35 mL = £4.38, 70 mL = £6.15. Label: 9 Excipients include aspartame 12.5 mg/5 mL (section 9.4.1) **Dose** CHILD 2 months–2 years 0.15 mL/kg twice daily, 2–6 years (13–21 kg) 2.5 mL twice daily, 7–12 years (22–40 kg) 5 mL twice daily, doubled in severe infections

**CO-FLUAMPICIL** A mixture of equal parts by mass of flucloxacillin and ampicillin

**Indications** mixed infections involving beta-lacta-
mase-producing staphylococci
5 Infections

**Side-effects**

- By mouth, co-fluampicil, 250/250 every 6 hours, dose doubled in severe infections; CHILD under 10 years half adult dose, dose doubled in severe infections.
- By intramuscular or slow intravenous injection or by intravenous infusion, co-fluampicil 250/250 every 6 hours, dose doubled in severe infections; CHILD under 2 years quarter adult dose, 2–10 years half adult dose, dose doubled in severe infections.

**Co-fluampicil (Non-proprietary)**

- Capsules, co-fluampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as trihydrate), net price 20-cap pack = £14.43. Label: 9, 22.
- Capsules, black/turquoise, co-fluampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as trihydrate), net price 20-cap pack = £4.00. Label: 9, 22.
- Syrup, co-fluampicil 125/125 (flucloxacillin 125 mg as magnesium salt, ampicillin 125 mg as trihydrate)/5 mL when reconstituted with water, net price 100 mL = £4.99. Label: 9, 22.

**Magnapen® (CP)**

- Capsules, 3.14 g/5 mL.
- Injection 500 mg, powder for reconstitution, co-fluampicil 250/250 (flucloxacillin 250 mg as sodium salt, ampicillin 250 mg as sodium salt), net price per vial = £1.33.

**Electrolytes**

- Na 1.3 mmol/vial.

---

**5.1.1 Penicillins**

**Contra-indications**

See under Ampicillin and Flucloxacillin.

**Dose**

- By intramuscular injection or slow intravenous injection or by intravenous infusion, ampicillin and flucloxacillin.

**Indications**

See preparations.

---

**5.1.4 Antipseudomonal penicillins**

The carboxypenicillin, ticarcillin, is principally indicated for serious infections caused by *Pseudomonas aeruginosa* although it also has activity against certain other Gram-negative bacilli including *Proteus* spp. and *Bacteroides fragilis*.

Ticarcillin is now available only in combination with clavulanic acid (section 5.1.1.3); the combination (*Timentin®*) is active against beta-lactamase-producing bacteria resistant to ticarcillin.

*Tazocin®* contains the ureidopenicillin *piperacillin* with the beta-lactamase inhibitor tazobactam. Piperacillin is more active than ticarcillin against *P. aeruginosa*. The spectrum of activity of *Tazocin®* is comparable to that of the carbapenems, imipenem and meropenem (section 5.1.2).

For pseudomonas septicaemias (especially in neutropenia or endocarditis) these antipseudomonal penicillins should be given with an aminoglycoside (e.g. gentamicin or endocarditis), these antipseudomonal penicillins should be given with an aminoglycoside (e.g. gentamicin or tobramycin) since they have a synergistic effect.

**Contra-indications**

See under Benzylpenicillin (section 5.1.1.1).

**Side-effects**

See under Benzylpenicillin (section 5.1.1.1); also nausea, vomiting, diarrhoea; *less commonly* stomatitis, dyspepsia, constipation, jaundice, hypotension, headache, insomnia, and injection-site reactions; *rarely* abdominal pain, hepatitis, oedema, fatigue, and eosinophilia; *very rarely* hypoglycaemia, hypokalaemia, pancytopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis.

**Dose**

- See preparations.

---

**5.1.5 Mecillinams**

Pivmecillinam has significant activity against many Gram-negative bacteria including *Escherichia coli*, klebsiella, enterobacter, and salmonellae. It is not active.
against *Pseudomonas aeruginosa* or enterococci. Pivmecillinam is hydrolysed to mecillinam, which is the active drug.

**PIVMECILLINAM HYDROCHLORIDE**

**Indications** see under Dose below

**Cautions** see under Benzylpenicillin (section 5.1.1.1); also liver and renal function tests required in long-term use; avoid in acute porphyria (section 9.8.2); pregnancy; **interactions**: Appendix 1 (penicillins)

**Contra-indications** see under Benzylpenicillin (section 5.1.1.1); also carotid insufficiency, oesophageal strictures, gastro-intestinal obstruction, infants under 3 months

**Side-effects** see under Benzylpenicillin (section 5.1.1.1); nausea, vomiting, dyspepsia; also reduced serum and total body carminite (especially with long-term or repeated use)

**Dose**

- Acute uncomplicated cystitis, **ADULT** and **CHILD** over 40 kg, initially 400 mg then 200 mg every 8 hours for 3 days
- Chronic or recurrent bacteriuria, **ADULT** and **CHILD** over 40 kg, 400 mg every 6–8 hours
- Urinary tract infections, **CHILD** under 40 kg, 20–40 mg/kg daily in 3–4 divided doses
- Salmonellosis, not recommended therefore no dose stated

**Counselling** Tablets should be swallowed whole with plenty of fluid during meals while sitting or standing

**Selexid®** (LEO) Tablets, I/c, pivmecillinam hydrochloride 200 mg, net price 10-pack tab £4.50. Label 9, 21, 27, counselling, posture (see Dose above)

### 5.1.2 Cephalosporins, carbapenems, and other beta-lactams

Antibiotics in this section include the cephalosporins, such as cefotaxime, ceftazidime, cefuroxime, cefalexin and cefradine, the monobactam, aztreonam, and the carbapenems, imipenem (a thienamycin derivative), meropenem, doripenem, and ertapenem.

#### 5.1.2.1 Cephalosporins

The cephalosporins are broad-spectrum antibiotics which are used for the treatment of septicaemia, pneumonia, meningitis, biliary-tract infections, peritonitis, and urinary-tract infections. The pharmacology of the cephalosporins is similar to that of the penicillins, excretion being principally renal. Cephalosporins penetrate the cerebrospinal fluid poorly unless the meninges are inflamed; cefotaxime is a suitable cephalosporin for infections of the CNS (e.g. meningitis).

The principal side-effect of the cephalosporins is hypersensitivity and about 0.5–6.5% of penicillin-sensitive patients will also be allergic to the cephalosporins. Patients with a history of immediate hypersensitivity to penicillin should not receive a cephalosporin. If a cephalosporin is essential in these patients because a suitable alternative antibacterial is not available, then cefixime, cefotaxime, ceftazidime, ceftriaxone, or cefuroxime can be used with caution; cefaclor, cefadroxil, cefalexin, and cefradine should be avoided.

Antibiotic-associated colitis may occur with the use of broad-spectrum cephalosporins.

Cefradine (cefdihidine) has generally been replaced by the newer cephalosporins.

Cefuroxime is a 'second generation' cephalosporin that is less susceptible than the earlier cephalosporins to inactivation by beta-lactamases. It is, therefore, active against certain bacteria which are resistant to the other drugs and has greater activity against *Haemophilus influenzae* and *Neisseria gonorrhoeae*.

Cefotaxime, ceftazidime and ceftriaxone are 'third generation' cephalosporins with greater activity than the 'second generation' cephalosporins against certain Gram-negative bacteria. However, they are less active than cefuroxime against Gram-positive bacteria, most notably *Staphylococcus aureus*. Their broad antibacterial spectrum may encourage superinfection with resistant bacteria or fungi.

Cefadroxil has good activity against pseudomonas. It is also active against other Gram-negative bacteria.

Ceftriaxone has a longer half-life and therefore needs to be given only once daily. Indications include serious infections such as septicemia, pneumonia, and meningitis. The calcium salt of ceftriaxone forms a precipitate in the gall bladder which may rarely cause symptoms but these usually resolve when the antibiotic is stopped.

**Orally active cephalosporins** The orally active 'first generation' cephalosporins, cefalexin (cephalexin), cefadroxil, and cefuroxime have a similar antimicrobial spectrum. They are useful for urinary-tract infections which do not respond to other drugs or which occur in pregnancy, respiratory-tract infections, otitis media, sinusitis, and skin and soft-tissue infections. Cefaclor has good activity against *H. influenzae*, but it is associated with protracted skin reactions especially in children. Cefadroxil has a long duration of action and can be given twice daily; it has poor activity against *H. influenzae*. Cefuroxime axetil, an ester of the 'second generation' cephalosporin cefuroxime, has the same antibacterial spectrum as the parent compound; it is poorly absorbed.

Cefixime has a longer duration of action than the other cephalosporins that are active by mouth. It is only licensed for acute infections.

Cefpodoxime proxetil is more active than the other oral cephalosporins against respiratory bacterial pathogens and it is licensed for upper and lower respiratory-tract infections.

For treatment of Lyme disease, see section 5.1.1.3.

**Oral infections** The cephalosporins offer little advantage over the penicillins in dental infections, often being less active against anaerobes. Infections due to oral streptococci (often termed viridans streptococci) which become resistant to penicillin are usually also resistant to cephalosporins. This is of importance in the case of patients who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin and cefradine have been used in the treatment of oral infections.
**Indications** infections due to sensitive Gram-positive and Gram-negative bacteria, but see notes above

**Cautions** sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also notes above and p. 290); renal impairment (Appendix 3); pregnancy and breast-feeding (but appropriate to use); false positive urinary glucose (if tested for reducing substances) and false positive Coombs’ test; **interactions**: Appendix 1 (cephalosporins)

**Contra-indications** cephalosporin hypersensitivity

**Side-effects** diarrhoea and rarely antibiotic-associated colitis (CSM has warned both more likely with higher doses), nausea and vomiting, abdominal discomfort, headache; allergic reactions including rashes, pruritus, urticaria, serum sickness-like reactions with rashes, fever and arthralgia, and anaphylaxis; Stevens-Johnson syndrome, toxic epidermal necrolysis reported; disturbances in liver enzymes, transient hepatitis and cholestatic jaundice; other side-effects reported include eosinophilia and blood dyscrasias (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hyperpnoea, and dizziness

**Dose**
- 250 mg every 8 hours, doubled for severe infections; max. 4 g daily; **CHILD** over 1 month, 20 mg/kg daily in 3 divided doses, doubled for severe infections, max. 1 g/day; or 1 month–1 year, 62.5 mg every 8 hours; 1–5 years, 125 mg; over 5 years, 250 mg; doses doubled for severe infections

**Cefaclor** (Non-proprietary) (Flynn)

- **Capsules**, cefaclor (as monohydrate) 250 mg, net price 21-cap pack = £4.52; 500 mg, 50-cap pack = £23.88. **Label**: 9

- **Brands include** Keftid

- **Suspension**, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 60 mL = £1.63; 250 mg/5 mL, 60 mL = £3.24; 500 mg/5 mL, 60 mL = £4.85. **Label**: 9

**Distaclovor** (Flynn) (Non-proprietary)

- **Capsules**, cefadroxil (as monohydrate) 500 mg (violet/grey), net price 20 = £17.33. **Label**: 9

- **Suspension**, both pink, cefadroxil (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £8.33; 250 mg/5 mL, 100 mL = £9.33. **Label**: 9

**Note** Sugar-free versions are available and can be ordered by specifying ‘sugar-free’ on the prescription **Brands include** Keftid

**Distaclovor MR** (Flynn) (Non-proprietary)

- **Tablets**, m/r, both blue, cefadroxil (as monohydrate) 375 mg. Net price 14-tab pack = £6.93. **Label**: 9, 21, 25

**Dose**
- 375 mg every 12 hours with food, dose doubled for pneumonia

Lower urinary-tract infections, 375 mg every 12 hours with food

**CEFADROXIL**

**Indications** see under Cefaclor; see also notes above

**Cautions** see under Cefaclor

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Dose**
- Patients over 40 kg, 0.5–1 g twice daily; skin, soft tissue, and simple urinary-tract infections, 1 g daily; **CHILD** under 1 year, 25 mg/kg daily in divided doses; 1–6 years, 250 mg twice daily; over 6 years, 500 mg twice daily

**Cefadroxil** (Non-proprietary) (Non-proprietary)

- **Capsules**, cefadroxil (as monohydrate) 500 mg, net price 20-cap pack = £5.25. **Label**: 9

**Baxan** (Bristol-Myers Squibb) (Galen)

- **Capsules**, cefadroxil (as monohydrate) 500 mg, net price 20-cap pack = £5.64. **Label**: 9

**Suspension**, cefadroxil (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 60 mL = £1.63; 250 mg/5 mL, 60 mL = £3.24; 500 mg/5 mL, 60 mL = £4.85. **Label**: 9

**CEFALEXIN** (Cefalexin)

**Indications** see under Cefaclor

**Cautions** see under Cefaclor

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Dose**
- 250 mg every 6 hours or 500 mg every 8–12 hours increased to 1–1.5 g every 6–8 hours for severe infections; **CHILD** 25 mg/kg daily in divided doses, doubled for severe infections, max. 100 mg/kg daily; or under 1 year 125 mg every 12 hours, 1–5 years 125 mg every 8 hours, 5–12 years 250 mg every 8 hours

**Prophylaxis of recurrent urinary-tract infection, ADULT 125 mg at night**

**Cefalexin** (Non-proprietary) (Wyn)

- **Capsules**, cefalexin 250 mg, net price 28-cap pack = £2.07; 500 mg, 21-cap pack = £2.61. **Label**: 9

**Tablets**, cefalexin 250 mg, net price 28-tab pack = £2.27; 500 mg, 21-tab pack = £2.84. **Label**: 9

**Oral suspension**, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.83; 250 mg/5 mL, 100 mL = £2.27. **Label**: 9

**Dental prescribing on NHS** Cefalexin Capsules, Tablets, and Oral Suspension may be prescribed

**Ceporex** (Galen) (Non-proprietary)

- **Capsules**, both caramel/grey, cefalexin 250 mg, net price 28-cap pack = £4.02; 500 mg, 28-cap pack = £7.85. **Label**: 9

**Tablets**, all pink, f/c, cefalexin 250 mg, net price 28-tab pack = £4.02; 500 mg, 28-tab pack = £7.85. **Label**: 9

**Syrup**, all orange, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £1.43; 250 mg/5 mL, 100 mL = £2.87; 500 mg/5 mL, 100 mL = £5.57. **Label**: 9

**Keflex** (Flynn) (Non-proprietary)

- **Capsules**, cefalexin 250 mg (green/white), net price 28-cap pack = £1.76; 500 mg (pale green/dark green), 21-cap pack = £2.66. **Label**: 9

**Tablets**, both peach, cefalexin 250 mg, net price 28-tab pack = £2.09; 500 mg (scored), 21-tab pack = £2.47. **Label**: 9
Suspension, cefalexin for reconstitution with water, 125 mg/5 mL, net price 100 mL = £8.89; 250 mg/5 mL, 100 mL = £11.51. Label: 9

### CEFIXIME

**Indications** see under Cefaclor (acute infections only); gonorrhoea; surgical prophylaxis

**Side-effects** see under Cefaclor

**Contra-indications** see under Cefaclor

**Dose**
- ADULT and CHILD over 10 years, 200–400 mg daily in 1–2 divided doses; CHILD over 6 months 8 mg/kg daily in 1–2 divided doses or 6 months–1 year 75 mg daily; 1–4 years 100 mg daily; 5–10 years 200 mg daily
- Gonorrhoea [unlicensed indication], 400 mg as a single dose

**Suprax®** (Rhône-Poulenc Rorer) (FMD)

Tablets, 1, 2, scored, cefixime 200 mg. Net price 7-tab pack = £15.23. Label: 9

Paediatric oral suspension, cefixime 100 mg/5 mL, when reconstituted with water, net price 50 mL (with double-ended spoon for measuring 3.75 mL or 5 mL since dilution not recommended) = £10.53, 100 mL = £18.91. Label: 9

### CEFOTAXIME

**Indications** see under Cefaclor; gonorrhoea; surgical prophylaxis: Haemophilus epiglottitis and meningitis (Table 1, section 5.1); see also notes above

**Cautions** see under Cefaclor

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor; rarely arrhythmias following rapid injection reported

**Dose**
- **By intramuscular** or **intravenous injection** or **by intravenous infusion**, 1 g every 12 hours increased in severe infections (e.g. meningitis) to 8 g daily in 4 divided doses; higher doses (up to 12 g daily in 3–4 divided doses) may be required; NEONATE 50 mg/kg daily in 2–4 divided doses increased to 150–200 mg/kg daily in severe infections; CHILD 100–150 mg/kg daily in 2–4 divided doses increased up to 200 mg/kg daily in very severe infections
- Gonorrhoea, 500 mg as a single dose

**Important** If bacterial meningitis and especially if meningococcal disease is suspected the patient should be transferred urgently to hospital. If benzylpenicillin cannot be given (e.g. because of an allergy), a single dose of cefotaxime may be given (if available) before urgent transfer to hospital. Suitable doses of cefotaxime by intravenous injection (or by intramuscular injection) are ADULT and CHILD over 12 years 1 g; CHILD under 12 years 50 mg/kg; chloramphenicol (section 5.1.7) may be used if there is a history of anaphylaxis to penicillins or cephalosporins

**Cefotaxime (Non-proprietary) (FMD)**

**Injection**, powder for reconstitution, cefotaxime (as sodium salt), net price 500-mg vial = £2.14; 1-g vial = £4.31; 2-g vial = £8.57

### CEPFodoxime

**Indications** see under Dose

**Cautions** see under Cefaclor

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Dose**
- Upper respiratory-tract infections (but in pharyngitis and tonsillitis reserved for infections which are recurrent, chronic, or resistant to other antibacterials), 100 mg twice daily (200 mg twice daily in sinusitis); CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours
- Lower respiratory-tract infections (including bronchitis and pneumonia), 100–200 mg twice daily; CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours
- Skin and soft-tissue infections, 200 mg twice daily; CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours
- Uncomplicated urinary-tract infections, 100 mg twice daily (200 mg twice daily in uncomplicated upper urinary-tract infections); CHILD 15 days–6 months 4 mg/kg every 12 hours, 6 months–2 years 40 mg every 12 hours, 3–8 years 80 mg every 12 hours, over 9 years 100 mg every 12 hours
- Uncomplicated gonorrhoea, 200 mg as a single dose

**Orelox®** (Hoechst Marion Roussel) (FMD)

Tablets, 1, 2, cefpodoxime 100 mg (as proxetil), net price 10-tab pack = £10.18. Label: 5, 9, 21

Oral suspension, cefpodoxime (as proxetil) for reconstitution with water, 40 mg/5 mL, net price 100 mL = £11.97. Label: 5, 9, 21

Excipients include aspartame (section 9.4.1)

### CEFRADINE

(Cephradine)

**Indications** see under Cefaclor; surgical prophylaxis

**Cautions** see under Cefaclor

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Dose**
- By mouth, 250–500 mg every 6 hours or 0.5–1 g every 12 hours; up to 1 g every 6 hours in severe infections; CHILD, 25–50 mg/kg daily in 2–4 divided doses
- By deep intramuscular injection or by intravenous injection over 3–5 minutes or by intravenous infusion, 0.5–1 g every 6 hours, increased to 8 g daily in severe infections; CHILD 50–100 mg/kg daily in 4 divided doses
- Surgical prophylaxis, by deep intramuscular injection or by intravenous injection over 3–5 minutes, 1–2 g at induction

**Cefradine (Non-proprietary) (FMD)**

Capsules, cefradine 250 mg, net price 20-cap pack = £8.97; 500 mg, 20-cap pack = £8.49. Label: 9

Brands include Nicef

Dental prescribing on NHS Cefradine Capsules may be prescribed

**Velosef®** (Squibb) (FMD)

Capsules, cefradine 250 mg (orange/blue), net price 20-cap pack = £5.42; 500 mg (blue), 20-cap pack = £11.22. Label: 9
**CEFADROME**

**Indications** see under Cefaclor; see also notes above

**Cautions** see under Cefaclor and notes above; surgical prophylaxis; prophylaxis of meningococcal disease in children

**Side-effects** see under Cefaclor; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobilised) or in gall bladder—consider discontinuation if symptomatic; rarely prolongation of prothrombin time, pancreatitis

**Dose**
- By deep intramuscular injection, or by intravenous injection over at least 2–4 minutes, or by intravenous infusion, 1 g daily; 2–4 g daily in severe infections; intramuscular doses over 1 g divided between more than one site; single intravenous doses above 1 g by intravenous infusion only
- Neonate by intravenous infusion over 60 minutes, 20–50 mg/kg daily (max. 50 mg/kg daily) infant and child under 50 kg, by deep intramuscular injection, or by intravenous injection over 2–4 minutes, or by intravenous infusion, 20–50 mg/kg daily; up to 80 mg/kg daily in severe infections; doses of 50 mg/kg and over by intravenous infusion only; 50 kg and over, adult dose
- Endocarditis caused by haemophilus, actinobacillus, carbiodermium, eikenella, and kingella species ("HACEK organisms") (in combination with another antibacterial, see Table 1, section 5.1; [unlicensed indication]), by intravenous infusion, 2–4 g daily
- Early syphilis [unlicensed indication], by deep intramuscular injection, 500 mg daily for 10 days
- Uncomplicated gonorrhoea, by deep intramuscular injection, 250 mg as a single dose
- Surgical prophylaxis, by deep intramuscular injection or by intravenous injection over at least 2–4 minutes, 1 g at induction; colorectal surgery, by deep intramuscular injection or by intravenous infusion, 2 g at induction; intramuscular doses over 1 g divided between more than one site

**CEFTRIAZONE**

**Indications** see under Cefaclor and notes above; surgical prophylaxis; prophylaxis of meningococcal meningitis [unlicensed indication] (Table 2, section 5.1)

**Cautions** see under Cefaclor; severe renal impairment (Appendix 3); hepatic impairment if accompanied by renal impairment (Appendix 2); premature neonates; may displace bilirubin from serum albumin, administer over 60 minutes in neonates (see also Contra-indications); treatment longer than 14 days, renal failure, dehydration—risk of ceftriaxone precipitation in gall bladder

**Contra-indications** see under Cefaclor; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding; concomitant treatment with calcium in children—risk of precipitation in urine and lungs of neonates (and possibly infants and older children)

**Side-effects** see under Cefaclor; calcium ceftriaxone precipitates in urine (particularly in very young, dehydrated or those who are immobilised) or in gall bladder—consider discontinuation if symptomatic; rarely prolongation of prothrombin time, pancreatitis

**Dose**
- By mouth (as cefuroxime axetil), 250 mg twice daily in most infections including mild to moderate lower respiratory tract infections (e.g. bronchitis); doubled for more severe lower respiratory tract infections or if pneumonia suspected
- Urinary tract infection, 125 mg twice daily, doubled in pyelonephritis
- Gonorrhoea, 1 g as a single dose
- Child over 3 months, 125 mg twice daily, if necessary doubled in child over 2 years with otitis media
- Lyme disease, adult and child over 12 years, 500 mg twice daily for 20 days
The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; imipenem, meropenem, and doripenem have good activity against Pseudomonas aeruginosa. The carbapenems are not active against meticillin-resistant Staphylococcus aureus and Enterococcus faecium.

Imipenem is partially inactivated in the kidney by enzymatic activity and is therefore administered in combination with cilastatin, a specific enzyme inhibitor, which blocks its renal metabolism. Meropenem, doripenem, and ertapenem are stable to the renal enzyme which inactivates imipenem and therefore can be given without cilastatin.

Side-effects of imipenem with cilastatin are similar to those of other beta-lactam antibiotics; neurotoxicity has been observed at very high dosage, in renal failure, or in patients with CNS disease. Ertapenem has been associated with seizures uncommonly. Meropenem has less seizure-inducing potential and can be used to treat central nervous system infection.

**DORIPENEM**

**Indications**
- hospital-acquired pneumonia; complicated intra-abdominal infections; complicated urinary-tract infections

**Cautions**
- sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 290); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (doripenem)

**Side-effects**
- nausea, diarrhoea; headache; phlebitis, pruritus, rash; less commonly antibiotic-associated colitis; also reported, neutropenia

**Dose**
- By intravenous infusion, ADULT over 18 years, 500 mg every 8 hours; max. duration of treatment 14 days

**Doribax®** (Janssen-Cilag) ►

**Intravenous infusion**, powder for reconstitution, doripenem (as monohydrate), net price 500-mg vial = £15.11

**ERTAPENEM**

**Indications**
- abdominal infections; acute gynaecological infections; community-acquired pneumonia; diabetic foot infections of the skin and soft-tissue; prophylaxis for colorectal surgery

**Cautions**
- sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 290); elderly, renal impairment (Appendix 3); CNS disorders—risk of seizures; pregnancy (Appendix 4); CNS disorders—risk of seizures; pregnancy (Appendix 4); interactions: Appendix 1 (ertapenem)

**Contra-indications**
- breast-feeding (Appendix 5)

**Side-effects**
- diarrhoea, nausea, vomiting, headache, injection-site reactions, rash, pruritus, raised platelet count; less commonly dry mouth, taste disturbances, dyspepsia, abdominal pain, anorexia, constipation, melena, antibiotic-associated colitis, bradycardia, hypotension, chest pain, oedema, pharyngeal discomfort, dyspnoea, dizziness, sleep disturbances, confusion, asthenia, seizures, vomiting, raised glucose, peptechiae; rarely dysphagia, cholestatics, liver disorder (including jaundice), arrhythmia, increase in blood pressure, syncope, nasal congestion, cough, wheezing, anxiety, depression, agitation, tremor, pelvic peritonitis, renal impairment, muscle cramp, scleral disorder, blood disorders (including neutropenia, thrombocytopenia, haemorrhage), hypoglycaemia, electrolyte disturbances; very rarely hallucinations
5.1.2 Cephalosporins, carbapenems, and other beta-lactams

**Dose**
- **By intravenous infusion**:
  - **ADULT and ADOLESCENT** over 13 years, 1 g once daily; **CHILD** 3 months–13 years, 15 mg/kg every 12 hours (max. 1 g daily)
  - Surgical prophylaxis, colostral surgery, **ADULT** over 18 years, 1 g completed within 1 hour before surgery

**Invanz** *(MSD)* *(Novartis)*
- **Intravenous infusion**, powder for reconstitution, ertapenem (as sodium salt), net price 1-g vial = £31.65

**IMIPENEM WITH CILASTATIN**

**Indications**
- aerobic and anaerobic Gram-positive and Gram-negative infections; surgical prophylaxis; hospital-acquired septicaemia (Table 1, section 5.1); not indicated for CNS infections

**Cautions**
- sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 290); renal impairment (Appendix 3); CNS disorders (e.g. epilepsy); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (imipenem with cilastatin)

**Side-effects**
- nausea, vomiting, diarrhoea (associated colitis reported), abdominal pain, disturbances in liver function tests; headache; thrombophlebitis; erythema, pain and induration, and thrombophlebitis

**Dose**
- **By intravenous infusion**, in terms of imipenem, 1–2 g daily (in 3–4 divided doses); less sensitive organisms, up to 50 mg/kg daily (max. 4 g daily) in 3–4 divided doses; **CHILD** 3 months and older, 60 mg/kg (up to max. of 2 g) daily in 4 divided doses; over 40 kg, adult dose
  - Surgical prophylaxis, 1 g at induction repeated after 3 hours, supplemented in high risk (e.g. colorectal) surgery by doses of 500 mg 8 and 16 hours after induction

**Primaxin** *(MSD)* *(Novartis)*
- **Intravenous infusion**, powder for reconstitution, imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg, net price per vial = £12.00

**MEROPEM**

**Indications**
- aerobic and anaerobic Gram-positive and Gram-negative infections

**Cautions**
- sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 290); hepatic impairment (monitor liver function; Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (meropenem)

**Side-effects**
- nausea, vomiting, diarrhoea (antibiotic-associated colitis reported), abdominal pain, disturbances in liver function tests; headache; thrombocytopenia, positive Coombs’ test; rash, pruritus, injection-site reactions; less commonly eosinophilia, thrombocytopenia; rarely convulsions; also reported paraesthesia, leucopenia, haemolytic anaemia, reduction in partial thromboplastin time, Stevens-Johnson syndrome, and toxic epidermal necrolysis

**Dose**
- **By intravenous injection** over 5 minutes or by intravenous infusion, 500 mg every 8 hours, dose doubled in hospital-acquired pneumonia, peritonitis, septicaemia and infections in neutropenic patients; **CHILD** 3 months–12 years [not licensed for injection in neutropenia] 10–20 mg/kg every 8 hours, over 50 kg body weight adult dose
  - Meningitis, 2 g every 8 hours; **CHILD** 3 months–12 years 40 mg/kg every 8 hours, over 50 kg body weight adult dose
  - Exacerbations of chronic lower respiratory-tract infection in cystic fibrosis, up to 2 g every 8 hours; **CHILD** 4–18 years 25–40 mg/kg every 8 hours

**Meronem** *(AstraZeneca)* *(Novartis)*
- **Injection**, powder for reconstitution, meropenem (as trihydrate), net price 500-mg vial = £8.60; 1-g vial = £17.19

**AZTREONAM**

**Other beta-lactam antibiotics**

**Aztreonam** is a monocyclic beta-lactam (‘monobactam’) antibiotic with an antibacterial spectrum limited to Gram-negative aerobic bacteria including *Pseudomonas aeruginosa*, *Neisseria meningitidis*, and *Haemophilus influenzae*; it should not be used alone for ‘blind’ treatment since it is not active against Gram-positive organisms. Aztreonam is also effective against *Neisseria gonorrhoeae* (but not against concurrent chlamydial infection). Side-effects are similar to those of the other beta-lactams although aztreonam may be less likely to cause hypersensitivity in penicillin-sensitive patients.

**AZTREONAM**

**Indications**
- Gram-negative infections including *Pseudomonas aeruginosa*, *Haemophilus influenzae*, and *Neisseria meningitidis*

**Cautions**
- hypersensitivity to beta-lactam antibiotics; hepatic impairment; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (aztreonam)

**Contra-indications**
- aztreonam hypersensitivity; pregnancy (Appendix 4)

**Side-effects**
- nausea, vomiting, diarrhoea, abdominal cramps; mouth ulcers, altered taste; jaundice and hepatitis; flushing; hypersensitivity reactions; blood disorders (including thrombocytopenia and neutropenia); rashes, injection-site reactions; rarely hypotension, seizures, asthenia, confusion, dizziness, headache, halitosis, and breast tenderness; very rarely antibiotic-associated colitis, gastro-intestinal bleeding, and toxic epidermal necrolysis

**Dose**
- **By deep intramuscular injection** or by intravenous injection over 3–5 minutes or by intravenous infusion, 1 g every 8 hours or 2 g every 12 hours; 2 g every 6–8 hours for severe infections (including systemic *Pseudomonas aeruginosa* and lung infec-
sections in cystic fibrosis); single doses over 1 g intravenously route only
Urinary-tract infections, 0.5–1 g every 8–12 hours
- CHILD over 1 week, by intravenous injection or infusion, 30 mg/kg every 6–8 hours increased in severe infections for child of 2 years or older to 50 mg/kg every 6–8 hours; max. 8 g daily
- Gonorrhoea, cystitis, by intramuscular injection, 1 g as a single dose

Azactam® (Squibb)® Injection, powder for reconstitution, aztreonam. Net price 500-mg vial = £5.00; 1-g vial = £9.98; 2-g vial = £19.98

5.13 Tetracyclines

The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. They remain, however, the treatment of choice for infections caused by chlamydia (trachoma, psittacosis, salpingitis, urethritis, and lymphogranuloma venereum), rickettsia (including Q-fever, brucella (doxycycline with either streptomycin or rifampicin), and the spirochaete, Borrelia burgdorferi (Lyme disease—see section 5.1.1.3). They are also used in respiratory and genitai mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic bronchitis (because of their activity against Haemophilus influenzae), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin).

For the role of tetracyclines in the management of meticillin-resistant Staphylococcus aureus (MRSA) infection, see p. 292.

Microbiologically, there is little to choose between the various tetracyclines, the only exception being minocycline which has a broader spectrum; it is active against Neisseria meningitidis and has been used for meningococcal prophylaxis but is no longer recommended because of side-effects including dizziness and vertigo (see section 5.1, table 2 for current recommendations). Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation.

Oral infections In adults, tetracyclines can be effective against oral anaerobes but the development of resistance (especially by oral streptococci) has reduced their usefulness for the treatment of acute oral infections; they may still have a role in the treatment of destructive (refractory) forms of periodontal disease. Doxycycline has a longer duration of action than tetracycline or oxytetracycline and need only be given once daily; it is reported to be more active against anaerobes than some other tetracyclines.

For the use of doxycycline in the treatment of recurrent aphthous ulceration, oral herpes, or as an adjunct to gingival scaling and root planing for periodontitis, see section 12.3.1 and section 12.3.2.

Cautions Tetracyclines should be used with caution in patients with hepatic impairment (Appendix 2) or those receiving potentially hepatotoxic drugs. Tetracyclines may increase muscle weakness in patients with myasthenia gravis, and exacerbate systemic lupus erythematosus. Antacids, and aluminium, calcium, iron, magnesium and zinc salts decrease the absorption of tetracyclines; milk also reduces the absorption of demeclocycline, oxytetracycline, and tetracycline. Other interactions: Appendix 1 (tetracyclines).

Contra-indications Depression of tetracyclines in growing bone and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia, and they should not be given to children under 12 years, or to pregnant (Appendix 4) or breast-feeding women (Appendix 5). However, doxycycline may be used in children for treatment and post-exposure prophylaxis of anthrax when an alternative antibacterial cannot be given [unlicensed indication]. With the exception of doxycycline and minocycline, the tetracyclines may exacerbate renal failure and should not be given to patients with kidney disease (Appendix 3). Tetracyclines should not be given to patients with acute porphyria (section 9.8.2)

Side-effects Side-effects of the tetracyclines include nausea, vomiting, diarrhoea (antibiotic-associated colitis reported occasionally), dysphagia, and oesophageal irritation. Other rare side-effects include hepatotoxicity, pancreatitis, blood disorders, photosensitivity (particularly with demeclocycline), and hypersensitivity reactions (including rash, exfoliative dermatitis, Stevens-Johnson syndrome, urticaria, angioedema, anaphylaxis, pericarditis). Headache and visual disturbances may indicate benign intracranial hypertension (discontinue treatment); bulging fontanelles have been reported in infants.

Tetracycline

Indications see notes above; acne vulgaris, rosacea (section 13.6)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; also acute renal failure, skin discoloration

Dose
- 250 mg every 6 hours, increased in severe infections to 500 mg every 6–8 hours
- Acne, see section 13.6.2
- Non-gonococcal urethritis, 500 mg every 6 hours for 7–14 days (21 days if failure or relapse after first course)

Counselling Tablets should be swallowed whole with plenty of fluid while sitting or standing

Tetracycline (Non-proprietary)® Tablets, coated, tetracycline hydrochloride 250 mg, net price 28-tab pack = £8.85. Label: 7, 9, 23, counselling, posture

Dental prescribing on NHS Tetracycline Tablets may be prescribed

DEMECLOCYCLINE HYDROCHLORIDE

Indications see notes above; also inappropriate secretion of antidiuretic hormone, section 6.5.2

Cautions see notes above, but photosensitivity more common (avoid exposure to sunlight or sun lamps)

Contra-indications see notes above
Side-effects see notes above; also reversible nephrogenic diabetes insipidus, acute renal failure

Dose
- 150 mg every 6 hours or 300 mg every 12 hours

Ledermycin® (Goldshield) [PH]
Capsules, red, demeclocycline hydrochloride 150 mg, net price 28-cap pack = £13.73. Label: 7, 9, 11, 23

DOXYCYCLINE

Indications see notes above; chronic prostatitis; sinusitis, syphilis, pelvic inflammatory disease (Table 1, section 5.1); treatment and prophylaxis of anthrax [unlicensed indication]; malaria treatment and prophylaxis (section 5.4.1); recurrent aphthous ulceration, adjunct to gingival scaling and root planing for periodontitis (section 12.3.1); oral herpes simplex (section 12.3.2); rosacea [unlicensed indication], acne vulgaris (section 13.6)

Cautions see notes above, but may be used in renal impairment; alcohol dependence; photosensitivity reported (avoid exposure to sunlight or sun lamps)

Contra-indications see notes above

Side-effects see notes above; also anorexia, flushing, and tinnitus

Dose
- 200 mg on first day, then 100 mg daily; severe infections (including refractory urinary-tract infections), 200 mg daily
- Early syphilis, 100 mg twice daily for 14 days; late latent syphilis, 100 mg twice daily for 28 days; neutrophils, 200 mg twice daily for 28 days
- Uncomplicated genital chlamydia, non-gonococcal urethritis, 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease, see also Table 1, section 5.1)
- Anthrax (treatment or post-exposure prophylaxis; see also section 5.1.12), 100 mg twice daily; CHILD (only if alternative antibacterial cannot be given) [unlicensed dose] 5 mg/kg daily in 2 divided doses (max. 200 mg daily)

Counselling Capsules should be swallowed whole with plenty of fluid during meals while sitting or standing

Note Doxycycline doses in BNF may differ from those in product literature

Doxycycline (Non-proprietary) [PH]
Capsules, doxycycline (as hylate) 50 mg, net price 28-cap pack = £1.78, 100 mg, 8-cap pack = £1.15. Label: 6, 9, 11, 27, counselling, posture

Brands include Doylax

Dental prescribing on NHS Doxycycline Capsules 100 mg may be prescribed

Vibramycin® (Pfizer) [PH]
Capsules, doxycycline (as hylate) 50 mg (green/ivory), net price 28-cap pack = £7.74. Label: 6, 9, 11, 27, counselling, posture

Vibramycin-D® (Pfizer) [PH]
Dispersible tablets, yellow, scored, doxycycline 100 mg, net price 8-tab pack = £4.91. Label: 6, 9, 11, 13

LYMECYCLINE

Indications see notes above

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose
- 408 mg every 12 hours, increased to 1.224–1.632 g daily in severe infections
- Acne, 408 mg daily for at least 8 weeks

Tetralysal 300® (Galderma) [PH]
Capsules, red/yellow, lymecycline 408 mg (= tetracycline 300 mg), net price 28-cap pack = £7.16, 56-cap pack = £14.26. Label: 6, 9

MINOCYCLINE

Indications see notes above; meningococcal carrier state; acne vulgaris (section 13.6.2)

Cautions see notes above, but may be used in renal impairment; if treatment continued for longer than 6 months, monitor every 3 months for hepatotoxicity, pigmentation and for systemic lupus erythematosus—discontinue if these develop or if pre-existing systemic lupus erythematosus worsens

Contra-indications see notes above

Side-effects see notes above; also dizziness and vertigo (more common in women); rarely anorexia, tinnitus, impaired hearing, hyperaesthesia, paraesthesia, acute renal failure, pigmentation (sometimes irreversible), and alopecia; very rarely systemic lupus erythematosus, discoloration of conjunctiva, tears, and sweat

Dose
- 100 mg twice daily
- Acne, see section 13.6.2 and under preparations, below

Prophylaxis of asymptomatic meningococcal carrier state (but no longer recommended, see notes above), 100 mg twice daily for 5 days usually followed by rifampicin

Counselling Tablets or capsules should be swallowed whole with plenty of fluid while sitting or standing

Minocycline (Non-proprietary) [PH]
Capsules, minocycline (as hydrochloride) 50 mg, net price 56-cap pack = £15.27; 100 mg, 28-cap pack = £13.09. Label: 6, 9, counselling, posture

Brands include Aknemin

Tablets, minocycline (as hydrochloride) 50 mg, net price 28-tab pack = £3.96, 100 mg, 28-tab pack = £8.43. Label: 6, 9, counselling, posture

Modified release

Acnamin® MR (Dexcel) [PH]
Capsules, m/r, buff/brown (enclosing pink and peach tablets), minocycline (as hydrochloride) 100 mg, net price 56-cap pack = £21.14. Label: 6, 25

Dose acne, 1 capsule daily

Minocin MR® (Meda) [PH]
Capsules, m/r, orange/brown (enclosing yellow and white pellets), minocycline (as hydrochloride) 100 mg. Net price 56-cap pack = £21.14. Label: 6, 25

Dose acne, 1 capsule daily

Sebomin MR® (Actavis) [PH]
Capsules, m/r, orange, minocycline (as hydrochloride) 100 mg, net price 56-cap pack = £21.14. Label: 6, 25

Dose acne, 1 capsule daily
**OXYTETRACYCLINE**

**Indications** see notes above; acne vulgaris, rosacea (section 13.6)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- 250–500 mg every 6 hours
- Acne, see section 13.6.2

**Oxytetracycline (Non-proprietary)**

Tablets, coated, oxytetracycline dihydrate 250 mg, net price 28-tab pack = £1.00. Label: 7, 9, 23

Brands include Oxytetracycline, Tygacil. By intravenous infusion

Oxytetracycline Tablets may be prescribed

**Tigecycline**

Tigecycline is a glycylcycline antibacterial structurally related to the tetracyclines; side-effects similar to those of the tetracyclines can potentially occur. Tigecycline is active against Gram-positive and Gram-negative bacteria, including tetracycline-resistant organisms, and some anaerobes. It is also active against meticillin-resistant Staphylococcus aureus and vancomycin-resistant enterococci, but *Pseudomonas aeruginosa* and many strains of *Proteus spp* are resistant to tigecycline. Tigecycline should be reserved for the treatment of complicated skin and soft-tissue infections and complicated abdominal infections caused by multiple-antibacterial resistant organisms.

**TIGECYCLINE**

**Indications** complicated intra-abdominal infections; complicated skin and soft-tissue infections

**Cautions** cholestasis, hepatic impairment (Appendix 2); breast-feeding (Appendix 5); interactions: Appendix 1 (tigecycline)

**Contra-indications** hypersensitivity to tetracyclines; pregnancy (Appendix 4)

**Side-effects** see notes above; also nausea, vomiting, abdominal pain, dyspepsia, diarrhoea, anorexia, bilirubinaemia, dizziness, headache, prolonged prothrombin time, prolonged activated partial thromboplastin time, rash, pruritus, and injection-site reactions; less commonly pancreatitis and hypoproteinaemia; also reported, antibiotic-associated colitis and thrombocytopenia

**Dose**
- By intravenous infusion, ADULT over 18 years, initially 100 mg, then 50 mg every 12 hours for 5–14 days
- *Tygaci* (Wyeth) ▼

  Intravenous infusion, powder for reconstitution, tigecycline, net price 50-mg vial = £32.31

**5.1.4 Aminoglycosides**

These include amikacin, gentamicin, neomycin, streptomycin, and tobramycin. All are bactericidal and active against some Gram-positive and many Gram-negative organisms. Amikacin, gentamicin, and tobramycin are also active against *Pseudomonas aeruginosa*; streptomycin is active against *Mycobacterium tuberculosis* and is now almost entirely reserved for tuberculosis (section 5.1.9).

The aminoglycosides are not absorbed from the gut (although there is a risk of absorption in inflammatory bowel disease and liver failure) and must therefore be given by injection for systemic infections. Excretion is principally via the kidney and accumulation occurs in renal impairment.

Most side-effects of this group of antibiotics are dose-related therefore care must be taken with dosage and whenever possible treatment should not exceed 7 days. The important side-effects are ototoxicity, and nephrotoxicity; they occur most commonly in the elderly and in patients with renal failure.

If there is impairment of renal function (or high pre-dose serum concentrations) the interval between doses must be increased; if the renal impairment is severe the dose itself should be reduced as well.

Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis; large doses given during surgery have been responsible for a transient myasthenic syndrome in patients with normal neuromuscular function.

Aminoglycosides should preferably not be given with potentially ototoxic diuretics (e.g. furosemide (frusemide)); if concurrent use is unavoidable administration of the aminoglycoside and of the diuretic should be separated by as long a period as practicable.

**Once daily dosage** Once daily administration of aminoglycosides is more convenient, provides adequate serum concentrations, and in many cases has largely superseded multiple daily dose regimens (given in 2–3 divided doses during the 24 hours). Local guidelines on dosage and serum concentrations should be consulted. A once-daily, high-dose regimen of an aminoglycoside should be avoided in patients with endocarditis, extensive burns of more than 20% of the total body surface area, or creatinine clearance less than 20 mL/minute.

**Serum concentrations** Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. In patients with normal renal function, aminoglycoside concentrations should be measured after 3 or 4 doses of a multiple daily dose regimen; patients with renal impairment may require earlier and more frequent measurement of aminoglycoside concentration.

For multiple daily dose regimens, blood samples should be taken approximately 1 hour after intramuscular or intravenous administration (‘peak’ concentration) and also just before the next dose (‘trough’ concentration). For once daily dose regimens, consult local guidelines on serum concentration monitoring.

Serum-aminoglycoside concentrations should be measured in all patients and must be determined in infants, in the elderly, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

**Endocarditis** Gentamicin is used in combination with other antibiotics for the treatment of bacterial endocarditis (Table 1, section 5.1). Serum-gentamicin concentration should be determined twice each week (more often in renal impairment). Streptomycin may be used
as an alternative in gentamicin-resistant enterococcal endocarditis.

Gentamicin is the aminoglycoside of choice in the UK and is used widely for the treatment of serious infections. It has a broad spectrum but is inactive against anaerobes and has poor activity against haemolytic streptococci and pneumococci. When used for the ‘blind’ therapy of undiagnosed serious infections it is usually given in conjunction with a penicillin or metronidazole (or both). Gentamicin is used together with another antibiotic for the treatment of endocarditis (see above and Table 1, section 5.1).

Loading and maintenance doses of gentamicin may be calculated on the basis of the patient’s weight and renal function (e.g. using a nomogram); adjustments are then made according to serum-gentamicin concentrations. High doses are occasionally indicated for serious infections, especially in the neonate, in the patient with cystic fibrosis, or in the immunocompromised patient. Whenever possible treatment should not exceed 7 days.

Amikacin is more stable than gentamicin to enzyme inactivation. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli.

Tobramycin has similar activity to gentamicin. It is less active against certain other Gram-negative bacteria. Tobramycin may be administered by nebuliser on a cyclical basis (28 days of tobramycin followed by a 28-day tobramycin-free interval) for the treatment of chronic pulmonary Ps. aeruginosa infection in cystic fibrosis; however, resistance may develop and some patients do not respond to treatment.

Neomycin is too toxic for parenteral administration and can only be used for infections of the skin or mucous membranes or to reduce the bacterial population of the colon prior to bowel surgery or in hepatic failure. Oral administration may lead to malabsorption. Small amounts of neomycin may be absorbed from the gut colon prior to bowel surgery or in hepatic failure. Oral Neomycin can only be used for infections of the skin or mucous membranes. It is too toxic for parenteral administration and patients do not respond to treatment.

**Dose**

- Multiple daily dose regimen, by intramuscular or by slow intravenous injection over at least 3 minutes or by intravenous infusion, 3–5 mg/kg daily (in divided doses every 8 hours), see also notes above; 
  - **CHILD** under 18 years see **BNF for Children**
  - Endocarditis (in combination with other antibiotics, see Table 1, section 5.1). **ADULT** 1 mg/kg every 8 hours

- Once daily dose regimen (see notes above and also consult local guidelines), by intravenous infusion, initially 5-7 mg/kg, then adjust according to serum-gentamicin concentration

- **By intrathecal injection**, seek specialist advice, 1 mg daily (increased if necessary to 5 mg daily)

**Note** For multiple daily dose regimen, one-hour (‘peak’) serum concentration should be 5–10 mg/litre (3–5 mg/litre for endocarditis); pre-dose (‘trough’) concentration should be less than 2 mg/litre (less than 1 mg/litre for endocarditis). For once-daily dose regimen, consult local guidelines on monitoring serum-gentamicin concentration

Gentamicin (Non-proprietary) (aminoglycosides)

**Injection**, gentamicin (as sulphate), net price 40 mg/mL, 1-mL amp = £1.40, 2-mL amp = £1.54, 2-mL vial = £1.48

Paediatric injection, gentamicin (as sulphate) 10 mg/mL, net price 2-mL vial = £1.80

Intrathecal injection, gentamicin (as sulphate) 5 mg/mL, net price 1-mL amp = 74p

Cidomycin® (Sanofi-Aventis) (aminoglycosides)

**Injection**, gentamicin (as sulphate) 40 mg/mL. Net price 2-mL amp or vial = £1.48

Gentamicin® (Amidpharm) (aminoglycosides)

**Injection**, gentamicin (as sulphate) 40 mg/mL. Net price 2-mL amp = £1.40

Isotonic Gentamicin Injection (Baxter) (aminoglycosides)

**Intravenous infusion**, gentamicin (as sulphate) 800 micrograms/mL in sodium chloride intravenous infusion 0.9%. Net price 100-mL (80-mg) Viaflex® bag = £1.61

Electrolytes Na 15.4 mmol/100-mL bag

**GENTAMICIN**

**Indications** septicaemia and neonatal sepsis; meningitis and other CNS infections; biliary-tract infection, acute pyelonephritis or prostatitis, endocarditis (see notes above); pneumonia in hospital patients, adjunct in listerial meningitis (Table 1, section 5.1); eye (section 11.3.1); ear (section 12.1.1)

**Cautions** pregnancy (Appendix 4), renal impairment, neonates, infants and elderly (adjust dose and monitor renal, auditory and vestibular function together with serum-gentamicin concentrations); avoid prolonged use; conditions characterised by muscular weakness; obesity (use ideal weight for height to calculate dose and monitor serum-gentamicin concentration closely); see also notes above; **interactions**: Appendix 1 (aminoglycosides)

**Contra-indications** myasthenia gravis

**Side-effects** vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis, stomatitis; also reported, nausea, vomiting, rash, blood disorders; see also notes above

**AMIKACIN**

**Indications** serious Gram-negative infections resistant to gentamicin

**Cautions** see under Gentamicin

**Contra-indications** see under Gentamicin

**Side-effects** see under Gentamicin

**Dose**

- By intramuscular or by slow intravenous injection or by infusion, 15 mg/kg daily in 2 divided doses, increased to 22.5 mg/kg daily in 3 divided doses in severe infections; max. 1.5 g daily for up to 10 days (max. cumulative dose 15 g); CHILD under 18 years see **BNF for Children**

**Note** One-hour (‘peak’) serum concentration should not exceed 30 mg/litre; pre-dose (‘trough’) concentration should be less than 10 mg/litre

> Amikacin (Non-proprietary) (Amdipharm) (proprietary)

**Injection**, amikacin (as sulphate) 250 mg/mL. Net price 2-mL vial = £10.14

Electrolytes Na 0.56 mmol/500-mg vial
**NEOMYCIN SULPHATE**

**Indications**  
bowel sterilisation before surgery, see also notes above

**Cautions**  
see under Gentamicin but too toxic for systemic use, see notes above

**Contra-indications**  
see under Gentamicin; intestinal obstruction; renal impairment (Appendix 3)

**Side-effects**  
see under Gentamicin but poorly absorbed on oral administration; increased salivation, stomatitis, impaired intestinal absorption with statorrhoea and diarrhoea

**Dose**  
- **By mouth**, pre-operative bowel sterilisation, 1 g every hour for 4 hours, then 1 g every 4 hours for 2–3 days
- Hepatic coma, up to 4 g daily in divided doses usually for 5–7 days

**Neomycin** (Non-proprietary)

**Tablets**, neomycin sulphate 500 mg. Net price 20 = £4.13

Brands include **Nivemycin**

---

**TOBRAMYCIN**

**Indications**  
see under Gentamicin and notes above

**Cautions**  
see under Gentamicin

**Specific cautions for inhaled treatment**  
Other inhaled drugs should be administered before tobramycin; monitor for bronchospasm with initial dose, measure peak flow before and after nebulisation—if bronchospasm occurs, repeat test using bronchodilator; monitor renal function before treatment and then annually; severe haemoptysis

**Contra-indications**  
see under Gentamicin

**Side-effects**  
see under Gentamicin; on inhalation, mouth ulcers, voice alteration, cough, bronchospasm (see Cautions)

**Dose**  
- **By intramuscular injection or by slow intravenous injection** or by intravenous infusion, 3 mg/kg daily in divided doses every 8 hours, see also notes above; in severe infections up to 5 mg/kg daily in divided doses every 6–8 hours (reduced to 3 mg/kg as soon as clinically indicated); **CHILD** under 18 years see BNF for Children
- **Urinary-tract infection**  
by intramuscular injection, 2–3 mg/kg daily as a single dose

**Note**  
One-hour (‘peak’) serum concentration should not exceed 10 mg/litre; pre-dose (‘trough’) concentration should be less than 2 mg/litre

**Tobramycin** (Non-proprietary)

**Injection**, tobramycin (as sulphate) 40 mg/mL, net price 1 mL (40-mg) vial = £4.00, 2-mL (80-mg) vial = £4.16, 6-mL (240-mg) vial = £19.20

**Tobi®** (Chiron)

**Nebuliser solution**, tobramycin 60 mg/mL, net price 56 × 5 mL (300-mg) unit = £1484.00

**Dose**  
chronic pulmonary *Pseudomonas aeruginosa* infection in cystic fibrosis patients, by inhalation of nebulised solution, **ADULT** and **CHILD** over 6 years, 300 mg every 12 hours for 28 days, courses repeated after 28-day interval
**Cautions** neonate under 2 weeks (risk of hypertrophic pyloric stenosis); predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); avoid in acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (not known to be harmful) and breastfeeding (only small amounts in milk); **Interactions:** Appendix 1 (macrolides)

**Side-effects** nausea, vomiting, abdominal discomfort, diarrhoea (antibiotic-associated colitis reported); less frequently urticaria, rashes and other allergic reactions; reversible hearing loss reported after large doses; choledochal jaundice, pancreatitis, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis also reported

**Dose**
- By mouth, **ADULT** and **CHILD** over 8 years, 250–500 mg every 6 hours or 0.5–1 g every 12 hours (see notes above); up to 4 g daily in divided doses in severe infections; **NEONATE** 12.5 mg/kg every 6 hours; **CHILD** 1 month–2 years 125 mg every 6 hours, 2–8 years 250 mg every 6 hours, doses doubled for severe infections
- Early syphilis, 500 mg 4 times daily for 14 days
- Uncomplicated genital chlamydia, non-gonococcal urethritis, 500 mg twice daily for 14 days
- By intravenous infusion, **ADULT** and **CHILD** severe infections, 50 mg/kg/day by continuous infusion or in divided doses every 6 hours; mild infections (oral treatment not possible), 25 mg/kg daily; **NEONATE** see BNF for Children

**Erythromycin (Non-proprietary)**

- **Capsules**, enclosing e/c microgranules, erythromycin 250 mg, net price 28-cap pack = £5.95. Label: 5, 9, 25
- **Brands** include Tilsoryth
- **Tablets**, e/c, erythromycin 250 mg, net price 28 = £1.93. Label: 5, 9, 25
- **Dental prescribing on NHS** Erythromycin Tablets e/c may be prescribed

**Erythromycin Ethyl Succinate (Non-proprietary)**

- **Oral suspension**, erythromycin (as ethyl succinate) for reconstitution with water 125 mg/5 mL (Suspension PI SF), net price 140 mL = £3.18; 250 mg/5 mL, 140 mL = £6.20; 500 mg/5 mL (Suspension SF Forte), 140 mL = £10.99. Label: 9

**Erythroped® (Abbott)**

- **Suspension SF**, sugar-free, banana-flavoured, erythromycin (as ethyl succinate) for reconstitution with water, 125 mg/5 mL (Suspension PI SF), net price 140 mL = £3.18; 250 mg/5 mL, 140 mL = £6.20; 500 mg/5 mL (Suspension SF Forte), 140 mL = £10.99. Label: 9

**Erythroped A® (Abbott)**

- **Tablets**, yellow, f/c, erythromycin 500 mg (as ethyl succinate). Net price 28-tab pack = £10.78. Label: 9
- **Dental prescribing on NHS** May be prescribed as Erythromycin Ethyl Succinate Tablets

**AZITHROMYCIN**

**Indications** respiratory-tract infections; otitis media; skin and soft-tissue infections; uncomplicated genital chlamydial infections and non-gonococcal urethritis (Table 1, section 5.1); mild or moderate typhoid due to multiple-antibacterial-resistant organisms [unlicensed indication]; prophylaxis of group A streptococcal infection (Table 2, section 5.1)

**Cautions** see under Erythromycin: pregnancy (Appendix 4) and breast-feeding (Appendix 5); **Interactions:** Appendix 1 (macrolides)

**Contra-indications** severe hepatic impairment (Appendix 2)

**Side-effects** see under Erythromycin; also anorexia, dyspepsia, flatulence, dizziness, headache, drowsiness, convulsions, arthralgia, and disturbances in taste and smell; rarely constipation, hepatitis, hepatic failure, syncope, insomnia, agitation, anxiety, asthma, paraesthesia, hyperactivity, thrombocytopenia, haemolytic anaemia, interstitial nephritis, acute renal failure, photosensitivity, tooth and tongue discoloration

**Dose**
- 500 mg once daily for 3 days or 500 mg on first day then 250 mg once daily for 4 days; **CHILD** over 6 months 10 mg/kg once daily for 3 days; or body-weight 15–25 kg, 200 mg once daily for 3 days; body-weight 26–35 kg, 300 mg once daily for 3 days; body-weight 36–45 kg, 400 mg once daily for 3 days
- Uncomplicated genital chlamydial infections and non-gonococcal urethritis, 1 g as a single dose
- Typhoid [unlicensed indication], 500 mg once daily for 7 days

**Azithromycin (Non-proprietary)**

- **1 Tablets**, azithromycin (as monohydrate hemi-ethanolate) 250 mg, net price 4-tab pack = £9.05; 500 mg, 3-tab pack = £9.19. Label: 5, 9
- **Capsules**, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £8.77, 6-cap pack = £13.16. Label: 5, 9, 23
1. Azithromycin tablets can be sold to the public for the treatment of confirmed, asymptomatic *Chlamydia trachomatis* genital infection in those over 16 years of age, and for the epidemiological treatment of their sexual partners, subject to max. single dose of 1 g, max. daily dose 1 g, and a pack size of 1 g

**Zithromax® (Pfizer)**

- **Capsules**, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £8.95, 6-cap pack = £13.43. Label: 5, 9, 23
- **Oral suspension**, cherry/banana-flavoured, azithromycin (as dihydrate) 200 mg/5 mL when reconsti-
tuted with water. Net price 15–mL pack = £5.08, 22.5-
ML pack = £7.62, 30–mL pack = £13.80. Label: 5, 9

**Indications**

**Clarithromycin**

respiratory-tract infections, mild to mod-
erate skin and soft tissue infections, otitis media; Helicobacter pylori eradication (section 1.3)

**Caution**

see under Erythromycin; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions:** Appendix 1 (macrolides)

**Side-effects**

see under Erythromycin; also dyspepsia,
tooth and tongue discoloration, smell and taste distur-
bances, stomatitis, glossitis, and headache; less com-
monly hepatitis, arthralgia, and myalgia; rarely
tinnitus; very rarely pancreatitis, dizziness, insomnia,
nightmares, anxiety, confusion, psychosis, paraes-
thesia, convulsions, hyperglycaemia, renal failure,
leucopenia, and thrombocytopenia; on intravenous
infusion, local tenderness, phlebitis

**Dose**

- **By mouth,** 250 mg every 12 hours for 7 days,
increased in severe infections to 500 mg every 12 hours for up to 14 days; **CHILD** body-weight under
8 kg, 7.5 mg/kg twice daily; 8–11 kg (1–2 years),
62.5 mg twice daily; 12–19 kg (3–6 years), 125 mg
twice daily; 20–29 kg (7–9 years), 187.5 mg twice
daily; 30–40 kg (10–12 years), 250 mg twice daily

- **By intravenous infusion** into larger proximal vein,
500 mg twice daily; **CHILD** under 12 years see BNF for Children

**Clarithromycin** (Non-proprietary)

- **Tablets,** clarithromycin 250 mg, net price 14-tab pack
  = £3.55; 500 mg, 14-tab pack = £7.02. Label: 9

**Clarosip®** (Grunenthal)

- **Granules,** clarithromycin 125 mg/straw, net price 14-
  straw pack = £6.70; 187.5 mg/straw, 14-straw pack
  = £9.70; 250 mg/straw, 14-straw pack = £12.70.

- **Counselling** Place straw in cold or warm drink such as water,
carbonated drink, or tea (but not full fat milk, milk-shake,
or drink with solid particles) and sip drink through straw; several sips may be required to obtain full dose

**Klaricid®** (Abbott)

- **Tablets,** both yellow, f/c, clarithromycin 250 mg, net
  price 14-tab pack = £7.43; 500 mg, 14-tab pack =

**Paediatric suspension**

clarithromycin for reconsti-
tution with water 125 mg/5 mL, net price 70 mL =
£5.58, 100 mL = £9.60; 250 mg/5 mL 70 mL = £11.16.
Label: 9

- **Granules,** clarithromycin 250 mg/sachet, net price
  14-sachet pack = £11.68. Label: 9, 13

**Intravenous infusion**

powder for reconstitution,
clarithromycin. Net price 500-mg vial = £11.46

**Electrolytes**

Na < 0.5 mmol/500-mg vial

**Klaricid XL®** (Abbott)

- **Tablets,** m/r, yellow, clarithromycin 500 mg, net
  price 7-tab pack = £6.72, 14-tab pack = £13.23. Label: 9, 21,
  25

**Dose**

500 mg once daily (doubled in severe infections) for 7–14 days

**Telithromycin**

**Indications** see notes above

**Cautions** hepatic impairment (Appendix 2; see also
Hepatic Disorders below); renal impairment (Appendix
3); pregnancy (Appendix 4); coronary heart dis-
ease, ventricular arrhythmias, bradycardia, hypokal-
aemia, hypomagnesaemia—risk of QT interval
prolongation; concomitant administration of drugs
that prolong QT-interval; **interactions:** Appendix 1
(telithromycin)

**Hepatic disorders** Patients should be told how to recognise
signs of liver disorder, and advised to discontinue treatment and seek prompt medical attention if symptoms such as
anorexia, nausea, vomiting, abdominal pain, jaundice, or
dark urine develop

**Driving** Visual disturbances or transient loss of consciousness
may affect performance of skilled tasks (e.g. driving);
effects may occur after the first dose. Administration at
time may reduce these side-effects. Patients should be
advised not to drive or operate machinery if affected

**Contra-indications** myasthenia gravis; history of telith-
romycin-associated hepatitis or jaundice; prolonga-
tion of QT interval; congenital or family history of
QT interval prolongation (if not excluded by ECG);
breast-feeding (Appendix 5)

**Side-effects** diarrhoea, nausea, vomiting, flatulence,
abdominal pain, taste disturbances; dizziness, head-
ache; less commonly constipation, stomatitis, anorexia,
hepatitis, flushing, palpitations, drowsiness, insomnia,
nervousness, eosinophilia, blurred vision, rash, urti-
caria, and pruritus; rarely cholestatic jaundice, arrhy-
thmias, hypotension, transient loss of consciousness,
par aesthesia, and diplopia; very rarely antibiotic-
associated colitis, altered sense of smell, muscle
cramp, erythema multiforme; also reported pan-
creatitis

**Dose**

- 800 mg once daily for 5 days for sinusitis or exacer-
bation of chronic bronchitis or for 7–10 days in com-
 munity-acquired pneumonia; **CHILD** under 18 years
  safety and efficacy not established

- **Tonsillitis** or pharyngitis caused by Streptococcus pyo-
genesis, **ADULT** and **CHILD** over 12 years, 800 mg once
daily for 5 days

**Ketek** (Aventis Pharma)

- **Tablets,** orange, f/c, telithromycin 400 mg, net price
  10-tab pack = £19.31. Label: 9, counselling, driving,
  hepatic disorders

**Clindamycin**

Clindamycin is active against Gram-positive cocci,
including streptococci and penicillin-resistant staphy-
occci, and also against many anaerobes, especially Bac-
teroides fragilis. It is well concentrated in bone and
excreted in bile and urine.

Clindamycin is recommended for staphylococcal joint
and bone infections such as osteomyelitis, and intra-
abdominal sepsis; it is an alternative to macrolides for
erysipelas or cellulitis in penicillin-allergic patients.
Clindamycin can also be used for infections associated
with meticillin-resistant Staphylococcus aureus (MRSA)
in bronchiectasis, bone and joint infections, and skin and
soft-tissue infections.

Clindamycin has been associated with antibiotic-asso-
ciated colitis (section 1.5), which may be fatal; it is most
common in middle-aged and elderly women, especially following an operation. Although antibiotic-associated colitis can occur with most antibacterials, it occurs more frequently with clindamycin. Patients should therefore discontinue treatment immediately if diarrhoea develops.

**Oral infections** Clindamycin should not be used routinely for the treatment of oral infections because it may be no more effective than penicillins against anaerobes and there may be cross-resistance with erythromycin-resistant bacteria. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

### CLINDAMYCIN

**Indications** see notes above; staphylococcal bone and joint infections, peritonitis; *falciparum* malaria (section 5.4.1)

**Cautions** discontinue immediately if diarrhoea or colitis develops; monitor liver and renal function on prolonged therapy and in neonates and infants; pregnancy (Appendix 4); breast-feeding (Appendix 5); avoid rapid intravenous administration; avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (clindamycin)

**Contra-indications** diarrhoeal states; avoid injections containing benzyl alcohol in neonates (see under preparations below)

**Side-effects** diarrhoea (discontinue treatment), abdominal discomfort, oesophagitis, oesophageal ulcers, taste disturbances, nausea, vomiting, antibiotic-associated colitis; jaundice; leucopenia, eosinophilia, and thrombocytopenia reported; rash, pruritus, urticaria, anaphylactic reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis reported; pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection

**Dose**
- **By mouth**, 150–300 mg every 6 hours; up to 450 mg every 6 hours in severe infections; **CHILD**, 3–6 mg/kg every 6 hours
- **Counselling** Patients should discontinue immediately and contact doctor if diarrhoea develops; capsules should be swallowed with a glass of water.
- **By deep intramuscular injection or by intravenous infusion**, 0.6–2.7 g daily (in 2–4 divided doses); life-threatening infection, up to 4.8 g daily; single doses above 600 mg by intravenous infusion only; single doses by intravenous infusion not to exceed 1.2 g; **CHILD** over 1 month, 15–40 mg/kg daily in 3–4 divided doses; severe infections; at least 300 mg daily regardless of weight

**Clindamycin** (Non-proprietary) [58]

<table>
<thead>
<tr>
<th>Capsules, clindamycin (as hydrochloride) 150 mg, net price 24-cap pack = £24.87. Label: 9, 27, counselling, see above (diarrhoea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental prescribing on NHS Clindamycin Capsules may be prescribed</td>
</tr>
</tbody>
</table>

**Dalacin C® (Pharmacia) [58]**

<table>
<thead>
<tr>
<th>Capsules, clindamycin (as hydrochloride) 75 mg (lavender), net price 24-cap pack = £7.45; 150 mg, (lavender/maroon), 24-cap pack = £13.72. Label: 9, 27, counselling, see above (diarrhoea)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental prescribing on NHS May be prescribed as Clindamycin Capsules</td>
</tr>
</tbody>
</table>

**Injection**, clindamycin (as phosphate) 150 mg/mL, net price 2-mL amp = £6.20; 4-mL amp = £12.35

**Excipients** include benzyl alcohol (avoid in neonates, see Excipients, p. 4)

### Chloramphenicol

Chloramphenicol is a potent broad-spectrum antibiotic; however, it is associated with serious haematological side-effects when given systemically and should therefore be reserved for the treatment of life-threatening infections, particularly those caused by *Haemophilus influenzae*, and also for typhoid fever.

Chloramphenicol eye drops (section 11.3.1) and chloramphenicol ear drops (section 12.1.1) are also available.

### CHLORAMPHENICOL

**Indications** see notes above

**Cautions** avoid repeated courses and prolonged treatment; reduce doses in hepatic impairment (Appendix 2); renal impairment (Appendix 3); blood counts required before and periodically during treatment; monitor plasma-chloramphenicol concentration in neonates (see below); interactions: Appendix 1 (chloramphenicol)

**Contra-indications** pregnancy (Appendix 4); breastfeeding (Appendix 5), acute porphyria (section 9.8.2)

**Side-effects** blood disorders including reversible and irreversible aplastic anaemia (with reports of resulting leukaemia), peripheral neuritis, optic neuritis, headache, depression, urticaria, erythema multiforme, nausea, vomiting, diarrhoea, stomatitis, glossitis, dry mouth; nocturnal haemoglobinuria reported; grey syndrome (abdominal distension, pallid cyanosis, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism

**Dose**
- **By mouth or by intravenous injection or infusion**, 50 mg/kg daily in 4 divided doses (exceptionally, can be doubled for severe infections such as septicaemia and meningitis, providing high doses reduced as soon as clinically indicated); **CHILD**, haemophilus epiglotitis and pyogenic meningitis, 50–100 mg/kg daily in divided doses (high dosages decreased as soon as clinically indicated); **NEONATE** under 2 weeks 25 mg/kg daily (in 4 divided doses); **INFANT** 2 weeks–1 year 50 mg/kg daily (in 4 divided doses)

**Note** Plasma concentration monitoring required in neonates and preferred in those under 4 years of age, in the elderly, and in hepatic impairment; recommended peak plasma concentration (approx. 1 hour after intravenous injection or infusion) 15–25 mg/litre; pre-dose (‘trough’) concentration should not exceed 15 mg/litre

**Chloramphenicol** (Non-proprietary) [78]

| Capsules, chloramphenicol 250 mg. Net price 60 = £377.00 |
Fusidic acid

Fusidic acid and its salts are narrow-spectrum antibiotics. The only indication for their use is in infections caused by penicillin-resistant staphylococci, especially osteomyelitis, as they are well concentrated in bone; they are also used for staphylococcal endocarditis. A second antistaphylococcal antibiotic is usually required to prevent emergence of resistance.

**SODIUM FUSIDATE**

**Indications** penicillin-resistant staphylococcal infection including osteomyelitis; staphylococcal endocarditis in combination with other antibacterials (Table 1, section 5.1)

**Cautions** monitor liver function with high doses, on prolonged therapy or in hepatic impairment (Appendix 2); elimination may be reduced in hepatic impairment or biliary disease or biliary obstruction; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (fusidic acid)

**Side-effects** nausea, vomiting, reversible jaundice, especially after high dosage or rapid infusion (withdrawal therapy if persistent); rarely hypersensitivity reactions, acute renal failure (usually with jaundice), blood disorders

**Dose**

- See under Preparations, below

**Sodium fusidate (LEO)**

*Intravenous infusion*, powder for reconstitution, sodium fusidate 500 mg (= fusidic acid 480 mg), with buffer; net price per vial (with diluent) = £70.04

*Electrolytes* Na 3.14 mmol/g

*Dose* as sodium fusidate, by intravenous infusion, ADULT over 50 kg, 500 mg 3 times daily; ADULT under 50 kg and CHILD, 6–7 mg/kg/3 times daily

**Fucidin® (LEO)**

*Tablets*, I/c, sodium fusidate 250 mg, net price 10-tab pack = £6.02. Label: 9

*Dose* as sodium fusidate, 500 mg every 8 hours, doubled for severe infections Skin infection, as sodium fusidate, 250 mg every 12 hours for 5–10 days

**Suspension**, off-white, banana- and orange-flavoured, fusidic acid 250 mg/5 mL., net price 50 mL = £6.73. Label: 9, 21

*Dose* as fusidic acid, ADULT 750 mg every 8 hours; CHILD up to 1 year 50 mg/kg/daily (in 3 divided doses), 1–5 years 250 mg every 8 hours, 5–12 years 500 mg every 8 hours

**Note** Fusidic acid is incompletely absorbed and doses recommended for suspension are proportionately higher than those for sodium fusidate tablets

**Vancomycin and teicoplanin**

The glycopeptide antibiotics vancomycin and teicoplanin have bactericidal activity against aerobic and anaerobic Gram-positive bacteria including multi-resistant staphylococci. However, there are reports of *Staphylococcus aureus* with reduced susceptibility to glycopeptides. There are increasing reports of glycopeptide-resistant enterococci. Vancomycin is used by the intravenous route in the treatment of endocarditis and other serious infections caused by Gram-positive cocci. It has a long duration of action and can therefore be given every 12 hours. Vancomycin (added to dialysis fluid) is also used in the treatment of peritonitis associated with peritoneal dialysis [unlicensed route] (Table 1 section 5.1).

Vancomycin given by mouth is effective in the treatment of *Clostridium difficile* infection (see also section 1.5); a dose of 125 mg every 6 hours for 7 to 10 days is considered adequate (higher dose may be considered if the infection fails to respond or if it is severe). Vancomycin should not be given by mouth for systemic infections since it is not significantly absorbed.

**Teicoplanin** is similar to vancomycin but has a significantly longer duration of action allowing once-daily administration. Unlike vancomycin, teicoplanin can be given by intramuscular as well as by intravenous injection; it is not given by mouth.

**VANCOMYCIN**

**Indications** see notes above

**Cautions** avoid rapid infusion (risk of anaphylactoid reactions, see Side-effects); rotate infusion sites; renal impairment (Appendix 3); elderly; avoid if history of deafness; all patients require plasma-vancomycin measurement (after 3 or 4 doses if renal function normal, earlier if renal impairment), blood counts, urinalysis, and renal function tests; monitor auditory function in elderly or if renal impairment; pregnancy (Appendix 4) and breast-feeding (Appendix 5); teicoplanin sensitivity; systemic absorption may follow oral administration especially in inflammatory bowel disorders or following multiple doses; interactions: Appendix 1 (vancomycin)

**Side-effects** after parenteral administration: nephrotoxicity including renal failure and interstitial nephritis; ototoxicity (discontinue if tinnitus occurs); blood disorders including neutropenia (usually after 1 week or cumulative dose of 25 g), rarely agranulocytosis and thrombocytopenia; nausea, chills, fever, eosinophilia, anaphylaxis, rashes (including exfoliative dermatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and vasculitis); phlebitis (irritant to tissue); on rapid infusion, severe hypotension (including shock and cardiac arrest), wheezing, dyspnoea, urticaria, pruritus, flushing of the upper body (‘red man’ syndrome), pain and muscle spasm of back and chest

**Dose**

- By mouth, *Clostridium difficile* infection, 125 mg every 6 hours for 7–10 days, see notes above; CHILD 5 mg/kg every 6 hours, over 5 years, half adult dose

**Note** Oral paediatric dose is lower than that on product literature but is adequate

- By intravenous infusion, 1–1.5 g every 12 hours;
  - ELDERLY over 65 years, 500 mg every 12 hours or 1 g once daily; CHILD over 1 month, 15 mg/kg every 8 hours (max. 2 g daily)

**Note** Plasma concentration monitoring required (see Cautions above); pre-dose (‘trough’) concentration should be 10–15 mg/litre (15–20 mg/litre for less sensitive strains of meticillin-resistant *Staphylococcus aureus*); vancomycin doses in BNF may differ from those in product literature
Vancomycin (Non-proprietary) (HM)
Capsules, vancomycin (as hydrochloride) 125 mg, net price 28-cap pack = £132.47; 250 mg, 28-cap pack = £132.47. Label: 9
Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 500-mg vial = £85.05; 1-g vial = £16.11
Note Can be used to prepare solution for oral administration

Vancocin® (Flynn) (HM)
Matrigel capsules, vancomycin (as hydrochloride) 125 mg, net price 28-cap pack = £88.31. Label: 9
Injection, powder for reconstitution, vancomycin (as hydrochloride), for use as an infusion, net price 500-mg vial = £85.05; 1-g vial = £16.11
Note Can be used to prepare solution for oral administration

TEICOPLANIN

Indications potentially serious Gram-positive infections including endocarditis, dialysis-associated peritonitis, and serious infections due to Staphylococcus aureus; prophylaxis in orthopaedic surgery at risk of infection with Gram-positive organisms

Cautions vancomycin sensitivity; blood counts and liver and kidney function tests required; monitor plasma-teicoplanin concentration if severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), endocarditis, renal impairment, in elderly, and in intravenous drug abusers; monitor renal and auditory function during prolonged treatment in renal impairment (Appendix 3) or if other nephrotoxic or neurotoxic drugs given; pregnancy (Appendix 4) and breast-feeding; interactions: Appendix 1 (teicoplanin)

Side-effects nausea, vomiting, diarrhoea; rash, pruritus, fever, bronchospasm, rigors, urticaria, angioedema, anaphylaxis; dizziness, headache; blood disorders including eosinophilia, leucopenia, neutropenia, and thrombocytopenia; disturbances in liver enzymes, transient increase of serum creatinine, renal failure; tinnitus, mild hearing loss, and vestibular disturbances; muscle effects (see Cautions), arthritis, myalgia, muscle weakness, and myositis; rhabdomyolysis is very rare. Monitor creatine kinase before treatment and then weekly during treatment (more frequently if creatine kinase elevated during treatment (more frequently if creatine kinase elevated before treatment, or if receiving another drug known to cause myopathy (preferably not salicylates)); discontinue if unexplained muscular symptoms and creatine kinase elevated markedly

Dose By intramuscular injection or by intravenous injection or infusion, initially 400 mg (for severe infections, by intravenous injection or infusion, initially 400 mg every 12 hours for 3 doses), then 200 mg once daily (400 mg once daily for severe infections); higher doses may be required in patients over 85 kg over 2 months or if other nephrotoxic or neurotoxic drugs given; monitor plasma-teicoplanin concentration if severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), endocarditis, renal impairment, in elderly, and in intravenous drug abusers; monitor renal and auditory function during prolonged treatment in renal impairment (Appendix 3) or if other nephrotoxic or neurotoxic drugs given; pregnancy (Appendix 4) and breast-feeding; interactions: Appendix 1 (teicoplanin)

Child over 2 months by intravenous injection or infusion, initially 10 mg/kg every 12 hours for 3 doses, subsequently 6 mg/kg once daily (severe infections or in neutropenia, 10 mg/kg once daily); subsequent doses can be given by intramuscular injection (but intravenous administration preferred in children); NEONATE by intravenous infusion, initially a single dose of 16 mg/kg, subsequently 8 mg/kg once daily

Streptococcal endocarditis, by intravenous injection or infusion, ADULT initially 6 mg/kg every 12 hours for 3 doses, then 6 mg/kg once daily

Enterococcal endocarditis, by intravenous injection or infusion, ADULT initially 10 mg/kg every 12 hours for 3 doses, then 10 mg/kg once daily

Orthopaedic surgery prophylaxis, by intravenous injection, 400 mg at induction of anaesthesia
Note Plasma-teicoplanin concentration is not measured routinely because a relationship between plasma concentration and toxicity has not been established. However, the plasma-teicoplanin concentration can be used to optimise treatment in some patients (see Cautions). Pre-dose (‘trough’) concentrations should be greater than 10 mg/litre (greater than 15–20 mg/litre in endocarditis) but less than 60 mg/litre

Targocid® (Aventis Pharma) (HM)
Injection, powder for reconstitution, teicoplanin, net price 200-mg vial (with diluent) = £17.58; 400-mg vial (with diluent) = £35.62
Electrolytes Na < 0.5 mmol/200- and 400-mg vial

Daptomycin

Daptomycin is a lipopeptide antibacterial with a spectrum of activity similar to vancomycin but its efficacy against enterococci has not been established. Daptomycin should be reserved for complicated skin and soft-tissue infections caused by resistant Gram-positive bacteria including meticillin-resistant Staphylococcus aureus (MRSA). It needs to be given with other antibacterials for mixed infections involving Gram-negative bacteria and some anaerobes.

The Scottish Medicines Consortium (p. 3) has advised (February 2008) that daptomycin (Cubicin®) is accepted for restricted use within NHS Scotland for the treatment of MRSA bacteraemia associated with right-sided endocarditis or with complicated skin and soft-tissue infections.

DAPTOMYCIN

Indications see under: Dose

Cautions interference with assay for prothrombin time and INR—take blood sample immediately before daptomycin dose; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (daptomycin)

Muscle effects Myalgia, muscle weakness, and myositis may occur uncommonly; rhabdomyolysis is very rare. Monitor creatine kinase before treatment and then weekly during treatment (more frequently if creatine kinase elevated more than 5 times upper limit of normal before treatment, or if receiving another drug known to cause myopathy (preferably not salicylates)); discontinue if unexplained muscular symptoms and creatine kinase elevated markedly

Contra-indications breast-feeding (Appendix 5)

Side-effects nausea, vomiting, diarrhoea; headache; rash, injection-site reactions; less commonly constipation, abdominal pain, dyspepsia, anorexia, taste disturbance, jaundice, hypertension, hypotension, flushing, arrhythmias, anxiety, insomnia, dizziness, fatigue, paraesthesia, hyperglycaemia, vaginitis, renal failure, anaemia, eosinophilia, thrombocytopenia, electrolyte disturbances, muscle effects (see Cautions), arthralgia, glossitis, and pruritus; also reported syncope, wheezing, and peripheral neuropathy
Dose

- By intravenous infusion, complicated skin and soft-tissue infections caused by Gram-positive bacteria, **ADULT** over 18 years, 4 mg/kg once daily; increased to 6 mg/kg once daily if associated with *Staphylococcus aureus* bacteraemia

Right-sided endocarditis caused by *Staphylococcus aureus*, **ADULT** over 18 years, 6 mg/kg once daily

Cubicin® (Novartis) ▼ [iir]

Intravenous infusion, powder for reconstitution, daptomycin, net price 350-mg vial = £62.00; 500-mg vial = £88.57

**Linezolid**

Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including meticillin-resistant *Staphylococcus aureus* (MRSA), and vanco-mycin-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid is an option if a glycopeptide, such as vancomycin, cannot be used to treat pneumonia or severe skin and soft-tissue infections caused by MRSA. Linezolid is not active against Gram-negative organisms and must be given with other antibacterials if the infection also involves Gram-negative organisms (the combination should be used for mixed skin and soft tissue infections only when other treatments are not available). A higher incidence of blood disorders and optic neuropathy have been reported in patients receiving linezolid for more than the maximum recommended duration of 28 days.

**Linezolid**

**Indications** pneumonia, complicated skin and soft-tissue infections caused by Gram-positive bacteria (initiated under expert supervision)

**Cautions** monitor full blood count (including platelet count) weekly (see also CSM Advice below); history of seizures; unless close observation and blood-pressure monitoring possible, avoid in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (MAOIs)

**CSM advice (blood disorders)** Haematopoietic disorders (including thrombocytopenia, anaemia, leucopenia, and pancytopenia) have been reported in patients receiving linezolid. It is recommended that full blood counts are monitored weekly. Close monitoring is recommended in patients who:

- receive treatment for more than 10–14 days;
- have pre-existing myelosuppression;
- are receiving drugs that may have adverse effects on haemoglobin, blood counts, or platelet function;
- have severe renal impairment.

If significant myelosuppression occurs, treatment should be stopped unless it is considered essential, in which case intensive monitoring of blood counts and appropriate management should be implemented.

**CHM advice (optic neuropathy)** Severe optic neuropathy may occur rarely, particularly if linezolid is used for longer than 28 days. The CHM recommends that:

- patients should be warned to report symptoms of visual impairment (including blurred vision, visual field defect, changes in visual acuity and colour vision) immediately;
- patients experiencing new visual symptoms (regardless of treatment duration) should be evaluated promptly, and referred to an ophthalmologist if necessary;
- visual function should be monitored regularly if treatment is required for longer than 28 days.

**Monoamine oxidase inhibition** Linezolid is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Patients should avoid consuming large amounts of tyramine-rich foods (such as mature cheese, yeast extracts, undistilled alcoholic beverages, and fermented soya bean products). In addition, linezolid should not be given with another MAOI or within 2 weeks of stopping another MAOI. Unless close observation and blood-pressure monitoring is possible, avoid in those receiving SSRIs, 5HT agonists (‘triptans’), tricyclic antidepressants, sympathomimetics, dopamine agonists, buspirone, pethidine and possibly other opioid analgesics. For other interactions see Appendix 1 (MAOIs)

**Contra-indications** breast-feeding (Appendix 5); see also Monoamine oxidase inhibition above

**Side-effects** diarrhoea (antibiotic-associated colitis reported), nausia, vomiting, taste disturbances; headache; less commonly thirst, dry mouth, glossitis, stomatitis, tongue discoloration, abdominal pain, dyspepsia, gastritis, constipation, pancreatitis, hypertension, fever, fatigue, dizziness, insomnia, hypoaesthesia, paraesthesia, tinnitus, polyuria, anaemia, leucopenia, thrombocytopenia, eosinophilia, electrolyte disturbances, blurred vision, rash, pruritus, diaphoresis, and injection-site reactions; very rarely transient ischaemic attacks, renal failure, pancytopenia and Stevens-Johnson syndrome; also reported convulsions, lactic acidosis; peripheral and optic neuropathy reported on prolonged therapy (see also CHM advice above)

**Dose**

- By mouth, 600 mg every 12 hours usually for 10–14 days (max. duration of treatment 28 days); **CHILD** [unlicensed] 1 week–12 years, 10 mg/kg every 8 hours; 12–18 years, adult dose

- By intravenous infusion over 30–120 minutes, 600 mg every 12 hours; **CHILD** [unlicensed] 1 week–12 years, 10 mg/kg every 8 hours; 12–18 years, adult dose

**Zyvox®** (Pharmacia) ▼ [iir]

**Tablets**, 1/g, linezolid 600 mg, net price 10-tab pack = £450.00. **Label**: 9, 10; patient information leaflet

**Suspension**, yellow, linezolid 100 mg/5 mL when reconstituted with water, net price 150 mL (orange-flavoured) = £222.50. **Label**: 9, 10; patient information leaflet

**Excipients** include aspartame 20 mg/5 mL (section 9.4.1)

**Intravenous infusion**, linezolid 2 mg/mL, net price 300-mL **Excel** bag = £44.50

**Excipients** include Na 5 mmol/300-mL bag, glucose 13.71 g/300-mL bag

**Quinupristin and dalfopristin**

A combination of the streptogramin antibiotics, quinupristin and dalfopristin (as Synercid®) is licensed for infections due to Gram-positive bacteria. The combination should be reserved for treating infections which have failed to respond to other antibacterials (e.g.
5 Infections

Meticillin-resistant *Staphylococcus aureus*, MRSA or for patients who cannot be treated with other antibacterials. Quinupristin and dalfopristin are not active against *Enterococcus faecalis* and they need to be given in combination with other antibacterials for mixed infections which also involve Gram-negative organisms.

### Quinupristin with Dalfopristin

**A mixture of quinupristin and dalfopristin (both as mesilate salts) in the proportions 3 parts to 7 parts**

**Indications**: Serious Gram-positive infections where no alternative antibacterial is suitable including hospital-acquired pneumonia, skin and soft-tissue infections, infections due to vancomycin-resistant *Enterococcus faecium*.

**Cautions**: Cardiac arrest, hypotension, bronchospasm, convulsions, thrombosis, thrombocytopenia and pancreatitis.

**Contra-indications**: Myasthenia gravis, pregnancy, hematological disorders, impaired renal and hepatic function.

**Side-effects**: Nausea, vomiting, diarrhoea; headache, asthenia; anaemia, leucopenia, eosinophilia, raised plasma-bilirubin concentration; hepatic impairment (avoid if severe; Appendix 3); predisposition to cardiac arrhythmias (including congenital QT syndrome, concomitant use of drugs that prolong QT interval, cardiac hypertrophy, dilated cardiomyopathy, hypokalaemia, hypomagnesaemia, bradycardia).

**Interactions**: Appendix 1 (quinupristin with dalfopristin).

**Dose**

- **Note**: Expressed as a combination of quinupristin and dalfopristin (in a ratio of 3:7)
- **ADULT** over 18 years, by intravenous infusion into central vein, 7.5 mg/kg every 8 hours for 7 days in skin and soft-tissue infections; for 10 days in hospital-acquired pneumonia; duration of treatment in *E. faecium* infection depends on site of infection.

**Synercid**

- **Nordic**
  - **Intravenous infusion**: Powder for reconstitution, quinupristin (as mesilate) 150 mg, dalfopristin (as mesilate) 350 mg, net price 500-mg vial = £37.00
  - **Electrolytes Na** approx. 16 mmol/500-mg vial

**Polyoxymyxins**

The polyoxymyxin antibiotic, colistin, is active against Gram-negative organisms including *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Klebsiella pneumoniae*. It is not absorbed by mouth and thus needs to be given by injection for a systemic effect. Intravenous administration of colistin should be reserved for Gram-negative infections resistant to other antibacterials; its major adverse effects are dose-related neurotoxicity and nephrotoxicity.

Colistin is used by mouth in bowel sterilisation regimens in neutropenic patients (usually with nystatin); it is not recommended for gastro-intestinal infections. It is also given by inhalation of a nebulised solution as an adjunct to standard antibacterial therapy in patients with cystic fibrosis.

Both colistin and polymyxin B are included in some preparations for topical application.

### Colistin

**Indications**: See notes above.

**Cautions**: Renal impairment (Appendix 3); acute porphyria (section 9.8.2); risk of bronchospasm on inhalation—may be prevented or treated with a selective beta agonist; interactions: Appendix 1 (polymyxins).

**Contra-indications**: Myasthenia gravis; pregnancy (Appendix 4); breast-feeding (Appendix 5).

**Side-effects**: Neurotoxicity reported especially with excessive doses (including apnoea, perioral and peripheral paralysis, vertigo; rarely vasomotor instability, slurred speech, confusion, psychosis, visual disturbances); nephrotoxicity; hypersensitivity reactions including rash; injection-site reactions; inhalation may cause sore throat, sore mouth, cough, bronchospasm.

**Dose**

- **By mouth**: Bowel sterilisation, 1.5–3 million units every 8 hours.
- **By slow intravenous injection** into a totally implantable venous access device, or by intravenous infusion (but see notes above).
- **ADULT** and **CHILD** body-weight under 60 kg, 50 000–75 000 units/kg daily in 3 divided doses; body-weight over 60 kg, 1–2 million units every 8 hours.

**Note**: Plasma concentration monitoring required in neonates, renal impairment, and in cystic fibrosis; recommended ‘peak’ plasma-colistin concentration (approx. 30 minutes after intravenous injection or infusion) 10–15 mg/litre (125–200 units/mL).

- **By inhalation of nebulised solution**: **ADULT** and **CHILD** over 2 years, 1–2 million units every 12 hours; **CHILD** under 2 years, 0.5–1 million units every 12 hours.

**Colomycin® (Forest)**

- **Tablets**: Scored, colistin sulphate 1.5 million units. Net price 50 = £58.28
- **Syrup**: Colistin sulphate 250 000 units/5 mL when reconstituted with water. Net price 80 mL = £3.48

**Injection**: Powder for reconstitution, colistimethate sodium (colistin sulphomethate sodium). Net price 500 000-unit vial = £1.14; 1 million-unit vial = £1.68; 2 million-unit vial = £3.09

**Electrolytes (before reconstitution)** Na < 0.5 mmol/500 000-unit, 1 million-unit, and 2 million-unit vial.

**Note**: Colomycin Injection (dissolved in physiological saline) may be used for nebulisation.

**Promixin® (Profile)**

- **Powder for nebuliser solution**: Colistimethate sodium (colistin sulphomethate sodium), net price 1 million-unit vial = £4.60
  - **Injection**: Powder for reconstitution, colistimethate sodium (colistin sulphomethate sodium), net price 1 million-unit vial = £2.30

**Electrolytes (before reconstitution)** Na < 0.5 mmol/1 million-unit vial.
### 5.1.8 Sulphonamides and trimethoprim

The importance of the sulphonamides has decreased as a result of increasing bacterial resistance and their replacement by antibacterials which are generally more active and less toxic.

Sulfamethoxazole (sulphamethoxazole) and trimethoprim are used in combination (as co-trimoxazole) because of their synergistic activity. However, co-trimoxazole is associated with rare but serious side-effects (e.g. Stevens-Johnson syndrome and blood dyscrasias, notably bone marrow depression and agranulocytosis) especially in the elderly (see CSM recommendations below).

#### Trimethoprim

Can be used alone for urinary- and respiratory-tract infections and for prostatitis, shigellosis, and invasive salmonella infections. Trimethoprim has irritatory-tract infections and for prostatitis, shigellosis, and systemic lupus erythematosus; rhabdomyolysis reported in HIV-infected patients.

**Side-effects**

- nausea, diarrhoea; headache; hyperkalaemia; rash (very rarely including Stevens-Johnson syndrome and blood dyscrasias, notably bone marrow depression and agranulocytosis) especially in the elderly (see CSM recommendations above).
- acute porphyria (section 9.8.2)

**Contra-indications**

- ketoacidosis; young infants (except for prophylaxis of pneumocystis pneumonia); hepatic impairment (avoid if severe); predisposition to folate deficiency or hyperkalaemia; elderly (see CSM recommendations above); asthma; G6PD deficiency (section 9.1.5); avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia); hepatic impairment (avoid if severe); renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (trimethoprim, sulfamethoxazole)

**Co-trimoxazole should be limited to the role of drug of choice in Pneumocystis jiroveci (Pneumocystis carinii) pneumonia; it is also indicated for toxoplasmosis and nocardiosis. It should now only be considered for use in acute exacerbations of chronic bronchitis and infections of the urinary tract when there is good bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibacterial; similarly it should only be used in acute otitis media in children when there is good reason to prefer it.**

**Cautions**

- avoid if severe; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (trimethoprim, sulfamethoxazole)

**Indications**

see CSM recommendations above

**Dose**

- By mouth, 960 mg every 12 hours; CHILD, every 12 hours, 6 weeks–5 months, 120 mg; 6–18 months, 240 mg; 6–12 years, 480 mg
- By intravenous infusion, 960 mg every 12 hours increased to 1.44 g every 12 hours in severe infections; CHILD 36 mg/kg daily in 2 divided doses increased to 54 mg/kg daily in severe infections
- Treatment of Pneumocystis jiroveci (Pneumocystis carinii) infections (undertaken where facilities for appropriate monitoring available—consult microbiologist and product literature), by mouth or by intravenous infusion, ADULT and CHILD over 4 weeks, 120 mg/kg daily in 2–4 divided doses for 14 days
- Prophylaxis of Pneumocystis jiroveci (Pneumocystis carinii) infections, by mouth, 960 mg once daily (may be reduced to 480 mg once daily to improve tolerance) or 960 mg on alternate days (3 times a week) or 960 mg twice daily on alternate days (3 times a week); CHILD 6 weeks–5 months, 120 mg twice daily on 3 consecutive or alternate days per week or on 7 days per week; 6 months–5 years, 240 mg; 6–12 years, 480 mg

**Note**

480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg

**Co-trimoxazole (Non-proprietary) (UK)**

<table>
<thead>
<tr>
<th>Tablets, co-trimoxazole 480 mg, net price 28-tab pack</th>
<th>£13.83, 960 mg, 20 = £4.69. Label: 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brands include Fectrim, Fectrim Forte</td>
<td></td>
</tr>
<tr>
<td>Paediatric oral suspension, co-trimoxazole 240 mg/5 mL, net price 100 mL = £1.12. Label: 9</td>
<td></td>
</tr>
<tr>
<td>Oral suspension, co-trimoxazole 480 mg/5 mL. Net price 100 mL = £4.41. Label: 9</td>
<td></td>
</tr>
<tr>
<td>Strong sterile solution, co-trimoxazole 96 mg/mL. For dilution and use as an intravenous infusion. Net price 5-mL amp = £1.58, 10-mL amp = £3.06</td>
<td></td>
</tr>
</tbody>
</table>

**Septin® (GSK) (UK)**

<table>
<thead>
<tr>
<th>Tablets, co-trimoxazole 480 mg. Net price 20 = £3.10. Label: 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forte tablets, scored, co-trimoxazole 960 mg. Net price 20 = £4.69. Label: 9</td>
</tr>
<tr>
<td>Adult suspension, co-trimoxazole 480 mg/5 mL. Net price 100 mL (vanilla-flavoured) = £4.41. Label: 9</td>
</tr>
<tr>
<td>Paediatric suspension, sugar-free, co-trimoxazole 240 mg/5 mL. Net price 100 mL (banana- and vanilla-flavoured) = £2.45. Label: 9</td>
</tr>
<tr>
<td>Intravenous infusion, co-trimoxazole 96 mg/mL. To be diluted before use. Net price 5-mL amp = £1.48</td>
</tr>
<tr>
<td>Excipients include propylene glycol, sulphites</td>
</tr>
</tbody>
</table>

**Sulfadiazine**

(Sulphadiazine)

**Indications**

prevention of rheumatic fever recurrence, toxoplasmosis [unlicensed]—see section 5.4.7

**Cautions**

see under Co-trimoxazole; renal impairment (avoid if severe; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (sulphonamides)
5.1.9 Antituberculosis drugs

Tuberculosis is treated in two phases—an initial phase using 4 drugs and a continuation phase using 2 drugs in fully sensitive cases. Treatment requires specialised knowledge, particularly where the disease involves resistant organisms or non-respiratory organs.

The regimens given below are recommended for the treatment of tuberculosis in the UK; variations occur in other countries. Either the unsupervised regimen or the supervised regimen described below should be used; the two regimens should not be used concurrently.

Initial phase The concurrent use of 4 drugs during the initial phase is designed to reduce the bacterial population as rapidly as possible and to prevent the emergence of drug-resistant bacteria. The drugs are best given as combination preparations unless one of the components cannot be given because of resistance or intolerance.

The treatment of choice for the initial phase is the daily use of isoniazid, rifampicin, pyrazinamide and ethambutol. Treatment should be started without waiting for culture results if clinical features or histology results are consistent with tuberculosis; treatment should be continued even if initial culture results are negative. The initial phase drugs should be continued for 2 months. Where a positive culture for M. tuberculosis has been obtained, but susceptibility results are not available after 2 months, treatment with rifampicin, isoniazid, pyrazinamide and ethambutol should be continued until full susceptibility is confirmed, even if this is for longer than 2 months.

Streptomycin is rarely used in the UK but it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced.

Continuation phase After the initial phase, treatment is continued for a further 4 months with isoniazid and rifampicin (preferably given as a combination preparation). Longer treatment is necessary for meningitis, direct spinal cord involvement, and for resistant organisms which may also require modification of the regimen.

Unsupervised treatment The following regimen should be used for patients who are likely to take antituberculous drugs reliably without supervision. Patients who are unlikely to comply with daily administration of antituberculous drugs should be treated with the regimen described under Supervised Treatment.

Recommended dosage for standard unsupervised 6-month treatment

Rifater® [rifampicin, isoniazid, and pyrazinamide] (for 2-month initial phase only)

Adult under 40 kg 3 tablets daily, 40–49 kg 4 tablets daily, 50–64 kg 5 tablets daily, over 65 kg 6 tablets daily

Ethambutol (for 2-month initial phase only)

Adult and child 15 mg/kg daily

Rifinah® [rifampicin and isoniazid] (for 4-month continuation phase following initial treatment with Rifater®)

Adult under 50 kg 3 tablets daily of Rifinah -150, 50 kg and over, 2 tablets daily of Rifinah -300 or (if combination preparations not appropriate):

Isoniazid (for 2-month initial and 4-month continuation phases)

Adult 300 mg daily; child 5–10 mg/kg (max. 300 mg) daily

Rifampicin (for 2-month initial and 4-month continuation phases)

Adult under 50 kg 450 mg daily, 50 kg and over 600 mg daily; child 10 mg/kg (max. 600 mg) daily

Pyrazinamide (for 2-month initial phase only)

Adult under 50 kg 1.5 g daily, 50 kg and over 2 g daily; child 35 mg/kg daily

Ethambutol (for 2-month initial phase only)

Adult and child 15 mg/kg daily

Pregnancy and breast-feeding The standard regimen (above) may be used during pregnancy and breastfeeding. Streptomycin should not be given in pregnant.
**Children**  Children are given isoniazid, rifampicin, pyrazinamide, and ethambutol for the first 2 months followed by isoniazid and rifampicin during the next 4 months. However, care is needed in young children receiving ethambutol because of the difficulty in testing eyesight and in obtaining reports of visual symptoms (see below).

**Supervised treatment**  Drug administration needs to be **fully supervised** (directly observed therapy, DOT) in patients who cannot comply reliably with the treatment regimen. These patients are given isoniazid, rifampicin, pyrazinamide and ethambutol (or streptomycin) 3 times a week under supervision for the first 2 months followed by isoniazid and rifampicin 3 times a week for a further 4 months.

**Recommended dosage for intermittent supervised 6-month treatment**

**Isoniazid** (for 2-month initial and 4-month continuation phases)

- **ADULT AND CHILD** 15 mg/kg (max. 900 mg) 3 times a week

**Rifampicin** (for 2-month initial and 4-month continuation phases)

- **ADULT** 600–900 mg 3 times a week; **CHILD** 15 mg/kg (max. 900 mg) 3 times a week

**Pyrazinamide** (for 2-month initial phase only)

- **ADULT** under 50 kg 2 g 3 times a week; 50 kg and over 2.5 g 3 times a week; **CHILD** 50 mg/kg 3 times a week

**Ethambutol** (for 2-month initial phase only)

- **ADULT AND CHILD** 30 mg/kg 3 times a week

**Immunocompromised patients**

Multi-resistant *Mycobacterium tuberculosis* may be present in immunocompromised patients. The organism should always be cultured to confirm its type and drug sensitivity. Confirmed *M. tuberculosis* infection sensitive to first-line drugs should be treated with a standard 6-month regimen; after completing treatment, patients should be closely monitored. The regimen may need to be modified if infection is caused by resistant organisms, and specialist advice is needed.

Specialist advice should be sought about tuberculosis treatment or chemoprophylaxis in a HIV-positive individual; care is required in choosing the regimen and in avoiding potentially hazardous interactions. Starting antiretroviral treatment in the first 2 months of antituberculosis treatment increases the risk of immune reconstitution syndrome.

Infection may also be caused by other mycobacteria e.g. *M. avium* complex in which case specialist advice on management is needed.

**Corticosteroids**  In meningeal or pericardial tuberculosis, a corticosteroid should be started at the same time as antituberculosis therapy.

**Prevention of tuberculosis**  Some individuals may develop tuberculosis owing to reactivation of previously latent disease. Chemoprophylaxis may be required in those who have evidence of latent tuberculosis and are receiving treatment with immnosuppressants (including cytotoxics and possibly long-term treatment with systemic corticosteroids). In these cases, chemoprophylaxis involves use of either isoniazid alone for 6 months or of isoniazid and rifampicin for 3 months, see Table 2, section 5.1; longer chemoprophylaxis is not recommended.

For prevention of tuberculosis in susceptible close contacts or those who have become tuberculin-positive, see Table 2, section 5.1. For advice on immunisation against tuberculosis, see section 14.4

**Monitoring**  Since isoniazid, rifampicin and pyrazinamide are associated with liver toxicity (see Appendix 2), **hepatic function** should be checked before treatment with these drugs. Those with pre-existing liver disease or alcohol dependence should have frequent checks particularly in the first 2 months. If there is no evidence of liver disease (and pre-treatment liver function is normal), further checks are only necessary if the patient develops fever, malaise, vomiting, jaundice or unexplained deterioration during treatment. In view of the need to comply fully with antituberculosis treatment on the one hand and to guard against serious liver damage on the other, patients and their carers should be informed carefully how to recognise signs of liver disorders and advised to discontinue treatment and seek immediate medical attention should symptoms of liver disease occur.

**Renal function** should be checked before treatment with antituberculosis drugs and appropriate dosage adjustments made. Streptomycin or ethambutol should preferably be avoided in patients with renal impairment, but if used, the dose should be reduced and the plasma-drug concentration monitored.

**Visual acuity** should be tested before ethambutol is used (see below).

Major causes of treatment failure are incorrect prescribing by the physician and inadequate compliance by the patient. Monthly tablet counts and urine examination (rifampicin imparts an orange-red colouration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist physician.

**Isoniazid** is cheap and highly effective. Like rifampicin it should always be included in any antituberculous regimen unless there is a specific contra-indication. Its only common side-effect is peripheral neuropathy which is more likely to occur where there are pre-existing risk factors such as diabetes, alcohol dependence, chronic renal failure, malnutrition and HIV infection. In these circumstances pyridoxine 10 mg daily (or 20 mg daily if suitable product not available) (section 9.6.2) should be given prophylactically from the start of treatment. Other side-effects such as hepatitis (important: see Monitoring above) and psychosis are rare.

**Rifampicin**, a rifamycin, is a key component of any antituberculous regimen. Like isoniazid it should always be included unless there is a specific contra-indication. During the first two months (‘initial phase’) of rifampicin administration transient disturbance of liver function with elevated serum transaminases is common but generally does not require interruption of treatment. Occasionally more serious liver toxicity requires a change of treatment particularly in those with pre-existing liver disease (important: see Monitoring above). On intermittent treatment six toxicity syndromes have been recognised—influenza-like, abdominal, and respiratory symptoms, shock, renal failure, and thrombocytopenic purpura—and can occur in 20 to 30% of patients.
**CAPREOMYCIN**

**Indications** in combination with other drugs, tuberculosis resistant to first-line drugs

**Cautions** hepatic impairment; renal impairment (Appendix 3); auditory impairment; monitor renal, hepatic, auditory, and vestibular function and electrolytes; pregnancy (teratogenic in animals, Appendix 4) and breast-feeding (Appendix 5); **interactions:** Appendix 1 (capreomycin)

**Side-effects** hypersensitivity reactions including urticaria and rashes; leucocytosis or leucopenia, rarely thrombocytopenia; changes in liver function tests; nephrotoxicity, electrolyte disturbances; hearing loss with tinnitus and vertigo; neuromuscular block after large doses, pain and induration at injection site

**Dose**
- By deep intramuscular injection, 1 g daily (not more than 20 mg/kg) for 2–4 months, then 1 g 2–3 times each week

**Capastat® (King)**

**Injection** powder for reconstitution, capreomycin sulphate 1 million units (= capreomycin approx. 1 g). Net price per vial = £22.89

**CYCLOSERINE**

**Indications** in combination with other drugs, tuberculosis resistant to first-line drugs

**Cautions** reduce dose in renal impairment (avoid if creatinine clearance less than 10 mL/minute); monitor haematological, renal, and hepatic function; pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions:** Appendix 1 (cycloserine)

**Contraindications** severe renal impairment, epilepsy, depression, severe anxiety, psychotic states, alcohol dependence, acute porphyria (section 9.8.2)

**Side-effects** mainly neurological, including headache, dizziness, vertigo, drowsiness, tremor, convulsions, confusion, psychosis, depression (discontinue or reduce dose if symptoms of CNS toxicity); rashes, allergic dermatitis (discontinue or reduce dose); megaloblastic anaemia; changes in liver function tests; heart failure at high doses reported

**Dose**
- Initially 250 mg every 12 hours for 2 weeks increased according to blood concentration and response to max. 500 mg every 12 hours; **CHILD** initially 10 mg/kg daily adjusted according to blood concentration and response

**Note** Blood concentration monitoring required especially in renal impairment or if dose exceeds 500 mg daily or if signs of toxicity; blood concentration should not exceed 30 mg/litre

**Cycloserine (King)**

**Capsules** red/grey cycloserine 250 mg, net price 100-cap pack = £303.45. Label: 2, 8

**ETHAMBUTOL HYDROCHLORIDE**

**Indications** tuberculosis, in combination with other drugs

**Cautions** reduce dose in renal impairment and if creatinine clearance less than 30 mL/minute, also monitor plasma-ethambutol concentration (Appendix 3); elderly; pregnancy; test visual acuity before treatment and warn patients to report visual changes—see

Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulphonylear, and anticoagulants; **interactions:** Appendix 1 (rifamycins). **Important:** the effectiveness of hormonal contraceptives is reduced and alternative family planning advice should be offered (section 7.3.1).

Rifabutin, a newly introduced rifamycin, is indicated for prophylaxis against *M. avium* complex infections in patients with a low CD4 count; it is also licensed for the treatment of non-tuberculous mycobacterial disease and pulmonary tuberculosis. **Important:** as with rifampicin it induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced requiring alternative family planning methods.

Pyrazinamide [unlicensed] is a bactericidal drug only active against intracellular dividing forms of *Pyrazinamide* and pulmonary tuberculosis. **Important:** its effectiveness is reduced when first-line drugs cause unacceptable side-effects, include amikacin, capreomycin, cycloserine, newer macrolides (e.g. azithromycin and clarithromycin), moxifloxacin and protionamide (prothionamide; no longer on UK market).
notes above; young children (see notes above)—routine ophthalmological monitoring recommended

**Contra-indications** optic neuritis, poor vision

**Side-effects** optic neuritis, red/green colour blindness, peripheral neuritis, rarely rash, pruritus, urti- caria, thrombocytopenia

**Dose**
- See notes above

**Note** Peak concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–12 mcg/ml/litre); ‘trough’ (pre-dose) concentration should be less than 1 mg/litre (4 mcg/ml/litre); see Cautions above; for advice on laboratory assay of ethambutol contact the Poisons Unit at New Cross Hospital (Tel (020) 7771 5360)

**Ethambutol** (Non-proprietary)  
Tablets, ethambutol hydrochloride 100 mg (yellow), net price 56-tab pack = £11.51; 400 mg (grey), 56-tab pack = £42.74. Label: 8

**ISONIAZID**

**Indications** tuberculosis, in combination with other drugs; prophylaxis—Table 2, section 5.1

**Cautions** hepatic impairment (Appendix 2; see also below); renal impairment (Appendix 3); slow acety- lator status (increased risk of side-effects); epilepsy; history of psychosis; alcohol dependence, malnutri- tion, diabetes mellitus, HIV infection (risk of periph- eral neuritis); pregnancy (Appendix 4) and breast- feeding (Appendix 5); acute porphyria (section 9.8.2); interactions: Appendix 1 (isoniazid)

**Hepatic disorders** Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

**Contra-indications** drug-induced liver disease

**Side-effects** nausea, vomiting, constipation, dry mouth; peripheral neuritis with high doses (pyridoxine prophylaxis, see notes above), optic neuritis, convulsions, psychotic episodes, vertigo; hypersensitivity reactions including fever, erythema multiforme, purpura; blood disorders including agranulocytosis, haemolytic anaemia, aplastic anaemia; hepatitis (especially over age of 35 years); systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia, and gynaecomastia reported; hearing loss and tinnitus (in patients with end-stage renal impairment)

**Dose**
- By mouth or by intramuscular or intravenous injection, see notes above

**Isoniazid** (Non-proprietary)  
Tablets, isoniazid 50 mg, net price 56-tab pack = £8.34; 100 mg, 28-tab pack = £8.29. Label: 8, 22

**Elixir** (BPC), isoniazid 50 mg, citric acid monohydrate 12.5 mg, sodium citrate 60 mg, concentrated anise water 0.05 mL, compound tartrazine solution 0.05 mL, glycerol 1 mL, double-strength chloroform water 2 mL, water to 5 mL. Label: 8, 22

‘Special order’ [unlicensed] product; contact Martindale, Rose- mont, or regional hospital manufacturing unit

**Injection** isoniazid 25 mg/mL, net price 2-mL amp = £11.04

**PYRAZINAMIDE**

**Indications** tuberculosis in combination with other drugs [unlicensed]

**Cautions** pregnancy (Appendix 4); hepatic impairment (monitor hepatic function, see also below and Appendix 2); diabetes; gout (avoid in acute attack); interactions: Appendix 1 (pyrazinamide)

**Hepatic disorders** Patients or their carers should be told how to recognise signs of liver disorder, and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop

**Contra-indications** acute porphyria (section 9.8.2)

**Side-effects** hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting, flushing, dysuria, arthralgia, sideroblastic anaemia, rash and occasionally photo-sensitivity

**Dose**
- See notes above

**Pyrazinamide** (Non-proprietary)  
Tablets, scored, pyrazinamide 500 mg. Label: 8

Available from ‘special order’ manufacturers or specialist-importing companies, see p. 939

**RIFABUTIN**

**Indications** see under Dose

**Cautions** see under Rifampicin; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); acute porphyria (section 9.8.2)

**Side-effects** nausea, vomiting; leucopenia, thrombo- cytopenia, anaemia, rarely haemolyis; raised liver enzymes, jaundice, rarely hepatitis; uveitis following high doses or administration with drugs which raise plasma concentration—see also interactions: Appendix 1 (rifamycins); arthralgia, myalgia, influenza-like syndrome, dyspnoea; also hypersensitivity reactions including fever, rash, eosinophilia, bronchospasm, shock; skin, urine, saliva and other body secretions coloured orange-red; asymptomatic corneal opacities reported with long-term use

**Dose**
- Prophylaxis of *Mycobacterium avium* complex infec- tions in immunosuppressed patients with low CD4 count (see product literature), 300 mg daily as a single dose
- Treatment of non-tuberculous mycobacterial disease, in combination with other drugs, 450–600 mg daily as a single dose for up to 6 months after cultures nega- tive
- Treatment of pulmonary tuberculosis, in combination with other drugs, 150–450 mg daily as a single dose for at least 6 months
- **CHILD** not recommended

**Mycobutin®** (Pharmacia)  
Capsules, red-brown, rifabutin 150 mg. Net price 30- cap pack = £90.38. Label: 8, 14, counselling, lenses, see under Rifampicin

**RIFAMPICIN**

**Indications** see under Dose

**Cautions** hepatic impairment (Appendix 2; liver func- tion tests and blood counts in hepatic disorders,
alcohol dependence, and on prolonged therapy, see also below); renal impairment (if above 600 mg daily); pregnancy and breast-feeding (see notes above and Appendix 4 and Appendix 5); acute porphyria (section 9.8.2); important: advise patients on hormonal contraceptives to use additional means (see also section 7.3.1); discolour soft contact lenses; see also notes above; interactions: Appendix 1 (rifamycins) Note If treatment interrupted re-introduce with low dosage and increase gradually; discontinue permanently if serious side-effects develop; hepatic disorders Patients or their carers should be told how to recognise signs of liver disorder; and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Contra-indications jaundice; side-effects gastro-intestinal symptoms including anorexia, nausea, vomiting, diarrhoea (antibiotic-associated colitis reported); headache, drowsiness; those occurring mainly on intermittent therapy include influenza-like symptoms (with chills, fever, dizziness, bone pain), respiratory symptoms (including shortness of breath), collapse and shock, haemolytic anaemia, thrombocytopenic purpura, disseminated intravascular coagulation, and acute renal failure; alterations of liver function, jaundice, flushing, urticaria, and rash; other side-effects reported include oedema, psychosis, renal insufficiency, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigoid reactions, leucopenia, dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, exfoliative dermatitis, and systemic lupus erythematosus. Discontinue treatment if symptoms develop and increase gradually; discontinue permanently if serious side-effects develop.

Dose
- Brucellosis, legionnaires’ disease, endocarditis and serious staphylococcal infections, in combination with other drugs, by mouth or by intravenous infusion, 0.6–1.2 g daily (in 2–4 divided doses)
- Tuberculosis, in combination with other drugs, see notes above
- Leprosy, section 5.1.10
- Prophylaxis of meningococcal meningitis and Haemophilus influenzae (type b) infection, section 5.1, table 2

Rifampicin (Non-proprietary) Rifadin® (Aventis Pharma)

Capsules, rifampicin 150 mg, net price 20 = £4.17; 300 mg, 20 = £10.44. Label: 8, 14, 22, counselling, see lenses above

Rifadin® (Aventis Pharma) Capsules, rifampicin 150 mg (blue/red), net price 20 = £3.81; 300 mg (red), 20 = £7.62. Label: 8, 14, 22, counselling, see lenses above

Syrup, red, rifampicin 100 mg/5 mL (raspberry-flavoured). Net price 120 mL = £3.70. Label: 8, 14, 22, counselling, see lenses above

Intravenous infusion, powder for reconstitution, rifampicin. Net price 600-mg vial (with solvent) = £7.98 Electrolytes Na < 0.5 mmol/vial

Rimactane® (Sandoz) Capsules, rifampicin 150 mg (red), net price 60-cap pack = £11.35; 300 mg (red/brown), 60-cap pack = £22.69. Label: 8, 14, 22, counselling, see lenses above

Combination preparations

Rifater® (Aventis Pharma)

Tablets, pink, s/c, rifampicin 120 mg, isoniazid 50 mg, pyrazinamide 300 mg. Net price 20 = £4.39. Label: 8, 14, 22, counselling, see lenses above

Dose initial treatment of pulmonary tuberculosis, patients up to 40 kg 3 tablets daily preferably before breakfast, 40–49 kg 4 tablets daily, 50–64 kg 5 tablets daily, 65 kg or more, 6 tablets daily; not suitable for use in children

Rifinah 150® (Aventis Pharma)

Tablets, pink, s/c, rifampicin 150 mg, isoniazid 100 mg, net price 84-tab pack = £16.55. Label: 8, 14, 22, counselling, see lenses above

Dose ADULT under 50 kg, 3 tablets daily; preferably before breakfast

Rifinah 300® (Aventis Pharma)

Tablets, orange, s/c, rifampicin 300 mg, isoniazid 150 mg, net price 56-tab pack = £21.87. Label: 8, 14, 22, counselling, see lenses above

Dose ADULT 30 kg and over, 2 tablets daily; preferably before breakfast

STREPTOMYCIN

Indications tuberculosis, in combination with other drugs; adjunct to doxycycline in brucellosis; enterococcal endocarditis (Table 1, section 5.1)

Cautions see under Aminoglycosides, section 5.1.4; interactions: Appendix 1 (aminoglycosides)

Contra-indications see under Aminoglycosides, section 5.1.4

Side-effects see under Aminoglycosides, section 5.1.4; also hypersensitivity reactions, paraesthesia of mouth

Dose
- By deep intramuscular injection, tuberculosis [unlicensed], see notes above; brucellosis, expert advice essential

Note One-hour (‘peak’) concentration should be 15–40 mg/litre; pre-dose (‘trough’) concentration should be less than 5 mg/litre (less than 1 mg/litre in renal impairment or in those over 50 years)

Streptomycin Sulphate (Non-proprietary)

Injection, powder for reconstitution, streptomycin (as sulphate), net price 1-g vial = £8.25 Available as an unlicensed preparation from UCB Pharma

5.1.10 Antileprotic drugs

Advice from a member of the Panel of Leprosy Opinion is essential for the treatment of leprosy (Hansen’s disease). Details of the Panel can be obtained from the Department of Health telephone (020) 7972 4480.

The World Health Organization has made recommendations to overcome the problem of dapsone resistance and to prevent the emergence of resistance to other antileprotic drugs. Drugs recommended are dapsone, rifampicin (section 5.1.9), and clofazimine. Other drugs with significant activity against Mycobacterium leprae include ofloxacin, minocycline and clarithromycin, but none of these are as active as rifampicin; at present they should be reserved as second-line drugs for leprosy.

A three-drug regimen is recommended for multibacillary leprosy (lepromatous, borderline-lepromatous, and border-line leprosy) and a two-drug regimen for paucibac-
**Multibacillary leprosy (3-drug regimen)**
- **Rifampicin**: 600 mg once-monthly, supervised (450 mg for adults weighing less than 35 kg)
- **Dapsone**: 100 mg daily, self-administered (50 mg daily or 1–2 mg/kg daily for adults weighing less than 35 kg)
- **Clofazimine**: 300 mg once-monthly, supervised, and 50 mg daily (or 100 mg on alternate days), self-administered

Multibacillary leprosy should be treated for at least 2 years. Treatment should be continued unchanged during both type I (reversal) or type II (erythema nodosum lepromatum) reactions. During reversal reactions neuritic pain or weakness can herald the rapid onset of permanent nerve damage. Treatment with prednisolone (initially 40–60 mg daily) should be instituted at once. Mild type II reactions may respond to aspirin. Severe type II reactions may require corticosteroids; thalidomide (unlicensed) is also useful in men and post-menopausal women who have become corticosteroid dependent, but it should be used under specialist supervision and it should never be used in women of child-bearing potential (significant teratogenic risk—for CSM guidance on prescribing, see Current Problems in Pharmacovigilance 1994; 20, 8). Increased doses of clofazimine 100 mg 3 times daily for the first month with subsequent reductions, are also useful but may take 4–6 weeks to attain full effect.

**Paucibacillary leprosy (2-drug regimen)**
- **Rifampicin**: 600 mg once-monthly, supervised (450 mg for those weighing less than 35 kg)
- **Dapsone**: 100 mg daily, self-administered (50 mg daily or 1–2 mg/kg daily for adults weighing less than 35 kg)

Paucibacillary leprosy should be treated for 6 months. If treatment is interrupted the regimen should be recommenced where it was left off to complete the full course. Neither the multibacillary nor the paucibacillary anti-leprosy regimen is sufficient to treat tuberculosis.

**Dapsone**

**Dose**
- Leprosy. 1–2 mg/kg daily, see notes above
- Dermatitis herpetiformis, see specialist literature

**Dapsone (Non-proprietary) [NHS]**

**Tablets**, dapsone 50 mg, net price 28-tab pack = £23.01; 100 mg, 28-tab pack = £33.74. Label: 

**CLOFAZIMINE**

**Indications**
- Leprosy

**Cautions**
- Hepatic and renal impairment; pregnancy; breast-feeding (Appendix 5); may discolour soft contact lenses; avoid if persistent abdominal pain and diarrhoea

**Side-effects**
- Nausea, vomiting (hospitalise if persistent), abdominal pain; headache, tiredness; brownish-black discoloration of lesions and skin including areas exposed to light; reversible hair discoloration; dry skin; red discoloration of faeces, urine and other body fluids; also rash, pruritus, photosensitivity, acne-like eruptions, anorexia, eosinophilic enteropathy, bowel obstruction, dry eyes, dimmed vision, macular and subepithelial corneal pigmentation; elevation of blood sugar, weight loss, splenic infarction, lymphadenopathy

**Dose**
- Leprosy, see notes above
- Lepromatous leprosy reactions, dosage increased to 300 mg daily for max. of 3 months

**Clofazimine (Non-proprietary) [NHS]**

**Capsules**, clofazimine 100 mg. Label: 8, 14, 21 Available on named-patient basis

**5.1.11 Metronidazole and tinidazole**

**Metronidazole** is an antimicrobial drug with high activity against anaerobic bacteria and protozoa; indications include trichomonal vaginitis (section 5.4.3), bacterial vaginosis (notably *Gardnerella vaginalis* infections), and *Entamoeba histolytica* and *Giardia lamblia* infections (section 5.4.2). It is also used for surgical and gynaecological sepsis in which its activity against colonic anaerobes, especially *Bacteroides fragilis*, is important. Metronidazole by the rectal route is an effective alternative to the intravenous route when oral administration is not possible. Intravenous metronidazole is used for the treatment of established cases of tetanus; diazepam (section 10.2.2) and tetanus immunoglobulin (section 14.5) are also used.

Metronidazole by mouth is effective for the treatment of *Clostridium difficile* infection, see also section 1.5; it can be given by intravenous infusion if oral treatment is inappropriate.

Topical metronidazole (section 13.10.1.2) reduces the odour produced by anaerobic bacteria in fungating tumours; it is also used in the management of rosacea (section 13.6).

**Tinidazole** is similar to metronidazole but has a longer duration of action.
**Oral infections** Metronidazole is an alternative to a penicillin for the treatment of many oral infections where the patient is allergic to penicillin or the infection is due to beta-lactamase-producing anaerobes (Table 1, section 5.1). It is the drug of first choice for the treatment of acute necrotising ulcerative gingivitis (Vincent’s infection) and pericoronitis; suitable alternatives are amoxicillin (section 5.1.1.3) and erythromycin (section 5.1.5). For these purposes metronidazole in a dose of 200 mg 3 times daily for 3 days is sufficient, but the duration of treatment may need to be longer in pericoronitis. Tinidazole is licensed for the treatment of acute ulcerative gingivitis.

---

**METRONIDAZOLE**

**Indications** anaerobic infections (including dental), see under Dose below; protozoal infections (section 5.4.2); *Helicobacter pylori* eradication (section 1.3); skin (section 13.10.1.2)

**Cautions** disulfiram-like reaction with alcohol, hepatic impairment and hepatic encephalopathy (Appendix 2); pregnancy (Appendix 4) and breast-feeding (Appendix 5); avoid in acute porphyria (section 9.8.2); clinical and laboratory monitoring advised if treatment exceeds 10 days; **interactions**: Appendix 1 (metronidazole)

**Side-effects** gastro-intestinal disturbances (including nausea and vomiting), taste disturbances, furred tongue, oral mucositis, anorexia; *very rarely* hepatitis, jaundice, pancreatitis, drowsiness, dizziness, headache, ataxia, psychic disorders, darkening of urine, thrombocytopenia, pancytopenia, myalgia, arthralgia, visual disturbances, rash, pruritus, and erythema multiforme; on prolonged or intensive therapy peripheral neuropathy, transient epileptiform seizures, and leucopenia

**Dose**
- Anaerobic infections (usually treated for 7 days and for 7–10 days in *Clostridium difficile* infection), by mouth, *either* 800 mg initially then 400 mg every 8 hours or 500 mg every 8 hours, **CHILD** 7.5 mg/kg every 8 hours; by rectum, 1 g every 8 hours for 3 days, then 1 g every 12 hours, **CHILD** every 8 hours for 3 days, then every 12 hours, age up to 1 year 125 mg, 1–5 years 250 mg, 5–10 years 500 mg, over 10 years, adult dose; by intravenous infusion over 20 minutes, 500 mg every 8 hours; **CHILD** 7.5 mg/kg every 8 hours
- Leg ulcers and pressure sores, by mouth, 400 mg every 8 hours for 7 days
- Bacterial vaginosis, by mouth, 400–500 mg twice daily for 5–7 days or 2 g as a single dose
- Pelvic inflammatory disease (see also Table 1, section 5.1), by mouth, 400 mg twice daily for 14 days
- Acute ulcerative gingivitis, by mouth, 200–250 mg every 8 hours for 3 days; **CHILD** 1–3 years 50 mg every 8 hours for 3 days; 3–7 years 100 mg every 12 hours; 7–10 years 100 mg every 8 hours
- Acute oral infections, by mouth, 200 mg every 8 hours for 3–7 days (see also notes above); **CHILD** 1–3 years 50 mg every 8 hours for 3–7 days; 3–7 years 100 mg every 12 hours; 7–10 years 100 mg every 8 hours
- Surgical prophylaxis, by mouth, 400–500 mg 2 hours before surgery; up to 3 further doses of 400–500 mg may be given every 8 hours for high-risk procedures; **CHILD** 7.5 mg/kg 2 hours before surgery; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

**By rectum**, 1 g 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures; **CHILD** 5–10 years 500 mg 2 hours before surgery; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures

**By intravenous infusion** (if rectal administration inappropriate), 500 mg at induction; up to 3 further doses of 500 mg may be given every 8 hours for high-risk procedures; **CHILD** 7.5 mg/kg at induction; up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures

**Note** Metronidazole doses in BNF may differ from those in product literature

**Metronidazole** (Non-proprietary)
- **Tablets**, metronidazole 200 mg, net price 21-tab pack = £1.10; 400 mg, 21-tab pack = £1.29. Label: 4, 9, 21, 25, 27
- Brands include Vaginyl
- **Tablets**, metronidazole 500 mg, net price 21-tab pack = £26.79. Label: 4, 9, 21, 25, 27
- **Suspension**, metronidazole (as benzoate) 200 mg/5 mL. Net price 100 mL = £9.07. Label: 4, 9, 23
- Brands include Norazol
- **Intravenous infusion**, metronidazole 5 mg/mL. Net price 20-mL amp = £1.56, 100-mL container = £3.41
- **Dental prescribing on NHS** Metronidazole Tablets and Oral Suspension may be prescribed

**Flagyl® (Winthrop)**
- **Tablets**, both f/c, ivory, metronidazole 200 mg, net price 21-tab pack = £4.67; 400 mg, 14-tab pack = £6.60. Label: 4, 9, 21, 25, 27
- **Suppositories**, metronidazole 500 mg, net price 10 = £15.80; 1 g, 10 = £24.00. Label: 4, 9

**Flagyl® (Aventis Pharma)**
- **Intravenous infusion**, metronidazole 5 mg/mL, net price 100-mL Viaflex® bag = £2.80
- **Electrolytes** Na 13.37 mmol/100-mL bag

**Flagyl S® (Winthrop)**
- **Suspension**, orange- and lemon-flavoured, metronidazole (as benzoate) 200 mg/5 mL. Net price 100 mL = £11.63. Label: 4, 9, 23

**Metroly® (Sandoz)**
- **Intravenous infusion**, metronidazole 5 mg/mL, net price 100-mL Steriflex® bag = £1.22
- **Electrolytes** Na 14.53 mmol/100-mL bag
- **Suppositories**, metronidazole 500 mg, net price 10 = £12.34; 1 g, 10 = £18.34. Label: 4, 9

---

**TINIDAZOLE**

**Indications** anaerobic infections, see under Dose below; protozoal infections (section 5.4.2); *Helicobacter pylori* eradication (section 1.3)

**Cautions** see under Metronidazole; pregnancy (manufacturer advises avoid in first trimester); avoid in acute porphyria (section 9.8.2); **interactions**: Appendix 1 (tinidazole)

**Side-effects** see under Metronidazole

**Dose**
- Anaerobic infections, 2 g initially, followed by 1 g daily or 500 mg twice daily, usually for 5–6 days
Fasigyn® (Pfizer)  ™  
Tablets, 1/2, tinidazole 500 mg. Net price 20-tab pack  
= £13.80. Label: 4, 9, 21, 25

## 5.1.12 Quinolones

### Nalidixic acid and norfloxacin are effective in uncomplicated urinary-tract infections.

**Ciprofloxacin** is active against both Gram-positive and Gram-negative bacteria. It is particularly active against Gram-negative bacteria, including salmonella, shigella, campylobacter, neisseria, and pseudomonas. Ciprofloxacin has only moderate activity against Gram-positive bacteria such as *Streptococcus pneumoniae* and *Enterococcus faecalis*; it should not be used for pneumococcal pneumonia. It is active against chlamydia and some mycobacteria. Most anaerobic organisms are not susceptible. Ciprofloxacin can be used for respiratory tract infections (but not for pneumococcal pneumonia), urinary-tract infections, infections of the gastro-intestinal system (including typhoid fever), bone and joint infections, gonorrhoea and septicaemia caused by sensitive organisms.

**Ofloxacin** is used for urinary-tract infections, lower respiratory-tract infections, gonorrhoea, and non-gonococcal urethritis and cervicitis.

**Levofloxacin** is active against Gram-positive and Gram-negative organisms. It has greater activity against pneumococci than ciprofloxacin. Levofloxacin is licensed for community-acquired pneumonia but it is considered to be second-line treatment for this indication.

Although ciprofloxacin, levofloxacin and ofloxacin are licensed for skin and soft-tissue infections, many staphylococci are resistant to the quinolones and their use should be avoided in MRSA infections.

**Moxifloxacin** should be reserved for the treatment of sinusitis, community-acquired pneumonia, or exacerbations of chronic bronchitis which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials. It has been associated with life-threatening hepatotoxicity. Moxifloxacin is active against Gram-positive and Gram-negative organisms. It has greater activity against Gram-positive organisms, including pneumococci, than ciprofloxacin. Moxifloxacin is not active against *Pseudomonas aeruginosa* or meticillin-resistant *Staphylococcus aureus* (MRSA).

**Anthrax** Inhalation or gastro-intestinal anthrax should be treated initially with either ciprofloxacin or doxycycline [unlicensed indication] (section 5.1.3) combined with one or two other antibacterials (such as amoxicillin, benzylpenicillin, chloramphenicol, clarithromycin, clindamyin, imipenem with cilastatin, rifampicin [unlicensed indication], and vancomycin). When the condition improves and the sensitivity of the *Bacillus anthracis* strain is known, treatment may be switched to a single antibacterial. Treatment should continue for 60 days because germination may be delayed.

**Cutaneous anthrax** should be treated with either ciprofloxacin [unlicensed indication] or doxycycline [unlicensed indication] (section 5.1.3) for 7 days. Treatment may be switched to amoxicillin (section 5.1.1.3) if the infecting strain is susceptible. Treatment may need to be extended to 60 days if exposure is due to aerosol. A combination of antibacterials for 14 days is recommended for cutaneous anthrax with systemic features, extensive oedema, or lesions of the head or neck.

Ciprofloxacin or doxycycline may be given for post-exposure prophylaxis. If exposure is confirmed, antibacterial prophylaxis should continue for 60 days. Antibacterial prophylaxis may be switched to amoxicillin after 10–14 days if the strain of *B. anthracis* is susceptible. Vaccination against anthrax (section 14.4) may allow the duration of antibacterial prophylaxis to be shortened.

**Cautions** Quinolones should be used with caution in patients with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency (section 9.1.5), myasthenia gravis (risk of exacerbation), in renal impairment (Appendix 3); pregnancy (Appendix 4), during breast-feeding (Appendix 5), and in children or adolescents (arthropathy has developed in weight-bearing joints in young animals—see below). Exposure to excessive sunlight should be avoided (discontinue if photosensitivity occurs). The CSM has warned that quinolones may induce convulsions in patients with or without a history of convulsions; taking NSAIDs at the same time may also induce them. Other interactions: Appendix 1 (quinolones).

**Use in children** Quinolones cause arthropathy in the weight-bearing joints of immature animals and are therefore generally not recommended in children and growing adolescents. However, the significance of this effect in humans is uncertain and in some specific circumstances short-term use of a quinolone in children may be justified. Nalidixic acid is used for urinary-tract infections in children over 3 months of age. Ciprofloxacin is licensed for pseudomonal infections in cystic fibrosis (for children above 5 years of age), and for treatment and prophylaxis of inhalational anthrax.

### Tendon damage

Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment; cases have also been reported several months after stopping a quinolone. Healthcare professionals are reminded that:

- quinolones are contra-indicated in patients with a history of tendon disorders related to quinolone use;
- patients over 60 years of age are more prone to tendon damage;
- kidney, heart, or lung transplant recipients are more prone to tendon damage;
- the risk of tendon damage is increased by the concomitant use of corticosteroids;
- if tendinitis is suspected, the quinolone should be discontinued immediately.

### Side-effects

Side-effects of the quinolones include nausea, vomiting, dyspepsia, abdominal pain, diarrhoea (rarely antibiotic-associated colitis), headache, dizziness, rash (very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis). Less frequent side-effects include anorexia, sleep disturbances, asthenia, confusion, anxiety, depression, hallucinations, tremor, blood disorders (including eosinophilia, leucopenia, thrombo-
cytopenia), arthralgia, myalgia, disturbances in vision and taste. Other side-effects reported rarely or very rarely include hepatic dysfunction (including jaundice and hepatitis), hypotension, vasculitis, dyspnoea (more frequent with moxifloxacin), convulsions, psychoses, paraesthesia, renal failure, interstitial nephritis, tendin inflammation and damage (see also Tendon Damage above), photosensitivity, disturbances in hearing and smell. The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions (neuralgic severe rash) occur.

## Ciprofloxacin

**Indications**  
see notes above and under Dose; eye infections (section 11.3.1)

**Cautions**  
see notes above; avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); interactions: Appendix 1 (quinolones)

Driving  
May impair performance of skilled tasks (e.g. driving); effects enhanced by alcohol

**Side-effects**  
see notes above; also flatulence, pain and phlebitis at injection site; rarely dysphagia, pancreatitis, chest pain, tachycardia, syncope, oedema, hot flushes, abnormal dreams, sweating, hyperglycaemia, and erythema nodosum; very rarely movement disorders, tinnitus, and tenosynovitis

**Dose**  
- **By mouth**, respiratory-tract infections, 250–750 mg twice daily
- Urinary-tract infections, 250–500 mg twice daily  
(100 mg twice daily for 3 days in acute uncomplicated cystitis in women)
- Chronic prostatitis, 500 mg twice daily for 28 days
- Gonorrhoea, 500 mg as a single dose
- Pseudomonal lower respiratory-tract infection in cystic fibrosis, 750 mg twice daily; **CHILD** 5–17 years (see Cautions above), up to 20 mg/kg (max. 750 mg) twice daily
- Most other infections, 500–750 mg twice daily
- Surgical prophylaxis, 750 mg 60–90 minutes before procedure
- Prophylaxis of meningococcal meningitis [not licensed], Table 2, section 5.1
- **By intravenous infusion** (over 30–60 minutes; 400 mg over 60 minutes), 200–400 mg twice daily  
Pseudomonal lower respiratory-tract infection in cystic fibrosis, 400 mg twice daily; **CHILD** 5–17 years (see Cautions above), up to 10 mg/kg (max. 400 mg) 3 times daily
- Urinary-tract infections, 100 mg twice daily
- Gonorrhoea, 100 mg as a single dose
- **CHILD** and **ADOLESCENT** not recommended (see Cautions above) but where benefit outweighs risk, **by mouth**, 5–15 mg/kg (max. 750 mg) twice daily or **by intravenous infusion**, 4–8 mg/kg (max. 400 mg) twice daily
- Anthrax (treatment and post-exposure prophylaxis, see notes above), **by mouth**, 500 mg twice daily; **CHILD** and **ADOLESCENT** 15 mg/kg (max. 500 mg) twice daily
- **By intravenous infusion**, 400 mg twice daily; **CHILD** and **ADOLESCENT** 10 mg/kg (max. 400 mg) twice daily

**Ciprofloxacin** (Non-proprietary)  
- **Tablets**, ciprofloxacin (as hydrochloride) 100 mg, net price 6-tab pack = £1.08; 250 mg, 10-tab pack = £1.12, 20-tab pack = £1.17; 500 mg, 10-tab pack = £1.19, 20-
  - **tab pack = £1.19**; 750 mg, 10-tab pack = £1.99.
  - Label: 7, 9, 25, counselling, driving

**Intravenous infusion**, ciprofloxacin (as lactate)  
2 mg/mL, net price 50-ml bottle = £8.00, 100-ml bottle = £15.00, 200-ml bottle = £22.00

**Ciproxin** *(Bayer)*  
- **Tablets**, all 1/2 c, ciprofloxacin (as hydrochloride) 100 mg, net price 6-tab pack = £2.80; 250 mg (scored), 10-tab pack = £7.50, 20-tab pack = £15.00; 500 mg (scored), 10-tab pack = £14.20, 20-tab pack = £28.40; 750 mg, 10-tab pack = £20.00. Label: 7, 9, 25, counselling, driving

**Suspension**, strawberry-flavoured, ciprofloxacin for reconstitution with diluent provided, 250 mg/5 mL, net price 100 mL = £16.50. Label: 7, 9, 25, counselling, driving

**Intravenous infusion**, ciprofloxacin (as lactate)  
2 mg/mL, in sodium chloride 0.9%, net price 50-ml bottle = £8.65, 100-ml bottle = £16.89, 200-ml bottle = £25.70

**Label**: 7, 9, 25, selling, driving

**Electrolytes**  
- **Na** 15.4 mmol/100-ml bottle

## Levofloxacín

**Indications**  
see under Dose

**Cautions**  
see notes above; predisposition to QT interval prolongation (including cardiac disease, congenital long QT syndrome, electrolyte disturbances, concomitant use with other drugs known to prolong QT interval); interactions: Appendix 1 (quinolones)

Driving  
May impair performance of skilled tasks (e.g. driving)

**Side-effects**  
see notes above; also flatulence, constipation; rarely tachycardia; very rarely pneumonitis, peripheral neuropathy, and hypoglycaemia; also reported, rhabdomyolysis and potentially life-threatening hepatic failure; local reactions and transient hypotension reported with infusion

**Dose**  
- **By mouth**, acute sinusitis, 500 mg daily for 10–14 days
- Exacerbation of chronic bronchitis, 250–500 mg daily for 7–10 days
- Community-acquired pneumonia, 500 mg once or twice daily for 7–14 days
- Urinary-tract infections, 250 mg daily for 7–10 days  
(for 3 days in uncomplicated infection)
- Chronic prostatitis, 500 mg once daily for 28 days
- Skin and soft tissue infections, 250 mg daily or 500 mg once or twice daily for 7–14 days
- **By intravenous infusion** (over at least 60 minutes for 500 mg), community-acquired pneumonia, 500 mg once or twice daily
- Complicated urinary-tract infections, 250 mg daily, increased in severe infections
- Skin and soft tissue infections, 500 mg twice daily

**Tavanic** *(Hoechst Marion Roussel)*  
- **Tablets**, yellow-red, f/c, scored, levofloxacin 250 mg, net price 5-tab pack = £7.23, 10-tab pack = £14.45; 500 mg, 5-tab pack = £12.93, 10-tab pack = £25.85. Label: 6, 9, 25, counselling, driving

**Intravenous infusion**, levofloxacin 5 mg/mL, net price 100-ml bottle = £26.40

**Label**: 7, 9, 25, selling, driving

**Electrolytes**  
- **Na** 15.4 mmol/100-ml bottle

### Intravenous infusion
- **Levofloxacin**  
  - **Tablets**, yellow-red, f/c, scored, levofloxacin 250 mg, net price 5-tab pack = £7.23, 10-tab pack = £14.45; 500 mg, 5-tab pack = £12.93, 10-tab pack = £25.85. Label: 6, 9, 25, counselling, driving
  - **Intravenous infusion**, levofloxacin 5 mg/mL, net price 100-ml bottle = £26.40
  
**Label**: 7, 9, 25, selling, driving

**Electrolytes**  
- **Na** 15.4 mmol/100-ml bottle

### Intravenous infusion
- **Levofloxacin**  
  - **Tablets**, yellow-red, f/c, scored, levofloxacin 250 mg, net price 5-tab pack = £7.23, 10-tab pack = £14.45; 500 mg, 5-tab pack = £12.93, 10-tab pack = £25.85. Label: 6, 9, 25, counselling, driving
  - **Intravenous infusion**, levofloxacin 5 mg/mL, net price 100-ml bottle = £26.40
  
**Label**: 7, 9, 25, selling, driving

**Electrolytes**  
- **Na** 15.4 mmol/100-ml bottle

### Intravenous infusion
- **Levofloxacin**  
  - **Tablets**, yellow-red, f/c, scored, levofloxacin 250 mg, net price 5-tab pack = £7.23, 10-tab pack = £14.45; 500 mg, 5-tab pack = £12.93, 10-tab pack = £25.85. Label: 6, 9, 25, counselling, driving
  - **Intravenous infusion**, levofloxacin 5 mg/mL, net price 100-ml bottle = £26.40
  
**Label**: 7, 9, 25, selling, driving

**Electrolytes**  
- **Na** 15.4 mmol/100-ml bottle

### Intravenous infusion
**MOXIFLOXACIN**

**Indications** sinusitis, community-acquired pneumonia, or exacerbations of chronic bronchitis which have failed to respond to other antibacterials or for patients who cannot be treated with other antibacterials

**Cautions** see notes above; conditions pre-disposing to arrhythmias, including myocardial ischaemia; **interactions:** Appendix 1 (quinolones)

**Driving** May impair performance of skilled tasks (e.g. driving)

**Contra-indications** see notes above; severe hepatic impairment; history of QT-interval prolongation, bradycardia, history of symptomatic arrhythmias, heart failure with reduced left ventricular ejection fraction, electrolyte disturbances, concomitant use with other drugs known to prolong QT-interval

**Side-effects** see notes above; also gastritis, flatulence, constipation, arrhythmias, palpitation, anemia, hypoglycaemia, altered mental state, hallucinations, hypotension, syncope, dysphagia, abnormal dreams, incoordination, amnesia, hyperglycaemia, hyperuricaemia, and stomatitis; very rarely potentially life-threatening hepatic failure

**Dose**

- 400 mg once daily for 10 days in community-acquired pneumonia, for 5–10 days in exacerbation of chronic bronchitis, for 7 days in sinusitis

**Avelox**® (Bayer)  ▼ (R)

**Tablets**, red, f/c, moxifloxacin (as hydrochloride)

400 mg, net price 5-tab pack = £11.95. Label: 6, 9, counselling, driving

**NALIDIXIC ACID**

**Indications** urinary-tract infections

**Cautions** see notes above; avoid in acute porphyria (section 9.8.2); liver disease; false positive urinary glucose (if tested for reducing substances); monitor blood counts, renal and liver function if treatment exceeds 2 weeks; **interactions:** Appendix 1 (quinolones)

**Side-effects** see notes above; also reported toxic psychosis, increased intracranial pressure, cranial nerve palsy, metabolic acidosis

**Dose**

- 900 mg every 6 hours for 7 days, reduced in chronic infections to 600 mg every 6 hours; **CHILD** over 3 months max. 50 mg/kg daily in divided doses; reduced in prolonged therapy to 30 mg/kg daily

**Uriben**® (Rosemont) ▼ (R)

**Suspension**, pink, nalidixic acid 300 mg/5 mL, net price 150 mL (raspberry- and strawberry-flavoured) = £11.42. Label: 9, 11

**Excipients** include sucrose 450 mg/5mL

**NORFLOXACIN**

**Indications** see under Dose

**Cautions** see notes above; interactions: Appendix 1 (quinolones)

**Driving** May impair performance of skilled tasks (e.g. driving)

**Side-effects** see notes above; also tinnitus, epiphora; rarely pancreatitis; very rarely arrhythmias; also reported, polyneuropathy and exfoliative dermatitis

**Dose**

- ‘Lower’ urinary-tract infections, 400 mg twice daily for 7–10 days (for 3 days in uncomplicated infections)
- Chronic relapsing ‘lower’ urinary-tract infections, 400 mg twice daily for up to 12 weeks; may be reduced to 400 mg once daily if adequate suppression within first 4 weeks
- Chronic prostatitis, 400 mg twice daily for 28 days

**Norfloxacin** (Non-proprietary) ▼ (R)

**Tablets**, norfloxacin 400 mg. net price 6-tab pack = £2.29, 14-tab pack = £3.07. Label: 7, 9, 23, counselling, driving

**Utinor**® (MSD) ▼ (R)

**Tablets**, scored, norfloxacin 400 mg. Net price 7-tab pack = £2.56, 14-tab pack = £5.11. Label: 7, 9, 23, counselling, driving

**OFLOXACIN**

**Indications** see under Dose

**Cautions** see notes above; hepatic impairment (Appendix 2); history of psychiatric illness; **interactions:** Appendix 1 (quinolones)

**Driving** May affect performance of skilled tasks (e.g. driving); effects enhanced by alcohol

**Side-effects** see notes above; also tachycardia; rarely abnormal dreams, unsteady gait, neuropathy, and extrapyramidal symptoms; very rarely changes in blood sugar; isolated cases of pneumonitis and rhabdomyolysis; on intravenous infusion, hypotension and local reactions (including thrombophlebitis)

**Dose**

- **By mouth**, urinary-tract infections, 200–400 mg daily preferably in the morning, increased if necessary in upper urinary-tract infections to 400 mg twice daily
- Chronic prostatitis, 200 mg twice daily for 28 days
- Lower respiratory-tract infections, 400 mg daily preferably in the morning, increased if necessary to 400 mg twice daily
- Skin and soft-tissue infections, 400 mg twice daily
  - Uncomplicated gonorrhoea, 400 mg as a single dose
  - Uncomplicated genital chlamydial infection, non-gonococcal urethritis, 400 mg daily in single or divided doses for 7 days
  - Pelvic inflammatory disease (see also section 5.1, table 1), 400 mg twice daily for 14 days
- **By intravenous infusion** (over at least 30 minutes for each 200 mg), complicated urinary-tract infection, 200 mg daily
- Lower respiratory-tract infection, 200 mg twice daily
- Septicaemia, 200 mg twice daily
- Skin and soft-tissue infections, 400 mg twice daily
- Severe or complicated infections, dose may be increased to 400 mg twice daily

**Ofloxacin** (Non-proprietary) ▼ (R)

**Tablets**, ofloxacin 200 mg, net price 10-tab pack = £5.56; 400 mg, 5-tab pack = £2.56, 10-tab pack = £5.42. Label: 6, 9, 11.
5.1.13 Urinary-tract infections

Urinary-tract infection is more common in women than in men; when it occurs in men there is frequently an underlying abnormality of the renal tract. Recurrent episodes of infection are an indication for radiological investigation especially in children in whom untreated pyelonephritis may lead to permanent kidney damage.

*Escherichia coli* is the most common cause of urinary-tract infection; *Staphylococcus saprophyticus* is also common in sexually active young women. Less common causes include Proteus and Klebsiella spp. *Pseudomonas aeruginosa* infections usually occur in the hospital setting and may be associated with functional or anatomical abnormalities of the renal tract. *Staphylococcus epidermidis* and *Enterococcus faecalis* infection may complicate catheterisation or instrumentation.

Uncomplicated lower urinary-tract infections often respond to trimethoprim, nitrofurantoin, amoxicillin, or nalidixic acid given for 7 days (3 days may be adequate for infections in women); those caused by fully sensitive organisms should be treated initially with an antibacterial which penetrates prostatic tissue such as trimethoprim, or some quinolones. Where infection is localised and associated with an indwelling catheter a bladder instillation is often effective (section 7.4.4).

Urinary-tract infection in pregnancy may be asymptomatic and requires prompt treatment to prevent progression to acute pyelonephritis. Penicillins and cephalosporins are suitable for treating urinary-tract infection during pregnancy. Nitrofurantoin may also be used but it should be avoided at term. Sulphonamides, quinolones, and tetracyclines should be avoided during pregnancy; trimethoprim should also preferably be avoided particularly in the first trimester.

In renal failure antibacterials normally excreted by the kidney accumulate with resultant toxicity unless the dose is reduced. This applies especially to the aminoglycosides which should be used with great caution; tetracyclines, methenamine, and nitrofurantoin should be avoided altogether.

Children

Urinary-tract infections in children require prompt antibacterial treatment to minimise the risk of renal scarring. Uncomplicated ‘lower’ urinary-tract infections in children over 3 months of age can be treated with trimethoprim, nitrofurantoin, a first generation cephalosporin (e.g. cefalexin), or amoxicillin for 3 days; children should be reassessed if they continue to be unwell 24–48 hours after the initial assessment. Amoxicillin should only be used if the organism causing the infection is sensitive to it.

Acute pyelonephritis in children over 3 months of age can be treated with a first generation cephalosporin or co-amoxiclav for 7–10 days. If the patient is severely ill, then the infection is best treated initially by injection of a broad-spectrum antibacterial such as cefotaxime or co-amoxiclav; gentamicin is an alternative.

*Children under 3 months of age* should be transferred to hospital and treated initially with intravenous antibacterial drugs such as ampicillin with gentamicin, or cefotaxime alone, until the infection responds; full doses of oral antibacterials are then given for a further period.

Recurrent episodes of infection are an indication for imaging tests. *Antibacterial prophylaxis* with low doses of trimethoprim or nitrofurantoin may be considered for children with recurrent infection, significant urinary-tract anomalies, or significant kidney damage.

---

**NITROFURANTOIN**

**Indications**

urinary-tract infections

**Cautions**

anaemia; diabetes mellitus; electrolyte imbalance; vitamin B and folate deficiency; pulmonary disease; hepatic impairment; monitor lung and liver function on long-term therapy, especially in the elderly (discontinue if deterioration in lung function); susceptibility to peripheral neuropathy; false positive urinary glucose (if tested for reducing substances); urine may be coloured yellow or brown; **interactions**: Appendix 1 (nitrofurantoin)

**Contra-indications**

renal impairment (Appendix 3); infants less than 3 months old, G6PD deficiency (including pregnancy at term, and breast-feeding of affected infants, see section 9.1.5 and Appendix 4 and Appendix 5), acute porphyria (section 9.8.2)

**Side-effects**

anorexia, nausea, vomiting, and diarrhoea; acute and chronic pulmonary reactions (pulmonary fibrosis reported; possible association with lupus erythematosus-like syndrome); peripheral
neuropathy; also reported, hypersensitivity reactions (including angioedema, anaphylaxis, sialadenitis, urticaria, rash and pruritus); rarely, cholestatic jaundice, hepatitis, exfoliative dermatitis, erythema multiforme, pancreatitis, arthralgia, blood disorders (including agranulocytosis, thrombocytopenia, and aplastic anaemia), benign intracranial hypertension, and transient alopecia.

**Dose**

- Acute uncomplicated infection, 50 mg every 6 hours with food for 7 days (3 days usually adequate in women); **CHILD** over 3 months, 3 mg/kg daily in 4 divided doses.
- Severe chronic recurrent infection, 100 mg every 6 hours with food for 7 days (dose reduced or discontinued if severe nausea).
- Prophylaxis (but see Cautions), 50–100 mg at night; **CHILD** over 3 months, 1 mg/kg at night.

**Nitrofurantoin** *(Non-proprietary)*

- **Tablets**, nitrofurantoin 50 mg, net price 28-tab pack = £1.84; 100 mg, 28-tab pack = £4.32. Label: 9, 14, 21
- **Oral suspension**, nitrofurantoin 25 mg/5 mL, net price 300 mL = £65.00. Label: 9, 14, 21

**Furadantin®** *(Goldshield)*

- **Tablets**, all yellow, scored, nitrofurantoin 50 mg, net price 20 = £1.96; 100 mg, 20 = £3.62. Label: 9, 14, 21

**Macrobid®** *(Goldshield)*

- **Capsules**, m/r, blue/yellow, nitrofurantoin 100 mg (as nitrofurantoin macrocystals and nitrofurantoin monohydrate). Net price 14-cap pack = £4.89. Label: 9, 14, 21, 25
- **Dose** uncomplicated urinary-tract infection, 1 capsule twice daily with food
- Genito-urinary surgical prophylaxis, 1 capsule twice daily on day of procedure and for 3 days after.

**Macrobidin®** *(Goldshield)*

- **Capsules**, nitrofurantoin 50 mg (yellow/white), net price 30-cap pack = £3.05; 100 mg (yellow/white), 20 = £3.84. Label: 9, 14, 21

**METHENAMINE HIPPURATE (Hexamine hippurate)**

**Indications** prophylaxis and long-term treatment of chronic or recurrent lower urinary-tract infections

**Cautions** pregnancy; avoid concurrent administration with sulphonamides (risk of crystalluria) or urinary alkalinising agents; **interactions**: Appendix 1 (methenamine)

**Contra-indications** hepatic impairment, renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3), severe dehydration, gout, metabolic acidosis

**Side-effects** gastrointestinal disturbances, bladder irritation, rash

**Dose**

- 1 g every 12 hours (may be increased in patients with catheters to 1 g every 8 hours); **CHILD** 6–12 years 500 mg every 12 hours

**Hiprex®** *(SM)*

- **Tablets**, scored, methenamine hippurate 1 g. Net price 60-tab pack = £6.58. Label: 9

---

### 5.2 Antifungal drugs

#### Treatment of fungal infections

The systemic treatment of common fungal infections is outlined below; specialist treatment is required in most forms of systemic or disseminated fungal infections. For local treatment of fungal infections, see section 7.2.2 (genital), section 7.4.4 (bladder), section 11.3.2 (eye), section 12.1.1 (ear), section 12.3.2 (opharynx), and section 13.10.2 (skin).

**Aspergillosis** Aspergillosis most commonly affects the respiratory tract but in severely immunocompromised patients, invasive forms can affect the sinuses, heart, brain, and skin. **Amphotericin** (liposomal formulation preferred if toxicity or renal impairment are concerns) or **voriconazole** can be used for the treatment of aspergillosis. **Caspofungin** or **itraconazole** are alternatives in patients who are refractory to, or intolerant of amphotericin. Itraconazole is also used as an adjunct for the treatment of allergic bronchopulmonary aspergillosis [unlicensed indication]. The Scottish Medicines Consortium (March 2003) does not recommend the use of caspofungin because of a lack of robust data on efficacy and safety in the treatment of invasive aspergillosis.

**Candidiasis** Many superficial candidal infections including infections of the skin (section 13.10.2) are treated locally; widespread or intractable infection requires systemic antifungal treatment. Vaginal candidiasis (section 7.2.2) may be treated with locally acting antifungals or with fluconazole given by mouth; for resistant organisms, itraconazole can be given by mouth.

**Oropharyngeal candidiasis** generally responds to topical therapy (section 12.3.2); fluconazole is given by mouth for unresponsive infections; it is effective and is reliably absorbed. Itraconazole may be used for fluconazole-resistant infections. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred.

For **deep and disseminated candidiasis**, **amphotericin** can be given by intravenous infusion. **Fluconazole** is an alternative for **Candida albicans** infection in clinically stable patients who have not received an azole antifungal recently. **Caspofungin** or **voriconazole** can be used for infections caused by fluconazole-resistant **Candida** spp. that have not responded to amphotericin, or in patients intolerant of amphotericin. In refractory cases, **flucytosine** can be used with intravenous amphotericin.

**Cryptococcosis** Cryptococcosis is uncommon but infection in the immunocompromised, especially in AIDS patients, can be life-threatening; cryptococcal meningitis is the most common form of fungal meningitis. The treatment of choice in cryptococcal meningitis is **amphotericin** by intravenous infusion and **flucytosine** by intravenous infusion for 2 weeks, followed by **fluconazole** by mouth for 8 weeks or until cultures are negative. In cryptococcosis, **fluconazole** is sometimes given alone as an alternative in AIDS patients with mild, localised infections or in those who cannot tolerate...
amphotericin. Following successful treatment, fluconazole can be used for prophylaxis against relapse until immunity recovers.

**Histoplasmosis** Histoplasmosis is rare in temperate climates; it can be life-threatening, particularly in HIV-infected persons. **Itraconazole** can be used for the treatment of immunocompetent patients with indolent non-meningeal infection including chronic pulmonary histoplasmosis. **Amphotericin** by intravenous infusion is preferred in patients with fulminant or severe infections. Following successful treatment, itraconazole can be used for prophylaxis against relapse.

**Skin and nail infections** Mild localised fungal infections of the skin (including tinea corporis, tinea cruris, and tinea pedis) respond to topical therapy (section 13.10.2). Systemic therapy is appropriate if topical therapy fails, if many areas are affected, or if the site of infection is difficult to treat such as in infections of the nails (onychomycosis) and of the scalp (tinea capitis). Oral imidazole or triazole antifungals (particularly itraconazole) and **terbinafine** are used more frequently than griseofulvin because they have a broader spectrum of activity and require a shorter duration of treatment.

*Tinea capitis* is treated systemically; additional topical application of an antifungal (section 13.10.2) may reduce transmission. **Griseofulvin** is used for tinea capitis in adults and children; it is effective against infections caused by *T. tonsurans* and Microsporum spp. **Terbinafine** is used for tinea capitis caused by *T. tonsurans* [unlicensed indication]. The role of terbinafine in the management of Microsporum infections is uncertain.

**Pityriasis versicolor** (section 13.10.2) may be treated with **itraconazole** by mouth if topical therapy is ineffective; **fluconazole** by mouth is an alternative. Oral **terbinafine** is not effective for pityriasis versicolor.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal is more effective than topical therapy. **Terbinafine** and **itraconazole** have largely replaced griseofulvin for the systemic treatment of onychomycosis, particularly of the toenail; terbinafine is considered to be the drug of choice. Itraconazole can be administered as intermittent ‘pulse’ therapy. For the role of topical antifungals in the treatment of onychomycosis, see section 13.10.2.

**Immunocompromised patients** Immunocompromised patients are at particular risk of fungal infections and may receive antifungal drugs prophylactically; oral imidazole or triazole antifungals are the drugs of choice for prophylaxis. **Fluconazole** is more reliably absorbed than itraconazole and ketoconazole and is considered less toxic than ketoconazole for long-term use. Amphotericin by intravenous infusion is used for the empirical treatment of serious fungal infections. Fluconazole is used for treating *Candida albicans* infection. Caspofungin is licensed for the empirical treatment of systemic fungal infections (such as those involving *Candida* spp. or *Aspergillus* spp.) in patients with neutropenia.

### Drugs used in fungal infections

**Polyene antifungals** The polyene antifungals include amphotericin and nystatin; neither drug is absorbed when given by mouth. They are used for oral, oropharyngeal, and perioral infections by local application in the mouth (section 12.3.2).

**Amphotericin** by intravenous infusion is used for the treatment of systemic fungal infections and is active against most fungi and yeasts. It is highly protein bound and penetrates poorly into body fluids and tissues. When given parenterally amphotericin is toxic and side-effects are common. Lipid formulations of amphotericin (*Abelcet*, *Ambisome*, and *Amphocin*) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contraindicated because of toxicity, especially nephrotoxicity or when response to conventional amphotericin is inadequate; lipid formulations are more expensive.

**Nystatin** is used principally for *Candida albicans* infections of the skin and mucous membranes, including oesophageal and intestinal candidiasis.

**Imidazole antifungals** The imidazole antifungals include clotrimazole, econazole, ketoconazole, sulconazole, and tioconazole. They are used for the local treatment of vaginal candidiasis (section 7.2.2) and for dermatophyte infections (section 13.10.2).

**Ketoconazole** is better absorbed by mouth than other imidazoles. It has been associated with fatal hepatotoxicity; the CSM has advised that prescribers should weigh the potential benefits of ketoconazole treatment against the risk of liver damage and should carefully monitor patients both clinically and biochemically. It should not be used by mouth for superficial fungal infections.

**Miconazole** (section 12.3.2) can be used locally for oral infections; it is also effective in intestinal infections. Systemic absorption may follow use of miconazole oral gel and may result in significant drug interactions.

**Triazole antifungals** Fluconazole is very well absorbed after oral administration. It also achieves good penetration into the cerebrospinal fluid to treat fungal meningitis.

**Itraconazole** is active against a wide range of dermatophytes. Itraconazole capsules require an acid environment in the stomach for optimal absorption. Itraconazole has been associated with liver damage and should be avoided or used with caution in patients with liver disease; fluconazole is less frequently associated with hepatotoxicity.

**Posaconazole** is licensed for the treatment of invasive fungal infections unresponsive to conventional treatment.

**Voriconazole** is a broad-spectrum antifungal drug which is licensed for use in life-threatening infections.

**Echinocandin antifungals** Caspofungin is active against *Aspergillus* spp. and *Candida* spp. *Anidulafungin* and *micafungin* are licensed for the treatment of invasive candidiasis.

**Other antifungals** Fluconazole is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly
in AIDS patients; weekly blood counts are necessary during prolonged therapy. Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment.

Griseofulvin is effective for widespread or intractable dermatophyte infections but has been superseded by newer antifungals, particularly for nail infections. It is the drug of choice for trichophyton infections in children. Duration of therapy is dependent on the site of the infection and may extend to a number of months.

Terbinafine is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.

### AMPHOTERICIN

(Amphotericin B)

**Indications** See under Dose

**Cautions** when given parenterally, toxicity common (close supervision necessary and test dose required; see Anaphylaxis below); renal impairment (Appendix 3); hepatic and renal function tests, blood counts, and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required; corticosteroids (avoid except to control reactions); pregnancy (Appendix 4); breast-feeding (Appendix 5); avoid rapid infusion (risk of arrhythmias); interac-
tions: Appendix 1 (amphotericin)

**Anaphylaxis** The CSM has advised that anaphylaxis occurs rarely with any intravenous amphotericin product and a test dose is advisable before the first infusion; the patient should be carefully observed for at least 30 minutes after the test dose. Fungylactic antipyriotics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin is essential)

**Side-effects** when given parenterally, anorexia, nausea and vomiting, diarrhoea, epigastric pain; febrile reactions, headache, muscle and joint pain; anaemia; disturbances in renal function (including hypokalaemia and hypomagnesaemia) and renal toxicity; also cardiovascular toxicity (including arrhythmias, blood pressure changes), blood disorders, neurological disorders (including hearing loss, diplopia, convulsions, peripheral neuropathy, encephalopathy), abnormal liver function (discon-
tinue treatment), rash, anaphylactoid reactions (see Anaphylaxis, above); pain and thrombophlebitis at injection site

**Dose**
- Oral and perioral infections, see section 12.3.2
- By intravenous infusion, see preparations

**Note** Different preparations of intravenous amphotericin vary in their pharmacodynamics, pharmacokinetics, dosage, and administration; these preparations should not be considered interchangeable. To avoid confusion, prescribers should specify the brand to be dispensed.

**Fungizone** (Squibb) [FWH]

**Intravenous infusion**, powder for reconstitution, amphotericin (as sodium deoxycholate complex), net price 50-mg vial = £4.12

**Dose** by intravenous infusion, systemic fungal infections, initial test dose of 1 mg over 20–30 minutes then 250 micrograms/kg daily, gradually increased over 2–4 days, if tolerated, to 1 mg/kg daily; max. (severe infection) 1.5 mg/kg daily or on alternate days

**Note** Prolonged treatment usually necessary; if interrupted for longer than 7 days recommence at 250 micrograms/kg daily and increase gradually

### Lipid formulations

**Abelcet** (Cephalon) [FWH]

**Intravenous infusion**, amphotericin 5 mg/mL as lipid complex with 1,2-dimyristoylphosphatidylcholine and 1,2-dimyristoylphosphatidylglycerol, net price 20-mL vial = £82.13 (hosp. only)

**Dose** by intravenous infusion, severe invasive candidiasis; severe systemic fungal infections in patients not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphot-
ericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in HIV patients, ADULT and CHILD, initial test dose 1 mg over 15 minutes then 5 mg/kg once daily for at least 14 days

**AmBisome** (Gilead) [FWH]

**Intravenous infusion**, powder for reconstitution, amphotericin 50 mg encapsulated in liposomes, net price 50-mg vial = £96.69

**Electrolytes** Na < 0.5 mmol/vial

**Excipients** include sucrose 900 mg/vial

**Dose** by intravenous infusion, severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin, ADULT and CHILD initial test dose 1 mg over 10 minutes then 1 mg/kg once daily increased gradually if necessary to 3 mg/kg once daily; max. 5 mg/kg once daily [unlicensed dose]

Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials, ADULT and CHILD, initial test dose 1 mg over 10 minutes then 3 mg/kg once daily until afebrile for 3 consecutive days; max. period of treatment 42 days; max. 5 mg/kg once daily [unlicensed dose]

Vesicular leishmaniasis, see section 5.4.5 and product literature

**Amphocil** (Beacon) [FWH]

**Intravenous infusion**, powder for reconstitution, amphotericin as a complex with sodium cholesteryl sulphate, net price 50-mg vial = £104.10, 100-mg vial = £190.05

**Electrolytes** Na < 0.5 mmol/vial

**Dose** by intravenous infusion, severe systemic or deep mycoses where toxicity or renal failure preclude use of conventional amphotericin, ADULT and CHILD initial test dose 2 mg over 10 minutes then 1 mg/kg once daily increased gradually if necessary to 3–4 mg/kg once daily; max. 6 mg/kg daily

### ANIDULAFUNGIN

**Indications** invasive candidiasis

**Cautions** pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** diarrhoea, nausea, vomiting; flushing; convulsion, headache; coagulopathy, hypokalaemia; raised serum creatinine; rash, pruritus; less commonly abdominal pain, cholestasis, hypertension, hyperglycaemia, urticaria, and injection-site pain; also reported, hepatitis

**Dose**
- By intravenous infusion, ADULT over 18 years, 200 mg on first day then 100 mg once daily

**Ecalta** (Pfizer) [FWH]

**Intravenous infusion**, net-price 100-mg vial = £299.99 (with solvent)

**Excipients** include alcohol 24%

### CASPOFUNGIN

**Indications** invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intoler-
ant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropaenia
Infections

**Invasive candidal infections** (including candidaemia and disseminated candidiasis) and cryptococcal meningitis (see Cryptococcosis, p. 327), adjunct to amphotericin B therapy. **Cautions** renal impairment (Appendix 3); pregnancy (Appendix 4). **Interactions:** amphotericin B, azole antifungals, itraconazole, fluconazole; coadministration may increase risk of myelotoxicity. **Signs of toxicity:** profound myelosuppression, hepatoxicity. **Preventative measures:** consider prophylactic use of one of the approved antifungal agents in severely immunocompromised patients; for 14 days in long-standing infections (see Cryptococcosis, p. 327), adjunct to amphotericin B therapy.

---

**Fluconazole**

**Indications** systemic yeast and fungal infections; adjunct to amphotericin in cryptococcal meningitis (see Cryptococcosis, p. 327), adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections.

**Cautions** renal impairment (Appendix 3); elderly; blood disorders; liver- and kidney-function tests and blood counts required (weekly in renal impairment or blood disorders); pregnancy (Appendix 4), breastfeeding (Appendix 5); **interactions:** Appendix 1 (antifungals, antiretrovirals); coadministration may increase risk of myelotoxicity. **Signs of toxicity:** profound myelosuppression, hepatoxicity. **Preventative measures:** consider prophylactic use of one of the approved antifungal agents in severely immunocompromised patients; for 14 days in long-standing infections (see Cryptococcosis, p. 327), adjunct to amphotericin B therapy.

**Side-effects** nausea, vomiting, diarrhoea, flatulence, headache, rash (discontinue treatment or monitor closely if rash is severe or systemic); less frequently dyspepsia, vomiting, taste disturbance, hepatic disorders, hypersensitivity reactions, anaphylaxis, dizziness, seizures, alopecia, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome (severe cutaneous reactions more likely in patients with a history of cutaneous reactions to drugs), toxic epidermal necrolysis, Stevens-Johnson syndrome, rash, pruritus, sweating; injection-site reactions; local injection-site reactions, anaphylaxis, dizziness, seizures, alopecia, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome, rash, pruritus, sweating.

**Dose**

- **By intravenous infusion**, **ADULT** over 18 years, 70 mg on first day then 50 mg once daily (70 mg once daily if body-weight over 80 kg).
- **Capsules**, fluconazole 50 mg (blue/white), net price 7-cap pack = £98p; 150 mg, single-capule pack = £91p; 200 mg, 7-cap pack = £2.02. Label: 9, (50 and 200 mg)
- **Oral suspension** fluconazole 50 mg, net price 7-cap pack = £98p; 150 mg, single-capule pack = £91p; 200 mg, 7-cap pack = £2.02. Label: 9, (50 and 200 mg)
- **Intravenous infusion**, fluconazole 2 mg/mL, net price 25-mL bottle = £7.32; 100-mL bottle = £29.28
- **Diflucan**: fluconazole 50 mg (blue/white), net price 7-cap pack = £66.42. Label: 9, (50 and 200 mg)
- **Oral suspension** orange-flavoured, fluconazole for reconstitution with water, 50 mg/5 mL, net price 35 mL = £16.61; 200 mg/5 mL, 35 mL = £66.42. Label: 9, (50 and 200 mg)
- **Intravenous infusion**, fluconazole 2 mg/mL, net price 25-mL bottle = £7.32; 100-mL bottle = £29.28
- **Electrolytes** Na 15 mmol/100-mL bottle

---

**Flucytosine**

**Indications** systemic yeast and fungal infections; adjunct to amphotericin in cryptococcal meningitis (see Cryptococcosis, p. 327), adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections.

**Cautions** renal impairment (Appendix 3); elderly; blood disorders; liver- and kidney-function tests and blood counts required (weekly in renal impairment or blood disorders); pregnancy (Appendix 4), breastfeeding (Appendix 5); **interactions:** Appendix 1 (fluconazole, amphotericin B); consider coadministration of amphotericin B and flucytosine in severely immunocompromised patients; for 14 days in long-standing infections (see Cryptococcosis, p. 327), adjunct to amphotericin B therapy.

**Side-effects** nausea, vomiting, diarrhoea, rashes; less frequently cardiotoxicity, confusion, hallucinations, convulsions, headache, sedation, vertigo, alterations in liver function tests (hepatitis and hepatic necrosis reported), and toxic epidermal necrolysis; blood disorders; pregnancy (Appendix 4), breastfeeding (Appendix 5); **interactions:** Appendix 1 (antifungals, antiretrovirals); coadministration may increase risk of myelotoxicity. **Signs of toxicity:** profound myelosuppression, hepatoxicity. **Preventative measures:** consider prophylactic use of one of the approved antifungal agents in severely immunocompromised patients; for 14 days in long-standing infections (see Cryptococcosis, p. 327), adjunct to amphotericin B therapy.

**Dose**

- **By intravenous infusion**, **CHILD** according to response (at least 8 weeks for cryptococcal meningitis); **CHILD** 6–12 mg/kg daily (every 72 hours in **NEONATE** up to 2 weeks old, every 48 hours in **NEONATE** 2–4 weeks old); max. 800 mg daily (unlicensed dose).
- **Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy, by mouth or by intravenous infusion**, 200 mg daily.
- **Prevention of fungal infections in immunocompromised patients, by mouth or by intravenous infusion**, 50–400 mg daily adjusted according to risk; 400 mg daily if high risk of systemic infections e.g. following bone-marrow transplantation; commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range; **CHILD** according to extent and duration of neutropenia, 3–12 mg/kg daily (every 72 hours in **NEONATE** up to 2 weeks old, every 48 hours in **NEONATE** 2–4 weeks old); max. 400 mg daily.
orders including thrombocytopenia, leucopenia, and aplastic anaemia reported

**Dose**
- **By intravenous infusion** over 20–40 minutes, **ADULT** and **CHILD**, 200 mg/kg daily in 4 divided doses usually for not more than 7 days; extremely sensitive organisms, 100–150 mg/kg daily may be sufficient

Cryptococcal meningitis (adjunct to amphotericin, see Cryptococcosis, p. 327) 100 mg/kg daily in 4 divided doses for 2 weeks [unlicensed duration]

**Note** For plasma concentration monitoring, blood should be taken shortly before starting the next infusion; plasma concentration for optimum response 25–50 mg/litre (200–400 micromol/litre)—should not be allowed to exceed 80 mg/litre (620 micromol/litre)

**Ancotil®** (Valeant) [PN]
- **Intravenous infusion**, flucytosine 10 mg/mL, net price 250-mL infusion bottle = £30.33 (hosp. only)
- **Electrolytes** Na 34.5 mmol/250-mL bottle

**Note** Flucytosine tablets [unlicensed] may be available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

---

**GRISEOFULVIN**

**Indications** dermatophyte infections of the skin, scalp, hair and nails with topical therapy has failed or is inappropriate

**Cautions** interactions: Appendix 1 (griseofulvin)
- **Driving** May impair performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** severe liver disease; systemic lupus erythematosus (risk of exacerbation); acute porphyria (section 9.8.2); pregnancy (avoid pregnancy during and for 1 month after treatment (Appendix 4); men should not father children within 6 months of treatment); breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, diarrhoea; headache; less frequently hepatotoxicity, dizziness, confusion, fatigue, sleep disturbances, impaired co-ordination, peripheral neuropathy, leucopenia, systemic lupus erythematosus, rash (including rarely erythema multiforme, toxic epidermal necrolysis), and photosensitivity

**Dose**
- Dermatophyte infections, 500 mg once daily or in divided doses; in severe infection dose may be doubled, reducing when response occurs; **CHILD** under 50 kg, 10 mg/kg once daily or in divided doses
- **Tinea capitis caused by Trichophyton tonsurans**, 1 g once daily or in divided doses; **CHILD** under 50 kg, 15–20 mg/kg once daily or in divided doses

**Note** Griseofulvin doses in BNF may differ from those in product literature

**Griseofulvin (Non-proprietary) [PN]**
- **Tablets**, griseofulvin 125 mg, net price 20 = £6.76; 500 mg, 20 = £17.52. Label: 9, 21, counselling, driving

---

**ITRACONAZOLE**

**Indications** see under Dose

**Cautions** absorption reduced in AIDS and neutropenia (monitor plasma-itraconazole concentration and increase dose if necessary); susceptibility to congestive heart failure (see also CSM advice below); renal impairment (Appendix 3); pregnancy (Appendix 4) and breast-feeding (Appendix 5); interactions: Appendix 1 (antifungals, triazole)

**Hepatotoxicity** Potentially life-threatening hepatotoxicity reported very rarely—discontinue if signs of hepatitis develop. Avoid or use with caution if history of hepatotoxicity with other drugs or in active liver disease (Appendix 2). Monitor liver function if treatment continues for longer than one month, if receiving other hepatotoxic drugs, if history of hepatotoxicity with other drugs, or in hepatic impairment

**Counselling** Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain or dark urine develop

---

**Contra-indications** acute porphyria (section 9.8.2)

**Side-effects** very rarely nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, constipation, jaundice, hepatitis (see also Hepatotoxicity above), heart failure (see CSM advice above), pulmonary oedema, headache, dizziness, peripheral neuropathy (discontinue treatment), menstrual disorder, hypokalaemia, rash, pruritus, Stevens-Johnson syndrome, and alopecia; with intravenous injection, very rarely hypertension and hyperglycaemia

**Dose**
- **By mouth**, oropharyngeal candidiasis, 100 mg once daily (200 mg once daily in AIDS or neutropaenia) for 15 days; see also under Sporanox® oral liquid below
- **Vulvovaginal candidiasis**, 200 mg twice daily for 1 day
- **Pityriasis versicolor**, 200 mg once daily for 7 days
- **Tinea corporis and tinea cruris**, either 100 mg once daily for 15 days or 200 mg once daily for 7 days
- **Tinea pedis and tinea manicum**, either 100 mg once daily for 30 days or 200 mg twice daily for 7 days
- **Onychomycosis**, either 200 mg once daily for 3 months or course (‘pulse’) of 200 mg twice daily for 7 days, subsequent courses repeated after 21-day interval; fingernails 2 courses, toenails 3 courses

- **Histoplasmosis**, 200 mg 1–2 times daily
- **Systemic aspergillosis**, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective, 200 mg once daily (candidiasis 100–200 mg once daily) increased in invasive or disseminated disease and in cryptococcal meningitis to 200 mg twice daily

- **Maintenance in AIDS patients** to prevent relapse of underlying fungal infection and prophylaxis in neutropaenia when standard therapy inappropriate, 200 mg once daily, increased to 200 mg twice daily if low plasma-itraconazole concentration (see Cautions)
- **Prophylaxis** in patients with haematological malignancy or undergoing bone-marrow transplant, see under Sporanox® oral liquid below

- **By intravenous infusion**, systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective, histoplasmosis, 200 mg every 12 hours for 2 days, then 200 mg once daily for max. 12 days

- **CHILD** and **ELDERLY** safety and efficacy not established
5.2 Antifungal drugs

**Sporanox®** (Janssen-Cilag)  
**Capsules**; blue/pink, enclosing coated beads, itraconazole 100 mg, net price 4-cap pack = £3.90; 15-cap pack = £20.96; 28-cap pack (Sporanox®-Pulse) = £27.30; 60-cap pack = £58.49. Label: 5, 9, 21, 25, counselling, hepatotoxicity

**Oral liquid**; sugar-free, cherry-flavoured, itraconazole 10 mg/mL, net price 150 mL (with 10-mL measuring cup) = £48.62. Label: 9, 23, counselling, administration, hepatotoxicity

**Dose** oral or oesophageal candidiasis in HIV-positive or other immunocompromised patients, 20 mL (2 measuring cups) daily in 1–2 divided doses for 1 week (continue for another week if no response)

Flucanazole-resistant oral or oesophageal candidiasis, 10–20 mL (1–2 measuring cups) twice daily for 2 weeks (continue for another 2 weeks if no response; the higher dose should not be used for longer than 2 weeks if no signs of improvement)

Prophylaxis of deep fungal infections (when standard therapy is inappropriate) in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic, 5 mg/kg daily in 2 divided doses; starting before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers; CHILD and ELDERLY safety and efficacy not established

**Counselling** Do not take with food; swish around mouth and swallow, do not rinse afterwards

**Concentrate for intravenous infusion**; itraconazole 10 mg/mL. For dilution before use. Net price 25-mL amp (with infusion bag and filter) = £66.43

**Excipients** include propylene glycol

**KETOCONAZOLE**

**Indications** see CSM recommendations, p. 328; dermatophytophyes and *Malassezia* folliculitis either resistant to fluconazole, terbinafine, or itraconazole or in patients intolerant of these antifungals; chronic mucocutaneous, cutaneous, and oropharyngeal candidiasis either resistant to fluconazole or itraconazole or in patients intolerant of these antifungals

**Cautions** predisposition to adrenocortical insufficiency; pregnancy (Appendix 4); interactions: Appendix 1 (antifungals, imidazole)

**Hepatotoxicity** Potentially life-threatening hepatotoxicity reported very rarely; risk of hepatotoxicity greater if given for longer than 10 days. Monitor liver function before treatment, then on weeks 2 and 4 of treatment, then every month. Avoid or use with caution if abnormal liver function tests (avoid in active liver disease) or if history of hepatotoxicity with other drugs. For CSM advice see p. 328

**Counselling** Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, jaundice, or dark urine develop

**Contra-indications** acute porphyria (section 9.8.2); hepatic impairment; breast-feeding

**Side-effects** nausea, vomiting, abdominal pain; pruritus; less commonly diarrhoea, headache, dizziness, drowsiness, and rash; also reported fatal liver damage (see Hepatotoxicity above), dyspepsia, raised intracranial pressure, paraesthesia, adrenocortical insufficiency, erectile dysfunction, menstrual disorders, azoospermia (with high doses), gynaecomastia, thrombocytopenia, photophobia, photosensitivity, and alopecia

**Dose**

- 200 mg once daily, increased if response inadequate to 400 mg once daily; continued until symptoms have cleared and cultures negative, but see Cautions (max. duration of treatment 4 weeks for *Malassezia* infection); CHILD body-weight 15–30 kg, 100 mg once daily; body-weight over 30 kg, adult dose

**Nizoral®** (Janssen-Cilag)  
**Tablets**; scored, ketoconazole 200 mg. Net price 30-tab pack = £14.59. Label: 5, 9, 21, counselling, hepatotoxicity

**MICAFUNGIN**

**Indications** see under Dose

**Cautions** monitor renal function; renal impairment; pregnancy (Appendix 4); breast-feeding (Appendix 5);

**Interactions** Appendix 1 (micafungin)

**Hepatotoxicity** Potentially life-threatening hepatotoxicity reported. Monitor liver function—discontinue if significant and persistent abnormalities in liver function tests develop. Use with caution in hepatic impairment (avoid if severe; Appendix 2) or if receiving other hepatotoxic drugs. Risk of hepatic side-effects greater in children under 1 year of age

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain; headache, fever; hypokalaemia, hypomagnesaemia, hypocalcaemia, leucopenia, anaemia; rash, phlebitis; less commonly dyspepsia, constipation, hepatomegaly, hepatitis and cholestasis (see also Hepatotoxicity above), taste disturbances, anorexia, tachycardia, palpitation, bradycardia, blood pressure changes, flushing, dyspnoea, sleep disturbances, anxiety, confusion, dizziness, tremor, pancytopenia, thrombocytopenia, eosinophilia, hyponatraemia, hypophosphataemia, hyperkalaemia, hyperhidrosis, and pruritus; rarely haemolytic anaemia; also reported renal failure (more frequent in children)

**Dose**

- By intravenous infusion, invasive candidiasis, ADULT, CHILD, and NEONATE, body-weight over 40 kg, 100 mg once daily (increased to 200 mg daily if inadequate response) for at least 14 days; body-weight under 40 kg, 2 mg/kg once daily (increased to 4 mg/kg daily if inadequate response) for at least 14 days Oesophageal candidiasis, ADULT and CHILD over 16 years, body-weight over 40 kg, 150 mg once daily; body-weight under 40 kg, 3 mg/kg once daily

Prophylaxis of candidiasis in patients undergoing bone-marrow transplantation or who are expected to become neutropenic for over 10 days, ADULT, CHILD, and NEONATE, body-weight over 40 kg, 50 mg once daily; body-weight under 40 kg, 1 mg/kg once daily; continue for at least 7 days after neutrophil count in desirable range

**Mycamine®** (Astellas)  
**Intravenous infusion**; powder for reconstitution, micafungin (as sodium), net price 50-mg vial = £196.08; 100-mg vial = £341.00

**NYSTATIN**

**Indications** candidiasis; oral infection (section 12.3.2); skin infection (section 13.10.2)

**Side-effects** nausea, vomiting, diarrhoea at high doses; oral irritation and sensitisation; rash (including urticaria) and rarely Stevens-Johnson syndrome reported

**Dose**

- By mouth, intestinal candidiasis 500 000 units every 6 hours, doubled in severe infection; NEONATE 100 000 units 4 times daily; CHILD 1 month–12 years, 100 000 units 4 times daily; immunocompromised children may require higher doses (e.g. 500 000 units 4 times daily)

**Note** Unlicensed for treatment of candidiasis in NEONATE.

Nystatin doses in BNF may differ from those in product literature
Nystan® (Squibb) [PHARMA]

**Tablets**, brown, s/c, nystatin 500 000 units, net price 56-tab pack = £4.37. Label: 9

**Suspension**, yellow, nystatin 100 000 units/mL, net price 30 mL with pipette = £1.91. Label: 9, counselling, use of pipette

POSACONAZOLE

**Indications** invasive aspergillosis either unresponsive to, or in patients intolerant of, amphotericin or itraconazole; fusariosis either unresponsive to, or in patients intolerant of, amphotericin; coccidiodomycosis either unresponsive to, or in patients intolerant of, amphotericin, itraconazole, or fluconazole; see also under Dose

**Cautions** cardiomyopathy, bradycardia, symptomatic arrhythmias, history of QT interval prolongation, concomitant use with other drugs known to cause QT-interval prolongation; monitor electrolytes (including potassium, magnesium, and calcium) before and during therapy, monitor liver function—consider discontinuing if impairment suspected (Appendix 2); pregnancy (ensure effective contraception during treatment; Appendix 4); **interactions**: Appendix 1 (antifungals, triazole)

**Contra-indications** acute porphyria (section 9.8.2); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea, dyspepsia, and flatulence); dizziness, headache, paraesthesia, drowsiness, fatigue, fever, anorexia; blood disorders (including anaemia, neutropenia, and thrombocytopenia), electrolyte disturbances; dry mouth; rash; less commonly angioedema, dizziness, malaise, paraesthesia, rash and urticaria occasionally with arthralgia or myalgia; less commonly thrombocytopenia, electrolyte disturbances, cardiomyopathy, bradycardia, symptomatic arrhythmias, history of QT interval prolongation; monitor electrolytes (including potassium, magnesium, and calcium) before and during therapy, monitor liver function—consider discontinuing if impairment suspected (Appendix 2); pregnancy (ensure effective contraception during treatment; Appendix 4); **interactions**: Appendix 1 (terbinafine)

**Dose**

- **By mouth**, 250 mg daily usually for 2–6 weeks in tinea pedis, 2–4 weeks in tinea cruris, 4 weeks in tinea corporis, 6 weeks–3 months in nail infections (occasionally longer in toenail infections); **CHILD** (unlicensed) usually for 4 weeks, tinea capitis, over 1 year, body-weight 10–20 kg, 62.5 mg once daily; body-weight 20–40 kg, 125 mg once daily; body-weight over 40 kg, 250 mg once daily

Terbinafine (Non-proprietary) [PHARMA]

**Tablets**, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £2.70, 28-tab pack = £3.43. Label: 9

Lamisil® (Novartis) [PHARMA]

**Tablets**, off-white, scored, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £23.16, 28-tab pack = £44.66. Label: 9

VORICONAZOLE

**Indications** invasive aspergillosis; serious infections caused by *Scedosporium* spp., *Fusarium* spp., or invasive fluconazole-resistant *Candida* spp. (including *C. krusei*)

**Cautions** electrolyte disturbances, cardiomyopathy, bradycardia, symptomatic arrhythmias, history of QT interval prolongation, concomitant use with other drugs that prolong QT interval; avoid exposure to sunlight; patients at risk of pancreatitis; monitor liver function before treatment and during treatment; haematological malignancy (increased risk of hepatic reactions); hepatic impairment (Appendix 2); monitor renal function; renal impairment (Appendix 3); pregnancy (ensure effective contraception during treatment—Appendix 4); **interactions**: Appendix 1 (antifungals, triazole)

**Contra-indications** acute porphyria (section 9.8.2); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances (including nausea, vomiting, abdominal pain, diarrhoea), jaundice; oedema, hypotension, chest pain; respiratory distress syndrome, sinusitis; headache, dizziness, asthenia, anxiety, depression, confusion, agitation,

---

**TERBINAFINE**

**Indications** dermatophyte infections of the nails, ringworm infections (including tinea pedis, cruris, and corporis) where oral therapy appropriate (due to site, severity or extent)

**Cautions** psoriasis (risk of exacerbation); autoimmune disease (risk of lupus-erythematosus-like effect); hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (terbinafine)

---

**BNF 57**

5.2 Antifungal drugs 333
hallucinations, paraesthesia, tremor; influenza-like symptoms; hypoglycaemia; haematuria; blood disorders (including anaemia, thrombocytopenia, leucopenia, pancytopenia), acute renal failure, hypokalaemia; visual disturbances including altered perception, blurred vision, and photophobia; rash, pruritus, photosensitivity, alopecia, cheilitis; injection-site reactions; less commonly cholecystitis, pancreatitis, hepatitis, constipation, arrhythmias (including QT interval prolongation), syncope, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia, nystagmus, hypoaesthesia, adrenocortical insufficiency, arthritis, blepharitis, optic neuritis, scleritis, glossitis, gingivitis, psoriasis, and Stevens-Johnson syndrome; rarely pseudomembranous colitis, convulsions, sleep disturbances, tinnitus, hearing disturbances, extrapyramidal effects, hypertonia, hypothyroidism, hyperthyroidism, discoid lupus erythematosus, toxic epidermal necrolysis, retinal haemorrhage, optic atrophy, and taste disturbances.

Dose
- By mouth, ADULT and ADOLESCENT over 12 years, body-weight over 40 kg, 400 mg every 12 hours for 2 doses then 200 mg every 12 hours, increased if necessary to 300 mg every 12 hours; body-weight under 40 kg, 200 mg every 12 hours for 2 doses then 100 mg every 12 hours, increased if necessary to 150 mg every 12 hours; CHILD 2–12 years, (oral suspension recommended) 200 mg every 12 hours.
- By intravenous infusion, 6 mg/kg every 12 hours for 2 doses, then 4 mg/kg every 12 hours (reduced to 3 mg/kg every 12 hours if not tolerated) for max. 6 months; CHILD 2–12 years, 7 mg/kg every 12 hours (reduced to 4 mg/kg every 12 hours if not tolerated) for max. 6 months.

Vfend® (Pfizer) Tablets, I/c, voriconazole 50 mg, net price 28-tablet pack = £275.68; 200 mg, 28-tab pack = £1102.74. Label: 9, 11, 23
Oral suspension, voriconazole 200 mg/5 mL when reconstituted with water, net common price 75 mL (orange-flavoured) = £551.37. Label: 9, 11, 23
Intravenous infusion, powder for reconstitution, voriconazole, net price 200-mg vial = £77.14
Excipients include sulphobutyl ether beta cyclodextrin sodium (risk of accumulation in renal impairment)
Electrolytes Na 9.47 mmol/vial

5.3 Antiviral drugs

5.3.1 HIV infection

There is no cure for infection caused by the human immunodeficiency virus (HIV) but a number of drugs slow or halt disease progression. Drugs for HIV infection (antiretrovirals) increase life expectancy considerably but they may be associated with serious side-effects. Treatment should be undertaken only by those experienced in their use.

Principles of treatment
Treatment is aimed at reducing the plasma viral load as much as possible and for as long as possible; it should be started before the immune system is irreversibly damaged. The need for early drug treatment should, however, be balanced against the risk of toxicity. Commitment to treatment and strict adherence over many years are required; the regimen chosen should take into account convenience and patient tolerance. The development of drug resistance is reduced by using a combination of drugs; such combinations should have synergistic or additive activity while ensuring that their toxicity is not additive. It is recommended that viral sensitivity to antiretroviral drugs is established before starting treatment or before switching drugs if the infection is not responding.

Initiation of treatment
The optimum time for initiating antiretroviral treatment depends primarily on the CD4 cell count; the plasma viral load and clinical symptoms may also help. The timing and choice of treatment should also take account of the possible effects of antiretroviral drugs on factors such as the risk of cardiovascular events. Treatment includes a combination of drugs known as ‘highly active antiretroviral therapy’. Treatment is initiated with 2 nucleoside reverse transcriptase inhibitors and a non-nucleoside reverse transcriptase inhibitor; the regimen of choice contain either tenofovir, emtricitabine, and efavirenz or abacavir, lamivudine, and efavirenz. Regimens containing 2 nucleoside reverse transcriptase inhibitors and a boosted protease inhibitor are reserved for patients with resistance to first-line regimens, women wishing to become pregnant, or patients with psychiatric illness. Patients who require treatment for both HIV and chronic hepatitis B should be treated with antivirals active against both diseases (section 5.3.3).

Switching therapy
Deterioration of the condition (including clinical and virological changes) may require a change in therapy. The choice of an alternative regimen depends on factors such as the response to previous treatment, tolerance and the possibility of cross-resistance.

Pregnancy and breast-feeding
Treatment of HIV infection in pregnancy aims to reduce the risk of toxicity to the fetus (although the teratogenic potential of most antiretroviral drugs is unknown), to minimise the viral load and disease progression in the mother, and to prevent transmission of infection to the neonate. All treatment options require careful assessment by a specialist. Zidovudine monotherapy reduces transmission of infection to the neonate. However, combination antiretroviral therapy maximises the chance of preventing transmission and represents optimal therapy for the mother. Combination antiretroviral therapy may be associated with a greater risk of preterm delivery. Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

The majority of virus infections resolve spontaneously in immunocompetent subjects. A number of specific treatments for viral infections are available, particularly for the immunocompromised. This section includes notes on herpes simplex and varicella-zoster, human immunodeficiency virus, cytomegalovirus, respiratory syncytial virus, viral hepatitis and influenza.
Children HIV disease in children has a different natural progression to adults. Children infected with HIV should be managed within a formal paediatric HIV clinical network by specialists with access to guidelines and information on antiretroviral drugs for children.

Post-exposure prophylaxis Prophylaxis with antiretroviral drugs [unlicensed indication] may be appropriate following exposure to HIV-contaminated material. Immediate expert advice should be sought in such cases; national guidelines on post-exposure prophylaxis for healthcare workers have been developed (by the Chief Medical Officer’s Expert Advisory Group on AIDS, www.dh.gov.uk) and local ones may also be available. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity. Prompt prophylaxis with antiretroviral drugs [unlicensed indication] is also appropriate following potential sexual exposure to HIV; recommendations have been developed by the British Association for Sexual Health and HIV, www.bashh.org

Drugs for HIV infection Zidovudine, a nucleoside reverse transcriptase inhibitor (or ‘nucleoside analogue’), was the first anti-HIV drug to be introduced. Other nucleoside reverse transcriptase inhibitors include abacavir, didanosine, emtricitabine, lamivudine, stavudine, and tenofovir.

The protease inhibitors include atazanavir, darunavir, fosamprenavir (a pro-drug of amprenavir), indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, and tipranavir. Ritonavir in low doses boosts the activity of atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, saquinavir, and tipranavir increasing the persistence of plasma concentrations of these drugs; at such a low dose, ritonavir has no intrinsic antiviral activity. A combination of lopinavir with low-dose ritonavir is available. The protease inhibitors are metabolised by cytochrome P450 enzyme systems and therefore have a significant potential for drug interactions. Protease inhibitors are associated with lipodystrophy and metabolic effects (see below).

The non-nucleoside reverse transcriptase inhibitors efavirenz, etravirine, and nevirapine are active against the subtype HIV-1 but not HIV-2, a subtype that is rare in the UK. These drugs may interact with a number of drugs metabolised in the liver. Nevirapine is associated with a high incidence of rash (including Stevens-Johnson syndrome) and occasionally fatal hepatitis. Rash is also associated with efavirenz and etravirine but it is usually milder. Psychiatric or CNS disturbances are common with efavirenz. CNS disturbances are often self-limiting and can be reduced by taking the dose at bedtime (especially in the first 2–4 weeks of treatment). Efavirenz treatment has also been associated with an increased plasma cholesterol concentration. Etravirine is used in regimes containing a boosted protease inhibitor for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors.

Enfuvirtide, which inhibits HIV from fusing to the host cell, is licensed for managing infection that has failed to respond to a regimen of other antiretroviral drugs; enfuvirtide should be combined with other potentially active antiretroviral drugs.

Maraviroc is an antagonist of the CCR5 chemokine receptor. It is licensed for patients exclusively infected with CCR5-tropic HIV. The Scottish Medicines Consortium (p. 3) has advised (March 2008) that maraviroc (Celsentri®) is not recommended for use within NHS Scotland.

Raltegravir is an inhibitor of HIV integrase. It is licensed for the treatment of HIV infection resistant to multiple antiretrovirals. The Scottish Medicines Consortium (p. 3) has advised (April 2008) that raltegravir (Isentress®) is accepted for restricted use within NHS Scotland for the treatment of patients with HIV infection resistant to 3 classes of antiretrovirals.

Immune reconstitution syndrome Improvement in immune function as a result of antiretroviral treatment may provoke a marked inflammatory reaction against residual opportunistic organisms.

Lipodystrophy syndrome Metabolic effects associated with antiretroviral treatment include fat redistribution, insulin resistance and dyslipidaemia; collectively these have been termed lipodystrophy syndrome. The usual risk factors for cardiovascular disease should be taken into account before starting antiretroviral therapy and patients should be advised about lifestyle changes to reduce their cardiovascular risk. Plasma lipids and blood glucose should be measured before starting antiretroviral therapy, after 3–6 months of treatment, and then annually.

Fat redistribution (with loss of subcutaneous fat, increased abdominal fat, ‘buffalo hump’ and breast enlargement) is associated with regimens containing protease inhibitors and nucleoside reverse transcriptase inhibitors. Stavudine (especially in combination with didanosine), and to a lesser extent zidovudine, are associated with a higher risk of lipodystrophy and should be used only if alternative regimens are not suitable.

Dyslipidaemia is associated with antiretroviral treatment, particularly with protease inhibitors. Protease inhibitors and nucleoside reverse transcriptase inhibitors are associated with insulin resistance and hyperglycaemia. Of the protease inhibitors, atazanavir and darunavir are less likely to cause dyslipidaemia, while saquinavir and atazanavir are less likely to impair glucose tolerance.

Osteonecrosis Osteonecrosis has been reported in patients with advanced HIV disease or following long-term exposure to combination antiretroviral therapy.

Nucleoside reverse transcriptase inhibitors

Cautions Nucleoside reverse transcriptase inhibitors should be used with caution in patients with chronic hepatitis B or C (greater risk of hepatic side-effects), in hepatic impairment (see also Lactic Acidosis below and Appendix 2), in renal impairment (Appendix 3), and in pregnancy (see also p. 334 and Appendix 4).

Lactic acidosis Life-threatening lactic acidosis associated with hepatomegaly and hepatic steatosis has been reported with nucleoside reverse transcriptase inhibitors. They should be used with caution in patients (particularly obese women) with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa...
and ribavirin), liver-enzyme abnormalities and with other risk factors for liver disease and hepatic steatosis (including alcohol abuse). Treatment with the nucleoside reverse transcriptase inhibitor should be discontinued in case of symptomatic hyperlactataemia, lactic acidosis, progressive hepatomegaly or rapid deterioration of liver function. Stavudine, especially with didanosine, is associated with a higher risk of lactic acidosis and should be used only if alternative regimens are not suitable.

### Side-effects

Side-effects of the nucleoside reverse transcriptase inhibitors include gastrointestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea), anorexia, pancreatitis, liver damage (see also Lactic Acidosis, above), dyspnœa, cough, headache, insomnia, dizziness, fatigue, blood disorders (including anaemia, neutropenia, and thrombocytopenia), myalgia, arthralgia, rash, urticaria, and fever. See notes above for metabolic effects and lipodystrophy (Lipodystrophy Syndrome), and Osteonecrosis.

<table>
<thead>
<tr>
<th><strong>ABACAVIR</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indications</strong></td>
</tr>
<tr>
<td><strong>Caution</strong></td>
</tr>
<tr>
<td><strong>Hypersensitivity reactions</strong></td>
</tr>
<tr>
<td><strong>Counselling</strong></td>
</tr>
<tr>
<td><strong>Contra-indications</strong></td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
</tr>
<tr>
<td><strong>Dose</strong></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Ziagen</strong> (GSK)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablets</strong>, yellow, f/c, scored, abacavir (as sulphate) 300 mg, net price 60-tab pack = £221.81. Counselling, hypersensitivity reactions</td>
</tr>
<tr>
<td><strong>Oral solution</strong>, sugar-free, banana and strawberry flavoured, abacavir (as sulphate) 20 mg/mL, net price 240-mL = £59.15. Counselling, hypersensitivity reactions</td>
</tr>
</tbody>
</table>

### With lamivudine

**For caution and side-effects see under individual drugs**

<table>
<thead>
<tr>
<th><strong>Kivexa</strong> (GSK)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablets</strong>, orange, f/c, abacavir (as sulphate) 600 mg, lamivudine 300 mg, net price 30-tab pack = £373.94. Counselling, hypersensitivity reactions</td>
</tr>
</tbody>
</table>

**Dose**
- **ADULT** and **CHILD** over 12 years, body-weight over 40 kg, 1 tablet once daily

### With lamivudine and zidovudine

**Note** For patients stabilised (for 6–8 weeks) on the individual components in the same proportions. For caution and side-effects see under individual drugs

<table>
<thead>
<tr>
<th><strong>Trizivir</strong> (GSK)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablets</strong>, blue-green, f/c, abacavir (as sulphate) 300 mg, lamivudine 150 mg, zidovudine 300 mg, net price 60-tab pack = £540.40. Counselling, hypersensitivity reactions</td>
</tr>
</tbody>
</table>

**Dose**
- **ADULT** over 18 years, 1 tablet twice daily

### DIDANOSINE

**(ddI, DDI)**

| **Indications** | HIV infection in combination with other antiretroviral drugs |
| **Caution** | see notes above; also history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaemia (see under Side-effects); ophthalmological examination (including visual acuity, colour vision, and dilated fundus examination) recommended annually or if visual changes occur; interactions: Appendix 1 (didanosine) |
| **Pancreatitis** | Suspend treatment if serum lipase raised (even if asymptomatic) or if symptoms of pancreatitis develop; discontinue if pancreatitis confirmed. Whenever possible avoid concomitant treatment with other drugs known to cause pancreatic toxicity (e.g. intravenous pentamidine isethionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if elevated |

### Contra-indications

**breast-feeding (Appendix 5)**

### Side-effects

**see notes above; also pancreatitis (see also under caution), liver failure, anaphylactic reactions, peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops), diabetes mellitus, hypoglycaemia, acute renal failure, rhabdomyolysis, dry eyes, retinal and optic nerve changes, dry mouth, parotid gland enlargement, sialadenitis, alopecia, hyperuricaemia (suspend if raised significantly)**

### **Dose**

- **ADULT** under 60 kg 250 mg daily in 1–2 divided doses, 60 kg and over 400 mg daily in 1–2 divided doses; **CHILD** over 3 months (under 6 years **Videx** tablets only), 240 mg/m daily (180 mg/m daily in combination with zidovudine) in 1–2 divided doses
EMTRICITABINE

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis); interactions: Appendix 1 (emtricitabine)

contra-indications breast-feeding (Appendix 5)

Side-effects see notes above; also abnormal dreams, pruritus, and hyperpigmentation

Dose

- See preparations below

Emtriva® (Gilead) Tablets, white/blue, emtricitabine 200 mg, net price 30-cap pack = £163.50; 200 mg, 30-cap pack = £81.84; 250 mg, 30-cap pack = £102.30; 400 mg, 30-cap pack = £163.68. Label: 25, counselling, administration, see below

Counselling Capsules to be taken at least 2 hours before or 2 hours after food

LAMIVUDINE (3TC)

Indications see preparations below

Cautions see notes above; interactions: Appendix 1 (lamivudine)

Chronic Hepatitis B Recurrent hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine. When treating chronic hepatitis B with lamivudine, monitor liver function tests every 3 months, and viral and serological markers of hepatitis B every 3–6 months, more frequently in patients with advanced liver disease or following transplantation (monitoring to continue after discontinuation)—consult product literature

contra-indications breast-feeding (Appendix 5)

Side-effects see notes above; also peripheral neuropathy, muscle disorders including rhabdomyolysis, nasal symptoms, alopecia

Dose

- See preparations below

Epivir® (GSK) Tablets, f/c, lamivudine 150 mg (scored, white), net price 60-tab pack = £152.14; 300 mg (grey), 30-tab pack = £167.21

oral solution, banana- and strawberry-flavoured, lamivudine 50 mg/5 mL, net price 240-mL pack = £41.41

Excipients include sucrose 1 g/5 mL

Dose HIV infection in combination with other antiretroviral drugs, 150 mg every 12 hours or 300 mg once daily; CHILD 3 months–12 years, 4 mg/kg (max. 150 mg) every 12 hours or body-weight 14–21 kg, 75 mg twice daily; body-weight 21–30 kg, 75 mg in the morning and 150 mg in the evening; body-weight over 30 kg, 150 mg twice daily

Stavudine (d4T)

Indications HIV infection in combination with other antiretroviral drugs

Cautions see notes above; also history of peripheral neuropathy (see under Side-effects); history of pancreatitis or concomitant use with other drugs associated with pancreatitis; interactions: Appendix 1 (stavudine)

contra-indications breast-feeding (Appendix 5)

Side-effects see notes above; also peripheral neuropathy (switch to another antiretroviral if peripheral neuropathy develops), abnormal dreams, cognitive dysfunction, drowsiness, depression, pruritus; less commonly anxiety, gynaecomastia

Dose

- ADULT under 60 kg, 30 mg every 12 hours preferably at least 1 hour before food; 60 kg and over, 40 mg every 12 hours; NEONATE under 2 weeks, 500 micrograms/kg every 12 hours; CHILD over 2 weeks, body-weight under 30 kg, 1 mg/kg every 12 hours; body-weight 30 kg and over, adult dose

With abacavir

See under Abacavir

With zidovudine

See under Zidovudine

With abacavir and zidovudine

See under Abacavir
Zerit® (Bristol-Myers Squibb) [PH]

Capsules, stavudine 20 mg (brown), net price 56-cap pack = £148.05; 30 mg (light orange/dark orange), 56-cap pack = £155.25; 40 mg (dark orange), 56-cap pack = £159.94 (all hosp. only)

Oral solution, cherry-flavoured, stavudine for reconstitution with water, 1 mg/mL, net price 200 mL = £24.35

TENEFOVIR DISOPROXIL

Indications HIV infection in combination with other antiretroviral drugs; chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis

Cautions see notes above; also test renal function and serum phosphate before treatment, then every 4 weeks (more frequently if at increased risk of renal impairment) for 1 year and then every 3 months, interrupt treatment if renal function deteriorates or serum phosphate decreases; concomitant or recent use of nephrotoxic drugs; on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis); interactions: Appendix 1 (tenofovir)

Contra-indications breast-feeding (Appendix 5)

Side-effects see notes above; hypophosphataemia; rarely renal failure; also reported nephrogenic diabetes insipidus, reduced bone density, hypokalaemia, myopathy, and rhabdomyolysis

Dose

- **ADULT** over 18 years, 245 mg once daily

Viread® (Gilead) ▼ [PH]

Tablets, f/c, blue, tenofovir disoproxil (as fumarate) 245 mg, net price 30-tab pack = £255.00. Label: 21, counselling, administration

Counselling Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste)

With emtricitabine

For cautions, contra-indications, and side-effects see under individual drugs

Truvada® (Gilead) [PH]

Tablets, blue, f/c, tenofovir disoproxil (as fumarate) 245 mg, emtricitabine 200 mg, net price 30-tab pack = £418.50. Label: 21, counselling, administration

Counselling Patients with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste)

Dose ADULT over 18 years, 1 tablet once daily

With efavirenz and emtricitabine

For cautions, contra-indications, and side-effects see under individual drugs

Atripla® (Gilead) [PH]

Tablets, pink, f/c, efavirenz 600 mg, emtricitabine 200 mg, tenofovir disoproxil (as fumarate) 245 mg, net price 30-tab pack = £626.90. Label: 23, 25

Dose HIV infection stabilised on antiretroviral therapy for more than 3 months, ADULT over 18 years, 1 tablet once daily

ZIDOVUDINE

(Azidothymidine, AZT)

Note The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug

Indications HIV infection in combination with other antiretroviral drugs; prevention of maternal-fetal HIV transmission (see notes above under Pregnancy and Breast-feeding)

Cautions see notes above; also haematological toxicity particularly with high dose and advanced disease—monitor full blood count after 4 weeks of treatment, then every 3 months; vitamin B deficiency (increased risk of neutropenia); if anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment; elderly; interactions: Appendix 1 (zidovudine)

Contra-indications abnormally low neutrophil counts or haemoglobin concentration (consult product literature); neonates with hyperbilirubinaemia requiring treatment other than phototherapy, or with raised transaminase (consult product literature); acute porphyria (section 9.8.2); breast-feeding (Appendix 5)

Side-effects see notes above; also anaemia (may require transfusion), taste disturbance, chest pain, influenza-like symptoms, paraesthesia, neuropathy, convulsions, dizziness, drowsiness, anxiety, depression, loss of mental acuity, myopathy, gynaecomastia, urinary frequency, sweating, pruritus, pigmentation of nails, skin and oral mucosa

Dose

- **By mouth**
  - **CHILD** 3 months–12 years, 360–480 mg/m daily in 3–4 divided doses; max. 200 mg every 6 hours
  - Prevention of maternal-fetal HIV transmission, seek specialist advice (combination therapy preferred)
  - Patients temporarily unable to take zidovudine by mouth, by intravenous infusion over 1 hour, 1–2 mg/kg every 4 hours (approximating to 1.5–3 mg/kg every 4 hours by mouth) usually for not more than 2 weeks; **CHILD** 3 months–12 years, 80–160 mg/m every 6 hours (120 mg/m every 6 hours approximates to 180 mg/m every 6 hours by mouth)

Retrovir® (GSK) [PH]

Capsules, zidovudine 100 mg (white/blue band), net price 100-cap pack = £110.98; 250 mg (blue/white/dark blue band), 40-cap pack = £110.98

Oral solution, sugar-free, strawberry-flavoured, zidovudine 50 mg/5 mL, net price 200-mL pack with 10-mL oral syringe = £22.20

Injection, zidovudine 10 mg/mL. For dilution and use as an intravenous infusion. Net price 20-mL vial = £11.14

With lamivudine

For cautions, contra-indications, and side-effects see under individual drugs

Combivir® (GSK) [PH]

Tablets, f/c, scored, zidovudine 300 mg, lamivudine 150 mg, net price 60-tab pack = £318.60

Dose ADULT and CHILD body-weight over 30 kg, 1 tablet twice daily; **CHILD** body-weight 14–21 kg, half a tablet twice daily; body-weight 21–30 kg, half a tablet in the morning and one tablet in the evening

Note Tablets may be crushed and mixed with semi-solid food or liquid just before administration

With abacavir and lamivudine

See under Abacavir
Protease inhibitors

Cautions  Protease inhibitors are associated with hyperglycaemia and should be used with caution in diabetes (see Lipodystrophy Syndrome, p. 335). Caution is also needed in patients with haemophilia who may be at increased risk of bleeding. Protease inhibitors should be used with caution in hepatic impairment (Appendix 2); the risk of hepatic side-effects is increased in patients with chronic hepatitis B or C. Atazanavir, darunavir, fosamprenavir, and tipranavir may be used at usual doses in patients with renal impairment, but other protease inhibitors should be used with caution in renal impairment (Appendix 3). Protease inhibitors should also be used with caution during pregnancy (Appendix 4).

Contra-indications  Protease inhibitors should not be given to patients with acute porphyria (section 9.8.2) or to women who are breast-feeding (Appendix 5).

Side-effects  Side-effects of the protease inhibitors include gastro-intestinal disturbances (including diarrhoea, nausea, vomiting, abdominal pain, flatulence), anorexia, hepatic dysfunction, pancreatitis; blood disorders including anaemia, neutropenia, and thrombocytopenia; sleep disturbances, fatigue, headache, dizziness, paraesthesia, myalgia, myositis, rhabdomyolysis; taste disturbances; rash, pruritus, Stevens-Johnson syndrome, hypersensitivity reactions including anaphylaxis; see also notes above for lipodystrophy and metabolic effects (Lipodystrophy Syndrome), and Osteonecrosis.

ATAZANAVIR

Indications  HIV infection in combination with other antiretroviral drugs

Cautions  see notes above; also concomitant use with drugs that prolong PR interval; cardiac conduction disorders; predisposition to QT interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); interactions: Appendix 1 (atazanavir)

Contra-indications  see notes above

Side-effects  see notes above; also peripheral neurological symptoms; less commonly mouth ulcers, hypertension, syncope, chest pain, dyspnoea, abnormal dreams, amnesia, disorientation, depression, anxiety, weight changes, increased appetite, gynaecomastia, nephrolithiasis, urinary frequency, haematuria, proteinuria, arthralgia, and alopecia; rarely hepatosplenomegaly, oedema, palpitation, and abnormal gait; also reported, Stevens-Johnson syndrome, hypersensitivity reactions including anaphylaxis; see also notes above for lipodystrophy and metabolic effects (Lipodystrophy Syndrome), and Osteonecrosis.

Dose  With low-dose ritonavir and food, ADULT over 18 years, 300 mg once daily with ritonavir 100 mg once daily.

Reyataz® (Bristol-Myers Squibb) ▼ (H)

Capsules, atazanavir (as sulphate) 150 mg (dark blue/ light blue), net price 60-cap pack = £315.69; 200 mg (dark blue), 60-cap pack = £315.69; 300 mg (red/ blue), 30-cap pack = £315.69. Label: 5, 21

DARUNAVIR

Indications  HIV infection (that has not responded to treatment with other protease inhibitors) in combination with other antiretroviral drugs

Cautions  see notes above; also sulphonamide sensitivity; interactions: Appendix 1 (darunavir)

Contra-indications  see notes above

Side-effects  see notes above; also myocardial infarction, angina, QT interval prolongation, transient ischaemic attack, syncope, tachycardia, hypertension, flushing, peripheral oedema, dyspnoea, cough, hiccups, peripheral neuropathy, anxiety, confusion, memory impairment, depression, abnormal dreams, abnormal coordination, weight gain, hyperthermia, hypothyroidism, osteoporosis, gynaecomastia, erectile dysfunction, dysuria, polyuria, nephrolithiasis, renal failure, hyponatraemia, arthralgia, keratoconjunctivitis sicca, conjunctival hyperaemia, salivation changes, mouth ulcers, increased sweating, and alopecia.

Dose  With low-dose ritonavir, ADULT over 18 years, 600 mg twice daily

Missed dose  If a dose is more than 6 hours late, the missed dose should not be taken and the next dose should be taken at the normal time.

Prezista® (Janssen-Cilag) ▼ (H)

Tablets, orange, f/c, darunavir (as ethanolate) 300 mg, net price 120-tab pack = £446.70. Label: 21

FOSAMPRENAVIR

Note  Fosamprenavir is a pro-drug of amprenavir

Indications  HIV infection in combination with other antiretroviral drugs

Cautions  see notes above; interactions: Appendix 1 (fosamprenavir)

Rash  Rash may occur, usually in the second week of therapy; discontinue permanently if severe rash with systemic or allergic symptoms or, mucosal involvement; if rash mild or moderate, may continue without interruption—rash usually resolves within 2 weeks and may respond to antihistamines

Contra-indications  see notes above

Side-effects  see notes above; also reported, rash including rarely Stevens-Johnson syndrome (see also Rash above)

Dose  With low-dose ritonavir, ADULT over 6 years, body-weight over 39 kg, 18 mg/kg twice daily; CHILD over 6 years, body-weight 25–39 kg, 18 mg/kg twice daily.

Note  700 mg fosamprenavir is equivalent to approx. 600 mg amprenavir

Telzir® (GSK) (H)

Tablets, f/c, pink, fosamprenavir (as calcium) 700 mg, net price 60-tab pack = £274.92

Oral suspension, fosamprenavir (as calcium) 50 mg/mL, net price 225-mL pack (grape-bubblegum—and peppermint-flavoured) (with 10-mL oral syringe) = £73.31. Counselling: administration

Counselling: In adults, oral suspension should be taken on an empty stomach; in children under 18 years, oral suspension should be taken with food.
INDINAVIR

**Indications** HIV infection in combination with nucleoside reverse transcriptase inhibitors

**Cautions** see notes above; also ensure adequate hydration (risk of nephrotoxicity especially in children); patients at risk of nephrotoxicity (monitor for nephrotoxicity); **interactions:** Appendix 1 (indinavir)

**Contra-indications** see notes above

**Side-effects** see notes above; also reported, dry mouth, hypoaesthesia, dry skin, hyperpigmentation, alopecia, paronychia, interstitial nephritis (with medullary calcification and cortical atrophy in asymptomatic severe leucocyturia), nephrotoxicity (may require interruption or discontinuation; more frequent in children), dysuria, haematuria, crystalluria, proteinuria, pyuria (in children), pyelonephritis; haemolytic anaemia

**Dose**
- 800 mg every 8 hours; **CHILD** and **ADOLESCENT** 4–17 years, 500 mg/m² every 8 hours (max. 800 mg every 8 hours); **CHILD** under 4 years, safety and efficacy not established

**Crixivan**

**Capsules** (MSD) Indinavir (as sulphate), 200 mg, net price 360-cap pack = £226.28; 400 mg, 90-cap pack = £113.15, 180-cap pack = £226.28. Label: 27, counselling, administration

**Counselling** Administer 1 hour before or 2 hours after a meal; may be administered with a low-fat light meal; in combination with didanosine tablets, allow 1 hour between each drug (antacids in didanosine tablets reduce absorption of indinavir); in combination with low-dose ritonavir, give with food

**Note** Dispense in original container (contains desiccant)

NELFINAVIR

**Indications** HIV infection in combination with other antiretroviral drugs

**Cautions** see notes above; **interactions:** Appendix 1 (nelfinavir)

**Contra-indications** see notes above

**Side-effects** see notes above; also reported, fever

**Dose**
- 1.25 g twice daily or 750 mg 3 times daily; **CHILD** 3–13 years, initially 50–55 mg/kg twice daily (max. 1.25 g twice daily) or 25–30 mg/kg 3 times daily (max. 750 mg 3 times daily)

**Viracept** (Roche) Nelfinavir (as mesilate) 250 mg, net price 300-tab pack = £273.16. Label: 21

**ITRANAVIR WITH RITONAVIR**

**Indications** HIV infection in combination with other antiretroviral drugs

**Cautions** see notes above; concomitant use with drugs that prolong QT or PR interval; cardiac conduction disorders, structural heart disease; pancreatitis (see below); **interactions:** Appendix 1 (lopinavir, ritonavir)

**Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

**Contra-indications** see notes above

**Side-effects** see notes and Cautions above; also electrolyte disturbances in children; less commonly dysphagia, appetite changes, weight changes, cholecystitis, hypertension, myocardial infarction, palpitation, thrombophlebitis, vasculitis, chest pain, oedema, dyspnoea, cough, agitation, anxiety, amnesia, ataxia, hypertonia, confusion, depression, abnormal dreams, extrapyramidal effects, neuropathy, influenza-like syndrome, Cushing’s syndrome, hypothyroidism, menorrhagia, amenorrhoea, sexual dysfunction, breast enlargement, dehydration, nephritis, hypercalciuria, lactic acidosis, arthralgia, hyperuricaemia, abnormal vision, otitis media, tinnitus, dry mouth, sialadenitis, mouth ulceration, periodontitis, acne, alopecia, dry skin, sweating, skin discoloration, nail disorders, rarely prolonged PR interval

**Dose**
- See preparations below

**Lopinavir with ritonavir**

**Indications** HIV infection in combination with other antiretroviral drugs

**Cautions** see notes above; concomitant use with drugs that prolong PR interval; cardiac conduction disorders, structural heart disease; pancreatitis (see below); **interactions:** Appendix 1 (ritonavir)

**Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

**Contra-indications** see notes above

**Side-effects** see notes and Cautions above; also diarrhoea (may impair absorption—close monitoring required), vasodilatation, cough, throat irritation, anxiety, perioral and peripheral paraesthesia, hypercholesterolaemia, fever, decreased blood thyroxine concentration, electrolyte disturbances, raised uric acid, dry mouth, mouth ulcers, and sweating; less commonly increased prothrombin time and dehydration; syncope, postural hypotension, seizures, menorrhagia, and renal failure also reported

**Dose**
- Initially 300 mg every 12 hours for 3 days, increased in steps of 100 mg every 12 hours over not longer than 14 days to 600 mg every 12 hours; **CHILD** over 2 years initially 250 mg/m² every 12 hours, increased by 50 mg/m² at intervals of 2–3 days to 350 mg/m² every 12 hours (max. 600 mg every 12 hours)
- Low-dose booster to increase effect of other protease inhibitors, 100–200 mg once or twice daily
Non-nucleoside reverse transcriptase inhibitors

**EFAVIRENZ**

**Indications**  HIV infection in combination with other antiretroviral drugs

**Cautions**  chronic hepatitis B or C (greater risk of hepatic side-effects), hepatic impairment (avoid if severe; Appendix 2); severe renal impairment (Appendix 3); pregnancy (Appendix 4); elderly; history of mental illness or seizures; **interactions:** Appendix 1 (efavirenz)

**Rash**  Rash, usually in the first 2 weeks, is the most common side-effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash mild or moderate, may continue without interruption—rash usually resolves within 1 month

**Psychiatric disorders**  Patients or their carers should be advised to seek immediate medical attention if symptoms such as severe depression, psychosis or suicidal ideation occur

**Contra-indications**  acute porphyria (section 9.8.2); breastfeeding (Appendix 5)

**Side-effects**  rash including Stevens-Johnson syndrome (see Rash above); abdominal pain, diarrhoea, nausea, vomiting; anxiety, depression, sleep disturbances, abnormal dreams, dizziness, headache, fatigue, impaired concentration (administration at bedtime especially in first 2–4 weeks reduces CNS effects); pruritus; *less commonly* pancreatitis, hepatitis, psychosis, mania, suicidal ideation, amnesia, ataxia, convulsions, and blurred vision; also reported hepatic failure, raised serum cholesterol (see Lipodystrophy Syndrome, p. 335), gynaecomastia, photosensitivity; see also Osteonecrosis, p. 335

**Dose**

- See preparations below

**Sustiva®**  (Bristol-Myers Squibb)  Tablets, efavirenz 50 mg (yellow/white), net price 30–cap pack = £17.41; 200 mg (yellow), 90–cap pack = £208.40. Label: 23

**Dose**

- ADULT and CHILD over 3 years, body-weight 13–14 kg, 200 mg once daily; body-weight 15–19 kg, 250 mg once daily, body-weight 20–24 kg, 300 mg once daily, body-weight 25–32.4 kg, 350 mg once daily, body-weight 32.5–39 kg, 400 mg once daily; body-weight 40 kg and over, 600 mg once daily

**Oral solution**, sugar-free, strawberry and mint flavour, efavirenz 30 mg/mL, net price 180–mL pack = £56.02

**Dose**

- ADULT and CHILD over 5 years, body-weight 13–14 kg, 270 mg once daily; body-weight 15–19 kg, 300 mg once daily, body-weight 20–24 kg, 360 mg once daily, body-weight 25–32.4 kg, 400 mg once daily, body-weight 32.5–39 kg, 510 mg once daily; body-weight 40 kg and over, 720 mg once daily, CHILD 3–4 years, body-weight 13–14 kg, 360 mg once daily; body-weight 15–19 kg, 390 mg once daily, body-weight 20–24 kg, 450 mg once daily, body-weight 25–32.4 kg, 510 mg once daily

**Note**  The bioavailability of Sustiva oral solution is lower than that of the capsules and tablets; the oral solution is not interchangeable with either capsules or tablets on a milligram-for-milligram basis

**With emtricitabine and tenofovir**

See under Tenofovir

---

**TIPRANAVIR**

**Indications**  HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in patients previously treated with antiretrovirals

**Cautions**  see notes above; also patients at risk of increased bleeding from trauma, surgery or other pathological conditions; concomitant use of drugs that increase risk of bleeding; **interactions:** Appendix 1 (tipranavir)

**Hepatotoxicity**  Potentially life-threatening hepatotoxicity reported; monitor liver function before treatment then every 2 weeks for 1 month, then every 3 months. Discontinue if signs or symptoms of hepatitis develop or if liver-function abnormality develops (consult product literature)

**Contra-indications**  see notes above

**Side-effects**  see notes above; also dyspnoea, anorexia, peripheral neuropathy, influenza-like symptoms, renal impairment and photosensitivity; rarely dehydration

**Dose**

- With low-dose ritonavir, ADULT over 18 years, 500 mg twice daily

**Aptivus®**  (Boehringer Ingelheim)  Capsules, pink, tipranavir 250 mg, net price 120–cap pack = £490.00. Label: 5, 21

---

**Norvir®**  (Abbott)  Capsules, ritonavir 100 mg, net price 84-cap pack = £94.35. Label 21

**Exipients** include alcohol 12%

**Oral solution**, sugar-free, ritonavir 400 mg/5 mL, net price 5 × 90–mL packs (with measuring cup) = £403.20. Label: 21, counselling, administration

**Counselling**  Oral solution contains 43% alcohol; bitter taste can be masked by mixing with chocolate milk; do not mix with water, measuring cup must be dry

**With lopinavir**

See under Lopinavir with ritonavir

**SAQUINAVIR**

**Indications**  HIV infection in combination with other antiretroviral drugs

**Cautions**  see notes above; also dyspnoea, increased appetite, peripheral neuropathy, convulsions, changes in libido, renal impairment, dry mouth, and alopecia

**Dose**

- With low-dose ritonavir, ADULT and ADOLESCENT over 16 years, 1 g every 12 hours

**Invirase®**  (Roche)  Capsules, brown/green, saquinavir (as mesilate) 200 mg, net price 270–cap pack = £240.06. Label: 21

**Tablets**, orange, f/c, saquinavir (as mesilate) 500 mg, net price 120–tab pack = £286.73. Label: 21

---

**With emtricitabine and tenofovir**

See under Tenofovir

---

5 Infections

5.3.1 HIV infection 341
ETRAVIRINE

Indications in combination with other antiretroviral drugs (including a boosted protease inhibitor) for HIV infection resistant to other non-nucleoside reverse transcriptase inhibitors and protease inhibitors

Cautions chronic hepatitis B or C (greater risk of hepatic side-effects); hepatic impairment (avoid if severe; Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (etravirine)

Rash Rash, usually in the second week, is the most common side-effect and appears more frequently in women; discontinue if severe rash; if rash mild or moderate, may continue without interruption—rash usually resolves within 2 weeks

Contra-indications acute porphyria (section 9.8.2); breast-feeding (Appendix 5); severe hepatic impairment; post-exposure prophylaxis

Side-effects rash including Stevens-Johnson syndrome, p. 335; rarely including toxic epidermal necrolysis (see also Cautions above); nausea, hepatitis (see also Hepatic Disease above), headache; commonly vomiting, abdominal pain, fatigue, fever, and myalgia; rarely diarrhoea, angioedema, anaphylaxis, hypersensitivity reactions (may involve hepatic reactions and rash, see Hepatic Disease above), arthralgia, anaemia, and granulocytopenia (more frequent in children); very rarely neuroendocrine reactions; see also Osteonecrosis, p. 335

Dose • ADULT over 18 years, 200 mg once daily for first 14 days then (if no rash present) 200 mg twice daily; NEONATE and CHILD under 8 years, 150 mg/m² (max. 200 mg) once daily for first 14 days, then (if no rash present) 150 mg/m² (max. 200 mg) twice daily or 4 mg/kg (max. 200 mg) once daily for first 14 days then (if no rash present) 7 mg/kg (max. 200 mg) twice daily; CHILD 8–16 years, 150 mg/m² (max. 200 mg) once daily for first 14 days then (if no rash present) 150 mg/m² (max. 200 mg) twice daily or 4 mg/kg (max. 200 mg) once daily for first 14 days then (if no rash present) 4 mg/kg (max. 200 mg) twice daily

Note Dose titration should be repeated if treatment interrupted for more than 7 days

Viramune® (Boehringer Ingelheim) Tablets, nevirapine 200 mg, net price 60-tab pack = £160.00. Counselling, hypersensitivity reactions

Suspension, nevirapine 50 mg/5 mL, net price 240-mL pack = £50.40. Counselling, hypersensitivity reactions

NEVIRAPINE

Indications HIV infection in combination with other antiretroviral drugs

Cautions hepatic impairment (see below and Appendix 2); chronic hepatitis B or C, high CD4 cell count, and women (all at greater risk of hepatic side-effects—manufacturer advises avoid in women with CD4 cell count greater than 250 cells/mm³ or in men with CD4 cell count greater than 400 cells/mm³ unless potential benefit outweighs risk); pregnancy (Appendix 4); interactions: Appendix 1 (nevirapine)

Hepatic disease Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in first 6 weeks; close monitoring required during first 18 weeks; monitor liver function before treatment then every 2 weeks for 2 months then after 1 month and then regularly; discontinue permanently if abnormalities in liver function tests accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy; hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe abnormalities in liver function tests but no hypersensitivity reaction—discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate abnormalities in liver function tests with no hypersensitivity reaction

Rash Rash, usually in first 6 weeks, is most common side-effect; incidence reduced if introduced at low dose and dose increased gradually; monitor closely for skin reactions during first 18 weeks; discontinue permanently if severe rash or if rash accompanied by blistering, oral lesions, conjunctivitis, facial oedema, general malaise or hypersensitivity reactions; if rash mild or moderate may continue without interruption but dose should not be increased until rash resolves

Counselling Patients should be told how to recognise hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if severe skin reaction, hypersensitivity reactions, or symptoms of hepatitis develop

Contra-indications acute porphyria (section 9.8.2); breast-feeding (Appendix 5); severe hepatic impairment; post-exposure prophylaxis

Side-effects rash including Stevens-Johnson syndrome and rarely, toxic epidermal necrolysis (see also Cautions above); nausea, hepatitis (see also Hepatic Disease above), headache, less commonly vomiting, abdominal pain, fatigue, fever, and myalgia; rarely diarrhoea, angioedema, anaphylaxis, hypersensitivity reactions (may involve hepatic reactions and rash, see Hepatic Disease above), arthralgia, anaemia, and granulocytopenia (more frequent in children); very rarely neuroendocrine reactions; see also Osteonecrosis, p. 335

Other antiretrovirals

ENFUVIRTIDE

Indications HIV infection in combination with other antiretroviral drugs for resistant infection or for patients intolerant to other antiretroviral regimens

Cautions chronic hepatitis B or C (possibly greater risk of hepatic side-effects); hepatic impairment (Appendix 2); pregnancy (Appendix 4)

Hypersensitivity reactions Hypersensitivity reactions including rash, fever, nausea, vomiting, chills, rigors, low blood pressure, respiratory distress, glomerulonephritis, and raised liver enzymes reported; discontinue immediately if any signs or symptoms of systemic hypersensitivity develop and do not rechallenge

Counselling Patients should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek immediate medical attention if symptoms develop

Contra-indications breast-feeding (Appendix 5)

Side-effects injection-site reactions; pancreatitis, gastro-oesophageal reflux disease, anorexia, weight loss; hypertriglyceridaemia; peripheral neuropathy, asthenia, tremor, anxiety, nightmares, irritability,
impacted concentration, vertigo; pneumonia, sinusitis, influenza-like illness; diabetes mellitus; haematuria; renal calculi, lymphadenopathy; myalgia; conjunctivitis; dry skin, acne, erythema, skin papilloma; less commonly hypersensitivity reactions (see Cautions); see also Osteonecrosis, p. 335

**Dose**

- **By subcutaneous injection,** ADULT and ADOLESCENT over 16 years, 90 mg twice daily; CHILD 6–15 years, 2 mg/kg twice daily (max. 90 mg twice daily)

**Fuzeon** (Roche) *(V)*

*Injection,* powder for reconstitution, enfuvirtide 108 mg (= enfuvirtide 90 mg/mL when reconstituted with 1 mL Water for Injections), net price 108 mg vial = £19.13 (with solvent, syringe, and alcohol swabs). Counselling, hypersensitivity reactions

### Maraviroc

**Indications** CCR5-tropic HIV infection in combination with other antiretroviral drugs in patients previously treated with antiretrovirals

**Cautions** cardiovascular disease; chronic hepatitis B or C; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (maraviroc)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, abdominal pain, dyspepsia, constipation, diarrhoea; cough; dizziness, paraesthesia, asthenia, sleep disturbances, headache, weight loss; muscle spasms, back pain; taste disturbances; rash, pruritus. less commonly pancreaticitis, hepatic cirrhosis, rectal bleeding, myocardial infarction, myocardial ischaemia, bronchospasm, seizures, hallucinations, loss of consciousness, polyneuropathy, pancytopenia, neutropenia, lymphadenopathy, renal failure, polyuria, and myositis; see also Osteonecrosis, p. 335

**Dose**

- **ADULT** over 18 years, 300 mg twice daily

**Celsentri** *(Pfizer)* *(V)*

*Tablets,* blue, f/c, maraviroc, 150 mg, net-price 60-tab pack = £551.10; 300 mg, 60-tab pack = £551.10

### Raltegravir

**Indications** in combination with other antiretroviral drugs for HIV infection resistant to multiple antiretrovirals

**Cautions** risk factors for myopathy or rhabdomyolysis; chronic hepatitis B or C (greater risk of hepatic side-effects); hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (raltegravir)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** abdominal pain, flatulence, constipation, lipodystrophy (see Lipodystrophy Syndrome, p. 335); dizziness, asthenia; arthralgia; pruritus, hyperhidrosis; less commonly vomiting, gastritis, hepatitis, myocardial infarction, hypertriglyceridaemia, allodynia, headache, renal failure, anaemia, neutropenia, and muscle spasm; also reported rash (including Stevens-Johnson syndrome); see also Osteonecrosis, p. 335

**Dose**

- **ADULT** and **CHILD** over 16 years, 400 mg twice daily

**Isentress** *(MSD)* *(V)*

*Tablets,* pink, f/c, raltegravir (as potassium salt) 400 mg, net price 60-tab pack = £647.29. Label: 25

### Herpes Simplex and Varicella-Zoster Infections

#### Herpes Simplex Infections

Herpes infection of the mouth and lips and in the eye is generally associated with herpes simplex virus serotype 1 (HSV-1); other areas of the skin may also be infected, especially in immunodeficiency. Genital infection is most often associated with HSV-2 and also HSV-1. Treatment of herpes simplex infection should start as early as possible and usually within 5 days of the appearance of the infection. In individuals with good immune function, mild infection of the eye (ocular herpes, section 11.3.3) and of the lips (herpes labialis or cold sores, section 13.10.3) is treated with a topical antiviral drug. Primary herpetic gingivostomatitis is managed by changes to diet and with analgesics (section 12.3.2). Severe infection, neonatal herpes infection or infection in immunocompromised individuals requires treatment with a systemic antiviral drug. Primary or recurrent genital herpes simplex infection is treated with an antiviral drug given by mouth. Persistence of a lesion or recurrence in an immunocompromised patient may signal the development of resistance.

Specialist advice should be sought for systemic treatment of herpes simplex infection in pregnancy.

#### Varicella-Zoster Infections

Regardless of immune function and the use of any immunoglobulins, neonates with chickenpox should be treated with a parenteral antiviral to reduce the risk of severe disease. Chickenpox in otherwise healthy children between 1 month and 12 years is usually mild and antiviral treatment is not usually required.

Chickenpox is more severe in adolescents and adults than in children; antiviral treatment started within 24 hours of the onset of rash may reduce the duration and severity of symptoms in otherwise healthy adults and adolescents. Antiviral treatment is generally recommended in immunocompromised patients and those at special risk (e.g. because of severe cardiovascular or respiratory disease or chronic skin disorder); in such cases, an antiviral is given for 10 days with at least 7 days of parenteral treatment.

Pregnant women who develop severe chickenpox may be at risk of complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.

Those who have been exposed to chickenpox and are at special risk of complications may require prophylaxis...
with varicella-zoster immunoglobulin (see under Specific Immunoglobulins, section 14.5).

In herpes zoster (shingles) systemic antiviral treatment can reduce the severity and duration of pain, reduce complications, and reduce viral shedding. Treatment with the antiviral should be started within 72 hours of the onset of rash and is usually continued for 7–10 days. Immunosuppressed patients at high risk of disseminated or severe infection should be treated with a parenteral antiviral drug.

Chronic pain which persists after the rash has healed or associated or severe infection should be treated with a par-...
Contraindications
- pregnancy (Appendix 4)
- renal impairment (Appendix 3); history of

Cautions
- Indications
- see under Dose

Genital herpes, Herpes zoster, 250 mg 3 times daily for 7 days

Dose
- Side-effects
- rarely

Intravenous infusion, aciclovir (as sodium salt), 25 mg/mL, net price 10-mL (250-mg) vial = £10.37; 20-mL (500-mg) vial = £19.21; 40-mL (1-g) vial = £40.44

Electrolytes Na 1.1 mmol/250-mg vial

Zovirax® (GSK) [H1]
- Tablets, all dispersible, f/c, aciclovir 200 mg, net price 25-tab pack = £18.80; 400 mg, 56-tab pack = £68.98; 800 mg (scored, Shingles Treatment Pack), 35-tab pack = £69.85. Label: 9
- Suspension, both off-white, sugar-free, aciclovir 200 mg/5 mL (banana-flavoured), net price 125 mL = £29.53; 400 mg/5 mL (Double Strength Suspension, orange-flavoured) 100 mL = £33.01. Label: 9
- Dental prescribing on NHS May be prescribed as Aciclovir 200 mg/5 mL oral Suspension

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt). Net price 250-mg vial = £10.15; 500-mg vial = £18.81

Electrolytes Na 1.1 mmol/250-mg vial

FAMCICLOVIR

Note Famiciclovir is a pro-drug of penciclovir

Indications treatment of herpes zoster, acute genital herpes simplex and suppression of recurrent genital herpes

Cautions hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4) and breast-feeding (Appendix 5); interactions: Appendix 1 (famciclovir)

Side-effects rarely nausea, headache, confusion; very rarely vomiting, jaundice, dizziness, drowsiness, hallucinations, rash, and pruritus; abdominal pain and fever have been reported in immunocompromised patients

Dose
- Herpes zoster, 250 mg 3 times daily for 7 days or 750 mg once daily for 7 days (in immunocompromised, 500 mg 3 times daily for 10 days)
- Genital herpes, first episode, 250 mg 3 times daily for 5 days (longer if new lesions appear during treatment or if healing incomplete); recurrent infection, 125 mg twice daily for 5 days (in immunocompromised or HIV-positive patients, all episodes, 500 mg twice daily for 5–10 days)
- Genital herpes, suppression, 250 mg twice daily (in HIV patients, 500 mg twice daily) interrupted every 6–12 months
- CHILD not recommended

Famvir® (Novartis) [H1]
- Tablets, all f/c, famciclovir 125 mg, net price 10-tab pack = £37.12; 250 mg, 15-tab pack = £111.35, 21-tab pack = £155.87; 56-tab pack = £415.67; 500 mg, 14-tab pack = £207.86, 30-tab pack = £445.28, 56-tab pack = £831.46; 750 mg, 7-tab pack = £148.79. Label: 9

Valaciclovir is a pro-drug of aciclovir

Indications treatment of herpes zoster; treatment of initial and suppression of recurrent herpes simplex infections of skin and mucous membranes including initial and recurrent genital herpes; reduction of transmission of genital herpes; prevention of cytomegalovirus disease following renal transplantation

Cautions see under Aciclovir; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

Side-effects see under Aciclovir but neurological reactions more frequent with high doses

Dose
- Herpes zoster, 1 g 3 times daily for 7 days; CHILD 12–18 years, see BNF for Children
- Herpes simplex, first episode, 500 mg twice daily for 5 days, longer if new lesions appear during treatment or if healing incomplete (1 g twice daily for 10 days for genital herpes in immunocompromised or HIV-positive patients); recurrent infection, 500 mg twice daily for 5 days (1 g twice daily for 5–10 days for genital herpes in immunocompromised or HIV-positive patients); CHILD 12–18 years, see BNF for Children
- Herpes simplex, suppression, 500 mg daily in 1–2 divided doses (in immunocompromised or HIV positive patients, 500 mg twice daily); CHILD 12–18 years, see BNF for Children
- Reduction of transmission of genital herpes, seek specialist advice, 500 mg once daily to be taken by the infected partner
- Prevention of cytomegalovirus disease following renal transplantation (preferably starting within 72 hours of transplantation), ADULT and CHILD over 12 years, 2 g 4 times daily usually for 90 days

INOSINE PRANOBEKX
(Inosine acedoben dimepranol)

Indications see under Dose

Cautions renal impairment (Appendix 3); history of gout or hyperuricaemia

Contra-indications pregnancy

Side-effects reversible increase in serum and urinary uric acid; less commonly nausea, vomiting, epigastric discomfort, headache, vertigo, fatigue, arthralgia, rashes and itching; rarely diarrhoea, constipation, anxiety, sleep disturbances, and polyuria

Dose
- Mucocutaneous herpes simplex, 1 g 4 times daily for 7–14 days
- Adjunctive treatment of genital warts, 1 g 3 times daily for 14–28 days
- Subacute sclerosing panencephalitis, 50–100 mg/kg daily in 6 divided doses

Imunovir® (Ardern) [H1]
- Tablets, scored, inosine pranobex 500 mg. Net price 100-tab pack = £39.50. Label: 9

VALACICLOVIR

Note Valaciclovir is a pro-drug of aciclovir

Indications treatment of herpes zoster; treatment of initial and suppression of recurrent herpes simplex infections of skin and mucous membranes including initial and recurrent genital herpes; reduction of transmission of genital herpes; prevention of cytomegalovirus disease following renal transplantation

Cautions see under Aciclovir; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

Side-effects see under Aciclovir but neurological reactions more frequent with high doses

Dose
- Herpes zoster, 1 g 3 times daily for 7 days; CHILD 12–18 years, see BNF for Children
- Herpes simplex, first episode, 500 mg twice daily for 5 days, longer if new lesions appear during treatment or if healing incomplete (1 g twice daily for 10 days for genital herpes in immunocompromised or HIV-positive patients); recurrent infection, 500 mg twice daily for 5 days (1 g twice daily for 5–10 days for genital herpes in immunocompromised or HIV-positive patients); CHILD 12–18 years, see BNF for Children
- Herpes simplex, suppression, 500 mg daily in 1–2 divided doses (in immunocompromised or HIV positive patients, 500 mg twice daily); CHILD 12–18 years, see BNF for Children
- Reduction of transmission of genital herpes, seek specialist advice, 500 mg once daily to be taken by the infected partner
- Prevention of cytomegalovirus disease following renal transplantation (preferably starting within 72 hours of transplantation), ADULT and CHILD over 12 years, 2 g 4 times daily usually for 90 days

Valtrex® (GSK) [H1]
- Tablets, f/c, valaciclovir (as hydrochloride) 250 mg, net price 60-tab pack = £130.87; 500 mg, 10-tab pack = £21.86, 42-tab pack = £91.61. Label: 9

5.3.2 Cytomegalovirus infection

Recommendations for the optimum maintenance therapy of cytomegalovirus (CMV) infections and the duration of treatment are subject to rapid change.

Ganciclovir is related to aciclovir but it is more active against cytomegalovirus; it is also much more toxic than aciclovir and should therefore be prescribed only when
the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the initial treatment of CMV infection. Ganciclovir causes profound myelosuppression when given with zidovudine; the two should not normally be given together particularly during initial ganciclovir therapy. The likelihood of ganciclovir resistance increases in patients with a high viral load or in those who receive the drug over a long duration; cross-resistance to cidofovir is common.

Valaciclovir (see p. 345) is licensed for prevention of cytomegalovirus disease following renal transplantation.

Valganciclovir is an ester of ganciclovir which is licensed for the initial treatment and maintenance treatment of CMV retinitis in AIDS patients. Valganciclovir is also licensed for preventing CMV disease following solid organ transplantation from a cytomegalovirus-positive donor.

Foscarnet is also active against cytomegalovirus; it is toxic and can cause renal impairment.

Cidofovir is given in combination with probenecid for CMV retinitis in AIDS patients when ganciclovir and foscarnet are contra-indicated. Cidofovir is nephrotoxic.

For local treatment of CMV retinitis, see section 11.3.3.

### Cidofovir

**Indications** cytomegalovirus retinitis in AIDS patients for whom other drugs are inappropriate

**Cautions** monitor renal function (serum creatinine and urinary protein) and neutrophil count within 24 hours before each dose; co-treatment with probenecid and prior hydration with intravenous fluids necessary to minimise potential nephrotoxicity (see below); diabetes mellitus (increased risk of ocular hypotony); interactions: Appendix 1 (cidofovir)

Nephrotoxicity Do not initiate treatment in renal impairment (assess creatinine clearance and proteinuria—consult product literature); discontinue treatment and give intravenous fluids if renal function deteriorates—consult product literature

Ocular disorders Regular ophthalmological examinations recommended; iritis and uveitis have been reported which may respond to a topical corticosteroid with or without a cycloplegic drug—discontinue cidofovir if no response to topical corticosteroid or if condition worsens, or if iritis or uveitis recurs after successful treatment

Contra-indications renal impairment (creatinine clearance 55 mL/minute or less); concomitant administration of potentially nephrotoxic drugs; discontinuation of potentially nephrotoxic drugs at least 7 days before starting cidofovir; pregnancy (avoid pregnancy during and for 1 month after treatment, men should not father a child during or within 3 months of treatment; Appendix 4); breast-feeding (Appendix 5)

Side-effects nephrotoxicity (see Cautions above); nausea, vomiting; dysphagia, abdominal pain, constipation, flatulence, dyspepsia, abdominal pain, constipation, flatulence, dyspepsia, headache, fever, asthenia; neutropenia; decreased intra-ocular pressure, iritis, uveitis (see Cautions above); alopecia, rash; less commonly Fanconi syndrome; also reported, hearing impairment and pancreatitis

**Dose**

- Initial (induction) treatment, ADULT over 18 years, by intravenous infusion over 1 hour, 5 mg/kg once weekly for 2 weeks (give probenecid and intravenous fluids with each dose, see below)
- Maintenance treatment, beginning 2 weeks after completion of induction, ADULT over 18 years, by intravenous infusion over 1 hour, 5 mg/kg once every 2 weeks (give probenecid and intravenous fluids with each dose, see below)

**Probenecid co-treatment** By mouth (preferably after food), probenecid 2 g 3 hours before cidofovir infusion followed by probenecid 1 g at 2 hours and 1 g at 8 hours after the end of cidofovir infusion (total probenecid 4 g); for cautions, contra-indications and side-effects of probenecid see section 10.1.4

**Prior hydration** Sodium chloride 0.9%, by intravenous infusion, 1 litre over 1 hour immediately before cidofovir infusion (if tolerated an additional 1 litre may be given over 1–3 hours, starting at the same time as the cidofovir infusion or immediately afterwards)

**Vistide®** (Pfizer) [TML] Intravenous infusion, cidofovir 75 mg/mL, net price £653.22

**Caution in handling** Cidofovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with water

### Vistide®

**Indications** life-threatening or sight-threatening cytomegalovirus infections in immunocompromised patients only; prevention of cytomegalovirus disease during immunosuppressive therapy following organ transplantation; local treatment of CMV retinitis (section 11.3.3)

**Cautions** close monitoring of full blood count (severe deterioration may require correction and possibly treatment interruption); history of neutropenia; low platelet count; potential carcinogen and teratogen; renal impairment (Appendix 3); radiotherapy; ensure adequate hydration during intravenous administration; vesicant—infuse into vein with adequate flow preferably using plastic cannula; children (possible risk of long-term carcinogenic or reproductive toxicity—not for neonatal or congenital cytomegalovirus disease); interactions: Appendix 1 (ganciclovir)

**Contra-indications** pregnancy (ensure effective contraception during treatment and barrier contraception for men during and for at least 90 days after treatment; Appendix 4); breastfeeding; hypersensitivity to ganciclovir or aciclovir; abnormally low hae-moglobin, neutrophil, or platelet counts (consult product literature)

### Side-effects
diarrhoea, nausea, vomitina, dyspepsia, abdominal pain, constipation, flatulence, dysphagia, hepatic dysfunction; dysphagia, chest pain, cough; headache, insomnia, convulsions, dizziness, neuropathy, depression, anxiety, confusion, abnormal thinking, fatigue, weight loss, anorexia; infection, fever, night sweats; anaemia, leukopenia, thrombocytopenia, pancytopenia, renal impairment; myalgia, arthralgia; macular oedema, retinal detachment, vitreous floaters, eye pain; ear pain, taste disturbance; dermatitis, pruritus; injection-site reactions; less commonly mouth ulcers, pancreatitis, arrhythmias, hypotension, anaphylactic reactions, psychosis, tremor, male infertility, haematuria, disturbances in hearing and vision, and alopecia

**Dose**

- By intravenous infusion, initially (induction) 5 mg/kg every 12 hours for 14–21 days for treatment or for 7–14 days for prevention; maintenance (for patients at risk of relapse of retinitis) 6 mg/kg daily on
5 days per week or 5 mg/kg daily until adequate recovery of immunity; if retinitis progresses initial induction treatment may be repeated

**Cymevene** (Roche) [NF]

Intravenous infusion, powder for reconstitution, ganciclovir (as sodium salt). Net price 500-mg vial = £31.60

Electrolytes Na 2 mmol/500-mg vial

Caution in handling Ganciclovir is toxic and personnel should be adequately protected during handling and administration; if solution comes into contact with skin or mucosa, wash off immediately with soap and water

**FOSCARNET SODIUM**

**Indications**
cytomegalovirus retinitis in AIDS patients; mucocutaneous herpes simplex virus infections unresponsive to aciclovir in immunocompromised patients

**Cautions**
renal impairment (reduce dose; consult product literature); monitor electrolytes, particularly calcium and magnesium; monitor serum creatinine every second day during induction and every week during maintenance; ensure adequate hydration; avoid rapid infusion; interactions: Appendix 1 (foscarnet)

**Contra-indications**
pregnancy; breast-feeding (Appendix 5)

**Side-effects**
nausea, vomiting, diarrhoea (occasionally constipation and dyspepsia), abdominal pain, anorexia, changes in blood pressure and ECG; headache, fatigue, mood disturbances (including psychosis), asthena, paraesthesia, convulsions, tremor, dizziness, and other neurological disorders; rash; impairment of renal function including acute renal failure; hypocalcaemia (sometimes symptomatic) and other electrolyte disturbances; abnormal liver function tests; decreased haemoglobin concentration, leucopenia, granulocytopenia, thrombocytopenia; thrombophlebitis if given undiluted by peripheral vein; genital irritation and ulceration (due to high concentrations excreted in urine); isolated reports of pancreatitis

**Dose**
- CMV retinitis, by intravenous infusion, induction 60 mg/kg every 8 hours for 2–3 weeks then maintenance, 60 mg/kg daily, increased to 90–120 mg/kg if tolerated; if retinitis progresses on maintenance dose, repeat induction regimen
- Mucocutaneous herpes simplex infection, by intravenous infusion, 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal

**Foscavir** (AstraZeneca) [NF]

Intravenous infusion, foscarnet sodium hexahydrate 24 mg/mL, net price 250-mL bottle = £34.49

**VALGANCICLOVIR**

**Note** Valganciclovir is a pro-drug of ganciclovir

**Indications** induction and maintenance treatment of cytomegalovirus retinitis in AIDS patients; prevention of cytomegalovirus disease following solid organ transplantation from a cytomegalovirus-positive donor.

**Cautions** see under Ganciclovir

**Side-effects** see under Ganciclovir

**Dose**
- CMV retinitis, induction, 900 mg twice daily for 21 days then 900 mg once daily; induction regimen may be repeated if retinitis progresses
- Prevention of cytomegalovirus disease following solid organ transplantation (starting within 10 days of transplantation), 900 mg once daily for 100 days
- CHILD under 18 years not recommended

**Note** Oral valganclovir 900 mg twice daily is equivalent to intravenous ganciclovir 5 mg/kg twice daily

**Valcyte** (Roche) [NF]

Tablets, pink, f/c, valganclovir (as hydrochloride) 450 mg, net price 60-tab pack = £1148.05. Label: 21

Caution in handling Valganclovir is a potential teratogen and carcinogen and caution is advised for handling of broken tablets; if broken tablets come into contact with skin or mucosa, wash off immediately with water

**5.3.3 Viral hepatitis**

Treatment for viral hepatitis should be initiated by a specialist. The management of uncomplicated acute viral hepatitis is largely symptomatic. Early treatment of acute hepatitis C with interferon alfa [unlicensed indication] may reduce the risk of chronic infection. Hepatitis B and hepatitis C viruses are major causes of chronic hepatitis. For details on immunisation against hepatitis A and B infections, see section 14.4 (active immunisation) and section 14.5 (passive immunisation).

**Chronic Hepatitis B** Peginterferon alfa-2a (section 8.2.4) is an option for the initial treatment of chronic hepatitis B (see NICE guidance below) and may be preferable to interferon alfa. The use of peginterferon alfa-2a and interferon alfa is limited by a response rate of 30–40% and relapse is frequent. Treatment should be discontinued if no improvement occurs after 4 months. The manufacturers of peginterferon alfa-2a and interferon alfa contraindicate use in decompensated liver disease but low doses can be used with great caution in these patients. Although interferon alfa is contraindicated in patients receiving immunosuppressant treatment (or who have received it recently), cautious use of peginterferon alfa-2a may be justified in some cases.

Adefovir dipivoxil, entecavir, lamivudine (see p. 337), telbivudine, or tenofovir disoproxil (see p. 338) are licensed for the treatment of chronic hepatitis B. Lamivudine or adefovir can also be used in patients with decompensated liver disease. Hepatitis B viruses with reduced susceptibility to lamivudine have emerged following extended therapy. Adefovir is effective in lamivudine-resistant chronic hepatitis B but telbivudine should not be used because cross-resistance may occur (see also NICE guidance below). Entecavir is effective in patients not previously treated with nucleoside analogues (see NICE guidance below). Resistance to entecavir can occur in patients who have received lamivudine.

If there is no toxicity or loss in efficacy, treatment with adefovir, entecavir, lamivudine, telbivudine, or tenofovir is usually continued until 6 months after adequate seroconversion has occurred. Treatment with lamivudine or adefovir is continued long-term in patients with decompensated liver disease.
Tenofvir, or a combination of tenofovir with either emtricitabine or lamivudine may be used with other antiretrovirals, as part of 'highly active antiretroviral therapy' (section 5.3.1) in patients who require treatment for both HIV and chronic hepatitis B. If patients infected with both HIV and chronic hepatitis B only require treatment for chronic hepatitis B, they should receive antivirals that are not active against HIV, such as peginterferon alfa-2a. Management of these patients should be co-ordinated between HIV and hepatology specialists.

NICE guidance

Adefovir dipivoxil and peginterferon alfa-2a for chronic hepatitis B (February 2006)

Peginterferon alfa-2a is an option for the initial treatment of chronic hepatitis B.

Adefovir dipivoxil is recommended as an option for the treatment of chronic hepatitis B if:

- treatment with interferon alfa or peginterferon alfa-2a has been unsuccessful, or
- a relapse occurs after successful initial therapy, or
- treatment with interferon alfa or peginterferon alfa-2a is poorly tolerated or contra-indicated.

Adefovir dipivoxil should not be given before treatment with lamivudine. It may be used either alone or in combination with lamivudine when treatment with lamivudine has resulted in viral resistance, or if lamivudine resistance is likely to occur rapidly and adversely affect the outcome.

NICE guidance

Entecavir and telbivudine for chronic hepatitis B (August 2008)

Entecavir is an option for the treatment of chronic hepatitis B.

Telbivudine is not recommended for the treatment of chronic hepatitis B. Patients currently receiving telbivudine can continue treatment until they and their clinician consider it appropriate to stop.

Chronic Hepatitis C

Before starting treatment, the genotype of the infecting hepatitis C virus should be determined and the viral load measured as this may affect the choice and duration of treatment. A combination of ribavirin (see p. 351) and peginterferon alfa (section 8.2.4) is used for the treatment of chronic hepatitis C (see NICE guidance, below). The combination of ribavirin and interferon alfa is less effective than the combination of peginterferon alfa and ribavirin. Peginterferon alfa alone should be used if ribavirin is contra-indicated or not tolerated. Ribavirin monotherapy is ineffective.

NICE guidance

Peginterferon alfa and ribavirin for mild chronic hepatitis C (August 2006)

The combination of peginterferon alfa and ribavirin can be used for treating mild chronic hepatitis C in patients over 18 years. Alternatively, treatment can be delayed until the disease has reached a moderate stage ('watchful waiting'). Peginterferon alfa alone can be used if ribavirin is contra-indicated or not tolerated.
Contra-indications breast-feeding (Appendix 5)

Side-effects nausea, vomiting, dyspepsia, diarrhoea, raised serum amylase and lipase; headache, fatigue, dizziness, sleep disturbances; less commonly thrombocytopenia; also reported, rash

Dose
- ADULT over 18 years, not previously treated with nucleoside analogues, 500 micrograms once daily
- ADULT over 18 years with lamivudine-resistant chronic hepatitis B, 1 mg once daily

Counselling To be taken at least 2 hours before or 2 hours after food

Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

TELBIVUDINE

Indications chronic hepatitis B infection with compensated liver disease, evidence of viral replication, and histologically documented active liver inflammation or fibrosis

Cautions monitor liver function tests every 3 months and viral and serological markers of hepatitis B every 3–6 months; discontinue if deterioration in liver function, hepatic steatosis, progressive hepatomegaly or unexplained lactic acidosis; hepatitis may recur on discontinuation; renal impairment (Appendix 3); pregnancy (Appendix 4). Interactions: Appendix 1 (telbivudine)

Counselling Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, or numbness, tingling or burning sensations

Contra-indications breast-feeding (Appendix 5)

Side-effects nausea, diarrhoea, abdominal pain, raised serum amylase and lipase; cough; dizziness, headache, fatigue; rash; less commonly peripheral neuropathy, arthralgia, myalgia, and myopathy

Dose
- ADULT and CHILD over 16 years, 600 mg once daily

Sebivo® (Novartis) Tablets, If/c, telbivudine 600 mg, net price 28-tab pack = £290.33. Counselling, muscle effects, peripheral neuropathy

5.3.4 Influenza

For advice on immunisation against influenza, see section 14.4.

Oseltamivir and zanamivir reduce replication of influenza A and B viruses by inhibiting viral neuraminidase. They are most effective for the treatment of influenza if started within a few hours of the onset of symptoms; they are licensed for use within 48 hours (within 36 hours for zanamivir in children) of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. Oseltamivir or zanamivir can reduce the risk of complications from influenza in the elderly and in patients with chronic disease (see also NICE guidance, p. 350).

Oseltamivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community (see also NICE guidance, below). Oseltamivir and zanamivir are also licensed for use in exceptional circumstances (e.g. when vaccination does not cover the infecting strain) to prevent influenza in an epidemic.

NICE guidance Oseltamivir, zanamivir, and amantadine for prophylaxis of influenza (September 2008)
The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza.

- Amantadine is not recommended for prophylaxis of influenza.
- Oseltamivir and zanamivir are not recommended for seasonal prophylaxis against influenza.
- When influenza is circulating in the community, either oseltamivir or zanamivir are recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk patients who are not effectively protected by influenza vaccine, and who have been in close contact with someone suffering from influenza-like illness in the same household or residential setting. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza. National surveillance schemes, including those run by the Health Protection Agency, should be used to indicate when influenza is circulating in the community.
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either oseltamivir or zanamivir may be used for post-exposure prophylaxis in at-risk patients (regardless of influenza vaccination) living in long-term residential or nursing homes.

At risk patients include those aged over 65 years or those who have one or more of the following conditions:
- chronic respiratory disease (including asthma treated with continuous or repeated use of inhaled or systemic corticosteroids or asthma with previous exacerbations requiring hospital admission);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.
Infections

2. The NICE guidelines on

1. The NICE guidelines on

Influenza A (see also notes above), Side-effects see section 4.9.1
Contra-indications see section 4.9.1
Cautions

350 5.3.4 Influenza BNF 57

NICE guidance
Oseltamivir, zanamivir, and amantadine for treatment of influenza (February 2003)
The drugs described here are not a substitute for vaccination, which remains the most effective way of preventing illness from influenza. When influenza A or influenza B is circulating in the community:

- amantadine is not recommended for treatment of influenza;
- oseltamivir or zanamivir are not recommended for treatment of otherwise healthy individuals with influenza;
- oseltamivir and zanamivir are recommended (in accordance with UK licensing) to treat at-risk adults who can start treatment within 48 hours of the onset of symptoms; oseltamivir is recommended for at-risk children who can start treatment within 48 hours of the onset of symptoms.

At-risk patients include those aged over 65 years or those who have one or more of the following conditions:

- chronic respiratory disease (including chronic obstructive pulmonary disease and asthma);
- significant cardiovascular disease (excluding hypertension);
- chronic renal disease;
- immunosuppression;
- diabetes mellitus.

Community-based virological surveillance schemes including those run by the Health Protection Agency and the Royal College of General Practitioners should be used to indicate when influenza is circulating in the community.

Amantadine is licensed for prophylaxis and treatment of influenza A but it is no longer recommended (see NICE guidance).

Information on pandemic influenza and avian influenza may be found at www.dh.gov.uk/pandemicflu and at www.hpa.org.uk

AMANTADINE HYDROCHLORIDE

Indications see under Dose; parkinsonism (section 4.9.1)
Cautions see section 4.9.1
Contra-indications see section 4.9.1
Side-effects see section 4.9.1

Dose

- Influenza A (see also notes above), ADULT and CHILD over 10 years, treatment, 100 mg daily for 4–5 days; prophylaxis, 100 mg daily usually for 6 weeks or with influenza vaccination for 2–3 weeks after vaccination

1. The NICE guidelines on Prophylaxis of Influenza (September 2008) also include patients with chronic liver disease or chronic neurological disease in the at-risk group.
2. The NICE guidelines on Prophylaxis of Influenza (September 2008) include patients with chronic heart disease in the at-risk group.

Lysovir® (Alliance) Capsules, red-brown, amantadine hydrochloride 100 mg, net price 5-cap pack = £2.40, 14-cap pack = £4.80. Counselling, driving

Symmetrel® (Alliance) Section 4.9.1

OSEL TAMIVIR

Indications see notes above
Cautions renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)
Side-effects nausea, vomiting, abdominal pain, diarrhoea; headache; conjunctivitis; less commonly rash; also reported, hepatitis, arrhythmias, neuropsychiatric disorders (in children and adolescents), visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Dose

- Prevention of influenza, ADULT and ADOLESCENT over 13 years, 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic; CHILD 1–13 years, body-weight under 15 kg, 30 mg once daily, body-weight 15–23 kg, 45 mg once daily, body-weight 23–40 kg, 60 mg once daily, body-weight over 40 kg, adult dose
- Treatment of influenza, ADULT and ADOLESCENT over 13 years, 75 mg every 12 hours for 5 days; CHILD 1–13 years, body-weight under 15 kg, 30 mg every 12 hours, body-weight 15–23 kg, 45 mg every 12 hours, body-weight 23–40 kg, 60 mg every 12 hours, body-weight over 40 kg, adult dose

1 Tamiflu® (Roche) Capsules, oseltamivir (as phosphate) 30 mg (yellow), net price 10-cap pack = £8.18; 45 mg (grey), 10-cap pack = £16.36; 75 mg (grey-yellow), 10-cap pack = £16.36. Label: 9
Suspension, sugar-free, tutti-frutti-flavoured, oseltamivir (as phosphate) for reconstitution with water, 60 mg/5 mL, net price 75 mL = £16.36. Label: 9
Excipients include sorbitol 1.7 g/5 mL

1. except for the treatment and prophylaxis of influenza as indicated in the notes above and NICE guidance; endorse prescription ‘SLS’

ZANAMIVIR

Indications see notes above
Cautions asthma and chronic pulmonary disease (risk of bronchospasm—short-acting bronchodilator should be available; avoid in severe asthma unless close monitoring possible and appropriate facilities available to treat bronchospasm); uncontrolled chronic illness; other inhaled drugs should be administered before zanamivir; pregnancy (Appendix 4)
Contra-indications breast-feeding (Appendix 5)
Side-effects very rarely, bronchospasm, respiratory impairment, angioedema, urticaria, and rash; also reported, neuropsychiatric disorders (especially in children and adolescents)
Side-effects

- fever, injection-site reactions, nervousness; less commonly diarrhoea, vomiting, constipation, haemorrhage, rhinitis, cough, wheeze, pain, drowsiness, asthenia, hyperkinesia, leucopenia, and rash; rarely apnoea, hypersensitivity reactions (including anaphylaxis)

Dose

- By intramuscular injection (preferably in anterolateral thigh), 15 mg/kg once a month during season of RSV risk (child undergoing cardiac bypass surgery, 15 mg/kg as soon as stable after surgery, then once a month during season of risk); injection volume over 1 mL should be divided between more than one site

- By inhalation of powder, post-exposure prophylaxis of influenza, ADULT and CHILD over 5 years, 10 mg once daily for 10 days

Prevention of influenza during an epidemic, ADULT and CHILD over 12 years, 10 mg once daily for up to 28 days

Treatment of influenza, ADULT and CHILD over 5 years, 10 mg twice daily for 5 days

Relenza® (GSK)

Dry powder for inhalation disks containing 4 blisters of zanamivir 5 mg/blister, net price 5 disks with Diskhaler® device = £16.36

Synagis® (Abbott)

Injection, powder for reconstitution, palivizumab, net price 50-mg vial = £360.40; 100-mg vial = £663.11

Ribavirin (tribavirin)

Indications severe respiratory syncytial virus bronchiolitis in infants and children; in combination with peginterferon alfa or interferon alfa for chronic hepatitis C in patients without liver decompensation (see also section 5.3.3)

Cautions

Specific cautions for inhaled treatment Maintain standard supportive respiratory and fluid management therapy; monitor electrolytes closely; monitor equipment for precipitation; pregnant women (and those planning pregnancy) should avoid exposure to aerosol

Specific cautions for oral treatment Exclude pregnancy before treatment; effective contraception essential during treatment and for 4 months after treatment in women and for 7 months after treatment in men; routine monthly pregnancy tests recommended; condoms must be used if partner of male patient is pregnant (ribavirin excreted in semen); renal impairment (Appendix 3); cardiac disease (assessment including ECG recommended before and during treatment—discontinue if deterioration); gout; determine full blood count, platelets, electrolytes, serum creatinine, liver function tests and uric acid before starting treatment and then on weeks 2 and 4 of treatment, then as indicated clinically—adjust dose if adverse reactions or laboratory abnormalities develop; consult product literature; eye examination recommended before treatment; eye examination also recommended during treatment if pre-existing ophthalmological disorder deteriorates or if new ophthalmological disorder develops; test thyroid function before treatment and then every 3 months in children

Contra-indications pregnancy (important teratogenic risk: see Cautions and Appendix 4); breastfeeding

Specific contra-indications for oral treatment Severe cardiac disease, including unstable or uncontrolled cardiac disease in previous 6 months; haemoglobinopathies; severe debilitating medical conditions; severe hepatic dysfunction or decompensated cirrhosis (Appendix 2); autoimmune disease (including autoimmune hepatitis); uncontrolled severe psychiatric condition; history of severe psychiatric condition in children

Side-effects Specific side-effects for inhaled treatment Worsening respiration, bacterial pneumonia, and pneumothorax reported; rarely non-specific anaemia and haemolysis

Specific side-effects for oral treatment Haemolytic anaemia (anaemia may be improved by epoetin); also (in combination with peginterferon alfa or interferon alfa) nausea, vomiting, dyspepsia, abdominal pain, peptic ulcer,
5.4 Antiprotozoal drugs

5.4.1 Antimalarials

**Advice on specific problems available from:**

**Advice for healthcare professionals**

HPA (Health Protection Agency) Malaria Reference Laboratory (020) 7636 3924 (prophylaxis only)

www.hpa.org.uk/infections/topics_az/malaria

National Travel Health Network and Centre 0845 602 6712

Travel Medicine Team, Health Protection Scotland (registered users of Travax only)

(weekdays 2–4 p.m. only)

www.travax.nhs.uk

Birmingham (0121) 424 0357

Liverpool (0151) 708 9393

London 0845 155 5000 (treatment)

Oxford (01865) 225 430

**Advice for travellers**

Hospital for Tropical Diseases

Travel Healthline 020 7950 7799

www.fitfortravel.nhs.uk

WHO advice on international travel and health

www.who.int/ith

National Travel Health Network and Centre (NaTHNaC)

www.nathnac.org/travel/index.htm

**5.4.4 Antigiardial drugs**

**5.4.5 Leishmaniacides**

**5.4.6 Trypanocides**

**5.4.7 Drugs for toxoplasmosis**

**5.4.8 Drugs for pneumocystis pneumonia**

### Infections

-扁桃体炎, 腹泻, 股骨坏死, 肝炎, 肺炎, 周围性水肿, 血压升高, 药物过敏反应, 口腔溃疡, 口腔干燥, 热射病, 高血脂, 高热, 糖尿病, 眼压升高, 青光眼, 视网膜疾病, 颅内出血, 空中血糖升高, 头痛, 高血压, 心动过缓, 尿潴留, 性功能障碍, 乏力, 记忆力下降, 精神分裂症, 自杀意念, 失眠, 疲劳, 注意力下降, 恶心, 呕吐, 腹痛, 腹泻, 胃炎, 胆囊炎, 胰腺炎, 肾炎, 肾功能不全, 肺栓塞, 咳嗽, 间质性肺炎, 睡眠障碍, 肿胀, 血压变化, 冲血, 心悸, 休克, 呼吸困难, 心律失常, 过敏反应, 过敏性休克, 肝功能不全, 肾功能不全, 呼吸功能不全, 血液系统异常, 出血, 动脉硬化, 血栓形成, 肿瘤, 恶性肿瘤, 脑炎, 病毒性脑炎, 呼吸道感染, 感染性休克, 病毒性肝炎, 肝硬化, 巨大细胞病毒感染, 6.5 g for reconstitution with 300 mL water for injections. Net price 3 × 6-g vials = £349.00

**Dose**

See preparations below

**Copegus®** (Roche) 

**Tablets**, f/c, ribavirin 200 mg (pink), net price 42-tab pack = £115.62, 112-tab pack = £308.31, 168-tab pack = £551.30. Label: 21

**Dose** chronic hepatitis C (in combination with interferon alfa or peginterferon alfa), AU**T**D**U**LT over 18 years, body-weight under 75 kg, 400 mg in the morning and 600 mg in the evening, body-weight 75 kg and over, 600 mg twice daily

**Note** Chronic hepatitis C genotype 2 or 3, or patients infected with HIV and hepatitis C require a lower dose of Copegus (in combination with peginterferon alfa), usual dose 400 mg twice daily

**Rebetol®** (Schering-Plough) 

**Capsules**, ribavirin 200 mg, net price 84-cap pack = £275.65, 140-cap pack = £459.42, 168-cap pack = £551.30. Label: 21

**Dose** chronic hepatitis C, AU**T**D**U**LT over 18 years (in combination with interferon alfa or peginterferon alfa), body-weight under 65 kg, 400 mg twice daily, body-weight 65–85 kg, 400 mg in the morning and 400 mg in the evening, body-weight 85–105 kg, 600 mg twice daily, body-weight over 105 kg, 600 mg in the morning and 400 mg in the evening, CHILD AND ADOLESCENT 3–17 years (in combination with interferon alfa), body-weight under 47 kg, 15 mg/kg daily in 2 divided doses; body-weight 47–50 kg, 200 mg in the morning and 400 mg in the evening, body-weight 50–65 kg, 400 mg twice daily; body-weight over 65 kg, as adult

**Virazole®** (Valeant) 

**Inhalation**, ribavirin 6 g for reconstitution with 300 mL water for injections. Net price 3 × 6-g vials = £349.00

**Dose** bronchiolitis, by aerosol inhalation or nebulisation (via small particle aerosol generator) of solution containing 20 mg/mL for 12–18 hours for at least 3 days; max. 7 days

Advice on specific problems available from:

**Advice for healthcare professionals**

HPA (Health Protection Agency) Malaria Reference Laboratory (020) 7636 3924 (prophylaxis only)

www.hpa.org.uk/infections/topics_az/malaria

National Travel Health Network and Centre 0845 602 6712

Travel Medicine Team, Health Protection Scotland (registered users of Travax only)

(weekdays 2–4 p.m. only)

www.travax.nhs.uk

Birmingham (0121) 424 0357

Liverpool (0151) 708 9393

London 0845 155 5000 (treatment)

Oxford (01865) 225 430

**Advice for travellers**

Hospital for Tropical Diseases

Travel Healthline 020 7950 7799

www.fitfortravel.nhs.uk

WHO advice on international travel and health

www.who.int/ith

National Travel Health Network and Centre (NaTHNaC)

www.nathnac.org/travel/index.htm

5.4.1 Antimalarials

**Recommendations on the prophylaxis and treatment of malaria reflect guidelines agreed by UK malaria specialists.**

The centres listed above should be consulted for advice on special problems.

**Treatment of malaria**

If the infective species is not known, or if the infection is mixed, initial treatment should be as for *falciparum malaria* with quinine, Malarone® (proguanil with atova-quine), or Riamet® (artemether with lumefantrine). Falciparum malaria can progress rapidly in unprotected individuals and antimalarial treatment should be considered in those with features of severe malaria and possible exposure, even if the initial blood tests for the organism are negative.
Falciparum malaria (treatment)

Falciparum malaria (malignant malaria) is caused by Plasmodium falciparum. In most parts of the world P. falciparum is now resistant to chloroquine which should not therefore be given for treatment.

Quinine, Malarone® (proguanil with atovaquone), or Riamet® (artemether with lumefantrine) can be given by mouth if the patient can swallow and retain tablets and there are no serious manifestations (e.g. impaired consciousness); quinine should be given by intravenous infusion (see below) if the patient is seriously ill or unable to take tablets. Mefloquine is now rarely used for treatment because of concerns about resistance.

Oral. The adult dosage regimen for quinine by mouth is:

- 600 mg (of quinine salt\(^1\)) every 8 hours for 5–7 days together with or followed by either doxycycline 200 mg once daily for 7 days or clindamycin 450 mg every 8 hours for 7 days [unlicensed indication].

If the parasite is likely to be sensitive, pyrimethamine 75 mg with sulfadoxine 1.5 g may be given as a single dose [unlicensed] together with or after a course of quinine.

Alternatively, Malarone® or Riamet® may be given instead of quinine. It is not necessary to give doxycycline, clindamycin or pyrimethamine with sulfadoxine after Malarone® or Riamet® treatment.

The adult dose of Malarone® by mouth is:

- 4 (‘standard’) tablets once daily for 3 days.

The dose of Riamet® by mouth for adult with body-weight over 35 kg is:

- 4 tablets initially, followed by 5 further doses of 4 tablets each given at 8, 24, 36, 48, and 60 hours (total 24 tablets over 60 hours).

Parenteral. If the patient is seriously ill or unable to take tablets, quinine should be given by intravenous infusion [unlicensed]. The adult dosage regimen for quinine by infusion is:

- loading dose\(^2\) of 20 mg/kg\(^3\) (up to maximum 1.4 g) of quinine salt\(^2\) infused over 4 hours then 8 hours after the start of the loading dose, maintenance dose of 10 mg/kg\(^2\) (up to maximum 700 mg) of quinine salt\(^2\) infused over 4 hours every 8 hours (until patient can swallow tablets to complete the 7-day course together with or followed by either doxycycline or clindamycin as above).

Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on oral treatment doses of quinine, infection acquired in quinine-resistant areas of south east Asia) because intravenous artesunate may be available for ‘named-patient’ use.

1. Valid for quinine hydrochloride, dihydrochloride, and sulphate; not valid for quinine biallate which contains a correspondingly smaller amount of quinine.
2. In intensive care units the loading dose can alternatively be given as quinine salt\(^1\) 7 mg/kg infused over 30 minutes followed immediately by 10 mg/kg over 4 hours then (after 8 hours) maintenance dose as described.
3. Important: the loading dose of 20 mg/kg should not be used if the patient has received quinine or mefloquine during the previous 12 hours.
4. Maintenance dose should be reduced to 5–7 mg/kg of salt in patients with severe renal impairment, severe hepatic impairment, or if parenteral treatment is required for more than 48 hours.

Children

Oral. Quinine is well tolerated by children although the salts are bitter. The dosage regimen for quinine by mouth for children is:

- 10 mg/kg (of quinine salt\(^1\)) every 8 hours for 7 days together with or followed by Clindamycin 7–13 mg/kg [max. 450 mg] every 8 hours for 7 days [unlicensed indication] or in children over 12 years, doxycycline 200 mg once daily for 7 days

or if the parasite is likely to be sensitive, pyrimethamine with sulfadoxine as a single dose [unlicensed]: up to 4 years and body-weight over 5 kg, pyrimethamine 12.5 mg with sulfadoxine 250 mg; 5–6 years, pyrimethamine 25 mg with sulfadoxine 500 mg; 7–9 years, pyrimethamine 37.5 mg with sulfadoxine 750 mg; 10–14 years, pyrimethamine 50 mg with sulfadoxine 1 g; 14–18 years, pyrimethamine 75 mg with sulfadoxine 1.5 g

Alternatively, Malarone® or Riamet® may be given instead of quinine; it is not necessary to give clindamycin, doxycycline, or pyrimethamine with sulfadoxine after Malarone® or Riamet® treatment. The dose regimen for Malarone® by mouth for children over 40 kg is the same as for adults (see above); the dose regimen for Malarone® for smaller children is reduced as follows:

- body-weight 5–8 kg, 2 ‘paediatric’ tablets once daily for 3 days; body-weight 9–10 kg, 3 ‘paediatric’ tablets once daily for 3 days; body-weight 11–20 kg, 1 ‘standard’ tablet once daily for 3 days; body-weight 21–30 kg, 2 ‘standard’ tablets once daily for 3 days; body-weight 31–40 kg, 3 ‘standard’ tablets once daily for 3 days.

The dose regimen of Riamet® by mouth for children over 12 years and body-weight over 35 kg is the same as for adults (see above). The dose regimen for Riamet® for children under 12 years is as follows:

- body-weight 5–15 kg: 1 tablet initially, followed by 5 further doses of 1 tablet each given at 8, 24, 36, 48, and 60 hours (total 6 tablets over 60 hours); body-weight 15–25 kg: 2 tablets initially, followed by 5 further doses of 2 tablets each given at 8, 24, 36, 48, and 60 hours (total 12 tablets over 60 hours);
- body-weight 25–35 kg: 3 tablets initially, followed by 5 further doses of 3 tablets each given at 8, 24, 36, 48, and 60 hours (total 18 tablets over 60 hours)

Parenteral. The dose regimen for quinine by intravenous infusion for children is calculated on a mg/kg basis as for adults (see above).

Pregnancy

Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The adult treatment doses of oral and intravenous quinine given above (including the loading dose) can safely be given to pregnant women. Clindamycin 450 mg every 8 hours for 7 days [unlicensed indication] should be given with or after quinine. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development); pyrimethamine with sulfadoxine, Malarone®, and Riamet® are also best avoided until more information is available.
Benign malarias (treatment)

Benign malaria is usually caused by *Plasmodium vivax* and less commonly by *P. ovale* and *P. malariae*. Chloroquine is the drug of choice for the treatment of benign malaria (but chloroquine-resistant *P. vivax* infection has been reported from Indonesia, New Guinea and some adjacent islands).

The adult dosage regimen for chloroquine by mouth is:

1. initial dose of 620 mg of base then
   2. a single dose of 310 mg of base after 6 to 8 hours then
   3. a single dose of 310 mg of base daily for 2 days

(approximate total cumulative dose of 25 mg/kg of base)

Chloroquine alone is adequate for *P. malariae* infections but in the case of *P. vivax* and *P. ovale*, a radical cure (to destroy parasites in the liver and thus prevent relapses) is required. This is achieved with primaquine [unlicensed] given after chloroquine; in *P. vivax* infection primaquine is given in an adult dosage of 30 mg daily for 14 days and for *P. ovale* infection it is given in an adult dosage of 15 mg daily for 14 days.

Children The dosage regimen of chloroquine for benign malaria in children is:

1. initial dose of 10 mg/kg of base (max. 620 mg) then
2. a single dose of 5 mg/kg of base (max. 310 mg) after 6–8 hours then
3. a single dose of 5 mg/kg of base (max. 310 mg) daily for 2 days

For a radical cure, primaquine [unlicensed] is then given to children over 6 months of age; specialist advice should be sought for children under 6 months of age. In *P. vivax* infection primaquine is given in a dose of 500 micrograms/kg (max. 30 mg) daily for 14 days, and for *P. ovale* infection it is given in a dose of 250 micrograms/kg (max. 15 mg) daily for 14 days.

Pregnancy The adult treatment doses of chloroquine can be given for benign malaria. In the case of *P. vivax* or *P. ovale*, however, the radical cure with primaquine should be postponed until the pregnancy is over; instead chloroquine should be continued at a dose of 310 mg each week during the pregnancy.

Prophylaxis against malaria

The recommendations on prophylaxis reflect guidelines agreed by UK malaria specialists; the advice is aimed at residents of the UK who travel to endemic areas. The choice of drug for a particular individual should take into account:

- risk of exposure to malaria;
- extent of drug resistance;
- efficacy of the recommended drugs;
- side-effects of the drugs;
- patient-related factors (e.g. age, pregnancy, renal or hepatic impairment, compliance with prophylactic regimen).

Protection against bites Prophylaxis is not absolute, and breakthrough infection can occur with any of the drugs recommended. Personal protection against being bitten is very important. Mosquito nets impregnated with permethrin provide the most effective barrier protection against insects; mats and vapourised insecticides are also useful. Diethyltoluamide (DEET) 20–50% in lotions, sprays, or roll-on formulations is safe and effective when applied to the skin of adults and children over 2 months of age. It can also be used during pregnancy and breast-feeding. The duration of protection varies according to the concentration of DEET and is longest for DEET 50%. Long sleeves and trousers worn after dusk also provide protection.

Length of prophylaxis In order to determine tolerance and to establish habit, prophylaxis should generally be started one week (preferably 2–3 weeks in the case of mefloquine) before travel into an endemic area (or if not possible at earliest opportunity up to 1 or 2 days before travel); Malarone or doxycycline prophylaxis should be started 1–2 days before travel. Prophylaxis should be continued for 4 weeks after leaving (except for Malarone prophylaxis which should be stopped 1 week after leaving).

In those requiring long-term prophylaxis, chloroquine and proguanil may be used for periods of over 5 years. Mefloquine is licensed for up to 1 year (although it has been used for up to 3 years without undue problems). Doxycycline can be used for up to 2 years. Malarone is licensed for use up to 28 days but can be used for up to 1 year (and possibly longer) with caution. Specialist advice should be sought for long-term prophylaxis.

Return from malarial region It is important to be aware that any illness that occurs within 1 year and especially within 3 months of return might be malaria even if all recommended precautions against malaria were taken. Travellers should be warned of this and told that if they develop any illness particularly within 3 months of their return they should go immediately to a doctor and specifically mention their exposure to malaria.

Children Prophylactic doses are based on guidelines agreed by UK malaria experts and may differ from advice in product literature. Weight is a better guide than age. If in doubt telephone centres listed on p. 352.

Epilepsy Both chloroquine and mefloquine are unsuitable for malaria prophylaxis in individuals with a his-
During pregnancy unless there is no suitable alternative. INR should be checked at regular intervals. After completing the course. For prolonged stays, the starting chemoprophylaxis, 7 days after starting, and stable before departure. It should be measured before for mefloquine before departure. The INR should be begun chemoprophylaxis at least 1 week (2–3 weeks contra-indicated during pregnancy. Malarone® should be avoided during pregnancy unless there is no suitable alternative. Pregnancy Travel to malarious areas should be avoided during pregnancy; if travel is unavoidable, effective prophylaxis must be used. Chloroquine and proguanil can be given in the usual doses during pregnancy, but these drugs are not appropriate for most areas because their effectiveness has declined, particularly in Sub-Saharan Africa; in the case of proguanil, folic acid 5 mg daily should be given. The centres listed on p. 352 should be consulted for advice on prophylaxis in chloroquine-resistant areas. The manufacturer advises that prophylaxis with mefloquine should be avoided as a matter of principle but studies of mefloquine in pregnancy (including use in the first trimester) indicate that it can be considered for travel to chloroquine-resistant areas. Doxycycline is contra-indicated during pregnancy. Malarone® should be avoided during pregnancy unless there is no suitable alternative.

Breast-feeding Prophylaxis is required in breast-fed infants; although antimalarials are present in milk, the amounts are too variable to give reliable protection.

Anticoagulants Travellers taking warfarin should begin chemoprophylaxis at least 1 week (2–3 weeks for mefloquine) before departure. The INR should be stable before departure. It should be measured before starting chemoprophylaxis, 7 days after starting, and after completing the course. For prolonged stays, the INR should be checked at regular intervals.

Specific recommendations

Where a journey requires two regimens, the regimen for the higher risk area should be used for the whole journey. Those travelling to remote or little-visited areas may require expert advice.

Risk may vary in different parts of a country—check under all risk levels

Important Settled immigrants (or long-term visitors) to the UK may be unaware that they will have lost some of their immunity and also that the areas where they previously lived may now be malarious.

North Africa, the Middle East, and Central Asia

**Very low risk** Risk very low in Algeria, Egypt (but low risk in El Faiyum, see below), Georgia (south-east, July–October), Kyrgyzstan (but low risk in south-west, see below), Libya, rural Morocco, most tourist areas of Turkey (but low risk in Adana and border with Syria, see below), Uzbekistan (extreme south-east only):

- chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever presents

**Low risk** Risk low in Armenia (June–October), Azerbaijan (southern border areas, June–September), Egypt (El Faiyum only, June–October), Iran (northern border with Azerbaijan, May–October; variable risk in rural south-east provinces; see below), rural north Iraq (May–November), Kyrgyzstan (south-west, May–October), north border of Syria (May–October), Turkey (plain around Adana and east of there, border with Syria, March–November), Turkmenistan (south-east only, June–October):

- preferably chloroquine or (if chloroquine not appropriate) proguanil hydrochloride

- chloroquine or (if chloroquine not appropriate) proguanil hydrochloride

**Variable risk** Risk variable and chloroquine resistance present in Afghanistan (below 2000 m, May–November), Iran (rural south-east provinces, March–November, see also Low risk above), Oman (remote rural areas only), Saudi Arabia (south-west and rural areas of western region; no risk in Mecca, Medina, Jeddah, or high-altitude areas of Asir Province), Tajikistan (June–October), Yemen (no risk in Sana’a):

- chloroquine + proguanil hydrochloride or (if chloroquine + proguanil not appropriate) doxycycline

Sub-Saharan Africa

No chemoprophylaxis recommended for Cape Verde (some risk on São Tiago) and Mauritius (but avoid mosquito bites and consider malaria if fever presents)

**Very high risk** Risk very high (or locally very high) and chloroquine resistance very widespread in Angola, Benin, Botswana (northern half, November–June), Burkina Faso, Burundi, Cameroon, Central African Republic, Chad, Comoros, Congo, Democratic Republic of the Congo (formerly Zaïre), Djibouti, Equatorial Guinea, Eritrea, Ethiopia (below 2000 m; no risk in Addis Ababa), Gabon, Gambia, Ghana, Guinea, Guinea-Bissau, Ivory Coast, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania (all year in south, July–October in north), Mozambique, Namibia (all year along Kavango and Kunene rivers; November–June in...
Infections

5

5.4.1 Antimalarials

Note In Zimbabwe and neighbouring countries, pyrimethamine with dapsone (also known as Deltaprim®) prophylaxis is used by local residents (sometimes with chloroquine)—this regimen is not recommended.

South Asia

Low risk Risk low in Bangladesh (but high risk in Chittagong Hill Tracts, see below), India (Kerala [southern states], Tamil Nadu, Karnataka, Southern Andhra Pradesh [including Hyderabad and Mumbai], Rajasthan [including Jaipur], Uttar Pradesh [including Aggra], Haraya, Uttarakanch, Himachal Pradesh, Jammu, Kashmir, Punjab, Delhi; variable risk in other areas, see below; high risk in Assam), Sri Lanka (but variable risk north of Vavuniya, see below):

Variable risk Risk variable and chloroquine resistance usually moderate in southern districts of Bhutan, India (low risk in some areas, see above; high risk in Assam, see below), Nepal (below 1500 m, especially Terai districts; no risk in Kathmandu), Pakistan (below 2000 m), Sri Lanka (north of Vavuniya; low risk in other areas, see above):

Variable to low risk in Singapore (below 1500 m), Thailand (except rural areas in western provinces of Thailand), Vietnam (south of Hanoi, and Mekong River until close to Cambodian border; substantial risk in other areas, see below):

chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever presents

Variable risk Risk variable and some chloroquine resistance in Indonesia (very low risk in Bali, and cities but substantial risk in Irian Jaya [West Papua] and Lombok, see below), rural Philippines below 600 m (no risk in cities, Cebu, Bohol, and Catanduanes), deep forests of peninsular Malaysia and Sarawak (but substantial risk in Sabah, see below):

choloroquine + proguanil hydrochloride or (if chloroquine + proguanil not appropriate) mefloquine or doxycycline or Malarone®

Substantial risk Risk substantial and drug resistance common in Cambodia (no risk in Phnom Penh; for western provinces, see below), China (Yunnan and Hainan; chloroquine prophylaxis appropriate for other remote areas; see also Very low risk above), East Timor, Irian Jaya [West Papua], Laos (no risk in Vientiane), Lombok, Malaysia (Sabah; see also Very low risk and Variable risk above), Myanmar (formerly Burma; see also Great risk below), Vietnam (very low risk in some areas, see above):

mefloquine or doxycycline or Malarone®

Great risk and drug resistance present Risk great and widespread chloroquine and mefloquine resistance present in western provinces of Cambodia, borders of Thailand with Cambodia, Laos and Myanmar (very low risk in Chang Ri and Kwai Bridge, see above), Myanmar (eastern Shan State):

doxycycline or Malarone®

Oceania

Risk Risk high and chloroquine resistance high in Papua New Guinea (below 1800 m), Solomon Islands, Vanuatu:

doxycycline or mefloquine or Malarone®

Central and South America and the Caribbean

Variable to low risk Risk variable to low in Argentina (rural areas along northern borders only), rural Belize (except Belize district), Costa Rica (Limon Province except Puerto Limon and northern canton of Pococci), Dominican Republic, El Salvador (Santa Ana province in west), Guatemala (below 1500 m), Haiti, Honduras,
Artemether with lumefantrine

Artemether with lumefantrine is licensed for the treatment of acute uncomplicated falciparum malaria.

### ARTEMETHER WITH LUMEFANTRINE

**Indications** treatment of acute uncomplicated falciparum malaria; treatment of benign malaria [unlicensed indication]

**Cautions** electrolyte disturbances, concomitant use with other drugs known to cause QT-interval prolongation; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); monitor patients unable to take food (greater risk of recrudescence); **interactions**: Appendix 1 (artemether with lumefantrine)

**Driving** Dizziness may affect performance of skilled tasks (e.g. driving)

**Contra-indications** history of arrhythmias, of clinically relevant bradycardia, and of congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or of congenital QT interval prolongation; breast-feeding (Appendix 5)

**Side-effects** abdominal pain, anorexia, diarrhoea, vomiting, nausea; palpitation; cough; headache, dizziness, sleep disturbances, asthenia, paraesthesia; arthralgia, myalgia; pruritus, rash; less commonly ataxia, hypoaesthesia

**Dose**
- Treatment of malaria, see p. 353

**Riamet** (Novartis) ▼

Tablets, yellow, artemether 20 mg, lumefantrine 120 mg, net price 24-tab pack = £22.50. Label: 21, counselling, driving

**Note** Tablets may be crushed just before administration

### Chloroquine

Chloroquine is used for the prophylaxis of malaria in areas of the world where the risk of chloroquine-resistant falciparum malaria is still low. It is also used with proguanil when chloroquine-resistant falciparum malaria is present but this regimen may not give optimal protection (see specific recommendations by country, p. 355).

Chloroquine is no longer recommended for the treatment of falciparum malaria owing to widespread resistance, nor is it recommended if the infective species is not known or if the infection is mixed; in these cases treatment should be with quinine, Malarone®, or Riamet® (for details, see p. 352). It is still recommended for the treatment of benign malarial (for details, see p. 354).

### CHLOROQUINE

**Indications** chemoprophylaxis and treatment of malaria; rheumatoid arthritis and lupus erythematosus (section 10.1.3)

**Cautions** moderate or severe hepatic impairment; renal impairment (see notes above); pregnancy (but for malaria benefit outweighs risk, see Appendix 4, Antimalarials); may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of
5.4.1 Antimalarials

Mefloquine

Mefloquine is used for the prophylaxis of malaria in areas of the world where there is a high risk of chloroquine-resistant *falciparum malaria* (for details, see specific recommendations by country, p. 355).

Mefloquine is now rarely used for the treatment of *falciparum malaria* because of increased resistance. It is rarely used for the treatment of benign malarial because better tolerated alternatives are available. Mefloquine should not be used for treatment if it has been used for prophylaxis.

The CSM has advised that travellers should be informed about adverse reactions of mefloquine and, if they occur, medical advice should be sought on alternative antimalarials before the next dose is due; the patient information leaflet, which describes adverse reactions should always be provided when dispensing mefloquine.

### MEFLOQUINE

#### Indications
chemoprophylaxis of malaria, treatment of malaria, see notes above

#### Cautions
pregnancy (see notes under Prophylaxis against malaria; Appendix 4)—manufacturer advises avoid pregnancy during and for 3 months after; breast-feeding (Appendix 5); avoid for chemoprophylaxis in severe hepatic impairment; cardiac conduction disorders; epilepsy (avoid for prophylaxis); not recommended in infants under 3 months (5 kg).

#### Interactions
Appendix 1 (mefloquine)

#### Driving
Dizziness or a disturbed sense of balance may affect performance of skilled tasks (e.g. driving); effects may persist for up to 3 weeks

#### Contra-indications
hypersensitivity to quinine; avoid for prophylaxis if history of psychiatric disorders (including depression) or convulsions

#### Side-effects
nausea, vomiting, diarrhoea, abdominal pain; dizziness, loss of balance, headache, sleep disorders (insomnia, drowsiness, abnormal dreams); less commonly neuropsychiatric reactions (including sensorimotor neuropathies, tremor, ataxia, anxiety, depression, panic attacks, agitation, hallucinations, psychosis, convulsions), tinnitus and vestibular disorders, visual disturbances, circulatory disorders (hypotension and hypertension), chest pain, tachycardia, palpitation, Bradycardia, cardiac conduction disorders, dyspnoea, muscle weakness, myalgia, arthralgia, rash (including Stevens-Johnson syndrome), urticaria, pruritus, alopecia, asthenia, malaise, fatigue, fever, loss of appetite, leucopenia or leucocytosis, thrombocytopenia; rarely suicidal ideation; very rarely AV block, pneumonitis, and encephalopathy

#### Dose

- **Prophylaxis of malaria, preferably started 2½ weeks before entering endemic area and continued for 4 weeks after leaving (see notes above), 310 mg once weekly; **infant up to 12 weeks body-weight under 6 kg, 37.5 mg once weekly; 12 weeks–1 year body-weight 6–10 kg, 75 mg once weekly; **child 1–4 years body-weight 10–16 kg, 112.5 mg once weekly; 4–8 years body-weight 16–25 kg, 150 mg once weekly; 8–13 years body-weight 25–45 kg, 225 mg once weekly; over 13 years body-weight over 45 kg, adult dose
  - Treatment of benign malarial, see p. 354

#### Counselling
Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above

Note: Chloroquine doses in BNF may differ from those in product literature

1. **Avloclor® (AstraZeneca)**
   - Tablets, scored, chloroquine phosphate 250 mg (= chloroquine base 155 mg). Net price 20-tab pack = £1.22. Label: 5, counselling, prophylaxis, see above

2. **Malarivon®**
   - Wallace Mfg)

3. **Nivaquine®**
   - Sanofi-Aventis)

4. With proguanil
   - For cautions and side-effects of proguanil see Proguanil; for dose see Chloroquine and Proguanil

5. **Paludrine/Avloclor®**
   - AstraZeneca

   - Tablets, travel pack of 14 tablets of chloroquine phosphate 250 mg (= chloroquine base 155 mg) and 98 tablets of proguanil hydrochloride 100 mg, net price 112-tab pack = £8.79. Label: 5, 21, counselling, prophylaxis, see above

1. Can be sold to the public provided it is licensed and labelled for the prophylaxis of malaria. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials are prescribed

2. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed
of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above.

Note: Mefloquine doses in BNF may differ from those in product literature.

1 Lariam® (Roche) Tablets, scored, mefloquine (as hydrochloride) 250 mg. Net price 8-tab pack = £14.53. Label: 21, 25, 27, counselling, driving, prophylaxis, see above.

Note: Tablet may be crushed and mixed with food such as jam or honey just before administration.

### Primquine

Primquine is used to eliminate the liver stages of *P. vivax* or *P. ovale* following chloroquine treatment (for details, see p. 354).

#### PRIMAQUINE

**Indications** adjunct in the treatment of *Plasmodium vivax* and *P. ovale* malaria (eradication of liver stages)

**Cautions** G6PD deficiency (test blood, see under Benign Malaria treatment, p. 354); systemic diseases associated with granulocytopenia (e.g. rheumatoid arthritis, lupus erythematosus); pregnancy (Appendix 4) and breast-feeding; **interactions**: Appendix 1 (primquine)

**Side-effects** nausea, vomiting, anorexia, abdominal pain; less commonly methaemoglobinemia, haemolytic anaemia especially in G6PD deficiency, leucopenia

**Dose**

- Treatment of benign malarial, see p. 354

**Primquine** (Non-proprietary)

- **Tablets**, primquine (as phosphate) 7.5 mg or 15 mg
  - Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

**Proguanil**

Proguanil is used (usually with chloroquine, but occasionally alone) for the prophylaxis of malaria, (for details, see specific recommendations by country, p. 355).

Proguanil used alone is not suitable for the treatment of malaria; however, Malarone® (a combination of atovaquone with proguanil) is licensed for the treatment of acute uncomplicated falciparum malaria. Malarone® is also used for the prophylaxis of falciparum malaria in areas of widespread mefloquine or chloroquine resistance. Malarone® is also used as an alternative to mefloquine or doxycycline. Malarone® is particularly suitable for short trips to highly chloroquine-resistant areas because it needs to be taken only for 7 days after leaving an endemic area.

#### PROGUANIL HYDROCHLORIDE

**Indications** chemoprophylaxis of malaria

**Cautions** renal impairment (see notes under Prophylaxis against malaria and Appendix 3); pregnancy (Appendix 4); **interactions**: Appendix 1 (proguanil)

**Side-effects** mild gastric intolerance, diarrhoea, and constipation; occasionally mouth ulcers and stomatitis; very rarely cholestasis, vasculitis, skin reactions, and hair loss

1 Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed

### Mefloquine

**Dose**

- Prophylaxis of malaria, preferably started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above), 200 mg once daily; INFANT up to 12 weeks body-weight under 6 kg, 25 mg once daily; 12 weeks–1 year body-weight 6–10 kg, 50 mg once daily; CHILD 1–4 years body-weight 10–16 kg, 75 mg once daily; 4–8 years body-weight 16–25 kg, 100 mg once daily; 8–13 years, body-weight 25–45 kg, 150 mg once daily; over 13 years body-weight over 45 kg, adult dose

**Counselling** Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above.

**Note** Mefloquine doses in BNF may differ from those in product literature.

1 Paludrine® (AstraZeneca) Tablets, scored, proguanil hydrochloride 100 mg. Net price 98-tab pack = £7.43. Label: 21, counselling, prophylaxis, see above

**Note** Tablet may be crushed and mixed with food such as milk, jam, or honey just before administration.

### With chloroquine

See under Chloroquine

#### PROGUANIL HYDROCHLORIDE WITH ATOVAQUONE

**Indications** treatment of acute uncomplicated falciparum malaria and prophylaxis of falciparum malaria, particularly where resistance to other antimalarial drugs suspected; treatment of benign malaria (unlicensed indication)

**Cautions** diarrhoea or vomiting (reduced absorption of atovaquone); efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: see Appendix 1 (proguanil, atovaquone)

**Side-effects** abdominal pain, nausea, vomiting, diarrhoea; cough; headache, dizziness, insomnia, abnormal dreams, depression, anorexia; fever; rash, pruritus; less frequently mouth ulcers, stomatitis, anxiety, blood disorders, hyponatraemia, palpitation, and hair loss; also reported, hepatitis, cholestasis, tachycardia, hallucinations, and vasculitis

**Dose**

- See preparations

**Counselling** Warn travellers about importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of immediate visit to doctor if ill within 1 year and especially within 3 months of return. For details, see notes above.

1 Malarone® (GSK) Tablets (‘standard’), pink, f/c, proguanil hydrochloride 100 mg, atovaquone 250 mg. Net price 12-tab pack = £25.21. Label: 21, counselling, prophylaxis, see above

**Dose**

- Prophylaxis of malaria, started 1–2 days before entering endemic area and continued for 1 week after leaving, ADULT and CHILD over 40 kg, 1 tablet daily

Treatment of malaria, ADULT and CHILD body-weight over 40 kg, 4 tablets once daily for 3 days; CHILD body-weight 11–21 kg 1 tablet daily for 3 days; body-weight 21–31 kg 2 tablets once daily for 3 days; body-weight 31–40 kg 3 tablets once daily for 3 days
Malarone® Paediatric (GSK)  
Paediatric tablets, pink, f/c proguanil hydrochloride 25 mg, atovaquone 62.5 mg, net price 12-tab pack = £6.26. Label: 21, counselling, prophylaxis, see above

Dose: prophylaxis of malaria, started 1–2 days before entering endemic area and continued for 1 week after leaving. CHILD body-weight 11–21 kg, 1 tablet once daily; body-weight 21–31 kg, 2 tablets once daily; body-weight 31–40 kg, 3 tablets once daily; body-weight over 40 kg use Malarone® ‘(standard)’ tablets

Treatment of malaria, CHILD body-weight 5–9 kg, 2 tablets once daily for 3 days; body-weight 9–11 kg, 3 tablets once daily for 3 days; body-weight 11 kg and over use Malarone® ‘(standard)’ tablets

Note: Tablets may be crushed and mixed with food or milky drink just before administration

Pyrimethamine

Pyrimethamine should not be used alone, but is used with sulfadoxine.

Pyrimethamine with sulfadoxine is not recommended for the prophylaxis of malaria, but it can be used in the treatment of falciparum malaria with (or following) quinine.

PYRIMETHAMINE

Indications: malaria (but used only in combined preparations incorporating sulfadoxine); toxoplasmosis—section 5.4.7

Cautions: hepatic or renal impairment, pregnancy (Appendix 4); breast-feeding (Appendix 5); blood counts required with prolonged treatment; history of seizures—avoid large loading doses; interactions: Appendix 1 (pyrimethamine)

Side-effects: depression of haemopoiesis with high doses, rashes, insomnia

Dose:

- Malaria, no dose stated because not recommended alone, see Pyrimethamine with Sulfadoxine below
- Toxoplasmosis, section 5.4.7

Daraprim® (GSK)  
Tablets, scored, pyrimethamine 25 mg. Net price 30-tab pack = £2.17

PYRIMETHAMINE WITH SULFADOXINE

Indications: adjunct to quinine in treatment of Plasmodium falciparum malaria; not recommended for prophylaxis

Cautions: see under Pyrimethamine and under Co-trimoxazole (section 5.1.8); pregnancy (Appendix 4); breast-feeding (Appendix 5); not recommended for prophylaxis (severe side-effects on long-term use); interactions: Appendix 1 (pyrimethamine, sulphonamides)

Contra-indications: see under Pyrimethamine and under Co-trimoxazole (section 5.1.8); sulphonamide allergy

Side-effects: see under Pyrimethamine and under Co-trimoxazole (section 5.1.8); pulmonary infiltrates (e.g. eosinophilic or allergic alveolitis) reported—discontinue if cough or shortness of breath

Dose:

- Treatment of malaria, see p. 353
- Prophylaxis, not recommended by UK malaria experts

Pyrimethamine with sulfadoxine (Non-proprietary)

Tablets, scored, pyrimethamine 25 mg, sulfadoxine 500 mg, net price 3-tab pack = 74p

Note: Also known as Fansidar

Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

Quinine

Quinine is not suitable for the prophylaxis of malaria. Quinine is used for the treatment of falciparum malaria or if the infective species is not known or if the infection is mixed (for details see p. 352).

QUININE

Indications: falciparum malaria; nocturnal leg cramps, see section 10.2.2

Cautions: cardiac disease (including atrial fibrillation, conduction defects, heart block), elderly—monitor ECG during parenteral treatment; renal impairment (Appendix 3); pregnancy (but appropriate for treatment of malaria; Appendix 4); monitor blood glucose and electrolyte concentration during parenteral treatment; G6PD deficiency (see section 9.1.5); interactions: Appendix 1 (quinine)

Contra-indications: haemoglobinuria, myasthenia gravis, optic neuritis, tinnitus

Side-effects: cinchonism, including tinnitus, headache, hot and flushed skin, nausea, abdominal pain, rashes, visual disturbances (including temporary blindness), confusion; cardiovascular effects (see Cautions); hypersensitivity reactions including angioedema; hypoglycaemia (especially after parenteral administration); blood disorders (including thrombocytopenia and intravascular coagulation); acute renal failure; photosensitivity; very toxic in overdosage—immediate advice from poisons centres essential (see also p. 32)

Dose:

- Treatment of malaria, see p. 353

Note: Quinine (anhydrous base) 100 mg = quinine bisulphate 169 mg = quinine dihydrochloride 122 mg = quinine hydrochloride 122 mg = quinine sulphate 121 mg. Quinine bisulphate 300-mg tablets are available but provide less quinine than 300 mg of the dihydrochloride, hydrochloride, or sulphate

Quinine Sulphate (Non-proprietary)

Tablets, coated, quinine sulphate 200 mg, net price 28-tab pack = £1.95; 300 mg, 28-tab pack = £1.88

Quinine Dihydrochloride (Non-proprietary)

Injection, quinine dihydrochloride 300 mg/mL. For dilution and use as an infusion. 1- and 2-mL amps Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

Note: Intravenous injection of quinine is so hazardous that it has been superseded by infusion

1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed
Tetracyclines

Doxycycline (section 5.1.3) is used for the prophylaxis of malaria in areas of widespread mefloquine or chloroquine resistance. Doxycycline is also used as an alternative to mefloquine or Malarone® (for details, see specific recommendations by country, p. 355).

Doxycycline is also used as an adjunct to quinine in the treatment of falciparum malaria (for details see p. 353).

DOXYCYCLINE

Indications  prophylaxis of malaria; adjunct to quinine in treatment of Plasmodium falciparum malaria; see also section 5.1.3

Cautions  section 5.1.3

Contra-indications  section 5.1.3

Side-effects  section 5.1.3

Dose

- Prophylaxis of malaria, started 1–2 days before entering endemic area and continued for 4 weeks after leaving (see notes above), 100 mg once daily
- Treatment of falciparum malaria, see p. 353

Preparations

Section 5.1.3

5.4.2 Amoebicides

Metronidazole is the drug of choice for acute invasive amoebic dysentery since it is very effective against vegetative forms of Entamoeba histolytica in faeces; it is given in an adult dose of 800 mg three times daily for 5 days. Tinidazole is also effective. Metronidazole and tinidazole are also active against amoebae which may have migrated to the liver. Treatment with metronidazole (or tinidazole) is followed by a 10-day course of diloxanide furoate.

Diloxanide furoate is the drug of choice for asymptomatic patients with E. histolytica cysts in the faeces; metronidazole and tinidazole are relatively ineffective. Diloxanide furoate is relatively free from toxic effects and the usual course is of 10 days, given alone for chronic infections or following metronidazole or tinidazole treatment.

For amoebic abscesses of the liver metronidazole is effective; tinidazole is an alternative. Aspiration of the abscess is indicated where it is suspected that it may rupture or where there is no improvement after 72 hours of metronidazole; the aspiration may need to be repeated. Aspiration aids penetration of metronidazole and, for abscesses with more than 100 mL of pus, if carried out in conjunction with drug therapy, may reduce the period of disability.

Diloxanide furoate is not effective against hepatic amoebiasis, but a 10-day course should be given at the completion of metronidazole or tinidazole treatment to destroy any amoebae in the gut.

DILOXANIDE FUROATE

Indications  see notes above; chronic amoebiasis and as adjunct to metronidazole or tinidazole in acute amoebiasis

Contra-indications  pregnancy (Appendix 4), breastfeeding (Appendix 5)

Side-effects  flatulence, vomiting, urticaria, pruritus

Dose

- 500 mg every 8 hours for 10 days; CHILD over 25 kg, 20 mg/kg daily in 3 divided doses for 10 days

See also notes above

Diloxanide (Sovereign) Tablets, diloxanide furoate 500 mg, net price 30-tab pack = £42.95. Label: 9

METRONIDAZOLE

Indications  see under Dose below; anaerobic infections, section 5.1.11

Cautions  section 5.1.11

Side-effects  section 5.1.11

Dose

- By mouth, invasive intestinal amoebiasis, 800 mg every 8 hours for 5 days; CHILD 1–3 years 200 mg every 8 hours; 3–7 years 200 mg every 6 hours; 7–10 years 400 mg every 8 hours
- Extra-intestinal amoebiasis (including liver abscess), 400–800 mg every 8 hours for 5–10 days; CHILD 1–3 years 100–200 mg every 8 hours; 3–7 years 100–200 mg every 6 hours; 7–10 years 200–400 mg every 8 hours
- Urogenital trichomoniasis, 200 mg every 8 hours for 7 days or 400–500 mg every 12 hours for 5–7 days, or 2 g as a single dose; CHILD 1–3 years 50 mg every 8 hours for 7 days; 3–7 years 100 mg every 12 hours; 7–10 years 100 mg every 8 hours
- Giardiasis, 2 g daily for 3 days or 400 mg 3 times daily for 5 days or 500 mg twice daily for 7–10 days; CHILD 1–3 years 500 mg daily for 3 days; 3–7 years 600–800 mg daily; 7–10 years 1 g daily

Preparations

Section 5.1.11

TINIDAZOLE

Indications  see under Dose below; anaerobic infections, section 5.1.11

Cautions  section 5.1.11

Side-effects  section 5.1.11

Dose

- Intestinal amoebiasis, 2 g daily for 2–3 days; CHILD 50–60 mg/kg daily for 3 days
- Amoebic involvement of liver, 1.5–2 g daily for 3–6 days; CHILD 50–60 mg/kg daily for 5 days
- Urogenital trichomoniasis and giardiasis, single 2 g dose; CHILD single dose of 50–75 mg/kg (repeated once if necessary)

Preparations

Section 5.1.11

5.4.3 Trichomonacides

Metronidazole (section 5.4.2) is the treatment of choice for Trichomonas vaginalis infection. Contact tracing is recommended and sexual contacts should be treated simultaneously. If metronidazole is ineffective, tinidazole (section 5.4.2) may be tried.
5.4.4 Antigiardial drugs

Metronidazole (section 5.4.2) is the treatment of choice for *Giardia lamblia* infections. Alternative treatments are tinidazole (section 5.4.2) or mecaprine hydrochloride.

MECAPRINE HYDROCHLORIDE

**Indications** giardiasis; discoid lupus erythematosus (Antimalarials, section 10.1.3)

**Cautions** hepatic impairment, elderly, history of psychosis; avoid in psoriasis; **Interactions**: Appendix 1 (mepacrine)

**Side-effects** gastro-intestinal disturbances; dizziness, headache; with large doses nausea, vomiting and occasionally transient acute toxic psychosis and CNS stimulation; on prolonged treatment yellow discoloration of skin and urine, chronic dermatoses (including severe exfoliative dermatitis), hepatitis, aplastic anaemia; also reported blue/black discoloration of palate and nails and cornal deposits with visual disturbances

**Dose**
- Giardiasis [unlicensed], 100 mg every 8 hours for 5–7 days

Mepacrine Hydrochloride

**Tablets**, mecaprine hydrochloride 100 mg. Label: 4, 9, 14, 21

Available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939

5.4.5 Leishmaniacides

Cutaneous leishmaniasis frequently heals spontaneously but if skin lesions are extensive or unsightly, treatment is indicated, as it is in visceral leishmaniasis (kala-azar). Leishmaniasis should be treated under specialist supervision.

Sodium stibogluconate, an organic pentavalent antimony compound, is used for visceral leishmaniasis. The dose is 20 mg/kg daily (max. 850 mg) by intramuscular or intravenous injection for 28 days in visceral leishmaniasis and for 20 days in cutaneous infection; the dosage varies with different geographical regions and expert advice should be obtained. Some early non-inflamed lesions of cutaneous leishmaniasis can be treated with intralesional injections of sodium stibogluconate under specialist supervision.

Amphotericin is used with or after an antimony compound for visceral leishmaniasis unresponsive to the antimonial alone; side-effects may be reduced by using liposomal amphotericin (*Ambisome*—section 5.2) at a dose of 1–3 mg/kg daily for 10–21 days to a cumulative dose of 21–30 mg/kg, or at a dose of 3 mg/kg for 5 consecutive days followed by a single dose of 3 mg/kg 6 days later. Other lipid formulations of amphotericin (*Abelcet* and *Amphocil*) are also likely to be effective but less information is available.

Pentamidine isethionate (pentamidine isethionate) (section 5.4.8) has been used in antimony-resistant visceral leishmaniasis, but although the initial response is often good, the relapse rate is high; it is associated with serious side-effects. Other treatments include paromomycin [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939).

SODIUM STIBOGLUCONATE

**Indications** leishmaniasis

**Cautions** intravenous injections must be given slowly over 5 minutes (to reduce risk of local thrombosis) and stopped if coughing or substernal pain; mucocutaneous disease (see below); monitor ECG before and during treatment; heart disease (withdraw if conduction disturbances occur); treat intercurrent infection (e.g. pneumonia); hepatic impairment; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Mucocutaneous disease Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around the lesions (may be life-threatening if pharyngeal or tracheal involvement)—may require corticosteroid

**Contra-indications** significant renal impairment

**Side-effects** anorexia, nausea, vomiting, abdominal pain, diarrhoea; ECG changes; coughing (see Cautions); headache, lethargy; arthralgia, myalgia; rarely jaundice, flushing, bleeding from nose or gum, subternal pain (see Cautions), vertigo, fever, sweating, and rash; also reported pancreatitis and anaphylaxis; pain and thrombosis on intravenous administration, intramuscular injection also painful

**Dose**
- See notes above

Pentostam® (GSK)

**Injection**, sodium stibogluconate equivalent to pentavalent antimony 100 mg/mL. Net price 100-mL bottle = £66.43

**Note** Injection should be filtered immediately before administration using a filter of 5 microns or less

5.4.6 Trypanocides

The prophylaxis and treatment of trypanosomiasis is difficult and differs according to the strain of organism. Expert advice should therefore be obtained.

5.4.7 Drugs for toxoplasmosis

Most infections caused by *Toxoplasma gondii* are self-limiting, and treatment is not necessary. Exceptions are patients with eye involvement (toxoplasma choroidoretinitis), and those who are immunosuppressed. Toxoplasmic encephalitis is a common complication of AIDS. The treatment of choice is a combination of pyrimethamine and sulfadiazine (sulphadiazine), given for several weeks (expert advice essential). Pyrimethamine is a folate antagonist, and adverse reactions to this combination are relatively common (folic acid supplements and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine with clindamycin or clari thromycin or azithromycin. Long-term secondary prophylaxis is required after treatment of toxoplasmosis in immunocompromised patients; prophylaxis should continue until immunity recovers.

If toxoplasmosis is acquired in pregnancy, transplacental infection may lead to severe disease in the fetus. Spiramycin [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) may reduce the risk of transmission of maternal infection to the fetus.
### 5.4.8 Drugs for pneumocystis pneumonia

Pneumonia caused by *Pneumocystis jiroveci* (*Pneumocystis carinii*) occurs in immunosuppressed patients; it is a common cause of pneumonia in AIDS. Pneumocystis pneumonia should generally be treated by those experienced in its management. Blood gas measurement is used to assess disease severity.

#### Treatment

**Mild to moderate disease** Co-trimoxazole (section 5.1.8) in high dosage is the drug of choice for the treatment of mild to moderate pneumocystis pneumonia.

Atovaquone is licensed for the treatment of mild to moderate pneumocystis infection in patients who cannot tolerate co-trimoxazole. A combination of dapsone 100 mg daily (section 5.1.10) with trimethoprim 5 mg/kg every 6–8 hours (section 5.1.8) is given by mouth for the treatment of mild to moderate disease [unlicensed indication].

A combination of clindamycin 600 mg by mouth every 8 hours (section 5.1.6) and primaquine 30 mg daily by mouth (section 5.4.1) is used in the treatment of mild to moderate disease [unlicensed indication]; this combination is associated with considerable toxicity.

Inhaled pentamidine isetionate is sometimes used for mild disease. It is better tolerated than parenteral pentamidine but systemic absorption may still occur.

**Severe disease** Co-trimoxazole (section 5.1.8) in high dosage, given by mouth or by intravenous infusion, is the drug of choice for the treatment of severe pneumocystis pneumonia. Pentamidine isetionate given by intravenous infusion is an alternative for patients who cannot tolerate co-trimoxazole, or who have not responded to it. Pentamidine isetionate is a potentially toxic drug that can cause severe hypotension during or immediately after infusion.

Corticosteroid treatment can be lifesaving in those with severe pneumocystis pneumonia (see Adjunctive Therapy below).

**Adjunctive therapy** In moderate to severe infections associated with HIV infection, prednisolone 50–80 mg daily is given by mouth for 5 days (alternatively, hydrocortisone may be given parenterally); the dose is then reduced to complete 21 days of treatment. Corticosteroid treatment should ideally be started at the same time as the anti-pneumocystis therapy and certainly no later than 24–72 hours afterwards. The corticosteroid should be withdrawn before anti-pneumocystis treatment is complete.

**Prophylaxis**

Prophylaxis against pneumocystis pneumonia should be given to all patients with a history of the infection. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised patients. Prophylaxis should continue until immunity recovers sufficiently. It should not be discontinued if the patient has oral candidiasis, continues to lose weight, or is receiving cytotoxic therapy or long-term immunosuppressant therapy.

**Co-trimoxazole** by mouth is the drug of choice for prophylaxis against pneumocystis pneumonia. It is given in a dose of 960 mg daily or 960 mg on alternate days (3 times a week); the dose may be reduced to co-trimoxazole 480 mg daily to improve tolerance.

Intermittent inhalation of pentamidine isetionate is used for prophylaxis against pneumocystis pneumonia in patients unable to tolerate co-trimoxazole. It is effective but patients may be prone to extrapulmonary infection. Alternatively, dapsone 100 mg daily (section 5.1.10) can be used. Atovaquone 750 mg twice daily has also been used for prophylaxis [unlicensed indication].

### ATOVAQUONE

**Indications** treatment of mild to moderate *Pneumocystis jiroveci* (*Pneumocystis carinii*) pneumonia in patients intolerant of co-trimoxazole

**Cautions** initial diarrhoea and difficulty in taking with food may reduce absorption (and require alternative therapy); other causes of pulmonary disease should be sought and treated; elderly; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); avoid breast-feeding (Appendix 5); **interactions**: Appendix 1 (atovaquone)

**Side-effects** nausea, diarrhoea, vomiting; headache; insomnia; fever; anaemia, neutropenia, hyponatraemia; rash, pruritus; also reported Stevens-Johnson syndrome

**Dose**

- 750 mg twice daily with food (particularly high fat) for 21 days; CHILD not recommended

**Wellvone® (GSK)**

**Suspension**, sugar-free, atovaquone 750 mg/5 mL, net price 210 mL (tutti-frutti-flavoured) = £405.31. Label: 21

**With proguanil hydrochloride**

See section 5.4.1

### PENTAMIDINE ISETIONATE

**Indications** see under Dose (should only be given by specialists)

**Cautions** risk of severe hypotension following administration (establish baseline blood pressure and administer with patient lying down; monitor blood pressure closely during administration, and at regular intervals, until treatment concluded); hypokalaemia, hypomagnesaemia, coronary heart disease, bradycardia, history of ventricular arrhythmias, concomitant use with other drugs which prolong QT-interval; hypertension or hypotension; hyperglycaemia or hypoglycaemia; leucopenia, thrombocytopenia, or anaemia; carry out laboratory monitoring according to product literature; care required to protect personnel during handling and administration; hepatic impairment; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (pentamidine isetionate)

**Side-effects** severe reactions, sometimes fatal, due to hypotension, hyperglycaemia, pancreatitis, and arrhythmias; also leucopenia, thrombocytopenia, acute
5 Infections

5.5 Anthelmintics

5.5.1 Drugs for threadworms (pinworms, Enterobius vermicularis)

Anthelmintics are effective in threadworm infections, but their use needs to be combined with hygienic measures to break the cycle of auto-infection. All members of the family require treatment.

Adult threadworms do not live for longer than 6 weeks and for development of fresh worms, ova must be swallowed and exposed to the action of digestive juices in the upper intestinal tract. Direct multiplication of worms does not take place in the large bowel. Adult female worms lay ova on the perianal skin which causes pruritus; scratching the area then leads to ova being transmitted on fingers to the mouth, often via food eaten with unwashed hands. Wasing hands and scrubbing nails before each meal and after each visit to the toilet is essential. A bath taken immediately after rising will remove ova laid during the night.

Mebendazole is the drug of choice for treating threadworm infection in patients of all ages over 2 years. It is given as a single dose; as reinfection is very common, a second dose may be given after 2 weeks.

Piperazine is available in combination with sennosides as a single-dose preparation.

Mebendazole

Indications threadworm, roundworm, whipworm, and hookworm infections

Cautions pregnancy (toxicity in rats); breast-feeding (Appendix 5); interactions: Appendix 1 (mebendazole)

Note The package insert in the Vermox pack includes the statement that it is not suitable for women known to be pregnant or children under 2 years

Side-effects very rarely abdominal pain, diarrhoea, convulsions (in infants) and rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis)

Dose

Threadworms, ADULT and CHILD over 2 years, 100 mg as a single dose; if reinfection occurs second dose may be needed after 2 weeks; CHILD under 2 years, see BNF for Children

Whipworms, ADULT and CHILD over 2 years, 100 mg twice daily for 3 days; CHILD under 2 years, see BNF for Children

Roundworms—section 5.5.2

Hookworms—section 5.5.4

1 Mebendazole (Non-proprietary) Tablets, chewable, mebendazole 100 mg

Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in adults and children over 2 years provided its container or package is labelled to show a max. single dose of 100 mg and it is supplied in a container or package containing not more than 800 mg

Vermox (Janssen-Cilag) Tablets, orange, scored, chewable, mebendazole 100 mg. Net price 6-tab pack = £1.42

Suspension, mebendazole 100 mg/5 mL. Net price 30 mL = £1.65

5.5 Anthelmintics

5.5.1 Drugs for threadworms

5.5.2 Ascaricides

5.5.3 Drugs for tapeworm infections

5.5.4 Drugs for hookworms

5.5.5 Schistosomicides

5.5.6 Filaricides

5.5.7 Drugs for cutaneous larva migrans

5.5.8 Drugs for strongyloidiasis

Advice on prophylaxis and treatment of helminth infections is available from:

Birmingham (0121) 424 0357
Scottish Centre for Infection and Environmental Health (registered users of Travax only) (0141) 300 1100 (weekdays 2–4 p.m. only)
Liverpool (0151) 708 9393
London (020) 7387 9300 (treatment)

renal failure, hypocalcaemia; also reported: azotaemia, abnormal liver-function tests, anaemia, hyperkalaemia, nausea and vomiting, dizziness, syncope, flushing, hyperglycaemia, rash, and taste disturbances; Stevens-Johnson syndrome reported; on inhalation, bronchoconstriction (may be prevented by prior use of bronchodilators), cough, and shortness of breath; discomfort, pain, induration, abscess formation, and muscle necrosis at injection site

Dose

• Pneumocystis jiroveci (Pneumocystis carinii) pneumonia, by intravenous infusion, 4 mg/kg once daily for at least 14 days (reduced according to product literature in renal impairment)

By inhalation of nebulised solution (using suitable equipment—consult product literature) 600 mg pentamidine isetionate once daily for 3 weeks; secondary prevention, 300 mg every 4 weeks or 150 mg every 2 weeks

• Visceral leishmaniasis (kala-azar, section 5.4.5), by deep intramuscular injection, 3–4 mg/kg on alternate days to max. total of 10 injections; course may be repeated if necessary

• Cutaneous leishmaniasis, by deep intramuscular injection, 3–4 mg/kg once or twice weekly until condition resolves (but see also section 5.4.5)

• Trypanosomiasis, by deep intramuscular injection or intravenous infusion, 4 mg/kg daily or on alternate days to total of 7–10 injections

Note Direct intravenous injection should be avoided whenever possible and never given rapidly; intramuscular injections should be deep and preferably given into the buttock

Pentacarinat® (Sanofi-Aventis) (Appendix 5); interactions:

Injection, powder for reconstitution, pentamidine isetionate, net price 300-mg vial = £30.45

Nebuliser solution, pentamidine isetionate, net price 300-mg bottle = £32.15

Caution in handling Pentamidine isetionate is toxic and personnel should be adequately protected during handling and administration—consult product literature

364 5.5 Anthelmintics

BNF 57

364 5.5 Anthelmintics

BNF 57
PIPERAZINE

Indications threadworm and roundworm infections

Cautions hepatic impairment (Appendix 2); renal impairment (Appendix 3); epilepsy; pregnancy (Appendix 4); packs on sale to the general public carry a warning to avoid in epilepsy, or in liver or kidney disease, and to seek medical advice in pregnancy; breast-feeding (Appendix 5)

Side-effects nausea, vomiting, colic, diarrhoea, allergic reactions including urticaria, bronchospasm, and rare reports of arthralgia, fever, Stevens-Johnson syndrome and angioedema; rarely dizziness, muscular incoordination (‘worm wobble’); drowsiness, nystagmus, vertigo, blurred vision, confusion and clonic contractions in patients with neurological or renal abnormalities

Dose
- See under Preparation, below

With sennosides
For cautions, contra-indications, side-effects of senna see section 1.6.2

Pripsen® (Thornton & Ross)
Oral powder, piperazine phosphate 4 g, total sennosides (calculated as sennoside B) 15.3 mg/sachet. Net price two-dose sachet pack = £1.53. Label: 13

Dose threadworms, stirred into milk or water; ADULT over 6 years, content of 1 sachet as a single dose (bedtime in adults or morning in children), repeated after 14 days; CHILD over 6 years, content of 1 sachet as a single dose (bedtime in adults or morning in children), repeated after 14 days; CHILD 1–6 years, 1 level 5-mL spoonful in the morning, repeated after 14 days
Roundworms, first dose as for threadworms; repeat at monthly intervals for up to 3 months if reinfection risk

5.5.2 Ascaricides
(common roundworm infections)

Mebendazole (section 5.5.1) is effective against Ascaris lumbricoides and is generally considered to be the drug of choice; the usual dose is 100 mg twice daily for 3 days.

Levamisole [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is an alternative. It is very well tolerated; mild nausea or vomiting has been reported in about 1% of treated patients; it is given as a single dose of 120–150 mg in adults.

Piperazine may be given in a single adult dose, see Piperazine, above.

5.5.3 Drugs for tapeworm infections

Taenicides

Niclosamide [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is the most widely used drug for tapeworm infections and side-effects are limited to occasional gastro-intestinal upset, lightheadedness, and pruritus; it is not effective against larval worms. Fears of developing cysticercosis in Taenia solium infections have proved unfounded. All the same, an antiemetic can be given before treatment and a laxative can be given 2 hours after niclosamide.

Praziquantel [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is as effective as niclosamide and is given as a single dose of 5–10 mg/kg after a light breakfast (a single dose of 25 mg/kg for Hymenolepis nana).

Hydatid disease

Cysts caused by Echinococcus granulosus grow slowly and asymptomatic patients do not always require treatment. Surgical treatment remains the method of choice in many situations. Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Alveolar echinococcosis due to E. multilocularis is usually fatal if untreated. Surgical removal with albendazole cover is the treatment of choice, but where effective surgery is impossible, repeated cycles of albendazole (for a year or more) may help. Careful monitoring of liver function is particularly important during drug treatment.

5.5.4 Drugs for hookworms
(ancylostomiasis, necatoriasis)

Hookworms live in the upper small intestine and draw blood from the point of their attachment to their host. An iron-deficiency anaemia may occur and, if present, effective treatment of the infection requires not only expulsion of the worms but treatment of the anaemia.

Mebendazole (section 5.5.1) has a useful broad-spectrum activity, and is effective against hookworms; the usual dose is 100 mg twice daily for 3 days. Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) given as a single dose of 400 mg, is an alternative.

5.5.5 Schistosomicides
(bilharziasis)

Adult Schistosoma haematobium worms live in the genito-urinary veins and adult S. mansoni in those of the colon and mesentry. S. japonicum is more widely distributed in veins of the alimentary tract and portal system.

Praziquantel [unlicensed] is available from Merck (Cysticide®) and is effective against all human schistosomes. The dose is 20 mg/kg followed after 4–6 hours by one further dose of 20 mg/kg (60 mg/kg in 3 divided doses on one day for S. japonicum infections). No serious adverse effects have been reported. Of all the available schistosomicides, it has the most attractive combination of effectiveness, broad-spectrum activity, and low toxicity.

Hycanthone, lucanthone, niridazole, oxamniquine, and sodium stibogluconate have now been superseded.
5.5.6 Filaricides

Diethylcarbamazine [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is effective against microfilariae and adults of *Loa loa*, *Wuchereria bancrofti*, and *Brugia malayi*. To minimise reactions treatment is commenced with a dose of diethylcarbamazine citrate 1 mg/kg on the first day and increased gradually over 3 days to 6 mg/kg daily in divided doses (up to 9 mg/kg daily in divided doses for *Loa loa*); this dosage is maintained for a further period. Close medical supervision is necessary particularly in the early phase of treatment.

In heavy infections there may be a febrile reaction, and in heavy *Loa loa* infection there is a small risk of encephalopathy. In such cases treatment must be given under careful in-patient supervision and stopped at the first sign of cerebral involvement (and specialist advice sought).

Ivermectin [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is very effective in onchocerciasis and it is now the drug of choice. A single dose of 150 micrograms/kg by mouth produces a prolonged reduction in microfilarial levels. Retreatment at intervals of 6 to 12 months depending on symptoms must be given until the adult worms die out. Reactions are usually slight and most commonly take the form of temporary aggravation of itching and rash. Diethylcarbamazine or suramin should no longer be used for onchocerciasis because of their toxicity.

5.5.7 Drugs for cutaneous larva migrans
(creeeping eruption)

Dog and cat hookworm larvae may enter human skin where they produce slowly extending itching tracks usually on the foot. Single tracks can be treated with topical thiabendazole (no commercial preparation available). Multiple infections respond to ivermectin, albendazole or thiabendazole (thiabendazole) by mouth [all unlicensed] and available from ‘special-order’ manufacturers or specialist importing companies, see p. 939).

5.5.8 Drugs for strongyloidiasis

Adult *Strongyloides stercoralis* live in the gut and produce larvae which penetrate the gut wall and invade the tissues, setting up a cycle of auto-infection. Ivermectin [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) in a dose of 200 micrograms/kg daily for 2 days is the treatment of choice for chronic *Strongyloides* infection.

Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist-importing companies, see p. 939) is an alternative given in a dose of 400 mg twice daily for 3 days, repeated after 3 weeks if necessary.
Diabetes mellitus occurs because of a lack of insulin or resistance to its action. It is diagnosed by measuring fasting or random blood-glucose concentration (and occasionally by oral glucose tolerance test). Although there are many subtypes, the two principal classes of diabetes are type 1 diabetes and type 2 diabetes.

**Type 1 diabetes** (formerly referred to as insulin-dependent diabetes mellitus (IDDM)), occurs as a result of a deficiency of insulin following autoimmune destruction of pancreatic beta cells. Patients with type 1 diabetes require administration of insulin.

**Type 2 diabetes** (formerly referred to as non-insulin-dependent diabetes (NIDDM)), is due either to reduced secretion of insulin or to peripheral resistance to the action of insulin. Although patients may be controlled on diet alone, many also require oral antidiabetic drugs or insulin (or both) to maintain satisfactory control. In overweight individuals, type 2 diabetes may be prevented by losing weight and increasing physical activity; use of drugs such as orlistat (section 4.5.1) or sibutramine (section 4.5.2) may be considered in obese patients.

**Treatment of diabetes** Treatment of all forms of diabetes should be aimed at alleviating symptoms and minimising the risk of long-term complications (see below); tight control of diabetes is essential.
Diabetes is a strong risk factor for cardiovascular disease (section 2.12). Other risk factors for cardiovascular disease such as smoking (section 4.10), hypertension (section 2.5), obesity (section 4.5), and hyperlipidaemia (section 2.12) should be addressed. Cardiovascular risk in patients with diabetes can be further reduced by the use of an ACE inhibitor (section 2.5.5.1), low-dose aspirin (section 2.9) and a lipid-regulating drug (section 2.12).

Prevention of diabetic complications Optimal glycaemic control in both type 1 diabetes and type 2 diabetes reduces, in the long term, the risk of microvascular complications including retinopathy, development of proteinuria and to some extent neuropathy. However, a temporary deterioration in established diabetic retinopathy may occur when normalising blood-glucose concentration. For reference to the use of an ACE inhibitor or an angiotensin-II receptor antagonist in the management of diabetic nephropathy, see section 6.1.5.

A measure of the total glycated (or glycosylated) haemoglobin (HbA1c) or a specific fraction (HbA1c) provides a good indication of glycaemic control over the previous 2–3 months. The ideal HbA1c concentration is between 6.5 and 7.5% but this cannot always be achieved, and those on insulin may have significantly increased risks of severe hypoglycaemia. Tight control of blood pressure in hypertensive patients with type 2 diabetes reduces mortality and protects visual acuity (by reducing considerably the risks of maculopathy and retinal photo-coagulation) (see also section 2.5).

Driving Drivers with diabetes are required to notify the Driver and Vehicle Licensing Agency (DVLA) of their condition if they are treated with insulin or if they are treated with oral antidiabetic drugs and also have complications. Detailed guidance on eligibility to drive is available from the DVLA (www.dvla.gov.uk/medical.aspx). Driving is not permitted when hypoglycaemic awareness is impaired or frequent hypoglycaemic episodes occur.

Drivers need to be particularly careful to avoid hypoglycaemia (see also above) and should be warned of the problems. Drivers treated with insulin should normally check their blood-glucose concentration before driving and, on long journeys, at 2-hour intervals; these precautions may also be necessary for drivers taking oral antidiabetic drugs who are at particular risk of hypoglycaemia. Drivers treated with insulin should ensure that a supply of sugar is always available in the vehicle and they should avoid driving if their meal is delayed. If hypoglycaemia occurs, or warning signs develop, the driver should:
- stop the vehicle in a safe place;
- switch off the ignition;
- eat or drink a suitable source of sugar;
- wait until recovery is complete before continuing journey; recovery may take 15 minutes or longer and should preferably be confirmed by checking blood-glucose concentration.

Insulin plays a key role in the regulation of carbohydrate, fat, and protein metabolism. It is a polypeptide hormone of complex structure. There are differences in the amino-acid sequence of animal insulins, human insulins and the human insulin analogues. Insulin may be extracted from pork pancreas and purified by crystallisation; it may also be extracted from beef pancreas, but beef insulins are now rarely used. Human sequence insulin may be produced semisynthetically by enzymatic modification of porcine insulin (emp) or biosynthetically by recombinant DNA technology using bacteria (crb, prb) or yeast (pyr).

All insulin preparations are to a greater or lesser extent immunogenic in man but immunological resistance to insulin action is uncommon. Preparations of human sequence insulin should theoretically be less immunogenic, but no real advantage has been shown in trials. Insulin is inactivated by gastro-intestinal enzymes, and must therefore be given by injection; the subcutaneous route is ideal in most circumstances. Insulin is usually injected into the upper arms, thighs, buttocks, or abdomen; absorption from a limb site may be increased if the limb is used in strenuous exercise after the injection. Generally subcutaneous insulin injections cause few problems; fat hypertrophy does, however, occur but can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Insulin is needed by all patients with ketoacidosis, and it is likely to be needed by most patients with:
- rapid onset of symptoms;
- substantial loss of weight;
- weakness;
- ketonuria;
- a first-degree relative who has type 1 diabetes.

Insulin is required by almost all children with diabetes. It is also needed for type 2 diabetes when other methods have failed to achieve good control, and temporarily in the presence of intercurrent illness or peri-operatively. Pregnant women with type 2 diabetes may be treated with insulin when diet alone fails. For advice on use of oral antidiabetic drugs in the management of diabetes in pregnancy, see section 6.1.2.

Management of diabetes with insulin The aim of treatment is to achieve the best possible control of blood-glucose concentration without making the patient obsessional and to avoid disabling hypoglycaemia; close co-operation is needed between the patient and the medical team because good control reduces the risk of complications.

Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual patient. For patients with acute-onset diabetes, treatment should be started with a short-acting insulin (e.g. soluble insulin, insulin aspart) given 3 times daily with intermediate-acting insulin at bedtime. For those less severely ill, treatment is usually started with a mixture of premixed short- and intermediate-acting
insulins (most commonly in a proportion of 30% soluble insulin and 70% isophane insulin) given twice daily; 8 units twice daily is a suitable initial dose for most ambulant patients. The proportion of the short-acting soluble component can be increased in those with excessive postprandial hyperglycaemia.

The dose of insulin is increased gradually, taking care to avoid troublesome hypoglycaemic reactions.

Insulin preparations can be divided into 3 types:

- those of short duration which have a relatively rapid onset of action, namely soluble insulin, insulin lispro and insulin aspart;
- those with an intermediate action, e.g. isophane insulin and insulin zinc suspension; and
- those whose action is slower in onset and lasts for long periods, e.g. insulin zinc suspension.

The duration of action of a particular type of insulin varies considerably from one patient to another, and needs to be assessed individually.

Examples of recommended insulin regimens

- Short-acting insulin mixed with intermediate-acting insulin: twice daily (before meals)
- Short-acting insulin mixed with intermediate-acting insulin: before breakfast
- Short-acting insulin: before evening meal
- Intermediate-acting insulin: at bedtime
- Short-acting insulin: three times daily (before breakfast, midday, and evening meal)
- Intermediate-acting insulin: at bedtime
- Intermediate-acting insulin with or without short-acting insulin: once daily either before breakfast or at bedtime suffices for some patients with type 2 diabetes who need insulin

Insulin requirements may be increased by infection, stress, accidental or surgical trauma, and during pregnancy. Requirements may be decreased in patients with renal impairment (Appendix 3) or hepatic impairment and in those with some endocrine disorders (e.g. Addison’s disease, hypopituitarism) or coeliac disease.

Pregnancy and breast-feeding During pregnancy and breast-feeding, insulin requirements may alter and doses should be assessed frequently by an experienced diabetes physician. The dose of insulin generally needs to be increased in the second and third trimesters of pregnancy. The short-acting insulin analogues, insulin aspart and insulin lispro, are not known to be harmful, and may be used during pregnancy and lactation. The safety of long-acting insulin analogues in pregnancy has not been established, therefore isophane insulin is recommended where longer-acting insulins are needed.

**NICE guidance**

**Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (type 1) (July 2008)**

Continuous subcutaneous insulin infusion is recommended as an option in adults and children over 12 years with type 1 diabetes:

- who suffer repeated or unpredictable hypoglycaemia, whilst attempting to achieve optimal glycaemic control with multiple-injection regimens, or
- whose glycaemic control remains inadequate (HbA over 8.5%) despite optimised multiple-injection regimens (including the use of long-acting insulin analogues where appropriate).

Continuous subcutaneous insulin infusion is also recommended as an option for children under 12 years with type 1 diabetes for whom multiple-injection regimens are considered impractical or inappropriate. Children on insulin pumps should undergo a trial of multiple-injection therapy between the ages of 12 and 18 years.

Soluble insulin by the intravenous route is reserved for urgent treatment, and for fine control in serious illness and in the peri-operative period (see under Diabetes and Surgery, below).

**Units** The word ‘unit’ should not be abbreviated.

**Monitoring** Many patients now monitor their own blood-glucose concentrations (section 6.1.6). Since blood-glucose concentrations vary substantially throughout the day, ‘normoglycaemia’ cannot always be achieved throughout a 24-hour period without causing damaging hypoglycaemia. It is therefore best to recommend that patients should maintain a blood-glucose concentration of between 4 and 9 mmol/litre for most of the time (4–7 mmol/litre before meals and less than 9 mmol/litre after meals), while accepting that on occasions, for brief periods, it will be above these values; strenuous efforts should be made to prevent the blood-glucose concentration from falling below 4 mmol/litre. Patients should be advised to look for ‘peaks’ and ‘troughs’ of blood glucose, and to adjust their insulin dosage only once or twice weekly. Overall it is ideal to aim for an HbA (glycosylated haemoglobin) concentration of 6.5–7.5% or less (reference range 4–6%) but this is not always possible without causing disabling hypoglycaemia; in those at risk of arterial disease, the aim should be to maintain the HbA concentration at 6.5% or less. HbA should be measured every 3–6 months. Fructosamine can also be used for assessment of control; this is simpler and cheaper but the measurement of HbA is generally a more reliable method.

**Insulin administration** Insulin is generally given by subcutaneous injection. Injection devices (‘pens’) (section 6.1.1.3), which hold the insulin in a cartridge and meter the required dose, are convenient to use. The conventional syringe and needle is still preferred by many and is also required for insulins not available in cartridge form.

For intensive insulin regimens multiple subcutaneous injections (3 to 4 times daily) are usually recommended. Short-acting injectable insulins (soluble insulin, insulin aspart, insulin glulisine, and insulin lispro) can also be given by continuous subcutaneous infusion using a portable infusion pump. This device delivers a continuous basal insulin infusion and patient-activated bolus doses at meal times. This technique is appropriate only for patients who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Patients on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration, and have expert training, advice and supervision from an experienced healthcare team.
The intake of energy and of simple and complex carbohydrates should be adequate to allow normal growth and development but obesity must be avoided. The carbohydrate intake needs to be regulated and should be distributed throughout the day. Fine control of plasma glucose can be achieved by moving portions of carbohydrate from one meal to another without altering the total intake.

**Hypoglycaemia** Hypoglycaemia is a potential problem with insulin therapy. All patients must be carefully instructed on how to avoid it.

Loss of warning of hypoglycaemia is common among insulin-treated patients and can be a serious hazard, especially for drivers and those in dangerous occupations. Very tight control of diabetes lowers the blood-glucose concentration needed to trigger hypoglycaemic symptoms; increase in the frequency of hypoglycaemic episodes reduces the warning symptoms experienced by the patient. Beta-blockers can also blunt hypoglycaemic awareness (and also delay recovery).

To restore the warning signs, episodes of hypoglycaemia must be minimised; this involves appropriate adjustment of insulin type, dose and frequency together with suitable timing and quantity of meals and snacks.

Some patients have reported loss of hypoglycaemia warning after transfer to human insulin. Clinical studies do not confirm that human insulin decreases hypoglycaemia awareness. If a patient believes that human insulin is responsible for the loss of warning it is reasonable to revert to animal insulin and essential to educate the patient about avoiding hypoglycaemia. Great care should be taken to specify whether a human or an animal preparation is required.

Few patients are now treated with beef insulins; when undertaking conversion from beef to human insulin, the total dose should be reduced by about 10% with careful monitoring for the first few days. When changing between pork and human-sequence insulins, a dose change is not usually needed, but careful monitoring is still advised.

**Diabetes and surgery** The following regimen is suitable when surgery in a patient with type 1 diabetes requires intravenous infusion of insulin for 12 hours or longer.

- Give an injection of the patient’s usual insulin on the night before the operation.
- Early on the day of the operation, start an intravenous infusion of glucose 5% or 10% containing potassium chloride 10 mmol/litre (provided that the patient is not hyperkalaemic) and infuse at a constant rate appropriate to the patient’s fluid requirements (usually 125 mL per hour); make up a solution of soluble insulin 1 unit/mL in sodium chloride 0.9% and infuse intravenously using a syringe pump piggy-backed to the intravenous infusion.
- The rate of the insulin infusion should normally be: Blood glucose < 4 mmol/litre, give 0.5 units/hour Blood glucose 4–15 mmol/litre, give 2 units/hour Blood glucose 15–20 mmol/litre, give 4 units/hour Blood glucose > 20 mmol/litre, review.
- In resistant cases (such as patients who are in shock or severely ill or those receiving corticosteroids or sympathomimetics) 2–4 times these rates or even more may be needed.

If a syringe pump is not available soluble insulin 16 units/litre should be added to the intravenous infusion of glucose 5% or 10% containing potassium chloride 10 mmol per litre (provided the patient is not hyperkalaemic) and the infusion run at the rate appropriate to the patient’s fluid requirements (usually 125 mL per hour) with the insulin dose adjusted as follows:

- Blood glucose < 4 mmol/litre, give 8 units/litre
- Blood glucose 4–15 mmol/litre, give 16 units/litre
- Blood glucose 15–20 mmol/litre, give 32 units/litre
- Blood glucose > 20 mmol/litre, review.

The rate of intravenous infusion depends on the volume depletion, cardiac function, age, and other factors. Blood-glucose concentration should be measured pre-operatively and then hourly until stable, thereafter every 2 hours. The duration of action of intravenous insulin is only a few minutes and the infusion must not be stopped unless the patient becomes overtly hypoglycaemic (blood glucose < 3 mmol/litre) in which case it should be stopped for up to 30 minutes. The amount of potassium chloride required in the infusion needs to be assessed by regular measurement of plasma electrolytes. Sodium chloride 0.9% infusion should replace glucose 5% or 10% if the blood glucose is persistently above 15 mmol/litre.

Once the patient starts to eat and drink, give subcutaneous insulin before breakfast and stop intravenous insulin 30 minutes later; the dose may need to be 10–20% more than usual if the patient is still in bed or unwell. If the patient was not previously receiving insulin, an appropriate initial dose is 30–40 units daily in four divided doses using soluble insulin before meals and intermediate-acting insulin at bedtime and the dose adjusted from day to day. Patients with hyperglycaemia often relapse after conversion back to subcutaneous insulin calling for one of the following approaches:

- additional doses of soluble insulin at any of the four injection times (before meals or bedtime) or
- temporary addition of intravenous insulin infusion (while continuing the subcutaneous regimen) until blood-glucose concentration is satisfactory or
- complete reversion to the intravenous regimen (especially if the patient is unwell).

### 6.1.1 Short-acting insulins

**Soluble insulin** is a short-acting form of insulin. For maintenance regimens it is usual to inject it 15 to 30 minutes before meals.

Soluble insulin is the most appropriate form of insulin for use in diabetic emergencies e.g. diabetic ketoacidosis (section 6.1.3) and at the time of surgery. It can be given intravenously and intramuscularly, as well as subcutaneously.

When injected subcutaneously, soluble insulin has a rapid onset of action (30 to 60 minutes), a peak action between 2 and 4 hours, and a duration of action of up to 8 hours.

When injected intravenously, soluble insulin has a very short half-life of only about 5 minutes and its effect disappears within 30 minutes.

The human insulin analogues, insulin aspart, insulin glulisine, and insulin lispro have a faster onset and
shorter duration of action than soluble insulin; as a result, compared to soluble insulin, fasting and preprandial blood-glucose concentration is a little higher, postprandial blood-glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently. Subcutaneous injection of insulin analogues may be convenient for those who wish to inject shortly before or, when necessary, shortly after a meal. They can also help those susceptible to hypoglycaemia before lunch and those who eat late in the evening and are prone to nocturnal hypoglycaemia. They can also be administered intravenously and can be used as alternatives to soluble insulin for diabetic emergencies and at the time of surgery.

**INSULIN**
(Insulin Injection; Neutral Insulin; Soluble Insulin)
A sterile solution of insulin (i.e. bovine or porcine) or of human insulin; pH 6.6–8.0

**Indications**
diabetes mellitus; diabetic ketoacidosis (section 6.1.3)

**Cautions**
see above; pregnancy (Appendix 4); reduce dose in renal impairment (Appendix 3); interactions: Appendix 1 (antidiabetics)

**Side-effects**
see notes above; transient oedema; local

**Dose**
- By subcutaneous, intramuscular or intravenous injection or intravenous infusion, according to requirements
- Highly purified animal
- Counselling Show container to patient and confirm that patient is expecting the version dispensed

**Hypurin**
Bovine Neutral (Wockhardt) (BN)
Injection, soluble insulin (bovine, highly purified)
100 units/mL. Net price 10-mL vial = £18.48; cartridges (for Autopen® Classic) 5 × 3 mL = £27.72

**Hypurin**
Porcine Neutral (Wockhardt) (BN)
Injection, soluble insulin (porcine, highly purified)
100 units/mL. Net price 10-mL vial = £16.80; cartridges (for Autopen® Classic) 5 × 3 mL = £25.20

**Human sequence**
- Counselling Show container to patient and confirm that patient is expecting the version dispensed

**Actrapid**
(Noovo Nordisk) (BN)
Injection, soluble insulin (human, por) 100 units/mL.
Net price 10-mL vial = £7.48
- Note Not recommended for use in subcutaneous insulin infusion pumps—may precipitate in catheter or needle

**Humulin S**
( Lilly) (BN)
Injection, soluble insulin (human, prb) 100 units/mL.
Net price 10-mL vial = £16.50; 5 × 3 mL cartridge (for most Autopen® Classic or Humulin®) = £28.12

**Insumin Rapid**
(Aventis Pharma) (BN)
Injection, soluble insulin (human, crb) 100 units/mL, net price 5 × 3-mL cartridge (for OptiPen® Pro I) = £23.43; 5 × 3-mL Insumin® Rapid OptiSet® prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £27.90
- Note Not recommended for use in subcutaneous insulin infusion pumps

**Mixed preparations**
- See Biphasic Isophane Insulin (section 6.1.1.2)

**INSULIN ASPART**
(Recombinant human insulin analogue)

**Indications**
diabetes mellitus

**Cautions**
see under Insulin; children (use only if benefit likely compared to soluble insulin)

**Side-effects**
see under Insulin

**Dose**
- By subcutaneous injection, immediately before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, intravenous injection or intravenous infusion, according to requirements

**NovoRapid**
(Noovo Nordisk) (BN)
Injection, insulin aspart (recombinant human insulin analogue) 100 units/mL. Net price 10-mL vial = £17.27; Penfill® cartridge (for NovoPen® devices) 5 × 3 mL = £29.45; 5 × 3 mL FlexPen® prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £32.00

**Counselling**
Show container to patient and confirm that patient is expecting the version dispensed

**INSULIN GLULISINE**
(Recombinant human insulin analogue)

**Indications**
diabetes mellitus

**Cautions**
see under Insulin

**Side-effects**
see under Insulin

**Dose**
- By subcutaneous injection, ADULT and CHILD over 6 years, immediately before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, ADULT and CHILD over 6 years, according to requirements

**Apidra**
(Sanoﬁ-Aventis) ▼ (BN)
Injection, insulin glulisine (recombinant human insulin analogue) 100 units/mL. Net price 10-mL vial = £17.27; 5 × 3 mL cartridge (for OptiPen® Pro I and Autopen® 2d) = £29.45; 5 × 3 mL OptiClik® cartridge (for OptiClik® Pen) = £31.50; 5 × 3 mL Apidra® Optiset® prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £29.45; 5 × 3 mL Apidra® SoloStar® prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £25.00

**Counselling**
Show container to patient and confirm that patient is expecting the version dispensed
- Note The Scottish Medicines Consortium (p. 3) has advised (October 2008) that Apidra is accepted for restricted use within NHS Scotland for the treatment of adults and children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate

**INSULIN LISPRO**
(Recombinant human insulin analogue)

**Indications**
diabetes mellitus

**Cautions**
see under Insulin; children (use only if benefit likely compared to soluble insulin)
**Endocrine system**

**Humalog® (Lilly) (R)**

Injection, insulin lispro (recombinant human insulin analogue) 100 units/mL. Net price 10-mL vial = £17.28; 5 × 3-mL cartridge (for OptiPen® Classic or HumaPen®) = £29.46; 5 × 3-mL Humalog®-Pen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46; 5 × 3-mL Humalog® KwikPen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46

**Counselling**

Show container to patient and confirm that patient is expecting the version dispensed

---

**6.1.1 Insulins**

**Humalog® (Lilly)**

Injection, insulin lispro (recombinant human insulin analogue) 100 units/mL. Net price 10-mL vial = £17.28; 5 × 3-mL cartridge (for OptiPen® Classic or HumaPen®) = £29.46; 5 × 3-mL Humalog®-Pen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46; 5 × 3-mL Humalog® KwikPen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46

**Counselling**

Show container to patient and confirm that patient is expecting the version dispensed

---

**INSULIN DETEMIR**

(Recombinant human insulin analogue—long acting)

**Indications**

diabetes mellitus

**Cautions**

see under Insulin (section 6.1.1.1); pregnancy (Appendix 4)

**Side-effects**

see under Insulin (section 6.1.1.1)

**Dose**

- By subcutaneous injection, ADULT and CHILD over 6 years, according to requirements

**Levemir® (Novo Nordisk)**

Injection, insulin detemir (recombinant human insulin analogue) 100 units/mL. Net price 5 × 3-mL cartridge (for NovoPen® devices) = £39.00; 5 × 3-mL FlexPen® prefilled disposable injection device (range 1–60 units, allowing 1-unit dosage adjustment) = £39.00; 5 × 3-mL Levemir InnoLet® prefilled disposable injection devices (range 1–50 units, allowing 1-unit dosage adjustment) = £44.85

**Counselling**

Show container to patient and confirm that patient is expecting the version dispensed

---

**INSULIN GLARGINE**

(Recombinant human insulin analogue—long acting)

**Indications**

diabetes mellitus

**Cautions**

see under Insulin (section 6.1.1.1); pregnancy (Appendix 4)

**Side-effects**

see under Insulin (section 6.1.1.1)

**Dose**

- By subcutaneous injection, ADULT and CHILD over 6 years, according to requirements

**Lantus® (Aventis Pharma)**

Injection, insulin glargine (recombinant human insulin analogue) 100 units/mL. Net price 10-mL vial = £26.00; 5 × 3-mL cartridge (for OptiPen® Pro 1 and Autopen® 24) = £39.00; 5 × 3-mL Opticlik® cartridge (for Opticlik® Pen®) = £42.00; 5 × 3-mL Lantus® OptiSet® prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £39.00; 5 × 3-mL Lantus® SoloStar® prefilled disposable injection devices (range 1–80 units, allowing 1-unit dosage adjustment) = £42.00

**Note**

The Scottish Medicines Consortium (p. 3) has advised (October 2002) that insulin glargine is accepted for restricted use within NHS Scotland for the treatment of type 1 diabetes:

- in those who are at risk of or experience unacceptable frequency or severity of nocturnal hypoglycaemia on attempting to achieve better hypoglycaemic control during treatment with other insulins
- as a once daily insulin therapy for patients who require a carer to administer their insulin.

It is not recommended for routine use in patients with type 2 diabetes unless they suffer from recurrent episodes of hypoglycaemia or require assistance with their insulin injections.

**Counselling**

Show container to patient and confirm that patient is expecting the version dispensed

---

**Side-effects**

see under Insulin

**Dose**

- By subcutaneous injection shortly before meals or when necessary shortly after meals, according to requirements
- By subcutaneous infusion, or intravenous injection, or intravenous infusion, according to requirements

- who would otherwise need twice-daily basal insulin injections in combination with oral antidiabetic drugs.

A trial of insulin glargine may be offered to those who have experienced significant nocturnal hypoglycaemia when treated with isophane insulin.
INSULIN ZINC SUSPENSION

(In insulin Zinc Suspension (Mixed)—long acting)

A sterile neutral suspension of bovine and/or porcine insulin or of human insulin in the form of a complex obtained by the addition of a suitable zinc salt; consists of rhombohedral crystals (10–40 microns) and of particles of no uniform shape (not exceeding 2 microns).

Indications  diabetes mellitus
Cautions  see under Insulin (section 6.1.1.1)
Side-effects  see under Insulin (section 6.1.1.1)

Dose  • By subcutaneous injection, according to requirements

Highly purified animal

Hypurin® Bovine Lente (Wockhardt) (Insulatard
Injection  insulin suspension (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £18.48
Counselling  Show container to patient and confirm that patient is expecting the version dispensed

ISOPHANE INSULIN

(Inophane Insulin Injection; Isophane Protamine Suspension; Isophane Insulin (NPH)—intermediate acting)

A sterile suspension of bovine or porcine insulin or of human insulin in the form of a complex obtained by the addition of protamine sulphate or another suitable protamine.

Indications  diabetes mellitus
Cautions  see under Insulin (section 6.1.1.1)
Side-effects  see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

Dose  • By subcutaneous injection, according to requirements

Highly purified animal

Counselling  Show container to patient and confirm that patient is expecting the version dispensed

Hypurin® Bovine Insophane (Wockhardt) (Humulin I-Pen
Injection  isophane insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £18.48
Counselling  Show container to patient and confirm that patient is expecting the version dispensed

Hypurin® Porcine Insophane (Wockhardt) (Humulin I-Pen
Injection  isophane insulin (porcine, highly purified) 100 units/mL. Net price 10-mL vial = £16.80; cartridges (for Autopen® Classic) 5 x 3 mL = £25.20

Human sequence

Counselling  Show container to patient and confirm that patient is expecting the version dispensed

Insulatard® (Novo Nordisk) (Insulatard
Injection  insophane insulin (human, pyr) 100 units/mL. Net price 10-mL vial = £7.48; Insulatard Penfil® cartridge (for Novopen® devices) 5 x 3 mL = £20.08; 5 x 3 mL Insulatard InnoLet® prefilled disposable injection devices (range 1–50 units, allowing 1-unit dosage adjustment) = £20.40

Humulin I® (Lilly) (Humulin I-Pen
Injection  insophane insulin (human, prb) 100 units/mL. Net price 10-mL vial = £16.50; 5 x 3 mL cartridge (for Autopen® Classic or HumaPen®) = £29.94; 5 x 3 mL Humulin I-Pen® prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.94

Insuman® Basal (Aventis Pharma) (Insulatard InnoLet
Injection  isophane insulin (human, crb) 100 units/mL. Net price 5-mL vial = £5.84; 5 x 3-mL cartridge (for OptiPen® Pro I) = £23.43; 5 x 3-mL Insuman® Basal OptiSet® prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £27.90

Mixed preparations

See Biphasic Isophane Insulin (p. 374)

PROTAMINE ZINC INSULIN

(Protamine Zinc Insulin Injection—long acting)

A sterile suspension of insulin in the form of a complex obtained by the addition of a suitable protamine and zinc chloride; this preparation was included in BP 1980 but is not included in BP 1988

Indications  diabetes mellitus
Cautions  see under Insulin (section 6.1.1.1); see also notes above
Side-effects  see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

Dose  • By subcutaneous injection, according to requirements

Hypurin® Bovine Protamine Zinc (Wockhardt) (Insulatard Protamine Zinc Injection—long acting)
Injection  protamine zinc insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £18.48
Counselling  Show container to patient and confirm that patient is expecting the version dispensed

Biphasic insulins

BIPHASIC INSULIN ASPART

(Intermediate-acting insulin)

Indications  diabetes mellitus
Cautions  see under Insulin and Insulin Aspart (section 6.1.1.1)
Side-effects  see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

Dose  • By subcutaneous injection, up to 10 minutes before or soon after a meal, according to requirements

NovoMix® 30 (Novo Nordisk) (Insulatard Protamine Zinc Injection, biphasic insulin aspart (recombinant human insulin analogue), 30% insulin aspart, 70% insulin aspart protamine, 100 units/mL. Net price 5 x 3 mL Penfil® cartridges (for Novopen® devices) = £29.43; 5 x 3 mL FlexPen® prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £32.00
Counselling  Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries)
6.1.1 Insulins

**BIPHASIC INSULIN LISPRO**
(Intermediate-acting insulin)

**Indications** diabetes mellitus

**Cautions** see under Insulin and Insulin Lispro (section 6.1.1.1)

**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

**Dose**
- By subcutaneous injection, up to 15 minutes before or soon after a meal, according to requirements

**Humalog® Mix25** *(Lilly)*

**Injection**, biphasic insulin lispro (recombinant human insulin analogue), 25% insulin lispro, 75% insulin lispro protamine, 100 units/mL, net price 5 × 3-mL cartridge *(for Autopen® Classic or HumaPen®)* = £29.46; 5 × 3-mL prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98. **Humalog® Mix25 KwikPen** prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98

**Counselling** Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries)

**Humalog® Mix50** *(Lilly)*

**Injection**, biphasic insulin lispro (recombinant human insulin analogue), 50% insulin lispro, 50% insulin lispro protamine, 100 units/mL, net price 5 × 3-mL cartridge *(for Autopen® Classic or HumaPen®)* = £29.46; 5 × 3-mL prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46; 5 × 3-mL **Humalog® Mix50 KwikPen** prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98

**Counselling** Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries)

**BIPHASIC ISOPHANE INSULIN**
(Biphasic Isophane Insulin Injection—intermediate acting)

A sterile buffered suspension of either porcine or human insulin complexed with protamine sulphate (or another suitable protamine) in a solution of insulin of the same species

**Indications** diabetes mellitus

**Cautions** see under Insulin (section 6.1.1.1)

**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

**Dose**
- By subcutaneous injection, according to requirements

**Highly purified animal**

**Counselling** Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries)

**Hyypurin® Porcine 30/70 Mix** *(Wockhardt)*

**Injection**, biphasic isophane insulin (porcine, highly purified), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £16.80; cartridges *(for Autopen® Classic)* 5 × 3 mL = £25.20

**Human sequence**

**Counselling** Show container to patient and confirm that patient is expecting the version dispensed; the proportions of the two components should be checked carefully (the order in which the proportions are stated may not be the same in other countries)

**Mixtard® 30** *(Novo Nordisk)*

**Injection**, biphasic isophane insulin (human, pyr), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £7.48; **Mixtard 30 Penfill® cartridge** *(for Novopen® devices)* 5 × 3 mL = £20.08; 5 × 3-mL **Mixtard 30 InnoLet®** prefilled disposable injection devices (range 1–50 units allowing 1-unit dosage adjustment) = £19.87

**Humulin M3®** *(Lilly)*

**Injection**, biphasic isophane insulin (human, prb), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £16.50; 5 × 3-mL cartridge *(for most Autopen® Classic or HumaPen®)* = £28.12

**Insuman® Comb 15** *(Aventis Pharma)*

**Injection**, biphasic isophane insulin (human, crb), 15% soluble, 85% isophane, 100 units/mL, net price 5 × 3-mL **Insuman® Comb 15 OptiSet®** prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £27.90

**Insuman® Comb 25** *(Aventis Pharma)*

**Injection**, biphasic isophane insulin (human, crb), 25% soluble, 75% isophane, 100 units/mL, net price 5-mL vial = £8.94; 5 × 3-mL cartridge *(for OptiPen® Pro I)* = £23.43; 5 × 3-mL **Insuman® Comb 25 OptiSet®** prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £27.90

**Insuman® Comb 50** *(Aventis Pharma)*

**Injection**, biphasic isophane insulin (human, crb), 50% soluble, 50% isophane, 100 units/mL, net price 5 × 3-mL cartridge *(for OptiPen® Pro I)* = £23.43; 5 × 3-mL **Insuman® Comb 50 OptiSet®** prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £27.90

**6.1.1.3 Hypodermic equipment**

Patients should be advised on the safe disposal of lancets, single-use syringes, and needles. Suitable arrangements for the safe disposal of contaminated waste must be made before these products are prescribed for patients who are carriers of infectious diseases.

**Injection devices**

**Autopen** *(Owen Mumford)*

**Injection device**, Autopen 24 *(for use with Sanofi-Aventis 3-mL insulin cartridges)*, allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2-unit dosage adjustment, max. 42 units (2-unit version), net price (both) = £15.55; **Autopen Classic** *(for use with Lilly and Wockhardt 3-mL insulin cartridges)*, allowing 1-unit dosage adjustment, max. 21 units (single-unit version) or 2-unit dosage adjustment, max. 42 units (2-unit version), net price (all) = £15.79

**HumaPen Luxura** *(Lilly)*

**Injection device**, for use with **Humulin** and **Humalog** 3-mL cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £26.36 (available in burgundy and champagne)
HumaPen Luxura HD (Lilly) Injection device, for use with Humulin and Humalog 3-mL cartridges, allowing 0.5-unit dosage adjustment, max. 30 units, net price = £26.36

mhi-500 (Medical House) Needle-free insulin delivery device for use with any 10-mL vial or any 3-mL cartridge of insulin (except the Novo Nordisk 3 mL penfills), allowing 0.5-unit dosage adjustment, max. 50 units, net price 3-month consumables pack for 10-mL adapter (13 nozzles, 5 insulin vial adaptors) = £23.43, for 3-mL adapter (13 nozzles, 5 insulin cartridge adaptors) = £35.81; vial adapter pack (6 insulin vial adaptors) = £7.66, cartridge adapter pack (6 insulin cartridge adaptors) = £7.87; nozzle pack (6 nozzles) = £7.81

NovoPen (Novo Nordisk) Injection device, for use with Penfill insulin cartridges; NovoPen Junior (for 3-mL cartridges), allowing 0.5-unit dosage adjustment, max. 35 units, net price = £25.02; NovoPen 4 (for 3-mL cartridges), allowing 1-unit dosage adjustment, max. 60 units, net price = £26.36 (available in silver and blue)

OptiClik (Sanofi-Aventis) Injection device, for use with Lantus OptiClik or Apidra Opticlutch insulin cartridges, allowing 1-unit dosage adjustment, max. 80 units, net price = £20.13 (available in blue and grey)

OptiPen Pro 1 (Aventis Pharma) Injection device, for use with Insuman insulin cartridges; allowing 1-unit dosage adjustment, max. 60 units, net price = £22.00

SQ-PEN (Medical House) Needle-free insulin delivery device for use with any 10-mL vial or any 3-mL cartridge of insulin, allowing 1-unit dosage adjustment, max. 50 units, net price starter pack (SQ-PEN device, 1 practice nozzle, 1 nozzle, 1 3-mL adapter, 1 10-mL adapter) = £147.83, 3-month consumables pack for 10-mL adapter (7 nozzles, 5 × 10-mL insulin vial adaptors) = £18.08, for 3-mL adapter (7 nozzles, 15 × 3-mL insulin cartridge adaptors) = £30.82; vial adapter pack (6 insulin vial adaptors) = £7.66, cartridge adapter pack (6 insulin cartridge adaptors) = £7.66; nozzle pack (6 nozzles) = £10.03

Lancets—sterile, single use (Drug Tariff)

<table>
<thead>
<tr>
<th>Product</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ascensia Microlet 100 = £3.69, 200 = £7.03</td>
<td>BD Micro-Fine + 100 = £3.16, 200 = £6.13</td>
</tr>
<tr>
<td>GlucoMen Fine 100 = £3.48, 200 = £6.74</td>
<td>Hypoguard Supreme 100 = £2.75</td>
</tr>
<tr>
<td>Monolet Extra 100 = £3.28, MFP Ultra Thin 100 = £3.30, Multiclix 204 = £3.92</td>
<td>One Touch UltraSoft 100 = £3.56</td>
</tr>
<tr>
<td>Thins 100 = £3.86, 200 = £7.39</td>
<td>Unilet ComforTouch 100 = £3.60, 200 = £6.85</td>
</tr>
<tr>
<td>28-gauge, 100 = £6.24, 200 = £12.20, Universal (formerly VitalCare), 200 = £6.32, Verso Soft, 23-gauge, 100 = £3.00, 200 = £5.70</td>
<td>Vitrex Gentle 28-gauge, 100 = £3.19, 200 = £6.13</td>
</tr>
</tbody>
</table>

Compatible finger-picking devices (unless indicated otherwise, see footnotes), all Autolet and Autolet Impression are also compatible finger-picking devices

Needles for Prefilled and Reusable Pen Injectors (Drug Tariff)

<table>
<thead>
<tr>
<th>Product</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD Micro-Fine +, NovoFine, Unifine Penpits Snap-on, needle length 6.1 mm or less, net price 100-needle pack = £12.53, 6.2–9.9 mm, 100-needle pack = £8.89, 10 mm or more, 100-needle pack = £8.89</td>
<td></td>
</tr>
<tr>
<td>Brands include BD Micro-Fine +, NovoFine, Unifine</td>
<td></td>
</tr>
</tbody>
</table>

Accessories

Needle Clipping (Chopping) Device (Drug Tariff) Consisting of a clipper to remove needle from its hub and container from which cut-off needles cannot be retrieved; designed to hold 1500 needles, not suitable for use with lancets. Net price = £1.32

Sharpguard (Drug Tariff) Net price 1-litre sharpsbin = 85p

6.1.2 Antidiabetic drugs

6.1.2.1 Sulphonylureas

6.1.2.2 Biguanides

6.1.2.3 Other antidiabetic drugs

Oral antidiabetic drugs are used for the treatment of type 2 diabetes mellitus. They should be prescribed only if the patient fails to respond adequately to at least 3 months’ restriction of energy and carbohydrate intake and an increase in physical activity. They should be used to augment the effect of diet and exercise, and not to replace them.

For patients not adequately controlled by diet and oral hypoglycaemic drugs, insulin may be added to the treatment regimen or substituted for oral therapy. When insulin is added to oral therapy, it is generally given as twice-daily injections of a biphasic insulin (or insophane insulin mixed with soluble insulin). Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain may be reduced if the insulin is given in combination with metformin.

Pregnancy and breast-feeding During pregnancy, women with either pre-existing or gestational diabetes may be treated with metformin [unlicensed use], either alone or in combination with insulin (section 6.1.1). Women with gestational diabetes should discontinue
hypoglycaemic treatment during breast-feeding for those with pre-existing diabetes.

Other oral hypoglycaemic drugs, including sulphonylureas, are contra-indicated in pregnancy (see also Appendix 4) and in breast-feeding (Appendix 5).

### 6.1.2 Sulphonylureas

The sulphonylureas act mainly by augmenting insulin secretion and consequently are effective only when some residual pancreatic beta-cell activity is present; during long-term administration they also have an extrapancreatic action. All may cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulphonylurea-induced hypoglycaemia may persist for many hours and must always be treated in hospital.

Sulphonylureas are considered for patients who are not overweight, or in whom metformin is contra-indicated or not tolerated. Several sulphonylureas are available and choice is determined by side-effects and the duration of action as well as the patient’s age and renal function. The long-acting sulphonylureas chlorpropamide and glibenclamide are associated with a greater risk of hypoglycaemia; for this reason they should be avoided in the elderly and shorter-acting alternatives, such as glipizide or tolbutamide, should be used instead. Chlorpropamide also has more side-effects than the other sulphonylureas (see below) and therefore it is no longer recommended.

When the combination of strict diet and sulphonylurea treatment fails other options include:

- combining with metformin (section 6.1.2.2) (reports of increased hazard with this combination remain unconfirmed);
- combining with acarbose (section 6.1.2.3), which may have a small beneficial effect, but flatulence can be a problem;
- combining with pioglitazone or rosiglitazone, but see section 6.1.2.3;
- combining with bedtime isophane insulin (section 6.1.1) but weight gain and hypoglycaemia can occur.

Insulin therapy should be instituted temporarily during intercurrent illness (such as myocardial infarction, coma, infection, and trauma). Sulphonylures should be omitted on the morning of surgery; insulin is required because of the ensuing hyperglycaemia in these circumstances.

**Contra-indications** Sulphonylureas should be avoided where possible in severe hepatic impairment (Appendix 2) and in acute porphyria (section 9.8.2). They should not be used during pregnancy (Appendix 4) and while breast-feeding (Appendix 5)—see section 6.1.2. Sulphonylureas are contra-indicated in the presence of ketoadiotosis.

**Side-effects** Side-effects of sulphonylureas are generally mild and infrequent and include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea and constipation.

Chlorpropamide has appreciably more side-effects, mainly because of its very prolonged duration of action and the consequent hazard of hypoglycaemia and it should no longer be used. It may also cause facial flushing after drinking alcohol; this effect does not normally occur with other sulphonylureas. Chlorpropamide may also enhance anti-diuretic hormone secretion and very rarely cause hyponatraemia (hyponatraemia is also reported with glimepiride and glipizide).

Sulphonylureas can occasionally cause a disturbance in liver function, which may rarely lead to cholestatic jaundice, hepatitis and hepatic failure. Hypersensitivity reactions can occur, usually in the first 6–8 weeks of therapy, they consist mainly of allergic skin reactions which progress rarely to erythema multiforme and exfoliative dermatitis, fever and jaundice; photosensitiv-ity has rarely been reported with chlorpropamide and glipizide. Blood disorders are also rare but may include leucopenia, thrombocytopenia, agranulocytosis, panc- topenia, haemolytic anaemia, and aplastic anaemia.

### CHLORPROPAMIDE

**Indications** type 2 diabetes mellitus (for use in dia-betes insipidus, see section 6.5.2)

**Cautions** see notes above; **interactions:** Appendix 1 (antidiabetics)

**Contra-indications** see notes above; **Side-effects** see notes above

**Dose**

- Initially 250 mg daily with breakfast (ELDERLY 100–125 mg but avoid—see notes above), adjusted according to response; max. 500 mg daily

**Chlorpropamide** (Non-proprietary) Tablets, chlorpropamide 100 mg, net price 20 = £1.70; 250 mg, 20 = £2.00. Label: 4

---

**GLIBENCAMIDE**

**Indications** type 2 diabetes mellitus

**Cautions** see notes above; **interactions:** Appendix 1 (antidiabetics)

**Contra-indications** see notes above; **Side-effects** see notes above
Dose
- Initially 5 mg daily with or immediately after breakfast; dose adjusted according to response in elderly; avoid, see notes above; max. 15 mg daily

Glibenclamide (Non-proprietary) (EH)
Tablets, glibenclamide 2.5 mg, net price 28-tab pack = £85p; 5 mg, 28-tab pack = £88p

Euglucon® (Aventis Pharma) (FH)
Tablets, glibenclamide 2.5 mg, net price 28-tab pack = £1.72

Gliclazide (Non-proprietary) (EH)
Indications type 2 diabetes mellitus
Cautions see notes above; interactions: Appendix 1 (antidiabetics)
Contra-indications see notes above
Side-effects see notes above
Dose
- Initially, 40–80 mg daily, adjusted according to response; up to 160 mg as a single dose; higher doses divided; max. 320 mg daily

GlaxoSmithKline
Tablets, scored, gliclazide 80 mg, net price 28-tab pack = £1.71

Note: DIAGLYK

Glucotrol
Tablets, scored, gliclazide 80 mg, net price 60-tab pack = £4.56

Modifed release

Diamicron® (Servier) (FH)
Tablets, m/r, gliclazide 30 mg, net price 28-tab pack = £3.08, 56-tab pack = £6.16. Label: 25

Dose
- Initially 30 mg daily with breakfast, adjusted according to response every 4 weeks (after 2 weeks if no decrease in blood glucose); max. 120 mg daily

Glibenclamide (Non-proprietary) (EH)
Tablets, scored, glibenclamide 2.5 mg, net price 28-tab pack = £1.48, 5 mg (scored), 28-tab pack = £1.26

Tolbutamide (Non-proprietary) (EH)
Tablets, tolbutamide 500 mg. Net price 28-tab pack = £1.51

6.1.2.2 Biguanides

Metformin, the only available biguanide, has a different mode of action from the sulphonylureas, and is not interchangeable with them. It exerts its effect mainly by decreasing gluconeogenesis and by increasing peripheral utilisation of glucose; since it acts only in the presence of endogenous insulin it is effective only if there are some residual functioning pancreatic islet cells.

Metformin is the drug of first choice in overweight patients in whom strict dieting has failed to control diabetes, if appropriate it may also be considered as an option in patients who are not overweight. It is also used when diabetes is inadequately controlled with sulphonylurea treatment. When the combination of strict diet and metformin treatment fails, other options include:

- combining with acarbose (section 6.1.2.3), which may have a small beneficial effect, but flatulence can be a problem;
- combining with insulin (section 6.1.1) but weight gain and hypoglycaemia can be problems (weight gain minimised if insulin given at night);
- combining with a sulphonylurea (section 6.1.2.1) (reports of increased hazard with this combination remain unconfirmed);
METFORMIN HYDROCHLORIDE

Indications diabetes mellitus (see notes above); polycystic ovary syndrome [unlicensed indication]; it improves insulin sensitivity, may aid weight reduction, helps to normalise menstrual cycle (increasing the rate of spontaneous ovulation), and may improve hirsutism.

Caution very rarely, metformin can provoke lactic acidosis which is most likely to occur in patients with renal impairment, see Lactic Acidosis below.

Lactic acidosis Metformin should be used cautiously in renal impairment because of the increased risk of lactic acidosis: it is contra-indicated in patients with significant renal impairment. NICE recommends that the dose of metformin should be reviewed if estimated glomerular filtration rate (eGFR) falls below 45 mL/minute/1.73 m² and to avoid if eGFR less than 30 mL/minute/1.73 m². To reduce the risk of lactic acidosis, metformin should be stopped temporarily withdrawn in those at risk of tissue hypoxia or sudden deterioration in renal function, such as those with dehydration, severe infection, shock, sepsis, acute heart failure, respiratory failure or hepatic impairment (Appendix 2), or those who have recently had a myocardial infarction.

Contra-indications ketoacidosis, see also Lactic Acidosis above; use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal) and use of general anaesthesia (suspend metformin on the morning of surgery and restart when renal function returns to normal); pregnancy (Appendix 4); breast-feeding (Appendix 5).

Side-effects anorexia, nausea, vomiting, diarrhoea (usually transient), abdominal pain, taste disturbance, rarely lactic acidosis (withdraw treatment), decreased vitamin-B₁₂ absorption, erythema, pruritus and urticaria; hepatitis also reported.

Dose
- Diabetes mellitus, ADULT and CHILD over 10 years initially 500 mg with breakfast for at least 1 week then 500 mg with breakfast and evening meal for at least 1 week then 500 mg with breakfast, lunch and evening meal; usual max. 2 g daily in divided doses.
- Polycystic ovary syndrome [unlicensed], initially 500 mg with breakfast for 1 week, then 500 mg with breakfast and evening meal for 1 week, then 1.5–1.7 g daily in 2–3 divided doses.

Note Metformin doses in the BNF may differ from those in the product literature.


Oral solution, sugar-free, metformin hydrochloride 500 mg/5 mL, net price 100 mL = £62.41. Label: 21.

Brands include Metol.

Glucophage® (Merck) Tablets, 1/2c, metformin hydrochloride 500 mg, net price 84-tab pack = £2.88; 850 mg, 56-tab pack = £3.20. Label: 21.

Modified release


Dose initially 500 mg once daily, increased every 10–15 days, max. 2 g once daily with evening meal, if control not achieved, use 1 g twice daily with meals, and if control still not achieved change to standard-release tablets.

Note Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of Bolamyn SR, not suitable if dose of standard-release tablets more than 2 g daily.


Dose initially 500 mg once daily, increased every 10–15 days, max. 2 g once daily with evening meal, if control not achieved, use 1 g twice daily with meals, and if control still not achieved change to standard-release tablets.

Note Patients taking up to 2 g daily of the standard-release metformin may start with the same daily dose of Glucophage SR, not suitable if dose of standard-release tablets more than 2 g daily.

The Scottish Medicines Consortium has advised (December 2005) that Glucophage SR is not recommended for the treatment of type 2 diabetes.

With pioglitazone See section 6.1.2.3.

With rosiglitazone See section 6.1.2.3.

With vildagliptin See section 6.1.2.3.

6.1.2.3 Other antidiabetic drugs

Acarbos, an inhibitor of intestinal alpha glucosidases, delays the digestion and absorption of starch and sucrose; it has a small but significant effect in lowering blood glucose. Use of acarbose is usually reserved for when other oral hypoglycaemics are not tolerated and are contra-indicated. Postprandial hyperglycaemia in type 1 diabetes can be reduced by acarbose, but it has been little used for this purpose. Flatulence deters some from using acarbose although this side-effect tends to decrease with time.

Nateglinide and repaglinide stimulate insulin release. Both drugs have a rapid onset of action and short duration of activity, and should be administered shortly before each main meal. Repaglinide may be given as...
monotherapy for patients who are not overweight or for those in whom metformin is contra-indicated or not tolerated, or it may be given in combination with metformin. Nateglinide is licensed only for use with metformin.

The thiazolidinediones, pioglitazone and rosiglitazone, reduce peripheral insulin resistance, leading to a reduction of blood-glucose concentration. Either drug can be used alone or in combination with metformin or with a sulphonylurea (if metformin inappropriate); the combination of a thiazolidinedione plus metformin is preferred to a thiazolidinedione plus sulphonylurea, particularly for obese patients. Inadequate response to a combination of metformin and sulphonylurea may indicate failing insulin release; the introduction of pioglitazone or rosiglitazone has a limited role in these circumstances and the initiation of insulin is often more appropriate. Blood-glucose control may deteriorate temporarily when a thiazolidinedione is substituted for an oral antidiabetic drug that is being used in combination with another. Long-term benefits of the thiazolidinediones have not yet been demonstrated. NICE (May 2008) has recommended that, when glycaemic control is inadequate with existing treatment, a thiazolidinedione can be added to:

- a sulphonylurea, if metformin is not tolerated
- metformin, if risks of hypoglycaemia with sulphonylurea are unacceptable
- combination of metformin and a sulphonylurea, if human insulin is likely to be unacceptable because of lifestyle or other personal issues, or the patient is obese or has metabolic syndrome.

The Scottish Medicines Consortium accepts use of a thiazolidinedione (rosiglitazone (June 2006), pioglitazone (February 2007)) with metformin and a sulphonylurea, for patients (especially if overweight) whose glycaemic control is inadequate despite the use of 2 oral hypoglycaemic drugs and who are unable or unwilling to take insulin; treatment should be initiated and monitored by an experienced diabetes physician.

**MHRA/CHM advice**

Rosiglitazone and pioglitazone cardiovascular safety (December 2007 and February 2008)

Rosiglitazone and pioglitazone should not be used in patients with heart failure or history of heart failure; incidence of heart failure is increased when rosiglitazone or pioglitazone is combined with insulin. Rosiglitazone should not be used in patients with acute coronary syndrome. Patients should be closely monitored for signs of heart failure. Rosiglitazone may be associated with a small increased risk of cardiac ischaemia particularly in combination with insulin. Rosiglitazone is not recommended for use in patients with ischaemic heart disease or peripheral arterial disease; in patients with history of ischaemic heart disease rosiglitazone should only be used after careful evaluation of the patient’s individual risk. The combination of rosiglitazone and insulin should be used only in exceptional cases, and under close supervision.

Sitagliptin and vildagliptin inhibit dipeptidylpeptidase-4 to increase insulin secretion and lower glucagon secretion. Both drugs are licensed for use in type 2 diabetes in combination with metformin or a sulphonylurea (if metformin inappropriate) or a thiazolidinedione, when treatment with either metformin or a sulphonylurea or a thiazolidinedione fails to achieve adequate glycaemic control. Sitagliptin is also licensed for use in combination with both metformin and a sulphonylurea when dual therapy with these drugs fails to achieve adequate glycaemic control.

The Scottish Medicines Consortium (p. 3) has advised (March 2008) that vildagliptin (Galvus®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in combination with metformin when addition of a sulphonylurea is inappropriate.

Exenatide, a synthetic form of exendin-4, is an incretin mimetic which increases insulin secretion, suppresses glucagon secretion, and slows gastric emptying. It is given by subcutaneous injection for the treatment of type 2 diabetes in combination with metformin or a sulphonylurea, or both, in patients who have not achieved adequate glycaemic control with these drugs alone or in combination. Exenatide use is associated with the prevention of weight gain and possible promotion of weight loss which can be beneficial in overweight patients.

The Scottish Medicines Consortium (p. 3) has advised (June 2007) that exenatide (Byetta®) is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes in combination with metformin or sulphonylurea (or both), as an alternative to treatment with insulin in patients where treatment with metformin or sulphonylurea (or both) at maximally tolerated doses has been inadequate, and treatment with insulin would be the next option.

**ACARBOSE**

**Indications** diabetes mellitus inadequately controlled by diet or by diet with oral antidiabetic drugs

**Cautions** monitor liver function; may enhance hypoglycaemic effects of insulin and sulphonylureas (hypoglycaemic episodes may be treated with oral glucose but not with sucrose); interactions: Appendix 1 (antidiabetics)

**Contra-indications** inflammatory bowel disease, predisposition to partial intestinal obstruction; hernia, previous abdominal surgery; hepatic impairment; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** flatulence, soft stools, diarrhoea (may need to reduce dose or withdraw), abdominal distention and pain; rarely, nausea, abnormal liver function tests and skin reactions; very rarely ileus, oedema, jaundice, and hepatitis

**Note** Antacids unlikely to be beneficial for treating side-effects

**Dose**

- Initially 50 mg daily increased to 50 mg 3 times daily, then increased if necessary after 6–8 weeks to 100 mg 3 times daily; max. 200 mg 3 times daily; CHILD and ADOLESCENT under 18 years not recommended

**Counselling** Tablets should be chewed with first mouthful of food or swallowed whole with a little liquid immediately before food. To counteract possible hypoglycaemia, patients receiving insulin or a sulphonylurea as well as acarbose need to carry glucose (not sucrose—acarbose interferes with sucrose absorption)
Glucobay® (Bayer) FILM TABLETS
Tablets, acarbose 50 mg, net price 90-tab pack = £6.60; 100 mg (scored), 90-tab pack = £12.51. Counselling, administration

EXENATIDE
Indications type 2 diabetes mellitus in combination with metformin or sulphonylurea (or with both) when metformin or a sulphonylurea or both inadequate
Cautions elderly; renal impairment (Appendix 3—avoid if creatinine clearance less than 30 mL/minute); pancreatitis (see below); interactions: Appendix 1 (antidiabetics)
Pancreatitis Severe pancreatitis (sometimes fatal), including haemorrhagic or necrotising pancreatitis, has been reported rarely. Patients or their carers should be told how to recognise signs and symptoms of pancreatitis and advised to seek prompt medical attention if symptoms such as abdominal pain, nausea, and vomiting develop; discontinue permanently if pancreatitis is diagnosed
Contra-indications ketoacidosis; severe gastro-intestinal disease; pregnancy (Appendix 4); breast-feeding (Appendix 5)
Side-effects gastro-intestinal disturbances including nausea, vomiting, diarrhoea, dyspepsia, abdominal pain and distension, gastro-oesophageal reflux disease, decreased appetite; headache, dizziness, asthenia; hypoglycaemia; increased sweating, injection-site reactions; antibody formation; very rarely anaphylactic reactions; also reported constipation, flatulence, dehydration, taste disturbance, renal impairment, pancreatitis (see Cautions above), drowsiness, rash, pruritus, urticaria, and angioedema
Dose
• By subcutaneous injection, ADULT over 18 years, initially 5 micrograms twice daily within 1 hour before 2 main meals (at least 6 hours apart), increased if necessary after at least 1 month to max. 10 micrograms twice daily Counselling If a dose is missed, continue with the next scheduled dose—do not administer after a meal. Some oral medications should be taken at least 1 hour before or 4 hours after exenatide injection—consult product literature for details
Byetta® (Lilly) FILM TABLETS
Injection, exenatide 250 micrograms/mL, net price 5 microgram/dose prefilled pen (60 doses) = £68.24, 10 microgram/dose prefilled pen (60 doses) = £88.24. Counselling, administration

NATEGLINIDE
Indications type 2 diabetes mellitus in combination with metformin (section 6.1.2.2) when metformin alone inadequate
Cautions substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit nateglinide on morning of surgery and recommence when eating and drinking normally); elderly, debilitated and malnourished patients; moderate hepatic impairment (avoid if severe—Appendix 2); interactions: Appendix 1 (antidiabetics)
Contra-indications ketoacidosis; pregnancy (Appendix 4) and breast-feeding (Appendix 5)
Side-effects hypoglycaemia; hypersensitivity reactions including pruritus, rashes and urticaria
Dose
• Initially 60 mg 3 times daily within 30 minutes before main meals, adjusted according to response up to max. 180 mg 3 times daily; CHILD and ADOLESCENT under 18 years not recommended
Starlix® (Novartis) FILM TABLETS
Tablets, f/c, nateglinide 60 mg (pink), net price 84-tab pack = £22.71; 120 mg (yellow), 84-tab pack = £25.88; 180 mg (red), 84-tab pack = £25.88

PIOGLITAZONE
Indications type 2 diabetes mellitus (alone or combined with metformin or a sulphonylurea, or with both, or with insulin—see also notes above)
Cautions monitor liver function (see below); cardiovascular disease or in combination with insulin (risk of heart failure—see MHRA/CHM advice p. 379); substitute insulin during peri-operative period (omit pioglitazone on morning of surgery and recommence when eating and drinking normally); increased risk of bone fractures in females in feet, lower leg, hands, and lower arms; interactions: Appendix 1 (antidiabetics)
Liver toxicity Rare reports of liver dysfunction; monitor liver function before treatment, and periodically thereafter; advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue and dark urine develop; discontinue if jaundice occurs
Contra-indications hepatic impairment, history of heart failure, pregnancy (Appendix 4), breast-feeding (Appendix 5)
Side-effects gastro-intestinal disturbances, weight gain, oedema, anaemia, headache, visual disturbances, dizziness, arthralgia, hypoesthesia, haematuria, impotence; less commonly hypoglycaemia, fatigue, insomnia, vertigo, sweating, altered blood lipids, proteinuria; see also Liver Toxicity above
Dose
• Initially 15–30 mg once daily increased to 45 mg once daily according to response
Actos® (Takeda) FILM TABLETS
Tablets, pioglitazone (as hydrochloride) 15 mg, net price 28-tab pack = £24.14; 30 mg, 28-tab pack = £33.54; 45 mg, 28-tab pack = £36.96
With metformin For cautions, contra-indications, and side-effects of metformin, see section 6.1.2.2
Competact® (Takeda) FILM TABLETS
Tablets, f/c, pioglitazone (as hydrochloride) 15 mg, metformin hydrochloride 850 mg, net price 56-tab pack = £31.56, Label: 21
Dose type 2 diabetes not controlled by metformin alone, 1 tablet twice daily. CHILD and ADOLESCENT under 18 years not recommended
Note Titration with the individual components (pioglitazone and metformin) desirable before initiating Competact

REPAGLINIDE
Indications type 2 diabetes mellitus (as monotherapy or in combination with metformin when metformin alone inadequate)
Cautions substitute insulin during intercurrent illness (such as myocardial infarction, coma, infection, and trauma) and during surgery (omit repaglinide on morning of surgery and recommence when eating and
drinking normally); debilitated and malnourished patients; renal impairment; interactions: Appendix 1 (antidiabetics)

**Contra-indications** ketoacidosis; severe hepatic impairment; pregnancy (Appendix 4) and breastfeeding (Appendix 5)

**Side-effects** abdominal pain, diarrhoea, constipation, nausea, vomiting; rarely hypoglycaemia, hypersensitivity reactions including pruritis, rashes, vasculitis, urticaria, and visual disturbances

**Dose**
- Initially 500 micrograms within 30 minutes before main meals (1 mg if transferring from another oral hypoglycaemic), adjusted according to response at intervals of 1–2 weeks; up to 4 mg may be given as a single dose, max. 16 mg daily; CHILD and ADOLESCENT under 18 years and ELDERLY over 75 years, not recommended

**Prandin** (Daichi Sankyo)  
Tablets, repaglinide 500 micrograms, net price 30-tab pack = £3.92, 90-tab pack = £11.76; 1 mg (yellow), 30-tab pack = £3.92, 90-tab pack = £11.76; 2 mg (peach), 90-tab pack = £11.76

Formerly marketed as NovoNorm

### ROSIGLITAZONE

**Indications** type 2 diabetes mellitus (alone or combined with metformin or with a sulphonylurea or with both—see also notes above)

**Cautions** monitor liver function (see below); cardiovascular disease or in combination with insulin (risk of heart failure and ischaemic heart disease—see MHRA/CHM advice p. 379); substitute insulin during peri-operative period (omit rosiglitazone on morning of surgery and recommence when eating and drinking normally); increased risk of bone fracture in females in feet, hands, and upper arms; renal impairment (Appendix 3); interactions: Appendix 1 (antidiabetics)

**Liver toxicity** Rare reports of liver dysfunction reported; monitor liver function before treatment and periodically thereafter; advise patients to seek immediate medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue, anorexia and dark urine develop; discontinue if jaundice occurs or liver enzymes significantly raised

**Contra-indications** hepatic impairment, history of heart failure or acute coronary syndrome, pregnancy (Appendix 4), breastfeeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances, cardiac ischaemia, headache, anaemia, altered blood lipids, weight gain, oedema, hypoglycaemia, bone fracture; less commonly increased appetite, heart failure, fatigue, paraesthesia, alopecia, dyspnoea; rarely pulmonary oedema, onset or worsening of macular oedema; very rarely angioedema, urticaria; see also Liver Toxicity above

**Dose**
- Initially 4 mg daily; may be increased after 8 weeks to 8 mg daily (in 1–2 divided doses) according to response; CHILD and ADOLESCENT under 18 years not recommended

**Avandia** (GSK)  
Tablets, f/c, rosiglitazone (as maleate) 4 mg (orange), net price 28-tab pack = £24.14, 56-tab pack = £48.28; 8 mg (red/brown), 28-tab pack = £36.96

### With metformin

For cautions, contra-indications, and side-effects of metformin, see section 6.1.2.2

**Avandamet** (GSK)  
Avandamet® 2 mg/500 mg tablets, f/c, pink, rosiglitazone (as maleate) 2 mg, metformin hydrochloride 500 mg, net price 112-tab pack = £36.96. Label: 21

**Avandamet® 2 mg/1 g tablets, f/c, yellow, rosiglitazone (as maleate) 2 mg, metformin hydrochloride 1 g, net price 56-tab pack = £24.14. Label: 21

**Avandamet® 4 mg/1 g tablets, f/c, pink, rosiglitazone (as maleate) 4 mg, metformin hydrochloride 1 g, net price 56-tab pack = £36.96. Label: 21

**Dose** type 2 diabetes mellitus not controlled by metformin alone, initially one Avandamet 2 mg/1 g tablet twice daily, increased after 8 weeks according to response to two Avandamet 2 mg/500 mg tablets twice daily or one Avandamet 4 mg/1 g tablet twice daily; max. 8 mg rosiglitazone and 2 g metformin hydrochloride daily; CHILD and ADOLESCENT under 18 years not recommended

**Note** Titration with the individual components (rosiglitazone and metformin) desirable before initiating Avandamet

### SITAGLIPTIN

**Indications** type 2 diabetes mellitus (in combination with metformin or with a thiazolidinedione or with a sulphonylurea or with metformin and a sulphonylurea—see notes above)

**Cautions** renal impairment (Appendix 3); interactions: Appendix 1 (antidiabetics)

**Contra-indications** ketoacidosis; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances; peripheral oedema; upper respiratory tract infection, nasopharyngitis; pain; osteoarthrits; less commonly anorexia, headache, drowsiness, dizziness, hypoglycaemia, osteoarthris

**Dose**
- ADULT over 18 years, 100 mg once daily

**Note** Dose of concomitant sulphonylurea may need to be reduced

**Januvia** (MSD)  
Tablets, beige, f/c, sitagliptin (as phosphate) 100 mg, net price 28-tab pack = £33.26

### VILDAGLIPTIN

**Indications** type 2 diabetes mellitus (in combination with metformin or with a sulphonylurea or with a thiazolidinedione—see also notes above)

**Cautions** elderly; monitor liver function (see below); heart failure (avoid if moderate or severe); renal impairment (avoid if creatinine clearance less than 50 mL/minute; Appendix 3); interactions: Appendix 1 (antidiabetics)

**Liver toxicity** Rare reports of liver dysfunction; monitor liver function before treatment and periodically thereafter; advise patients to seek prompt medical attention if symptoms such as nausea, vomiting, abdominal pain, fatigue, anorexia and dark urine develop; discontinue if jaundice or other signs of liver dysfunction occur

**Contra-indications** ketoacidosis; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Side-effects** nausea; peripheral oedema; headache, tremor, asthenia, dizziness; less commonly constipation; hypoglycaemia; rarely hepatic dysfunction (see
also Liver Toxicity above); very rarely nasopharyngitis; upper respiratory tract infection and arthralgia also reported

**Dose**
- **ADULT** over 18 years, in combination with metformin or a thiazolidinedione, 50 mg twice daily; in combination with a sulphonylurea, 50 mg daily in the morning

**Galvus®** (Novartis) ▼ (p48)
- Tablets, pale yellow, vildagliptin 50 mg, net price 56-tab pack = £31.76

**With metformin**
For cautions, contra-indications, and side-effects of metformin, see section 6.1.2.2

**Eucreas®** (Novartis) ▼ (p48)
- **Eucreas®** 50 mg/850 mg tablets, f/c, yellow, vildagliptin 50 mg, metformin hydrochloride 850 mg, net price 60-tab pack = £31.76. Label: 21
- **Eucreas®** 50 mg/1 g tablets, f/c, dark yellow, vildagliptin 50 mg, metformin hydrochloride 1 g, net price 60-tab pack = £31.76. Label: 21

**Dose**
- type 2 diabetes mellitus not controlled by metformin alone, **ADULT** over 18 years, 1 Eucreas® tablet twice daily (based on patient’s current metformin dose)

The Scottish Medicines Consortium (p. 3) has advised (June 2008) that Eucreas® is accepted for restricted use within NHS Scotland for the treatment of type 2 diabetes mellitus in patients unable to achieve adequate glycaemic control with metformin alone or those already treated with vildagliptin and metformin as separate tablets

**6.1.3 Diabetic ketoacidosis**

Soluble insulin, used intravenously, is the most appropriate form of insulin for the management of diabetic ketoacidotic and hyperosmolar non-ketotic coma. It is preferable to use the type of soluble insulin that the patient has been using previously. It is necessary to achieve and to maintain an adequate plasma-insulin concentration until the metabolic disturbance is brought under control.

Insulin is best given by intravenous infusion, using an infusion pump, and diluted to 1 unit/mL (care in mixing, see Appendix 6). Adequate plasma-insulin concentration can usually be maintained with infusion rates of 6 units/hour for adults and 0.1 units/kg/hour for children. Blood glucose is expected to decrease by about 5 mmol/litre/hour; if the response is inadequate the infusion rate can be doubled or quadrupled. When the blood-glucose concentration has fallen to 10 mmol/litre the infusion rate can be reduced to 3 units/hour for adults (about 0.05 units/kg/hour for children) and continued until the patient is ready to take food by mouth. The insulin infusion should not be stopped before subcutaneous insulin has been started.

No matter how large, a bolus intravenous injection of insulin can provide an adequate plasma concentration for a short time only; therefore if facilities for intravenous infusion are not available the insulin is given by intramuscular injection. An initial loading dose of 20 units intramuscularly is followed by 6 units intramuscularly every hour until the blood-glucose concentration falls to 10 mmol/litre; intramuscular injections are then given every 2 hours. Although absorption of insulin is usually rapid after intramuscular injection, it may be impaired in the presence of hypotension and poor tissue perfusion; moreover insulin may accumulate during treatment and late hypoglycaemia should be watched for and treated appropriately.

Intravenous replacement of fluid and electrolytes (section 9.2.2) with sodium chloride intravenous infusion is an essential part of the management of ketoacidosis; potassium chloride is included in the infusion as appropriate to prevent the hypokalaemia induced by the insulin. Sodium bicarbonate infusion (1.26% or 2.74%) is used only in cases of extreme acidosis and shock since the acid-base disturbance is normally corrected by the insulin. When the blood glucose has fallen to approximately 10 mmol/litre glucose 5% is infused (maximum 2 litres in 24 hours), but insulin infusion must continue.

**6.1.4 Treatment of hypoglycaemia**

Initially glucose 10–20 g is given by mouth either in liquid form or as granulated sugar or sugar lumps. Approximately 10 g of glucose is available from 2 teaspoons of sugar, 3 sugar lumps. Glucophage® (formerly known as Hypostop Gel® glucose 10 g/25 g tube, available from BBI Healthcare), and non-diet versions of Lucozade® Energy Original 55 mL, Coca-Cola® 90 mL, Ribena® Original 15 mL (to be diluted). If necessary this may be repeated in 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, and biscuits) or the next meal, if it is due, can prevent blood-glucose concentration from falling again.

Hypoglycaemia which causes unconsciousness is an emergency. Glucagon, a polypeptide hormone produced by the alpha cells of the islets of Langerhans, increases plasma-glucose concentration by mobilising glycogen stored in the liver. In hypoglycaemia, if sugar cannot be given by mouth, glucagon can be given by injection. Carbohydrates should be given as soon as possible to restore liver glycogen; glucagon is not appropriate for chronic hypoglycaemia. It may be issued to close relatives of insulin-treated patients for emergency use in hypoglycaemic attacks. It is often advisable to prescribe on an ‘if necessary’ basis to hospitalised insulin-treated patients, so that it may be given rapidly by the nurses during an hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, 50 mL of glucose intravenous infusion 20% (section 9.2.2) may be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Alternatively, 25 mL of glucose intravenous infusion 50% may be given, but this higher concentration is more irritant and viscous making administration difficult. Glucose intravenous infusion 10% may also be used but larger volumes are needed. Close monitoring is necessary in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Patients whose hypoglycaemia is caused by an oral anti-diabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs may persist for many hours.

For advice on the emergency management of hypoglycaemia in dental practice, see p. 23
GLUCAGON

Indications see notes above and under Dose

Cautions see notes above, insulinoma, glucagonoma; ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency

Contra-indications phaeochromocytoma

Side-effects nausea, vomiting, abdominal pain, hypokalaemia, hypotension, rarely hypersensitivity reactions

Dose
- Insulin-induced hypoglycaemia, by subcutaneous, intramuscular, or intravenous injection, ADULT and CHILD over 8 years (or body-weight over 25 kg), 1 mg; CHILD under 8 years (or body-weight under 25 kg), 500 micrograms; if no response within 10 minutes intravenous glucose must be given
- Diagnostic aid, consult product literature
- Beta-blocker poisoning, see p. 32
- Note 1 unit of glucagon = 1 mg of glucagon

1 Glucagen® HypoKit (Novo Nordisk) injection, powder for reconstitution, glucagon (rbs) as hydrochloride with lactose, net price 1-mg vial with prefilled syringe containing water for injection = £11.52

Chronic hypoglycaemia

Diazoxide, administered by mouth, is useful in the management of patients with chronic hypoglycaemia from excess endogenous insulin secretion, either from an islet cell tumour or islet cell hyperplasia. It has no place in the management of acute hypoglycaemia.

DIAZOXIDE

Indications chronic intractable hypoglycaemia (for use in hypertensive crisis see section 2.5.1)

Cautions ischaemic heart disease, pregnancy (Appendix 4), labour, impaired renal function (Appendix 3); monitor blood pressure; during prolonged use monitor white cell and platelet count, and in children, regularly assess growth, bone, and psychological development; interactions Appendix 1 (diazoxide)

Side-effects anorexia, nausea, vomiting, hyperuricemia, hypotension, oedema, tachycardia, arrhythmias, extrapyramidal effects; hypertrichosis on prolonged treatment

Dose
- By mouth, ADULT and CHILD, initially 5 mg/kg daily in 2–3 divided doses

Eudemine® (UCB Pharma) tablets, diazoxide 50 mg. Net price 20 = £9.29

Injection, see section 2.5.1

Diabetic neuropathy

Regular review of diabetic patients should include an annual test for urinary protein (using Albustix®) and serum creatinine measurement. If the urinary protein test is negative, the urine should be tested for microalbuminuria (the earliest sign of nephropathy). If reagent strip tests (Micro-Test II® or Micrubumintest®) are used and prove positive, the result should be confirmed by laboratory analysis of a urine sample. Provided there are no contra-indications, all diabetic patients with nephropathy causing proteinuria or with established microalbuminuria (at least 3 positive tests) should be treated with an ACE inhibitor (section 2.5.5.1) or an angiotensin-II receptor antagonist (section 2.5.5.2) even if the blood pressure is normal; in any case, to minimise the risk of renal deterioration, blood pressure should be carefully controlled (section 2.5).

ACE inhibitors can potentiate the hypoglycaemic effect of insulin and oral antidiabetic drugs; this effect is more likely during the first weeks of combined treatment and in patients with renal impairment.

For the treatment of hypertension in diabetes, see section 2.5.
**6.1.6 Diagnostic and monitoring agents for diabetes mellitus**

### Blood monitoring

Blood glucose monitoring using a meter gives a direct measure of the glucose concentration at the time of the test and can detect hypoglycaemia as well as hyperglycaemia. Patients should be properly trained in the use of blood glucose monitoring systems and to take appropriate action on the results obtained. Inadequate understanding of the normal fluctuations in blood glucose can lead to confusion and inappropriate action.

For patients treated with insulin, it is ideal to observe the ‘peaks’ and ‘troughs’ of blood glucose over 24 hours and make adjustments to their insulin no more than once or twice weekly. Daily alterations to the insulin dose are highly undesirable (except during illness).

Self-monitoring of blood-glucose concentration is appropriate for patients with type 2 diabetes:

- who are treated with insulin;
- who are treated with oral hypoglycaemic drugs e.g. sulphonylureas, to provide information on hypoglycaemia;
- to monitor changes in blood-glucose concentration resulting from changes in lifestyle or medication, and during intercurrent illness;
- to ensure safe blood-glucose concentration during activities, including driving.

**Note** In the UK blood-glucose concentration is expressed in mmol/litre and Diabetes UK advises that these units should be used for self-monitoring of blood glucose. In other European countries units of mg/100 mL (or mg/dL) are commonly used. It is advisable to check that the meter is pre-set in the correct units.

If the patient is unwell and diabetic ketoacidosis is suspected, blood ketones should be measured according to local guidelines (section 6.1.3). Patients and their carers should be trained in the use of blood ketone monitoring systems and to take appropriate action on the results obtained, including when to seek medical attention.

#### Test strips

**Active** (Roche Diagnostics)
- **Reagent strips**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Glucotrend and Accu-Chek Active meters only. Net price 50-strip pack = £14.76

**Advantage Plus** (Roche Diagnostics)
- **Sensor strips**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Accu-Chek Advantage meter only. Net price 50-strip pack = £14.76

**Ascensia Autodiost (Bayer Diabetes Care)**
- **Sensor discs**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Ascensia Breeze and Ascensia Esprit meters only. Net price 5 × 10-disc pack = £14.62

**Aviva (Roche Diagnostics)**
- **Sensor strips**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Accu-Chek Aviva meter only. Net price 50-strip pack = £14.49

**BM-Accutest** (Roche Diagnostics)
- **Reagent strips**, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with Accu-Chek Accutest meters only. Net price 50-strip pack = £14.31

**Breeze 2** (Bayer Diabetes Care)
- **Sensor discs**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with the Breeze 2 meter only. Net price 5 × 10-disc pack = £14.34

**Compact** (Roche Diagnostics)
- **Reagent strips**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Accu-Chek Compact and Accu-Chek Compact Plus meters only. Net price 3 × 17-strip pack = £14.88

**Contour** (Bayer Diabetes Care)
- **Sensor strips**, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Contour meter only. Net price 50-strip pack = £14.74

**Note** Formerly Ascensia Microfil

**FreeStyle** (Abbott)
- **Sensor strips**, for blood glucose monitoring, range 1.1–27.8 mmol/litre, for use with FreeStyle meter only. Net price 50-strip pack = £14.62

**Freestyle Lite** (Abbott)
- **Sensor strips**, for blood glucose monitoring, range 1.1–27.8 micromol/litre, for use with Freestyle Lite meter only. Net price 50-strip pack = £14.62

**GlucoMen** (Menarini Diagnostics)
- **Sensor strips**, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with GlucoMen Glyco and Glucomen PC meters only. Net price 50-strip pack = £13.67

**GlucoMen LX** (Menarini Diagnostics)
- **Sensor strips**, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with GlucoMen LX meter only. Net price 50-strip pack = £14.33

**GlucoMen Visio Sensor** (Menarini Diagnostics)
- **Sensor strips**, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with GlucoMen Visio meter. Net price 50-strip pack = £14.33

**Hypoguard Supreme** (Hypoguard)
- **Reagent strips**, for blood glucose monitoring, range 2.2–27.7 mmol/litre, for use with Hypoguard Supreme meter. Net price 50-strip pack = £12.00

---

**Endocrine system**

- **phate** (section 1.4.2) is the best drug, but other anti-diarrhoeal preparations can be tried. An antiemetic which promotes gastric transit, such as metoclopramide or domperidone (section 4.8), is helpful for gastroparesis. In rare cases when an antiemetic does not help, erythromycin (especially when given intravenously) may be beneficial but this needs confirmation.

For the management of erectile dysfunction, see section 7.4.5.

In *neuropathic postural hypotension* increased salt intake and the use of the mineralocorticoid fludrocortisone 100–400 micrograms daily [unlicensed use] (section 6.3.1) help by increasing plasma volume, but uncomfortable oedema is a common side-effect. Fludrocortisone can also be combined with *flurbiprofen* (section 10.1.1) and *ephrinephrine hydrochloride* (section 3.1.1.2) [both unlicensed]. Midodrine [unlicensed], an alpha agonist, may also be useful in postural hypotension.

*Gustatory sweating* can be treated with an anti-muscarinic such as propantheline bromide (section 1.2); side-effects are common. For the management of hyperhidrosis, see section 13.12.

In some patients with *neuropathic oedema*, *ephrinephrine hydrochloride* [unlicensed use] 30–60 mg 3 times daily offers effective relief.
**BNF 57**

6.1.6 Diagnostic and monitoring agents for diabetes mellitus

---

**GlucoMen Visio** (Menarini Diagnostics)

**GlucoMen LX** (Menarini Diagnostics)

**Abbott**

**Contour** (Roche Diagnostics)

**Accu-Chek Compact Plus** (Roche Diagnostics)

**TRUETrack** (Home Diagnostics)

**TRUEone** (LifeScan)

**Prestige** (LifeScan)

**Optium Plus** (LifeScan)

---

**BNF 57 6.1.6 Diagnostic and monitoring agents for diabetes mellitus385**

£14.53

---

**PocketScan** (LifeScan)

---

**MediSense G2** (Abbott)

Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with MediSense Precision QID, meter only. Net price 50-strip pack = £13.67

- **MediSense Soft-Sense Plus** (Abbott)
  - Sensor strips, for blood glucose monitoring, range 1.7–25 mmol/litre, for use with Optium Xceed meter only. Net price 50-strip pack = £14.52

- **One Touch** (LifeScan)
  - Reagent strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with One Touch II, Profile and Basic meters only. Net price 50-strip pack = £14.37

- **One Touch Ultra** (LifeScan)
  - Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with One Touch Ultra, One Touch Ultra 2, One Touch Ultra Smart, and One Touch UltraEasy meters only. Net price 50-strip pack = £14.53

- **One Touch Vita** (LifeScan)
  - Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre for use with One Touch Vita meter only. Net price 50-strip pack = £14.59

- **Optium β-ketone test strips** (Abbott)
  - Reagent Strips, for blood ketone monitoring, range 0–8 mmol/litre, for use with Optium or Optium Xceed meters only. Net price 10-strip pack = £19.55

- **Optium Plus** (Abbott)
  - Sensor strips (formerly MediSense Optium Plus), for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with Optium Xceed meter only. Net price 50-strip pack = £14.53

- **PocketScan** (LifeScan)
  - Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with PocketScan meter only. Net price 50-strip pack = £14.19

- **Prestige** (Home Diagnostics)
  - Reagent strips, for blood glucose monitoring, range 1.4–33.3 mmol/litre, for use with Prestige meter only. Net price 50-strip pack = £14.51

- **TRUEone** (Home Diagnostics)
  - Sensor strips with meter, for blood glucose monitoring, range 1.1–33.3 mmol/litre. Meter built into top of sensor strip pot. Net price 50-strip and meter pack = £14.25

- **TRUETrack** (Home Diagnostics)
  - Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with TRUETrack meter only. Net price 50-strip pack = £14.25

---

**Meters**

- **Accu-Chek Aviva** (Roche Diagnostics)
  - Meter, for blood glucose monitoring (for use with Aviva test strips). Accu-Chek Aviva system = £12.99

- **Accu-Chek Compact Plus** (Roche Diagnostics)
  - Meter, for blood glucose monitoring (for use with Compact test strips). Accu-Chek Compact Plus system = £12.99

- **Breeze 2** (Bayer Diabetes Care)
  - Meter, for blood glucose monitoring (for use with Breeze 2 Sensor discs) = £10.29

- **Contour** (Bayer Diabetes Care)
  - Meter, for blood glucose monitoring (for use with Ascensia Microfill sensor strips) = £10.29

- **Freestyle** (Abbott)
  - Meters, for blood glucose monitoring (for use with Freestyle and Freestyle Lite test strips). Freestyle Lite meter = £7.79; Freestyle Freedom Lite meter = £5.99

- **GlucoMen LX** (Menarini Diagnostics)
  - Meter, for blood glucose monitoring (for use with GlucoMen LX sensor strips) = £12.99

- **GlucoMen Visio** (Menarini Diagnostics)
  - Meter, for blood glucose monitoring (for use with GlucoMen Visio Sensor strips) = £12.99

- **Optium Plus** (LifeScan)
  - Meter, for blood glucose monitoring (for use with Medisense Optium Plus, and Optium Optium Xceed meter only. Net price 50-strip pack = £14.53

---

**Urinalysis**

Tests for glucose range from reagent strips specific to glucose to reagent tablets which detect all reducing sugars. Few patients still use Clinistix®; Clinistix® is suitable for screening purposes only. Tests for ketones by patients are rarely required unless they become unwell—see section 6.1.6. Microalbuminuria can be detected with Microlab Test IP® or Microalbumintest®, but this should be followed by confirmation in the laboratory, since false positive results are common.

- **Glucose**
  - **Clinistix** (Bayer Diabetes Care)
    - Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £3.25

- **Clinitest** (Bayer Diabetes Care)
  - Reagent tablets, for detection of glucose and other reducing substances in urine. Net price 36-tab pack = £2.00

- **Diabur-Test 5000** (Roche Diagnostics)
  - Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.79

- **Diastix** (Bayer Diabetes Care)
  - Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £2.76

- **Medi-Test Glucose** (BHR)
  - Reagent strips, for detection of glucose in urine. Net price 50-strip pack = £2.30

- **Ketones**
  - **Ketostix** (Bayer Diabetes Care)
    - Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £2.92

- **Ketur Test** (Roche Diagnostics)
  - Reagent strips, for detection of ketones in urine. Net price 50-strip pack = £2.68
6.2 Thyroid and antithyroid drugs

6.2.1 Thyroid hormones

Thyroid hormones are used in hypothyroidism (myxoedema), and also in diffuse non-toxic goitre, Hashimoto’s thyroiditis (lymphadenoid goitre), and thyroid carcinoma. Neonatal hypothyroidism requires prompt treatment for normal development. Levothyroxine sodium (thyroxine sodium) is the treatment of choice for maintenance therapy.

In infants and children with congenital hypothyroidism and juvenile myxoedema, the dose of levothyroxine should be titrated according to clinical response, growth assessment, and measurements of plasma thyroxine and thyroid-stimulating hormone. See BNF for Children (section 6.2.1) for suitable dosage regimens.

Liothyronine sodium has a similar action to levothyroxine but is more rapidly metabolised and has a more rapid effect; 20 micrograms is equivalent to 100 micrograms of levothyroxine. Its effects develop after a few hours and disappear within 24 to 48 hours of discontinuing treatment. It may be used in severe hypothyroid states when a rapid response is desired.

Liothyronine by intravenous injection is the treatment of choice in hypothyroid coma. Adjunctive therapy includes intravenous fluids, hydrocortisone, and treatment of infection; assisted ventilation is often required.

6.2.2 Antithyroid drugs

Indications hypothyroidism; see also notes above

Cautions panhypopituitarism or predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting levothyroxine), elderly, cardiovascular disorders (including hypertension, myocardial insufficiency or myocardial infarction, see Initial Dosage below), long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (dose of antidiabetic drugs including insulin may need to be increased); pregnancy (Appendix 4); interactions: Appendix 1 (thyroid hormones)

Initial dosage Baseline ECG is valuable because changes induced by hypothyroidism can be confused with ischaemia. If metabolism increases too rapidly (causing diarrhoea, nervousness, rapid pulse, insomnia, tremors and sometimes anginal pain where there is latent myocardial ischaemia), reduce dose or withhold for 1–2 days and start again at a lower dose

Contra-indications thyrotoxicosis

Side-effects usually at excessive dosage (see Initial Dosage above) include diarrhoea, vomitings, anginal pain, arrhythmias, palpitation, tachycardia, tremor, restlessness, excitability, insomnia, headache, flushing, sweating, fever, heat intolerance, weight-loss, muscle cramp, and muscular weakness; transient hair loss in children; hypersensitivity reactions including rash, pruritus and oedema also reported

Dose

- ADULT, initially 50–100 micrograms once daily, preferably before breakfast, adjusted in steps of 25–50 micrograms every 3–4 weeks according to response (usual maintenance dose 100–200 micrograms once daily); in cardiac disease, severe hypothyroidism, and patients over 50 years, initially 25 micrograms once daily, adjusted in steps of 25 micrograms every 4 weeks according to response; usual maintenance dose 50–200 micrograms once daily;
- CHILD under 12 years see BNF for Children (section 6.2.1)

Levothyroxine (Non-proprietary)

Tablets, levothyroxine sodium 25 micrograms, net price 28-tab pack = £1.80; 50 micrograms, 28-tab pack = £1.10; 100 micrograms, 28-tab pack = £1.22

Brands include Eltroxin

Oral solution, levothyroxine sodium 25 micrograms/5 mL, net price 100 mL = £44.90; 100 micrograms/5 mL, 100 mL = £52.75

Brands include Eutrox (sugar-free)
Antithyroid drugs

Antithyroid drugs are used for hyperthyroidism either to prepare patients for thyroidectomy or for long-term management. In the UK carbimazole is the most commonly used drug. Propylthiouracil may be used in patients who suffer sensitivity reactions to carbimazole as sensitivity is not necessarily displayed to both drugs. Both drugs act primarily by interfering with the synthesis of thyroid hormones.

**LIOTHYRONINE SODIUM**
(=Tri-iodothyronine sodium)

**Indications** see notes above

**Cautions** see under Levothyroxine Sodium; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (thyroid hormones)

**Contra-indications** see under Levothyroxine Sodium

**Side-effects** see under Levothyroxine Sodium

**Dose**
- By mouth, initially 10–20 micrograms daily gradually increased to 60 micrograms daily in 2–3 divided doses; ELDERLY smaller initial doses; CHILD, adult dose reduced in proportion to body-weight
- By slow intravenous injection, hypothyroid coma, 5–20 micrograms repeated every 12 hours or as often as every 4 hours if necessary; alternatively 50 micrograms initially then 25 micrograms every 8 hours reducing to 25 micrograms twice daily

Liothyronine sodium (Goldshield) ¶¶

Tablets, scored, liothyronine sodium 20 micrograms, net price 28-tab pack = £20.00

Triiodothyronine (Goldshield) ¶¶

Injection, powder for reconstitution, liothyronine sodium (with dextran). Net price 20-microgram amp = £37.92

6.2.2 Antithyroid drugs

Antithyroid drugs only need to be given once daily because of their prolonged effect on the thyroid. Over-treatment can result in the rapid development of hypothyroidism and should be avoided particularly during pregnancy because it can cause fetal goitre.

A combination of carbimazole, 40 to 60 mg daily with levothyroxine, 50 to 150 micrograms daily; may be used in a blocking-replacement regimen; therapy is usually given for 18 months. The blocking-replacement regimen is not suitable during pregnancy.

**Iodine** has been used as an adjunct to antithyroid drugs for 10 to 14 days before partial thyroidectomy; however, there is little evidence of a beneficial effect. Iodine should not be used for long-term treatment because its antithyroid action tends to diminish.

Radioactive sodium iodide (I) solution is used increasingly for the treatment of thyrotoxicosis at all ages, particularly where medical therapy or compliance is a problem, in patients with cardiac disease, and in patients who relapse after thyroidectomy.

**Propranolol** is useful for rapid relief of thyrotoxic symptoms and may be used in conjunction with antithyroid drugs or as an adjunct to radioactive iodine. Beta-blockers are also useful in neonatal thyrotoxicosis and in supraventricular arrhythmias due to hyperthyroidism. Propranolol has been used in conjunction with iodine to prepare mildly thyrotoxic patients for surgery but it is preferable to make the patient euthyroid with carbimazole. Laboratory tests of thyroid function are not altered by beta-blockers. Most experience in treating thyrotoxicosis has been gained with propranolol but nadolol is also used. For doses and preparations of beta-blockers see section 2.4.

**Thyrotoxic crisis** (‘thyroid storm’) requires emergency treatment with intravenous administration of fluids, propranolol (5 mg) and hydrocortisone (100 mg every 6 hours, as sodium succinate), as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

**Pregnancy and breast-feeding** Radioactive iodine therapy is contra-indicated during pregnancy. Propylthiouracil and carbimazole can be given but the blocking-replacement regimen (see above) is not suitable. Both propylthiouracil and carbimazole cross the placenta and in high doses may cause fetal goitre and hypothyroidism—the lowest dose that will control the hyperthyroid state should be used (requirements in Graves’ disease tend to fall during pregnancy). Rarely, carbimazole has been associated with congenital defects, including aplasia cutis of the neonate.

Carbimazole and propylthiouracil appear in breast milk but this does not preclude breast-feeding as long as neonatal development is closely monitored and the lowest effective dose is used.
CARBIMAZOLE

Indications hyperthyroidism

Cautions hepatic impairment (avoid if severe; Appendix 2); pregnancy and breast-feeding (see notes above)

Contra-indications severe blood disorders

Side-effects nausea, mild gastro-intestinal disturbances, taste disturbance, headache; fever, malaise; rash, pruritus, arthralgia; rarely myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis, see CSM warning above), and jaundice

Counselling Warn patient to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops

Dose

• See notes above

Carbimazole (Non-proprietary) Tablets, carbimazole 5 mg, net price 100-tab pack = £5.51; 20 mg, 100-tab pack = £19.12. Counselling, blood disorder symptoms

Neo-Mercazole® (Amidpharm) Tablets, both pink, carbimazole 5 mg, net price 100-tab pack = £5.15; 20 mg, 100-tab pack = £19.12. Counselling, blood disorder symptoms

IODINE AND IODIDE

Indications thyrotoxicosis (pre-operative)

Cautions pregnancy, children; not for long-term treatment

Contra-indications breast-feeding

Side-effects hypersensitivity reactions including cor- yza-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes; on prolonged treatment depression, insomnia, impotence; goitre in infants of mothers taking iodides

Dose

• See under preparation

Aqueous Iodine Oral Solution (Lugol’s Solution), iodine 5%, potassium iodide 10% in purified water, freshly boiled and cooled, total iodine 130 mg/mL. Net price 100 mL = £1.19. Label: 27

Dose 0.1–0.3 mL 3 times daily well diluted with milk or water

PROPYLTHIOURACIL

Indications hyperthyroidism

Cautions see under Carbimazole; hepatic impairment (Appendix 2), renal impairment (Appendix 3)

Side-effects see under Carbimazole; leucopenia; rarely cutaneous vasculitis, thrombocytopenia, aplastic anaemia, hypoprothrombinaemia, hepatitis, encephalopathy, hepatic necrosis, nephritis, lupus erythematosus-like syndromes

Dose

• See notes above

Propylthiouracil (Non-proprietary) Tablets, propylthiouracil 50 mg. Net price 56-tab pack = £34.85

6.3 Corticosteroids

6.3.1 Replacement therapy

The adrenal cortex normally secretes hydrocortisone (cortisol) which has glucocorticoid activity and weak mineralocorticoid activity. It also secretes the mineralocorticoid aldosterone.

In deficiency states, physiological replacement is best achieved with a combination of hydrocortisone (section 6.3.2) and the mineralocorticoid fludrocortisone; hydrocortisone alone does not usually provide sufficient mineralocorticoid activity for complete replacement.

In Addison’s disease or following adrenalectomy, hydrocortisone 20 to 30 mg daily by mouth is usually required. This is given in 2 doses, the larger in the morning and the smaller in the evening, mimicking the normal diurnal rhythm of cortisol secretion. The optimum daily dose is determined on the basis of clinical response. Glucocorticoid therapy is supplemented by fludrocortisone 50 to 300 micrograms daily.

In acute adrenocortical insufficiency, hydrocortisone is given intravenously (preferably as sodium succinate) in doses of 100 mg every 6 to 8 hours in sodium chloride intravenous infusion 0.9%.

In hypopituitarism glucocorticoids should be given as in adrenocortical insufficiency, but since production of aldosterone is also regulated by the renin-angiotensin system a mineralocorticoid is not usually required. Additional replacement therapy with levotyroxine (section 6.2.1) and sex hormones (section 6.4) should be given as indicated by the pattern of hormone deficiency.

FLUDROCORTISONE ACETATE

Indications mineralocorticoid replacement in adre- nocortical insufficiency

Cautions section 6.3.2; interactions: Appendix 1 (corticosteroids)

Contra-indications section 6.3.2

Side-effects section 6.3.2

Dose

• 50–300 micrograms daily; CHILD 5 micrograms/kg daily

Florinef® (Squibb) Tablets, scored, fludrocortisone acetate 100 micro- grams. Net price 100-tab pack = £5.36. Label: 10, steroid card

6.3.2 Glucocorticoid therapy

In comparing the relative potencies of corticosteroids in terms of their anti-inflammatory (glucocorticoid) effects it should be borne in mind that high glucocorticoid activity in itself is of no advantage unless it is accom- panied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids below). The minera-
locorticoid activity of fludrocortisone (section 6.3.1) is so high that its anti-inflammatory activity is of no clinical relevance. The table below shows equivalent anti-inflammatory doses.

### Equivalent anti-inflammatory doses of corticosteroids

This table takes no account of mineralocorticoid effects, nor does it take account of variations in duration of action.

<table>
<thead>
<tr>
<th>Prednisolone</th>
<th>5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone</td>
<td>750 micrograms</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>25 mg</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>6 mg</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>750 micrograms</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>20 mg</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>4 mg</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4 mg</td>
</tr>
</tbody>
</table>

The relatively high mineralocorticoid activity of cortisone and hydrocortisone, and the resulting fluid retention, make them unsuitable for disease suppression on a long-term basis. However, they can be used for adrenal replacement therapy (section 6.3.1); hydrocortisone is preferred because cortisone requires conversion in the liver to hydrocortisone. Hydrocortisone is used on a short-term basis by intravenous injection for the emergency management of some conditions. The relatively moderate anti-inflammatory potency of hydrocortisone also makes it a useful topical corticosteroid for the management of inflammatory skin conditions because side-effects (both topical and systemic) are less marked (section 13.4); cortisone is not active topically.

Prednisolone has predominantly glucocorticoid activity and is the corticosteroid most commonly used by mouth for long-term disease suppression.

Betamethasone and dexamethasone have very high glucocorticoid activity in conjunction with insignificant mineralocorticoid activity. This makes them particularly suitable for high-dose therapy in conditions where fluid retention would be a disadvantage.

Betamethasone and dexamethasone also have a long duration of action and this, coupled with their lack of mineralocorticoid action, makes them particularly suitable for conditions which require suppression of corticotropin (corticotrophin) secretion (e.g. congenital adrenal hyperplasia). Some esters of betamethasone and of beclometasone (beclomethasone) exert a considerably more marked topical effect (e.g. on the skin or the lungs) than when given by mouth; use is made of this to obtain topical effects whilst minimising systemic side-effects (e.g. for skin applications and asthma inhalations).

Deflazacort has a high glucocorticoid activity; it is derived from prednisolone.

### Use of corticosteroids

Dosages of corticosteroids vary widely in different diseases and in different patients. If the use of a corticosteroid can save or prolong life, as in exfoliative dermatitis, pemphigus, acute leukaemia or acute transplant rejection, high doses may need to be given, because the complications of therapy are likely to be less serious than the effects of the disease itself.

When long-term corticosteroid therapy is used in some chronic diseases, the adverse effects of treatment may become greater than the disabilities caused by the disease. To minimise side-effects the maintenance dose should be kept as low as possible.

When potentially less harmful measures are ineffective corticosteroids are used topically for the treatment of inflammatory conditions of the skin (section 13.4). Corticosteroids should be avoided or used only under specialist supervision in psoriasis (section 13.5).

Corticosteroids are used both topically (by rectum) and systemically (by mouth or intravenously) in the management of ulcerative colitis and Crohn’s disease (section 1.5). They are also included in locally applied creams for haemorrhoids (section 1.7.2).

Use can be made of the mineralocorticoid activity of fludrocortisone to treat postural hypotension in autonomic neuropathy (section 6.1.5).

High-dose corticosteroids should be avoided for the management of septic shock. However, there is evidence that administration of lower doses of hydrocortisone (50 mg intravenously every 6 hours) and fludrocortisone (50 micrograms daily by mouth) is of benefit in adrenocortical insufficiency resulting from septic shock.

Dexamethasone and betamethasone have little if any mineralocorticoid action and their long duration of action makes them particularly suitable for suppressing corticotropin secretion in congenital adrenal hyperplasia where the dose should be tailored to clinical response and by measurement of adrenal androgens and 17-hydroxyprogesterone. In common with all glucocorticoids their suppressive action on the hypothalamic-pituitary-adrenal axis is greatest and most prolonged when they are given at night. In most individuals a single dose of 1 mg of dexamethasone at night, is sufficient to inhibit corticotropin secretion for 24 hours. This is the basis of the ‘overnight dexamethasone suppression test’ for diagnosing Cushing’s syndrome.

Betamethasone and dexamethasone are also appropriate for conditions where water retention would be a disadvantage.

A corticosteroid may be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy (see also p. 16); high doses of betamethasone or dexamethasone are generally used. However, a corticosteroid should not be used for the management of head injury or stroke because it is unlikely to be of benefit and may even be harmful.

In acute hypersensitivity reactions such as angioedema of the upper respiratory tract and anaphylactic shock, corticosteroids are indicated as an adjunct to emergency treatment with adrenaline (epinephrine) (section 3.4.3). In such cases hydrocortisone (as sodium succinate) by intravenous injection in a dose of 100 to 300 mg may be required.

Corticosteroids are preferably used by inhalation in the management of asthma (section 3.2) but systemic therapy in association with bronchodilators is required for the emergency treatment of severe acute asthma (section 3.1.1).

Corticosteroids may also be useful in conditions such as autoimmune hepatitis, rheumatoid arthritis and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia (section 9.1.3), and some cases of the nephrotic syndrome (particularly in children) and thrombocytopenic purpura (section 9.1.4).
Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus, temporal arteritis, and polyarteritis nodosa; the effects of the disease process may be suppressed and symptoms relieved, but the underlying condition is not cured, although it may ultimately remit. It is usual to begin therapy in these conditions at fairly high dose, such as 40 to 60 mg prednisolone daily, and then to reduce the dose to the lowest commensurate with disease control.

For other references to the use of corticosteroids see Prescribing in Palliative Care, section 8.2.2 (immunosuppression), section 10.1.2 (rheumatic diseases), section 11.4 (eye), section 12.1.1 (otitis externa), section 12.2.1 (allergic rhinitis), and section 12.3.1 (aphthous ulcers).

**Administration**

Whenever possible local treatment with creams, intra-articular injections, inhalations, eye-drops, or enemas should be used in preference to systemic treatment. The suppressive action of a corticosteroid on cortisol secretion is least when it is given as a single dose in the morning. In an attempt to reduce pituitary-adrenal suppression further, the total dose for two days can sometimes be taken as a single dose on alternate days; alternate-day administration has not been very successful in the management of asthma (section 3.2). Pituitary-adrenal suppression can also be reduced by means of intermittent therapy with short courses. In some conditions it may be possible to reduce the dose of corticosteroid by adding a small dose of an immunosuppressive drug (section 8.2.1).

**Cautions and contra-indications of corticosteroids**

**Adrenal Suppression**

During prolonged therapy with corticosteroids, adrenal atrophy develops and can persist for years after stopping. Abrupt withdrawal after a prolonged period can lead to acute adrenal insufficiency, hypotension or death (see Withdrawal of Corticosteroids, below). Withdrawal can also be associated with fever, myalgia, arthralgia, rhinitis, conjunctivitis, painful itchy skin nodules and weight loss.

To compensate for a diminished adrenocortical response caused by prolonged corticosteroid treatment, any significant intercurrent illness, trauma, or surgical procedure requires a temporary increase in corticosteroid dose, or if already stopped, a temporary reintroduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate postoperative period, anaesthetists must know whether a patient is taking or has been taking a corticosteroid by adding a small dose of an immunosuppressive drug (section 8.2.1).

- **Minor surgery under general anaesthesia**—usual oral corticosteroid dose on the morning of surgery or hydrocortisone 25–50 mg (usually the sodium succinate) intravenously at induction; the usual oral corticosteroid dose is recommenced after surgery.

- **Moderate or major surgery**—usual oral corticosteroid dose on the morning of surgery and hydrocortisone 25–50 mg intravenously at induction, followed by hydrocortisone 25–50 mg 3 times a day by intravenous injection for 24 hours after moderate surgery or for 48–72 hours after major surgery; the usual pre-operative oral corticosteroid dose is recommenced on stopping hydrocortisone injections.

Patients on long-term corticosteroid treatment should carry a Steroid Treatment Card (see p. 392) which gives guidance on minimising risk and provides details of prescriber, drug, dosage and duration of treatment.

**Infections**

Prolonged courses of corticosteroids increase susceptibility to infections and severity of infections; clinical presentation of infections may also be atypical. Serious infections e.g. septicaemia and tuberculosis may reach an advanced stage before being recognised, and amoebiasis or strongyloidiasis may be activated or exacerbated (exclude before initiating a corticosteroid in those at risk or with suggestive symptoms). Fungal or viral ocular infections may also be exacerbated (see also section 11.4.1).

**Chickenpox**

Unless they have had chickenpox, patients receiving oral or parenteral corticosteroids for purposes other than replacement should be regarded as being at risk of severe chickenpox (see Steroid Treatment Card). Manifestations of fulminant illness include pneumonia, hepatitis and disseminated intravascular coagulation; rash is not necessarily a prominent feature. Passive immunisation with varicella-zoster immunoglobulin (section 14.5) is needed for exposed non-immune patients receiving systemic corticosteroids or for those who have used them within the previous 3 months. Confirmed chickenpox warrants specialist care and urgent treatment (section 5.3.2.1). Corticosteroids should not be stopped and dosage may need to be increased.

Topical, inhaled or rectal corticosteroids are less likely to be associated with an increased risk of severe chickenpox.

**Measles**

Patients taking corticosteroids should be advised to take particular care to avoid exposure to measles and to seek immediate medical advice if exposure occurs. Prophylaxis with intramuscular normal immunoglobulin (section 14.5) may be needed.

**Withdrawal of corticosteroids**

The CSM has recommended that gradual withdrawal of systemic corticosteroids should be considered in those whose disease is unlikely to relapse and have:

- recently received repeated courses (particularly if taken for longer than 3 weeks);
- taken a short course within 1 year of stopping long-term therapy;
- other possible causes of adrenal suppression;
- received more than 40 mg daily prednisolone (or equivalent);
- been given repeat doses in the evening;
- received more than 3 weeks’ treatment.

Systemic corticosteroids may be stopped abruptly in those whose disease is unlikely to relapse and who have...
received treatment for 3 weeks or less and who are not included in the patient groups described above.

During corticosteroid withdrawal the dose may be reduced rapidly down to physiological doses (equivalent to prednisolone 7.5 mg daily) and then reduced more slowly. Assessment of the disease may be needed during withdrawal to ensure that relapse does not occur.

Psychiatric reactions

Systemic corticosteroids, particularly in high doses, are linked to psychiatric reactions including euphoria, nightmares, insomnia, irritability, mood lability, suicidal thoughts, psychotic reactions, and behavioural disturbances. A serious paranoid state or depression with risk of suicide can be induced, particularly in patients with a history of mental disorder. These reactions frequently subside on reducing the dose or discontinuing the corticosteroid but they may also require specific management. Patients should be advised to seek medical advice if psychiatric symptoms (especially depression and suicidal thoughts) occur and they should also be alert to the rare possibility of such reactions during withdrawal of corticosteroid treatment.

Systemic corticosteroids should be prescribed with care in those predisposed to psychiatric reactions, including those who have previously suffered corticosteroid-induced psychosis, or who have a personal or family history of psychiatric disorders.

Pregnancy and breast-feeding

Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM has concluded:

- corticosteroids vary in their ability to cross the placenta; betamethasone and dexamethasone cross the placenta readily while 88% of prednisolone is inactivated as it crosses the placenta;
- there is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities such as cleft palate or lip;
- when administration is prolonged or repeated during pregnancy, systemic corticosteroids increase the risk of intra-uterine growth restriction; there is no evidence of intra-uterine growth restriction following short-term treatment (e.g. prophylactic treatment for neonatal respiratory distress syndrome);
- any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important;
- prednisolone appears in small amounts in breast milk but maternal doses of up to 40 mg daily are unlikely to cause systemic effects in the infant; infants should be monitored for adrenal suppression if the mothers are taking a higher dose.

See also Appendix 4 and Appendix 5.

Other cautions and contra-indications

Other cautions include: children and adolescents (growth restriction possibly irreversible), elderly (close supervision required particularly on long-term treatment); frequent monitoring required if history of tuberculosis (or X-ray changes), hypertension, recent myocardial infarction (rupture reported), congestive heart failure, hepatic impairment (Appendix 2), renal impairment, diabetes mellitus including family history, osteoporosis (post-menopausal women at special risk), glaucoma (including family history), ocular herpes simplex—risk of corneal perforation, severe affective disorders (particularly if history of steroid-induced psychosis—see also Psychiatric Reactions, above), epilepsy, peptic ulcer, hypothroidism, history of steroid myopathy, ulcerative colitis, diverticulitis, recent intestinal anastomoses,
thromboembolic disorders; myasthenia gravis; interactions: Appendix 1 (corticosteroids)

Other contra-indications include: systemic infection (unless specific therapy given); avoid live virus vaccines in those receiving immunosuppressive doses (serum antibody response diminished)

Side-effects of corticosteroids

Overdosage or prolonged use can exaggerate some of the normal physiological actions of corticosteroids leading to mineralocorticoid and glucocorticoid side-effects.

Mineralocorticoid side-effects include hypertension, sodium and water retention, and potassium and calcium loss. They are most marked with fludrocortisone, but are significant with cortisone, hydrocortisone, corticotropin, and tetracosactide (tetracosactrin). Mineralocorticoid actions are negligible with the high potency glucocorticoids, betamethasone and dexamethasone, and occur only slightly with methylprednisolone, prednisolone, and triamcinolone.

Glucocorticoid side-effects include diabetes and osteoporosis (section 6.6), which is a danger, particularly in the elderly, as it can result in osteoporotic fractures for example of the hip or vertebrae; in addition high doses are associated with avascular necrosis of the femoral head. Muscle wasting (proximal myopathy) can also occur. Corticosteroid therapy is also weakly linked with peptic ulceration and perforation (the potential advantage of soluble or enteric-coated preparations to reduce the risk is speculative only). See also Psychiatric Reactions, p. 391.

High doses of corticosteroids can cause Cushing’s syndrome, with moon face, striae, and acne; it is usually reversible on withdrawal of treatment, but this must always be gradually tapered to avoid symptoms of acute adrenal insufficiency (important: see also Adrenal Suppression, p. 390).

In children, administration of corticosteroids may result in suppression of growth. For the effect of corticosteroids given in pregnancy, see Pregnancy and Breastfeeding, p. 391.

Side-effects can be minimised by using lowest effective dose for minimum period possible.

Other side-effects include: gastrointestinal effects: dyspepsia, abdominal distension, acute pancreatitis, oesophageal ulceration and candidiasis; musculoskeletal effects: muscle weakness, vertebral and long bone fractures, tendon rupture; endocrine effects: menstrual irregularities and amenorrhoea, hirsutism, weight gain, negative nitrogen and calcium balance, increased appetite; increased susceptibility to and severity of infection, reactivation of dormant tuberculosis; neuropsychiatric effects: psychological dependence, insomnia, increased intracranial pressure with papilloedema in children (usually after withdrawal), aggravation of schizophrenia, aggravation of epilepsy; ophthalmic effects: glaucoma, papilloedema, posterior subcapsular cataracts, corneal or scleral thinning and exacerbation of ophthalmic viral or fungal disease, increased intra-ocular pressure, exophthalmos; also impaired healing, petechiae, ecchymoses, facial erythema, suppression of skin test reactions, urtica, hyperhidrosis, skin atrophy, bruising, telangiectasia, myocardial rupture following recent myocardial infarction, congestive heart failure, leucocytosis, hyperglycaemia, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise, hiccups, headache, vertigo.

For other references to the side-effects of corticosteroids see section 3.2 (asthma), section 11.4 (eye) and section 13.4 (skin).

**STEROID TREATMENT CARD**

I am a patient on STEROID treatment which must not be stopped suddenly

- If you have been taking this medicine for more than three weeks, the dose should be reduced gradually when you stop taking steroids unless your doctor says otherwise.
- Read the patient information leaflet given with the medicine.
- Always carry this card with you and show it to anyone who treats you (for example a doctor, nurse, pharmacist or dentist). For one year after you stop the treatment, you must mention that you have taken steroids.
- If you become ill, or if you come into contact with anyone who has an infectious disease, consult your doctor promptly. If you have never had chickenpox, you should avoid close contact with people who have chickenpox or shingles. If you do come into contact with chickenpox, see your doctor urgently.
- Make sure that the information on the card is kept up to date.

**BETAMETHASONE**

**indications** suppression of inflammatory and allergic disorders; congenital adrenal hyperplasia; see also notes above; ear (section 12.1.1); eye (section 11.4.1); nose (section 12.2.1); oral ulceration (section 12.3.1)

**Cautions** see notes above; transient effect on fetal movements and heart rate

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- **By mouth**, usual range 0.5–5 mg daily; see also Administration (above)
- **By intramuscular injection or slow intravenous injection or infusion**, 4–20 mg, repeated up to 4 times in 24 hours; **CHILD, by slow intravenous injection**, up to 1 year 1 mg, 1–5 years 2 mg, 6–12 years 4 mg, repeated up to 4 times in 24 hours according to response
Betanel® (UCB Pharma) 
Tablets, scored, betamethasone 500 micrograms. Net price 100-tab pack = £4.39. Label: 10, steroid card, 21

Betnesol® (UCB Pharma) 
Soluble tablets, pink, scored, betamethasone 500 micrograms (as sodium phosphate). Net price 100-tab pack = £5.17. Label: 10, steroid card, 13, 21

CORTISONE ACETATE

Indications see under Dose but now superseded, see also notes above

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose

- For replacement therapy, 25–37.5 mg daily in divided doses

Contra-indications see notes above

Cautions see notes above

Indications suppression of inflammatory and allergic disorders

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose

- Usual maintenance 3–18 mg daily (acute disorders, initially up to 120 mg daily); see also Administration (above)
- CHILD 0.25–1.5 mg/kg daily (or on alternate days); see also Administration (above)

Calcort® (Shire) 
Tablets, deflazacort 6 mg, net price 60-tab pack = £16.46. Label: 5, 10, steroid card

DEFLAZACORT

Indications suppression of inflammatory and allergic disorders; diagnosis of Cushing’s disease, congenital adrenal hyperplasia; cerebral oedema associated with malignancy; croup (section 3.1); nausea and vomiting with chemotherapy (section 8.1); rheumatic disease (section 10.1.2); eye (section 11.4.1); skin (section 13.4)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose

- By mouth, usual range 0.5–10 mg daily; CHILD 10–100 micrograms/kg daily; see also Administration (above)
- By intramuscular injection or slow intravenous injection or infusion (as dexamethasone phosphate), initially 0.5–24 mg; CHILD 200–400 micrograms/kg daily

Dexamethasone (Non-proprietary) 
Tablets, dexamethasone 2 mg, net price 20 = £1.75. Label: 10, steroid card, 21

Available from Organon

Oral solution, sugar-free, dexamethasone (as dexamethasone sodium phosphate) 2 mg/5 mL, net price 150-mL = £42.30. Label: 10, steroid card, 21

Brands include Dexsol

Injection, dexamethasone phosphate (as dexamethasone sodium phosphate) 4 mg/mL, net price 1-mL amp = £1.00, 2-mL vial = £1.98; 24 mg/mL, 5-mL vial = £16.66. Label: 10, steroid card

Available from Hospira

Injection, dexamethasone (as dexamethasone sodium phosphate) 4 mg/mL, net price 1-mL amp = 91p, 2-mL vial = £1.27. Label: 10, steroid card

Available from Organon

HYDROCORTISONE

Indications adrenocortical insufficiency (section 6.3.1); shock; see also notes above; hypersensitivity reactions e.g. anaphylactic shock and angioedema (section 3.4.3); asthma (section 3.1); severe inflammatory bowel disease (section 1.5); haemorrhoids (section 1.7.2); rheumatic disease (section 10.1.2); eye (section 11.4.1); skin (section 13.4)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; also phosphate ester associated with paraesthesia and pain (particularly in the perineal region)

Dose

- By mouth, replacement therapy, 20–30 mg daily in divided doses—see section 6.3.1; CHILD 10–30 mg

- By intramuscular injection or slow intravenous injection or infusion, 100–500 mg, 3–4 times in 24 hours or as required; CHILD by slow intravenous injection up to 1 year 25 mg, 1–5 years 50 mg, 6–12 years 100 mg

Hydrocortisone (Non-proprietary) 
Tablets, scored, hydrocortisone 10 mg, net price 30-tab pack = 70p; 20 mg, 30-tab pack = £1.07. Label: 10, steroid card, 21

Efcortesol® (Sovereign) 
Injection, hydrocortisone 100 mg (as sodium phosphate)/mL, net price 1-mL amp = 75p, 5-mL amp = £4.48. Label: 10, steroid card

Note Paraeesthesia and pain (particularly in the perineal region) may follow intravenous injection of the phosphate ester

1. Restriction does not apply where administration is for saving life in emergency
Sex hormones

6.4

6.4.1 Female sex hormones

6.4.2 Male sex hormones and antagonists

6.4.3 Anabolic steroids

6.4.1.1 Oestrogens and HRT

6.4.1.2 Progestogens

6.4.1.1 Oestrogens and HRT

Oestrogens are necessary for the development of female secondary sexual characteristics; they also stimulate myometrial hypertrophy with endometrial hyperplasia.

PREDNISOLONE

Indications suppression of inflammatory and allergic disorders; see also notes above; inflammatory bowel disease (section 1.5); asthma, section 3.1 and section 3.2; immunosuppression, section 8.2.2; rheumatic disease, section 10.1.2; eye, section 11.4.1; ear, section 12.1.1

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose

• By mouth, initially, up to 10–20 mg daily (severe disease, up to 60 mg daily), preferably taken in the morning after breakfast; can often be reduced within a few days but may need to be continued for several weeks or months

Maintenance, usual range, 2.5–15 mg daily, but higher doses may be needed; cushingoid side-effects increasingly likely with doses above 7.5 mg daily

• By intramuscular injection, prednisolone acetate (section 10.1.2.2), 25–100 mg once or twice weekly

Prednisolone (Non-proprietary)

Tablets, prednisolone 1 mg, net price 28-tab pack = 88p; 5 mg, 28-tab pack = 98p; 25 mg, 56-tab pack = £20.00. Label: 10, steroid card, 21

Tablets, both e/c, prednisolone 2.5 mg (brown), net price 30-tab pack = £4.81; 5 mg (red), 30-tab pack = £4.88. Label: 5, 10, steroid card, 25

Brands include DeltaCortril Enetic

Soluble tablets, prednisolone 5 mg (as sodium phosphate), net price 30-tab pack = £7.45. Label: 10, steroid card, 13, 21

Injection, see section 10.1.2.2

TRIAMCINOLONE

Indications suppression of inflammatory and allergic disorders; see also notes above; rheumatic disease, section 10.1.2; mouth, section 12.3.1; skin, section 13.4

Cautions see notes above; also high dosage may cause proximal myopathy, avoid in chronic therapy

Contra-indications see notes above

Side-effects see notes above

Dose

• By deep intramuscular injection, into gluteal muscle, 40 mg of acetone depot for depot effect, repeated at intervals according to the patient’s response; max. single dose 100 mg

Kenalog® Intra-articular/Intramuscular (Squibb)

Injection (aqueous suspension), triamcinolone acetonide 40 mg/mL, net price 1-mL vial = £1.70; 1-mL prefilled syringe = £2.11; 2-mL prefilled syringe = £3.66. Label: 10, steroid card

Note Intramuscular needle with prefilled syringe should be replaced for intra-articular injection
In terms of oestrogenic activity natural oestrogens (estradiol (estradiol), estrone (oestrone), and estriol (oestradiol)) have a more appropriate profile for hormone replacement therapy (HRT) than synthetic oestrogens (ethinylestradiol (ethinyl-oestradiol) and mestranol). Tibolone has oestrogenic, progestogenic and weak androgenic activity.

Oestrogen therapy is given cyclically or continuously for a number of gynaecological conditions. If long-term therapy is required in women with a uterus, a progestogen should normally be added to reduce the risk of cystic hyperplasia of the endometrium (or of endometriotic foci in women who have had a hysterectomy) and possible transformation to cancer.

Oestrogens are no longer used to suppress lactation because of their association with thromboembolism.

### Hormone replacement therapy

Hormone replacement therapy (HRT) with small doses of an oestrogen (together with a progestogen in women with a uterus) is appropriate for alleviating menopausal symptoms such as vaginal atrophy or vasomotor instability. Oestrogen given systemically in the perimenopausal and postmenopausal period or tibolone given in the postmenopausal period also diminish postmenopausal osteoporosis (section 6.6.1) but other drugs (section 6.6) are preferred. Menopausal atrophic vaginitis may respond to a short course of a topical vaginal oestrogen preparation (section 7.2.1) used for a few weeks and repeated if necessary.

Systemic therapy with an oestrogen or drugs with oestrogenic properties alleviates the symptoms of oestrogen deficiency such as vasomotor symptoms. Tibolone combines oestrogenic and progestogenic activity with weak androgenic activity; it is given continuously, without cyclical progestogen.

HRT may be used in women with early natural or surgical menopause (before age 45 years), since they are at high risk of osteoporosis. For early menopause, HRT can be given until the approximate age of natural menopause (i.e. until age 50 years). Alternatives to HRT should be considered if osteoporosis is the main concern (section 6.6).

Clonidine (section 2.5.2 and section 4.7.4.2) may be used to reduce vasomotor symptoms in women who cannot take an oestrogen, but clonidine may cause unacceptable side-effects.

HRT increases the risk of venous thromboembolism, stroke, endometrial cancer (reduced by a progestogen), breast cancer, and ovarian cancer; there is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause. For details of these risks see HRT Risk table below.

The CSM advises that the minimum effective dose of HRT should be used for the shortest duration. Treatment should be reviewed at least annually and for osteoporosis alternative treatments considered (section 6.6). HRT does not prevent coronary heart disease or protect against a decline in cognitive function and it should not be prescribed for these purposes. Experience of treating women over 65 years with HRT is limited.

For the treatment of menopausal symptoms the benefits of short-term HRT outweigh the risks in the majority of women, especially in those aged under 60 years.

### Risk of breast cancer

The CSM has estimated that using all types of HRT, including tibolone, increases the risk of breast cancer within 1–2 years of initiating treatment, see HRT Risk table below for details. The increased risk is related to the duration of HRT use (but not to the age at which HRT is started) and this excess risk disappears within 5 years of stopping.

Radiological detection of breast cancer can be made more difficult as mammographic density can increase with HRT use; tibolone has only a limited effect on mammographic density.

### Risk of endometrial cancer

The increased risk of endometrial cancer depends on the dose and duration of oestrogen-only HRT, see HRT Risk table below for details.

In women with a uterus, the addition of a progestogen cyclically (for at least 10 days per 28-day cycle) reduces the additional risk of endometrial cancer; this additional risk is eliminated if a progestogen is given continuously. However, this should be weighed against the increased risk of breast cancer.

### Risk of ovarian cancer

Long-term use of combined HRT or oestrogen-only HRT is associated with a small increased risk of ovarian cancer, see HRT Risk table below for details; this excess risk disappears within a few years of stopping.

### Risk of venous thromboembolism

Women using combined or oestrogen-only HRT are at an increased risk of deep vein thrombosis and of pulmonary embolism especially in the first year of use, see HRT Risk table below for details.

In women who have predisposing factors (such as a personal or family history of deep vein thrombosis or pulmonary embolism, severe varicose veins, obesity, trauma, or prolonged bed-rest) it may be prudent to review the need for HRT as in some cases the risks of HRT may exceed the benefits. See below for advice on surgery.

### Risk of stroke

Risk of stroke increases with age, therefore older women have a greater absolute risk of stroke. Combined HRT or oestrogen-only HRT slightly increases the risk of stroke, see HRT Risk table below for details.

### Risk of coronary heart disease

HRT does not prevent coronary heart disease and should not be prescribed for this purpose. There is an increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause, see HRT Risk table below for details. Although very little information is available on the risk of coronary heart disease in younger women who start HRT close to the menopause, studies suggest a lower relative risk compared with older women.

### Choice

The choice of HRT for an individual depends on an overall balance of indication, risk, and convenience. A woman with a uterus normally requires oestrogen with cyclical progestogen for the last 12 to 14 days of the cycle or a preparation which involves continuous...
administration of an oestrogen and a progestogen (or one which provides both oestrogenic and progestogenic activity in a single preparation). Continuous combined preparations or tibolone are not suitable for use in the perimenopause or within 12 months of the last menstrual period; women who use such preparations may bleed irregularly in the early stages of treatment—if bleeding continues endometrial abnormality should be ruled out and consideration given to changing to cyclical HRT.

An oestrogen alone is suitable for continuous use in women without a uterus. However, in endometriosis, endometrial foci may remain despite hysterectomy and the addition of a progestogen should be considered in these circumstances.

An oestrogen may be given by mouth or it may be given by subcutaneous or transdermal administration, which avoids first-pass metabolism. In the case of subcutaneous implants, recurrence of vasomotor symptoms at supraphysiological plasma concentrations may occur; moreover, there is evidence of prolonged endometrial stimulation after discontinuation (calling for continued cyclical progestogen). For the use of topical HRT preparations see section 7.2.1.

Contraception

HRT does not provide contraception and a woman is considered potentially fertile for 2 years after her last menstrual period if she is under 50 years, and for 1 year if she is over 50 years. A woman who is under 50 years and free of all risk factors for venous and arterial disease can use a low-oestrogen combined oral contraceptive pill (section 7.3.1) to provide both relief of menopausal symptoms and contraception; it is recommended that the oral contraceptive be stopped at 50 years of age since there are more suitable alternatives.

<table>
<thead>
<tr>
<th>Risk</th>
<th>Age range (years)</th>
<th>Background incidence per 1000 women in Europe not using HRT</th>
<th>Additional cases per 1000 women using oestrogen only HRT (estimated)</th>
<th>Additional cases per 1000 women using combined (oestrogen-progestogen) HRT (estimated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Over 5 years</td>
<td>Over 10 years</td>
<td>For 5 years use</td>
</tr>
<tr>
<td>Breast cancer¹</td>
<td>50–59</td>
<td>10</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 5 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>15</td>
<td>30</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 5 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td>Endometrial cancer² ³</td>
<td>50–59</td>
<td>2</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 5 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 5 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>50–59</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>3</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 5 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td>Venous thromboembolism⁴⁵</td>
<td>50–59</td>
<td>5</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 5 years use</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>8</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td>Stroke⁶</td>
<td>50–59</td>
<td>4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For 10 years use</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>9</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>Coronary heart disease⁷⁸</td>
<td>70–79</td>
<td>29–44</td>
<td>2</td>
<td>15</td>
</tr>
</tbody>
</table>

Note Where background incidence or additional cases have not been included in the table, this indicates a lack of available data. NS indicates a non-significant difference.

Taken from MHRA/CHM (Drug Safety Update 2007; 1 (2): 2–6 available at www.mhra.gov.uk/mhra/drugsafetyupdate

1. Tibolone increases the risk of breast cancer but to a lesser extent than with combined HRT.
2. Evidence suggests an increased risk of endometrial cancer with tibolone. After 2.7 years of use (in women of average age 68 years), 1 extra case of endometrial hyperplasia and 4 extra cases of endometrial cancer were diagnosed compared with placebo users.
3. The risk of endometrial cancer cannot be reliably estimated in those using combined HRT because the addition of progestogen for at least 10 days per 28-day cycle greatly reduces the additional risk, and addition of a daily progestogen eliminates the additional risk. The risk of endometrial cancer in women who have not used HRT increases with body mass index (BMI); the increased risk of endometrial cancer in users of oestrogen-only HRT or tibolone is more apparent in women who are not overweight.
4. Limited data does not suggest an increased risk of thromboembolism with tibolone compared to combined HRT or women not taking HRT.
5. Although the level of risk of thromboembolism associated with non-oral routes of administration of HRT has not been established, it may be lower for the transdermal route.
6. Tibolone use increases the risk of stroke about 2.2 times from the first year of treatment; risk of stroke is age-dependent and therefore the absolute risk of stroke with tibolone increases with age.
7. Increased risk of coronary heart disease in women who start combined HRT more than 10 years after menopause.
8. There is insufficient data to draw a conclusion on the risk of coronary heart disease with tibolone.
any potentially fertile woman needs HRT, non-hormonal contraceptive measures (such as condoms) are necessary. Measurement of follicle-stimulating hormone can help to determine fertility, but high measurements alone (particularly in women aged under 50 years) do not necessarily preclude the possibility of becoming pregnant.

**Surgery** Major surgery under general anaesthesia, including orthopaedic and vascular leg surgery, is a predisposing factor for venous thromboembolism and it may be prudent to stop HRT 4–6 weeks before surgery (see Risk of Venous Thromboembolism, above); it should be restarted only after full mobilisation. If HRT is continued or if discontinuation is not possible (e.g. in non-elective surgery), prophylaxis with heparin may be prudent to stop HRT 4–6 weeks before surgery (see Risk of Venous Thromboembolism, above); it should be restarted only after full mobilisation. If HRT is continued or if discontinuation is not possible (e.g. in non-elective surgery), prophylaxis with heparin, including orthopaedic and vascular leg surgery, is a predisposing factor for venous thromboembolism and it may be prudent to stop HRT 4–6 weeks before surgery (see Risk of Venous Thromboembolism, above); it should be restarted only after full mobilisation.

**Withdrawal bleeding**: Cyclical HRT (where a progestogen is taken for 12–14 days of each 28-day oestrogen treatment cycle) usually results in regular withdrawal bleeding towards the end of the progestogen. The aim of continuous combined HRT (where a combination of oestrogen and progestogen is taken, usually in a single tablet, throughout each 28-day treatment cycle) is to avoid bleeding, but irregular bleeding may occur during the early treatment stages (if it continues endometrial abnormality should be excluded and consideration given to cyclical HRT instead).

**Dose**
- See under preparations

**Counselling on patches**: Patch should be removed after 3–4 days (or once a week in case of 7-day patch) and replaced with fresh patch on slightly different site; recommended sites: clean, dry, unbroken areas of skin on trunk below waistline; not to be applied on or near breasts or under waistband. If patch falls off in bath allow skin to cool before applying new patch.

**OESTROGENS FOR HRT**

**Note** Relates only to small amounts of oestrogens given for hormone replacement therapy

**Indications** see notes above and under preparations

**Cautions** prolonged exposure to unopposed oestrogens may increase risk of developing endometrial cancer (see notes above); migraine (or migraine-like headaches); diabetes (increased risk of heart disease); history of breast nodules or fibrocystic disease—closed monitor breast status (risk of breast cancer, see notes above); risk factors for oestrogen-dependent tumours (e.g. breast cancer in first-degree relative); uterine fibroids may increase in size, symptoms of endometriosis may be exacerbated; factors predisposing to thromboembolism (see notes above); presence of antiphospholipid antibodies (increased risk of thrombotic events); increased risk of gall-bladder disease reported; hypophysal tumours; acute porphyria (see section 9.8.2); interactions: Appendix 1 (oestrogens)

**Other conditions** The product literature advises caution in other conditions including hypertension, renal disease, asthma, epilepsy, sickle-cell disease, melanoma, otosclerosis, multiple sclerosis, and systemic lupus erythematosus (but care required if antiphospholipid antibodies present, see above). Evidence for caution in these conditions is unsatisfactory and many women with these conditions may stand to benefit from HRT.

**Contra-indications** pregnancy; oestrogen-dependent cancer, history of breast cancer, active thrombophlebitis, active or recent arterial thromboembolic disease (e.g. angina or myocardial infarction), venous thromboembolism, or history of recurrent venous thromboembolism (unless already on anticoagulant treatment), liver disease (where liver function tests have failed to return to normal), Dubin-Johnson and Rotor syndromes (or monitor closely), untreated endometrial hyperplasia, undiagnosed vaginal bleeding, breast-feeding

**Side-effects** see notes above for risks of long-term use; nausea and vomiting, abdominal cramps and bloating, weight changes, breast enlargement and tenderness, premenstrual-like syndrome, sodium and fluid retention, cholestatic jaundice, glucose intolerance, altered blood lipids—may lead to pancreatitis, rashes and chloasma, changes in libido, depression, mood changes, headache, migraine, dizziness, leg cramps (rule out venous thrombosis), vaginal candidiasis, contact lenses may irritate; transdermal delivery systems may cause contact sensitisation (possible severe hypersensitivity reaction on continued exposure), and headache has been reported on vigorous exercise.

**Premarie**: (Wyeth) (HR)

- **Premarie Low Dose tablets**, s/c, ivory, conjugated oestrogen (equine) 300 micrograms and medroxyprogesterone acetate 1.5 mg, net price 3 × 28-tab pack = £29.85
- **Dose** menopausal symptoms in women with a uterus, 1 tablet daily continuously

- **Premarie tablets**, s/c, blue, conjugated oestrogen (equine) 625 micrograms and medroxyprogesterone acetate 5 mg, Net price 3 × 28-tab pack = £27.14
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously (starting on day 1 of menstruation if cycles have not ceased)

- **Premarie Cycle Calendar pack**, all s/c, 14 white tablets, conjugated oestrogens (equine) 625 micrograms; 14 green tablets, conjugated oestrogens (equine) 625 micrograms and medroxyprogesterone acetate 10 mg, net price 3 × 28-tab pack = £24.87
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 white tablet daily for 14 days, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) then 1 green tablet daily for 14 days; subsequent courses are repeated without interval

- **Premarap-C**: (Wyeth) (HR)

- **Premarap-C 0.625 Calendar pack**, s/c, 28 maroon tablets, conjugated oestrogens (equine) 625 micrograms; 12 light brown tablets, norgestrel 150 micrograms (≡ levonorgestrel 75 micrograms). Net price 3 × 40-tab pack = £17.67
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 maroon tablet daily continuously, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent), and 1 brown tablet daily on days 17–28 of each 28-day treatment cycle; subsequent courses are repeated without interval

- **Premarap-C 1.25 Calendar pack**, s/c, 28 yellow tablets, conjugated oestrogens (equine) 1.25 mg; 12 light brown tablets, norgestrel 150 micrograms (≡ levonorgestrel 75 micrograms). Net price 3 × 40-tab pack = £17.87
- **Dose** see under 0.625 Calendar pack, but taking 1 yellow tablet daily continuously (instead of 1 maroon tablet) if symptoms not fully controlled with lower strength
Endocrine system

Female sex hormones

Estradiol with progestogen

Angeliq® (Schering Health) (PAP)

Tablets, f/c, red, estradiol 1 mg, drospirenone 2 mg. Net price 3 × 28-tab pack = £25.80

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously (if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase)

Cautions use with care if an increased concentration of potassium might be hazardous; renal impairment (Appendix 3)

Note Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

Climestag® (Novartis) (PAP)

Climestag® 1-mg tablets, 16 grey-blue, estradiol valerate 1 mg; 12 white, estradiol valerate 1 mg and norethisterone 1 mg. Net price 28-tab pack = £5.74; 3 × 28-tab pack = £16.69

Dose menopausal symptoms, a 1 grey-blue tablet daily for 16 days, starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent) then 1 white tablet for 12 days; subsequent courses are repeated without interval

Climestag® 2-mg tablets, 16 blue, estradiol valerate 2 mg; 12 yellow, estradiol valerate 2 mg and norethisterone 1 mg. Net price 28-tab pack = £5.74; 3 × 28-tab pack = £16.69

Dose see Climestag 1-mg, but starting with 1 blue tablet daily (instead of 1 grey-blue tablet) if symptoms not controlled with lower strength

Climesse® (Novartis) (PAP)

Tablets, pink, estradiol valerate 2 mg, norethisterone 700 micrograms. Net price 1 × 28-tab pack = £10.34; 3 × 28-tab pack = £31.03

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus. 1 tablet daily continuously

Note Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

Clinorette® (ReSource Medical) (PAP)

Tablets, f/c, 16 white, estradiol 2 mg; 12 pink, estradiol 2 mg and norethisterone 1 mg, net price 3 × 28-tab pack = £9.23

Dose menopausal symptoms, in women with a uterus, 1 white tablet daily for 16 days starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 pink tablet daily for 12 days; subsequent courses are repeated without interval

Cyclo-Progynova® (Viatris) (PAP)

Cyclo-Progynova® 2-mg tablets, all s/c, 11 white, estradiol valerate 2 mg; 10 brown, estradiol valerate 2 mg and norgestrel 500 micrograms (= levonorgestrel 250 micrograms). Net price per pack = £3.11

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily on a continuous basis (if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase)

Elette-Duet Conti® tablets, f/c, grey, estradiol 2 mg, norethisterone acetate 1 mg. Net price 3 × 28-tab pack = £17.97

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily on a continuous basis (if changing from cyclical HRT begin treatment the end of scheduled bleed)

Note Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

Estracombi® (Novaris) (PAP)

Combination pack, self-adhesive patches of Estraderm TTS® 50 (releasing estradiol approx. 50 micrograms/24 hours) and of Estragest TTS® (releasing estradiol approx. 50 micrograms/24 hours and norethisterone acetate 250 micrograms/24 hours); net price 1-month pack (4 of each) = £13.37, 3-month pack (12 of each) = £40.11. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), 1 Estraderm TTS® 50 patch to be applied twice weekly for 2 weeks followed by 1 Estragest TTS® patch twice weekly for 2 weeks; subsequent courses are repeated without interval

Evorel® (Janssen-Cilag) (PAP)

Evorel® Conti patches, self-adhesive, (releasing estradiol approx. 50 micrograms/24 hours and norethisterone acetate approx. 170 micrograms/24 hours), net price 8-patch pack = £12.00, 24-patch pack = £35.99. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 patch to be applied twice weekly continuously

Evorel® Sequel combination pack, 4 self-adhesive patches of Evorel® 50 (releasing estradiol approx. 50 micrograms/24 hours) and 4 self-adhesive patches of Evorel® Conti (releasing estradiol approx. 50 micrograms/24 hours and norethisterone acetate approx. 170 micrograms/24 hours), net price 8-patch pack = £10.23. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 Evorel® 50 patch to be applied twice weekly for 2 weeks followed by 1 Evorel® Conti patch twice weekly for 2 weeks; subsequent courses are repeated without interval

Femapak® (Solvay) (PAP)

Femapak® 40 combination pack of 8 self-adhesive patches of Fematrix® 40 (releasing estradiol approx. 40 micrograms/24 hours) and 14 tablets of dydrogesterone 10 mg. Net price per pack = £7.61. Counselling, administration

Dose see under Femapak 80

Femapak® 80 combination pack of 8 self-adhesive patches of Fematrix® 80 (releasing estradiol approx. 80 micrograms/24 hours) and 14 tablets of dydrogesterone 10 mg. Net price per pack = £8.06. Counselling, administration

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6) in case of Femapak® 80 only), in women with a uterus, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent), apply 1 patch twice weekly continuously and take 1 tablet daily on days 15–28 of each 28-day treatment cycle; therapy should be initiated with Femapak® 40 in those with menopausal symptoms, prolonged oestrogen deficiency or anticipated intolerance to higher strengths, subsequently adjusted to lowest effective dose

Femoston® (Solvay) (PAP)

Femoston® 1/10 tablets, both f/c, 14 white, estradiol 1 mg, 14 grey, estradiol 1 mg, dydrogesterone 10 mg. Net price 3 × 28-tab pack = £13.47

Dose menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 white tablet daily for 14 days...
days, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent) then 1 grey tablet for 14 days, subsequent courses repeated without interval.

**Femoston®**
- 2/10 tablets, both f/c, 14 red, estradiol 2 mg; 14 yellow, estradiol 2 mg, dydrogesterone 10 mg. Net price 3 x 28-tab pack = £13.47
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 red tablet daily for 14 days, starting within 5 days of onset of menstruation (or any time if cycles have ceased or are infrequent) then 1 yellow tablet daily for 14 days; subsequent courses repeated without interval; therapy required for menopausal symptoms alone, Femoston 1/10 given initially and Femoston 2/10 substituted if symptoms not controlled
- **Note** Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

**FemSeven® Conti**
- (Merck)
- **Patches**, self-adhesive (releasing estradiol approx. 50 micrograms/24 hours and levonorgestrel approx. 7 micrograms/24 hours); net price 4-patch pack = £15.48, 12-patch pack = £ 44.12. Counseling, administration
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously (if changing from cyclical HRT begin treatment the day after finishing oestrogen plus progestogen phase)
- **Note** Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

**FemSeven® Sequi**
- (Merck)
- **Combination pack**, self-adhesive patches of FemSeven Sequi Phase 1 (releasing estradiol approx. 50 micrograms/24 hours) and of FemSeven Sequi Phase 2 (releasing estradiol approx. 50 micrograms/24 hours and levonorgestrel approx. 10 micrograms/24 hours); net price 1-month pack (2 of each) = £13.18, 3-month pack (6 of each) = £37.54. Counseling, administration
- **Dose** menopausal symptoms in women with a uterus, 1 patch to be applied once a week continuously
- **Note** Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

**Indivina®**
- (Orion)
- **Indivina® 1 mg/2.5 mg tablets**, estradiol valerate 1 mg, medroxyprogesterone acetate 2.5 mg, net price 3 x 28-tab pack = £21.49
- **Indivina® 1 mg/5 mg tablets**, estradiol valerate 1 mg, medroxyprogesterone acetate 5 mg, net price 3 x 28-tab pack = £21.49
- **Indivina® 2 mg/5 mg tablets**, estradiol valerate 2 mg, medroxyprogesterone acetate 5 mg, net price 3 x 28-tab pack = £21.49
- **Indivina® 2 mg/10 mg tablets**, estradiol valerate 2 mg, medroxyprogesterone acetate 10 mg, net price 3 x 28-tab pack = £21.49
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously; start at end of scheduled bleed if changing from cyclical HRT
- **Note** Less suitable for use in perimenopausal women or within 3 years of last menstrual period—see Choice above

**Kliofem®**
- (Novo Nordisk)
- **Tablets**, f/c, yellow, estradiol 2 mg, norethisterone acetate 1 mg. Net price 3 x 28-tab pack = £11.43
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously; start at end of scheduled bleed if changing from cyclical HRT
- **Note** Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

**Kliovance®**
- (Novo Nordisk)
- **Tablets**, f/c, estradiol 1 mg, norethisterone acetate 500 micrograms, net price 3 x 28-tab pack = £14.67
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously; start at end of scheduled bleed if changing from cyclical HRT
- **Note** Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

**Novofem®**
- (Novo Nordisk)
- **Tablets**, f/c, 16 red, estradiol 1 mg; 12 white, estradiol 1 mg, norethisterone acetate 1 mg, net price 3 x 28-tab pack = £13.50
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 red tablet daily for 16 days then 1 white tablet daily for 12 days; subsequent courses are repeated without interval; start treatment with red tablet at any time or if changing from cyclical HRT, start treatment the day after finishing oestrogen plus progestogen phase

**Nuvelle®**
- (Schering Health)
- **Nuvelle® tablets**, all s/c, 16 white, estradiol valerate 2 mg; 12 pink, estradiol valerate 2 mg and levonorgestrel 75 micrograms. Net price 3 x 28-tab pack = £12.87
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 white tablet daily for 16 days, starting on day 1 of menstruation (or any time if cycles have ceased or are infrequent) then 1 pink tablet daily for 12 days; subsequent courses are repeated without interval
- **Nuvelle® Continuous tablets**, f/c, pink, estradiol 2 mg, norethisterone acetate 1 mg, net price 3 x 28-tab pack = £16.85
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 tablet daily continuously; start at end of scheduled bleed if changing from cyclical HRT
- **Note** Unsuitable for use in perimenopausal women or within 12 months of last menstrual period—see Choice above

**Tridestra®**
- (Orion)
- **Tablets**, 70 white, estradiol valerate 2 mg; 14 blue, estradiol valerate 2 mg and medroxyprogesterone acetate 20 mg; 7 yellow, inactive. Net price 91-tab pack = £80.40
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 white tablet daily for 70 days, then 1 blue tablet daily for 14 days, then 1 yellow tablet daily for 7 days; subsequent courses are repeated without interval

**Trisequens®**
- (Novo Nordisk)
- **Tablets**, 12 blue, estradiol 2 mg; 10 white, estradiol 2 mg, norethisterone acetate 1 mg; 6 red, estradiol 1 mg, net price 3 x 28-tab pack = £11.10
- **Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), in women with a uterus, 1 blue tablet daily, starting on day 5 of menstruation (or at any time if cycles have ceased or are infrequent), then 1 tablet daily in sequence (without interruption)

### Conjugated oestrogens only

**Premarin®**
- (Wyeth)
- **Tablets**, all s/c, conjugated oestrogens (equine) 300 microigrams (green) net price 3 x 28-tab pack = £9.72, 625 micrograms (maroon), 3 x 28-tab pack = £9.72, 1.25 mg (yellow), 3 x 28-tab pack = £13.19
- **Dose** menopausal symptoms, 0.3–1.25 mg daily continuously; osteoporosis prophylaxis (see section 6.6), 0.625–1.25 mg daily continuously; with cyclical progesteron for 12–14 days of each cycle in women with a uterus

### Estradiol only

**Estradiol implants**
- (Organon)
- **Implant**, estradiol 25 mg, net price each = £12.95; 50 mg, each = £21.08
- **Dose** by implantation, oestrogen replacement, and osteoporosis prophylaxis (see section 6.6) with cyclical progesteron for 12–14 days of each cycle in women with a uterus, see notes above.
6.4.1 Female sex hormones

100 mg as required (usually every 4–8 months) according to oestrogen levels—check before each implant.

Note: On cessation of treatment or if implants are removed from those with a uterus, cyclical progestogen should be continued until withdrawal bleed stops.

**Bedrol** (ReSource Medical)

**Tablets**, 1/c, estradiol 2 mg, net price 3 × 28-tab pack = £5.07.

**Dose** menopausal symptoms, with cyclical progestogen for 12–14 days of each cycle in women with a uterus; therapy should be initiated with 1 patch to be applied weekly continuously, starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent).

**Climaval** (Novartis)


**Dose** menopausal symptoms (if patient has had a hysterectomy), 1–2 mg daily.

**Eleste-Solo** (Meda)

**Eleste-Solo** 1 mg tablets, estradiol 1 mg. Net price 3 × 28-tab pack = £5.34.

**Dose** menopausal symptoms, with cyclical progestogen for 12–14 days of each cycle in women with a uterus, 1 mg daily starting on day 1 of menstruation (or at any time if cycles have ceased or are infrequent).

**Eleste-Solo** 2 mg tablets, orange, estradiol 2 mg. Net price 3 × 28-tab pack = £5.34.

**Dose** menopausal symptoms not controlled with lower strength oestrogen deficiency or anticipated intolerance to higher strength, dosage may be increased if required, subsequently adjusted to lowest effective dose.

**Estraderm MX** (Novartis)

**Tablets**, self-adhesive, estradiol, MX 40 patch (releasing approx. 40 micrograms/24 hours), net price 8-patch pack = £5.19; MX 80 patch (releasing approx. 80 micrograms/24 hours), 8-patch pack = £5.99. Counselling, administration.

**Dose** menopausal symptoms (and osteoporosis prophylaxis in case of Estraderm TTS 50 only; see section 6.6), 1 patch to be applied twice weekly continuously, with cyclical progesterone for 12 days of each cycle in women with a uterus; therapy should be initiated with TTS 50 for first month, subsequently adjusted to lowest effective dose.

**Estraderm TTS** (Novartis)

**Tablets**, self-adhesive, estradiol, TTS 25 patch (releasing approx. 25 micrograms/24 hours), net price 8-patch pack = £7.45, 24-patch pack = £22.36; TTS 50 patch (releasing approx. 50 micrograms/24 hours), 8-patch pack = £7.48, 24-patch pack = £22.43; TTS 100 patch (releasing approx. 100 micrograms/24 hours), 8-patch pack = £9.02, 24-patch pack = £27.16, 20-patch pack (hosp. only) = £16.76. Counselling, administration.

**Dose** menopausal symptoms (and osteoporosis prophylaxis in case of Estraderm TTS 50 only; see section 6.6), 1 patch to be applied twice weekly continuously, with cyclical progestogen for 12 days of each cycle in women with a uterus; therapy should be initiated with TTS 50 for first month, subsequently adjusted to lowest effective dose.

**Estradot** (Novartis)

**Patches**, self-adhesive, estradiol, ’25’ patch (releasing approx. 25 micrograms/24 hours), net price 8-patch pack = £5.20; ’37.5’ patch (releasing approx. 37.5 micrograms/24 hours), 8-patch pack = £5.21; ’50’ patch (releasing approx. 50 micrograms/24 hours), 8-patch pack = £5.22, ’75’ patch (releasing approx. 75 micrograms/24 hours), 8-patch pack = £6.08; ’100’ patch (releasing approx. 100 micrograms/24 hours), 8-patch pack = £6.31. Counselling, administration.

**Dose** menopausal symptoms (all strengths) and osteoporosis prophylaxis (Estradot ‘50’; ‘75’; and ‘100’ only; see section 6.6), 1 patch to be applied twice weekly continuously, with cyclical progesterone for 12 days of each cycle in women with a uterus; for osteoporosis prophylaxis therapy should be initiated with ’50’ patch.

**Evorel** (Janssen-Cilag)

**Patches**, self-adhesive, estradiol, ’25’ patch (releasing approx. 25 micrograms/24 hours), net price 8-patch pack = £2.86; ’50’ patch (releasing approx. 50 micrograms/24 hours), 8-patch pack = £3.24, 24-patch pack = £9.72; ’75’ patch (releasing approx. 75 micrograms/24 hours), 8-patch pack = £3.44; ’100’ patch (releasing approx. 100 micrograms/24 hours), 8-patch pack = £3.57. Counselling, administration.

**Dose** menopausal symptoms and osteoporosis prophylaxis (except Evorel 25; see section 6.6), 1 patch to be applied twice weekly continuously, with cyclical progesterone for at least 12 days of each cycle in women with a uterus; therapy should be initiated with ’50’ patch for first month, subsequently adjusted to lowest effective dose.

**Fematrix** (Solvay)

**Fematrix** 40 patch, self-adhesive, estradiol, ‘40’ patch (releasing approx. 40 micrograms/24 hours). Net price 8-patch pack = £4.95. Counselling, administration.

**Dose** menopausal symptoms, 1 patch to be applied twice weekly continuously starting within 5 days of onset of menstruation (or at any time if cycles have ceased or are infrequent), with cyclical progesterone for 12–14 days of each cycle in women with a uterus; therapy should be initiated with MX 40 in those with menopausal symptoms, prolonged oestrogen deficiency or anticipated intolerance to higher strength, dosage may be increased if required, subsequently adjusted to lowest effective dose.

**Fematrix** 80 patch, self-adhesive, estradiol (releasing approx. 80 micrograms/24 hours). Net price 8-patch pack = £5.40. Counselling, administration.

**Dose** menopausal symptoms and osteoporosis prophylaxis (see section 6.6), as for Fematrix 40, therapy should be initiated with Fematrix 40 in those with menopausal symptoms, prolonged oestrogen deficiency or anticipated intolerance to higher strength.

**FemSeven** (Merck)

**Patches**, self-adhesive, estradiol, ’50’ patch (releasing approx. 50 micrograms/24 hours), net price 4-patch pack = £6.04, 12-patch pack = £18.02; ’75’ patch (releasing approx. 75 micrograms/24 hours), net price 4-patch pack = £6.98; ’100’ patch (releasing approx.
100 micrograms/24 hours), net price 4-patch pack = £7.28. Counselling, administration

**Dose**  menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1 patch to be applied once a week continuously, with cyclical progestogen for at least 10 days of each cycle in women with a uterus; therapy should be initiated with FemSeven 50 patches for the first few months, subsequently adjusted according to response

**Oestrogel**<sup>®</sup> (Ferring) <sup>[fn]</sup>

**Gel**, estradiol 0.06%, net price 64-dose pump pack = £7.39. Counselling, administration

**Dose**  menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 2 measures (estradiol 1.5 mg) to be applied over an area twice that of the template provided once daily continuously, starting within 5 days of menstruation (or anytime if cycles have ceased or are infrequent), with cyclical progestogen for 12 days of each cycle in women with a uterus; for menopausal symptoms may be increased if necessary after 1 month to max. 4 measures daily

**Counselling**  Apply gel to clean, dry, intact skin such as arms, shoulders or inner thighs and allow to dry for 5 minutes before covering with clothing. Not to be applied on or near breasts or on vulval region. Avoid skin contact with another person (particularly male) and avoid other skin products or washing the area for at least 1 hour after application

**Progynova**<sup>®</sup> (Schering Health) <sup>[fn]</sup>

**Tablets**, both s/c, estradiol valerate 1 mg (beige), net price 3 x 28-tab pack = £6.56; 2 mg (blue), 3 x 28-tab pack = £6.56

**Dose**  menopausal symptoms, 1–2 mg daily continuously; osteoporosis prophylaxis (see section 6.6), 2 mg daily continuously, with cyclical progestogen for 12 days of each cycle in women with a uterus

**Progynova**<sup>®</sup> TS (Schering Health) <sup>[fn]</sup>

**Patches**, self-adhesive, Progynova TS 50 (releasing estradiol approx. 50 micrograms/24 hours), net price 12-patch pack = £16.71; Progynova TS 100 (releasing estradiol approx. 100 micrograms/24 hours), 12-patch pack = £18.39. Counselling, administration

**Dose**  menopausal symptoms and osteoporosis prophylaxis (Progynova TS 50 only; see section 6.6), 1 patch to be applied once a week continuously or 1 patch per week for 3 weeks followed by a 7-day patch-free interval (cyclical), with cyclical progestogen for 12–14 days of each cycle in women with a uterus; in those with menopausal symptoms, therapy should be initiated with Progynova TS 50, dosage may be increased if required, subsequently adjusted to lowest effective dose

**Note**  Women receiving Progynova TS 100 patches for meno-pausal symptoms may continue with this strength for osteoporosis prophylaxis (see section 6.6)

**Sandrena**<sup>®</sup> (Organon) <sup>[fn]</sup>

**Gel**, estradiol (0.1%), 500 microgram/500 mg sachet, net price 28-sachet pack = £5.28, 1 mg/1 g sachet, 28-sachet pack = £6.08. Counselling, administration

**Excipients**  include propylene glycol (see section 13.1.3)

**Dose**  menopausal symptoms, estradiol 1 mg (1 g gel) to be applied once daily over area 1–2 times size of hand, with cyclical progestogen for 12–14 days of each cycle in women with a uterus; dose may be adjusted after 2–3 cycles to a usual dose of estradiol 0.5–1.5 mg (0.5–1.5 g gel) daily

**Counselling**  Apply gel to intact areas of skin such as lower trunk or thighs, using right and left sides on alternate days. Wash hands after application. Not to be applied on the breasts or face and avoid contact with eyes. Allow area of application to dry for 5 minutes and do not wash area for at least 1 hour

**Zumenon**<sup>®</sup> (Govaly) <sup>[fn]</sup>

**Tablets**, f/c, estradiol 1 mg, net price 84-tab pack = £6.89; 2 mg (red), 84-tab pack = £6.89

**Dose**  menopausal symptoms, initially 1 mg daily starting on day 5 of menstruation (or any time if cycles have ceased or are infrequent) adjusted to 1–4 mg daily according to response; osteoporosis prophylaxis (see section 6.6), 2 mg daily; with cyclical progestogen for 10–14 days of each cycle in women with a uterus

### Estradiol, estril and estrene

**Hormonin**<sup>®</sup> (Shire) <sup>[fn]</sup>

**Tablets**, pink, estradiol 600 micrograms, estril 270 micrograms, estrone 1.4 mg. Net price 84-tab pack = £6.61

**Dose**  menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1–2 tablets daily, with cyclical progestogen for 12–14 days of each cycle in women with a uterus

**Note**  Hormonin tablets can be given continuously or cyclically (21 days out of 28)

### Estril only

**Ovestin**<sup>®</sup> (Organon) <sup>[fn]</sup>

**Tablets**, scored, estril 1 mg. Net price 30-tab pack = £3.91. Label: 25

**Dose**  genito-urinary symptoms associated with oestrogen-deficiency states, 0.5–3 mg daily, as single dose, for up to 1 month, then 0.5–1 mg daily until restoration of epithelial integrity (short-term use); infertility due to poor cervical penetration, 0.25–1 mg daily on days 6–15 of cycle

**Estropipate only**

**Harmogen**<sup>®</sup> (Pharmacia) <sup>[fn]</sup>

**Tablets**, peach, scored, estopipate 1.5 mg. Net price 28-tab pack = £3.77

**Dose**  menopausal symptoms and osteoporosis prophylaxis (see section 6.6), 1.5 mg daily continuously (with cyclical progestogen for 10–13 days of each cycle in women with a uterus), up to 3 mg daily (in single or divided doses) for vasomotor symptoms and menopausal vaginitis

### TIBOLONE

**Indications**  short-term treatment of symptoms of oestrogen deficiency (including women being treated with gonadotrophin releasing hormone analogues); osteoporosis prophylaxis in women at risk of fractures (second-line)

**Cautions**  see notes above and under Oestrogens for HRT; vaginal bleeding (investigate for endometrial cancer if bleeding continues beyond 6 months or after stopping treatment); renal impairment, history of liver disease (Appendix 2), epilepsy, migraine, diabetes mellitus, hypercholesterolaemia; withdraw if signs of thromboembolic disease, abnormal liver function tests or cholestatic jaundice; see also Note below; interactions: Appendix 1 (tibolone)

**Contra-indications**  see notes above and under Oestrogens for HRT; hormone-dependent tumours, history of cardiovascular or cerebrovascular disease (e.g. thrombophlebitis, thromboembolism), uninvestigated vaginal bleeding, severe liver disease, pregnancy, breast-feeding

**Side-effects**  see notes above; also abdominal pain, weight changes, vaginal bleeding, leukorrhoea, facial hair, and rarely amnesia; gastro-intestinal disturbances, oedema, dizziness, headache, migraine, depression, breast cancer (see notes above and section 6.4.1.1), arthralgia, myalgia, visual disturbances, seborrhoeic dermatitis, rash and pruritus also reported

**Dose**

- 2.5 mg daily

**Note**  Unsuitable for use in the premenopause (unless being treated with gonadotrophin-releasing hormone analogue) and as (or with) an oral contraceptive; also unsuitable for use within 12 months of last menstrual period (may cause irregular bleeding); induce withdrawal bleed with progestogen if transferring from another form of HRT
Ethinylestradiol

Ethinylestradiol (ethinyloestradiol) is licensed for short-term treatment of symptoms of oestrogen deficiency, for osteoporosis prophylaxis if other drugs (section 6.6) cannot be used and for the treatment of female hypogonadism and menstrual disorders.

Ethinylestradiol is occasionally used under specialist supervision for the management of hereditary haemorrhagic telangiectasia (but evidence of benefit is limited). Side-effects include nausea, fluid retention, and thrombosis. Impotence and gynaecomastia have been reported in men.

For use in prostate cancer, see section 8.3.1.

Ethinylestradiol (Ethinyloestradiol)

**Indications** see notes above

**Cautions** cardiovascular disease (sodium retention with oedema, thromboembolism), hepatic impairment (jaundice), see also under Combined Hormonal Contraceptives (section 7.3.1) and under Oestrogens for HRT (p. 397)

**Contra-indications** see under Combined Hormonal Contraceptives (section 7.3.1) and under Oestrogens for HRT (p. 397)

**Side-effects** feminising effects in men; see also under Combined Hormonal Contraceptives (section 7.3.1) and under Oestrogens for HRT (p. 397)

**Dose**
- Menopausal symptoms and osteoporosis prophylaxis, (with intact uterus), 10–50 micrograms daily for 21 days, repeated after 7-day tablet-free period
- Female hypogonadism, 10–50 micrograms daily, usually on cyclical basis; initial oestrogen therapy should be followed by combined oestrogen and progestogen therapy
- Menstrual disorders, 20–50 micrograms daily from day 5 to 25 of each cycle, with progestogen added either throughout the cycle or from day 15 to 25

**Ethinylestradiol** (Non-proprietary) Tablets, ethinylestradiol 10 micrograms, net price 21-tab pack = £18.55; 50 micrograms, 21-tab pack = £18.55; 1 mg, 28-tab pack = £34.53

**Raloxifene**

Raloxifene is licensed for the treatment and prevention of postmenopausal osteoporosis; unlike hormone replacement therapy, raloxifene does not reduce menopausal vasomotor symptoms.

Raloxifene may reduce the incidence of oestrogen-receptor-positive breast cancer but its role in established breast cancer is not yet clear. The manufacturer advises avoiding its use during treatment for breast cancer.
molecular weight heparin (section 2.8.1) may decrease the risk of fetal loss (use under specialist supervision only).

Hormone replacement therapy In women with a uterus a progestogen needs to be added to long-term oestrogen therapy for hormone replacement, to prevent cystic hyperplasia of the endometrium and possible transformation to cancer; it can be added on a cyclical or a continuous basis (see section 6.4.1.1). Combined packs incorporating suitable progestogen tablets are available, see p. 397.

Oral contraception Desogestrel, etynodiol (ethynodiol), gestodene, levonorgestrel, norethisterone, and norgestimate are used in combined oral contraceptives and in progestogen-only contraceptives (section 7.3.1 and section 7.3.2).

Cancer Progestogens also have a role in neoplastic disease (section 8.3.2).

Cautions Progestogens should be used with caution in conditions that may worsen with fluid retention e.g. epilepsy, hypertension, migraine, cardiac or renal dysfunction, and in those susceptible to thromboembolism (particular caution with high dose). Care is also required in liver impairment (avoid if severe), and in those with a history of depression. Progestogens can decrease glucose tolerance and diabetes should be monitored closely. For interactions see Appendix 1 (progestogens).

Contra-indications Progestogens should be avoided in patients with a history of liver tumours, and in severe liver impairment. They are also contra-indicated in those with a history of liver tumours, and in severe hepatic, hepatic, renal impairment, and in those susceptible to thromboembolism (particular caution with high dose). Care is also required in liver impairment (avoid if severe), and in those with a history of depression. Progestogens can decrease glucose tolerance and diabetes should be monitored closely. For interactions see Appendix 1 (progestogens).

Side-effects Side-effects of progestogens include menstrual disturbances, premenstrual-like syndrome (including bloating, fluid retention, breast tenderness), weight change, nausea, headache, dizziness, insomnia, drowsiness, depression, change in libido; also skin reactions (including urticaria, pruritus, rash, and acne), hirsutism and alopecia. Jaundice and anaphylactoid reactions have also been reported.

**DYROGESTERONE**

**Indications** HRT (section 6.4.1.1)

**Contra-indications** see notes above; pregnancy (Appendix 4)

**Side-effects** see notes above; indigestion

**Dose**
- By mouth, 2.5–10 mg daily for 5–10 days beginning on day 16 to 21 of cycle, repeated for 2 cycles in dysfunctional uterine bleeding and 3 cycles in secondary amenorrhoea
- Mild to moderate endometriosis, 10 mg 3 times daily for 90 consecutive days, beginning on day 1 of cycle
- Progestogenic opposition of oestrogen HRT, 10 mg daily for the last 14 days of each 28-day oestrogen HRT cycle

**Prorad®** (Pharmacia) tablets, all scored, medroxyprogesterone acetate 2.5 mg (orange), net price 30-tab pack = £1.84; 5 mg (blue), 10-tab pack = £1.23; 10 mg (white), 10-tab pack = £2.47, 90-tab pack = £22.16

**Climanor®** (ReSource Medical) Tablets, f/c, medroxyprogesterone acetate 5 mg, net price 28-tab pack = £3.27

**Combined preparations** Section 6.4.1.1

**NORETHISTERONE**

**Indications** see under Dose; HRT (section 6.4.1.1); contraception (section 7.3.1 and section 7.3.2); malignant disease (section 8.3.2)

**Contra-indications** see notes above; breast-feeding (Appendix 5)

**Side-effects** see notes above; pregnancy (Appendix 4)

**Dose**
- Endometriosis, by mouth, 10–15 mg daily for 4–6 months or longer, starting on day 5 of cycle (if spotting occurs increase dose to 20–25 mg daily, reduced once bleeding has stopped)
- Dysfunctional uterine bleeding, menorrhagia (but see notes above), by mouth, 5 mg 3 times daily for 10 days to arrest bleeding; to prevent bleeding 5 mg twice daily from day 19 to 26
- Dysmenorrhoea (but see notes above), by mouth, 5 mg 3 times daily from day 5 to 24 for 3–4 cycles
- Premenstrual syndrome (but not recommended, see notes above), by mouth, 5 mg 2–3 times daily from day 19 to 26 for several cycles
- Postponement of menstruation, by mouth, 5 mg 3 times daily starting 3 days before expected onset (menstruation occurs 2–3 days after stopping)

**Tablets of 5 mg**

**Norethisterone** (Non-proprietary) tablets, norethisterone 5 mg, net price 30-tab pack = £2.65

**Primolut N** (Schering Health) Tablets, norethisterone 5 mg. Net price 30-tab pack = £2.01

**Urovian®** (Pharmacia) tablets, norethisterone 5 mg. Net price 30-tab pack = £1.40, 90-tab pack = £4.21

**Combined preparations** Section 6.4.1.1
Androgens cause masculinisation; they may be used as replacement therapy in castrated adults and in those who are hypogonadal due to either pituitary or testicular disease. In the normal male they inhibit pituitary gonadotrophin secretion and depress spermatogenesis. Androgens also have an anabolic action which led to the development of anabolic steroids (section 6.4.3).

Androgens are useless as a treatment of impotence and impaired spermatogenesis unless there is an associated hypoandrogenism; they should not be given until the hypoandrogenism has been properly investigated. Treatment should be under expert supervision.

When given to patients with hypopituitarism they can lead to normal sexual development and potency but not to fertility. If fertility is desired, the usual treatment is with gonadotrophins or pulsatile gonadotrophin-releasing hormone (section 6.5.1) which will stimulate spermatogenesis as well as androgen production.

Caution should be used when androgens or chorionic gonadotrophin are used in treating boys with delayed puberty since the fusion of epiphyses is hastened and may result in short stature; skeletal maturation should be monitored.

Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate, propionate or undecanoate, or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, may be used. Satisfactory replacement therapy can sometimes be obtained with 1 mL of Sustanon 250®, given by intramuscular injection once a month, although more frequent dose intervals are often necessary. Implants of testosterone can be used for hypogonadism; the implants are replaced every 4 to 5 months.

Testosterone implants can be used in postmenopausal women as an adjunct to hormone replacement therapy. A testosterone patch is also licensed to improve libido in surgically induced menopausal women (receiving concomitant oestrogen therapy).

## TESTOSTERONE AND ESTERS

**Indications** see under preparations

**Cautions** cardiac, renal, or hepatic impairment

(Appendix 2), elderly, ischaemic heart disease, hypertension, epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of hypercalcaemia), undertaken regular examination of the prostate and breast during treatment; monitor full blood count, lipid profile and liver function; pre-pubertal boys (see notes above and under Side-effects); **interactions**: Appendix 1 (testosterone)

**Women** Regularly assess for androgenic side-effects; women should be advised to report any signs of virilisation e.g. deepening of the voice or hirsutism

**Contra-indications** breast cancer in men, prostate cancer, history of primary liver tumours, hypercalcaemia, pregnancy (Appendix 4), breast-feeding (Appendix 5), nephrotic syndrome

**Side-effects** prostate abnormalities and prostate cancer, headache, depression, gastro-intestinal bleeding, nausea, vomiting, cholestatic jaundice, changes in libido, gynaecomastia, polycystic ovaries, anxiety, irritability, nervousness, asthenia, paraesthesia, hypertension, electrolyte disturbances including sodium retention with oedema and hypercalcaemia, weight gain; increased bone growth, muscle cramps, atherosclerosis; androgenic effects such as hirsutism, male-pattern baldness, seborrhoea, acne, pruritus, excessive frequency and duration of penile erection, precocious sexual development and premature closure of epiphyses in pre-pubertal males, suppression of spermatogenesis in men and virilism in women; rarely liver tumours; sleep apnoea also reported; **with patches, buccal tablets, and gel**, local irritation and allergic reactions (including burn-like lesions with patches), and taste disturbances

**Dose** See under preparations
Virormone  

- Testosterons (Organon)  
  Capsules, orange, testosterone undecanoate 40 mg in oily solution. Net price 30-cap pack = £8.89; 60-cap pack = £17.79. Label: 21, 25  
  **Dose** androgen deficiency, 120–160 mg daily for 2–3 weeks; maintenance 60–120 mg daily

**Buccal**

- Striant® SR (Ardana)  
  Mucoadhesive buccal tablets, m/r, testosterone 30 mg, net price 60-tab pack = £45.84. Counselling, see under Dose below  
  **Dose** hypogonadism, 30 mg every 12 hours; CHILD and ADOLESCENT under 18 years not recommended  
  **Counselling** Place rounded side of tablet on gum above front teeth and hold lip firmly over the gum for 30 seconds. If tablet detaches within 4 hours of next dose, replace with new tablet which is considered the second dose for the day.

**Intramuscular**

- Testosterone Enantate (Cambridge)  
  **Injection** (oily), testosterone enantate 250 mg/mL. Net price 1-mL amp = £11.01  
  **Dose** by slow intramuscular injection, hypogonadism, initially 250 mg every 2–3 weeks; maintenance 250 mg every 3–6 weeks  
  **Breast cancer** 250 mg every 2–3 weeks; maintenance 250 mg every 3–6 weeks  
  **Note** under 18 years not recommended

- Nebido® (Bayer)  
  **Injection** (oily), testosterone undecanoate 250 mg/mL. Net price 4-mL amp = £76.70  
  **Dose** by deep intramuscular injection, hypogonadism in men over 18 years, 1 g every 10–14 weeks; if necessary, second dose may be given after 6 weeks to achieve rapid steady state plasma testosterone levels and then every 10–14 weeks

- Sustanon 100® (Organon)  
  **Injection** (oily), testosterone propionate 20 mg, testosterone phenylpropionate 40 mg, and testoster-

- Sustanon 250® (Organon)  
  **Injection** (oily), testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 40 mg/mL. Net price 1-mL amp = £1.09  
  **Excipients** include arachis (peanut) oil, benzyl alcohol (see Excipients p 2)  
  **Dose** by deep intramuscular injection, androgen deficiency, 1 mL every 2 weeks

- Transdermal preparations

- Andropatch® (GSK)  
  **Patches**, self-adhesive, releasing testosterone approx. 2.5 mg/24 hours, net price 60-patch pack = £49.10; releasing testosterone approx. 5 mg/24 hours, net price 30-patch pack = £49.10. Counselling, administration  
  **Dose** androgen deficiency in men (over 15 years) associated with primary or secondary hypogonadism, apply to clean, dry, unbroken skin on back, abdomen, upper arms or thighs, removing after 24 hours and siting replacement patch on a different area (with an interval of 7 days before using the same site), initially apply patches equivalent to testosterone 5 mg/24 hours (2.5 mg/24 hours in non-virilised patients) at night (approx. 10 p.m.), then adjust to 2.5 mg to 7.5 mg every 24 hours according to plasma-testosterone concentration (those with a body-weight over 130 kg may require 7.5 mg every 24 hours)

- Intrinsa® (Procter & Gamble)  
  **Patches**, self-adhesive, releasing testosterone approx. 300 micrograms/24 hours, net price 8-patch pack = £28.00. Counselling, administration  
  **Dose** hypoactive sexual desire disorder associated with surgically induced menopause (in women receiving concomitant oestrogen therapy (section 6.4.1.1)), apply 1 patch twice weekly continuously to clean, dry, unbroken skin on lower abdomen below waistline; site replacement patch on a different area (avoid using same area for 7 days); assess treatment after 3–6 months, discontinue if no benefit

  **Note** Not recommended for women naturally menopausal or those taking conjugated oestrogens. Safety and efficacy of use beyond 1 year not established

- Testim® (Ipsen)  
  **Gel**, testosterone 50 mg/5 g tube, net price 30-tube pack = £33.00. Counselling, administration  
  **Excipients** include propylene glycol (see section 13.1.3)  
  **Dose** hypogonadism due to testosterone deficiency in men (over 18 years), 50 mg testosterone (5 g gel) applied once daily, subsequent application adjusted according to response; max. 100 mg (10 g gel) daily  
  **Counselling** Squeeze entire content of tube on to one palm and apply as a thin layer on clean, dry, healthy skin of shoulder or upper arm, preferably in the morning after washing or bathing (if 2 tubes required use 1 per shoulder or upper arm); rub in and allow to dry before putting on clothing to cover site; wash hands with soap after application; avoid washing application site for at least 6 hours  
  **Avoid skin contact with application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature

- Testogel® (Schering Health)  
  **Gel**, testosterone 50 mg/5 g sachet, net price 30-sachet pack = £33.00. Counselling, administration  
  **Dose** hypogonadism due to androgen deficiency in men (over 18 years), 50 mg testosterone (5 g gel) to be applied once daily; subsequent application adjusted according to response in 25-mg (2.5 g gel) increments to max. 100 mg (10 g gel) daily  
  **Counselling** Apply thin layer of gel on clean, dry, healthy skin such as shoulders, arms or abdomen, immediately after sachet is opened. Not to be applied on genital area as high alcohol content may cause local irritation. Allow to dry for 3–5 minutes before dressing. Wash hands with soap and water after applying gel, avoid shower or bath for at least 6 hours  
  **Avoid skin contact with gel application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature

- Tostran® (ProStrakan)  
  **Gel**, testosterone 2% (10 mg/ metered application), net price 60-g multidose dispenser = £26.67. Counselling, administration  
  **Excipients** include butyric acid, propylene glycol (see section 13.1.3)  
  **Dose** hypogonadism due to testosterone deficiency in men (over 18 years), initially 60 mg testosterone (3 g gel) applied once daily;  
  **Note** Testosterone transfer to other people, especially pregnant women and children—consult product literature
Cyproterone acetate

Anti-androgens

Cyproterone acetate

Dose

Side-effects

Contra-indications

Indications

Cautions

Applying gel on clean, dry, intact skin of abdomen or both inner thighs, preferably in the morning. Gently rub in with a finger until dry before dressing. Wash hands with soap and water after applying gel; avoid washing application site for at least 2 hours. Not to be applied on genital area. Avoid skin contact with gel application sites to prevent testosterone transfer to other people, especially pregnant women and children—consult product literature.

MESTEROLONE

Indications see under Dose

Cautions see under Testosterone and Esters

Contra-indications see under Testosterone and Esters

Side-effects see under Testosterone and Esters but spermatogenesis unimpaired

Dose

Androgen deficiency and male infertility associated with hypogonadism, 25 mg 3–4 times daily for several months, reduced to 50–75 mg daily in divided doses for maintenance; CHILD not recommended

Pro-Viron® (Schering Health)

Tablets, scored, mesterolone 25 mg. Net price 30-tab pack = £4.44

Anti-androgens

Cyproterone acetate

Cyproterone acetate is an anti-androgen used in the treatment of severe hypersexuality and sexual deviation in the male. It inhibits spermatogenesis and produces reversible infertility (but is not a male contraceptive); abnormal sperm forms are produced. Fully informed consent is recommended and an initial spermatogram. As hepatic tumours have been produced in animal studies, careful consideration should be given to the risk/benefit ratio before treatment. Cyproterone acetate is also used as an adjunct in prostatic cancer (section 8.3.4.2) and in the treatment of acne and hirsutism in women (section 13.6.2).

CYPROTERONE ACETATE

Indications see notes above; prostate cancer (section 8.3.4.2)

Cautions ineffective for male hypersexuality in chronic alcoholism (relevance to prostate cancer not known); blood counts initially and throughout treatment; monitor hepatic function regularly (liver function tests should be performed before treatment, see also under Side-effects below); monitor adrenocortical function regularly; diabetes mellitus (see also Contra-indications)

Driving Fatigue and lassitude may impair performance of skilled tasks (e.g. driving)

Contra-indications do not apply in prostate cancer hepatic disease (Appendix 2), severe diabetes (with vascular changes); sickle-cell anaemia, malignant or wasting disease, severe depression, history of thrombo-embolic disorders; youths under 18 years (may arrest bone maturation and testicular development)

Side-effects fatigue and lassitude, breathlessness, weight changes, reduced sebum production (may clear acne), changes in hair pattern, gynaecomastia (rarely leading to galactorrhoea and benign breast nodules); rarely hypersensitivity reactions, rash and osteoporosis; inhibition of spermatogenesis (see notes above); hepatotoxicity reported (including jaundice, hepatitis and hepatic failure usually in men given 200–300 mg daily for prostatic cancer, see section 8.3.4.2 for details and warnings)

Dose

Male hypersexuality, 50 mg twice daily after food

Cyproterone Acetate (Non-proprietary)

Tablets, cyproterone acetate 50 mg. net price 56-tab pack = £31.54. Label: 21 counselling, driving

Androcur® (Schering Health)

Tablets, scored, cyproterone acetate 50 mg. Net price 56-tab pack = £25.89. Label: 21 counselling, driving

Dutasteride and finasteride

Dutasteride and finasteride are specific inhibitors of the enzyme 5α-reductase, which metabolises testosterone into the more potent androgen, dihydrotestosterone. This inhibition of testosterone metabolism leads to reduction in prostate size, with improvement in urinary flow rate and in obstructive symptoms. Dutasteride and finasteride are alternatives to alpha-blockers (section 7.4.1) particularly in men with a significantly enlarged prostate. Finasteride is also licensed for use with doxazosin in the management of benign prostatic hyperplasia.

A low strength of finasteride is licensed for treating male-pattern baldness in men (section 13.9).

Cautions Dutasteride and finasteride decrease serum concentration of prostate cancer markers such as prostate-specific antigen; reference values may need adjustment. Both dutasteride and finasteride are excreted in semen and use of a condom is recommended if sexual partner is pregnant or likely to become pregnant. Women of childbearing potential should avoid handling crushed or broken tablets of finasteride and leaking capsules of dutasteride.

Contra-indications Dutasteride and finasteride are contra-indicated in women, children, and adolescents.

Side-effects The side-effects of dutasteride and finasteride include impotence, decreased libido, ejaculation disorders, and breast tenderness and enlargement.

DUTASTERIDE

Indications benign prostatic hyperplasia

Cautions see notes above; interactions: Appendix 1 (dutasteride)

Contra-indications see notes above; also severe hepatic impairment

Side-effects see notes above

Dose

500 micrograms daily (may require 6 months’ treatment before benefit is obtained)

Avodart® (GSK)

Capsules, yellow, dutasteride 500 micrograms, net price 30-cap pack = £24.81. Label: 25
6.4.3 Anabolic steroids

Anabolic steroids have some androgenic activity but they cause less virilisation than androgens in women. They are used in the treatment of some aplastic anaemias (section 9.1.3). Anabolic steroids have been given for osteoporosis in women but they are no longer advocated for this purpose.

The protein-building properties of anabolic steroids have not proved beneficial in the clinical setting. Their use as body builders or tonics is quite unjustified; some athletes abuse them.

NANDROLONE

Indications osteoporosis in postmenopausal women (but not recommended, see notes above); aplastic anaemia (section 9.1.3)

Cautions cardiac and renal impairment, hepatic impairment (Appendix 2), hypertension, diabetes mellitus, epilepsy, migraine; monitor skeletal maturation in young patients; skeletal metastases (risk of hypercalcaemia); interactions: Appendix 1 (anabolic steroids)

Contra-indications severe hepatic impairment, prostate cancer, male breast cancer, pregnancy (Appendix 4) and breast-feeding, alcohol dependence, susceptibility to radiation, hepatoma, breast carcinoma

Side-effects acne, sodium retention with oedema, virilisation with high doses including voice changes (sometimes irreversible), amenorrhoea, inhibition of spermatogenesis, premature epiphyseal closure; abnormal liver-function tests reported with high doses; liver tumours reported occasionally on prolonged treatment with anabolic steroids

Dose

See below

Deca-Durabolin® (Organon) (oil) Injection (oily), nandrolone decanoate 50 mg/mL, net price 1-mL amp = £3.29

Exipients include arachis (peanut) oil, benzyl alcohol (see Excipients, p. 2)

Dose by deep intramuscular injection, 50 mg every 3 weeks

6.5 Hypothalamic and pituitary hormones and anti-oestrogens

6.5.1 Hypothalamic and anterior pituitary hormones and anti-oestrogens

Anti-oestrogens

The anti-oestrogens clomifene (clomiphene) and tamoxifen (section 8.3.4.1) are used in the treatment of female infertility due to oligomenorrhoea or secondary amenorrhoea (e.g. associated with polycystic ovarian disease). They induce gonadotrophin release by occupying oestrogen receptors in the hypothalamus, thereby interfering with feedback mechanisms; chiorionic gonadotrophin is sometimes used as an adjunct. Patients should be warned that there is a risk of multiple pregnancy (rarely more than twins).

CLOMIFENE CITRATE

(Clamiphene Citrate)

Indications anovulatory infertility—see notes above

Cautions see notes above; polycystic ovary syndrome (cysts may enlarge during treatment), ovarian hyperstimulation syndrome, ectopic pregnancy, incidence of multiple births increased (consider ultrasound monitoring), visual symptoms (discontinue and initiate ophthalmological examination); breast-feeding (Appendix 5)

CSM Advice The CSM has recommended that clomifene should not normally be used for longer than 6 cycles (possibly increased risk of ovarian cancer)

Contra-indications hepatic disease (Appendix 2), ovarian cysts, hormone-dependent tumours or abnormal uterine bleeding of undetermined cause, pregnancy (exclude before treatment; Appendix 4)

Side-effects visual disturbances (withdraw), ovarian hyperstimulation (withdraw), hot flushes, abdominal discomfort, occasionally nausea, vomiting, depression, insomnia, breast tenderness, headache, intermenstrual spotting, minor and endometriosis, convulsions, weight gain, rashes, dizziness, hair loss

Dose

50 mg daily for 5 days, starting within about 5 days of onset of menstruation (preferably on 2nd day) or at any time (normally preceded by a progestogen-induced withdrawal bleed) if cycles have ceased;
second course of 100 mg daily for 5 days may be given in absence of ovulation; most patients who are going to respond will do so to first course; 3 courses should constitute adequate therapeutic trial; long-term cyclical therapy not recommended—see CSM advice, above

Clomifene (Non-proprietary) Tablets, clomifene citrate 50 mg, net price 30-tab pack = £11.35

Clomid® (Aventis Pharma) Tablets, yellow, scored, clomifene citrate 50 mg. Net price 30-tab pack = £8.80

Anterior pituitary hormones

Corticotrophins

Tetracosactide (tetracosactrin), an analogue of corticotropin (ACTH), is used to test adrenocortical function; failure of the plasma cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency. Both corticotropin and tetracosactide were formerly used as alternatives to corticosteroids in conditions such as Crohn’s disease or rheumatoid arthritis; their value was limited by the variable and unpredictable therapeutic response and by the waning of their effect with time.

TETRACOSACTIDE

(Tetracosactrin)

Indications see notes above

Cautions as for corticosteroids, section 6.3.2; important: risk of anaphylaxis (medical supervision; consult product literature); Interactions: Appendix 1 (corticosteroids)

Contra-indications as for corticosteroids, section 6.3.2; avoid injections containing benzyl alcohol in neonates (see under preparations)

Side-effects as for corticosteroids, section 6.3.2

Dose

• See under preparations below

Synacthen® (Alliance) Injection, tetracosactide 250 micrograms (as acetate)/mL. Net price 1-ml amp = £2.93

Dose diagnostic (30-minute test), by intramuscular or intra-venous injection, 250 micrograms as a single dose

Synacthen Depot® (Alliance) Injection (aqueous suspension), tetracosactide acetate 1 mg/mL, with zinc phosphate complex. Net price 1-ml amp = £4.18

Excipients include benzyl alcohol (avoid in neonates, see Excipients p. 2)

Dose diagnostic (5-hour test), by intramuscular injection, 1 mg as a single dose

Note Formerly used therapeutically by intramuscular injection, in an initial dose of 1 mg daily (or every 12 hours in acute cases), reduced to 1 mg every 2–3 days, then 1 mg weekly (or 500 micrograms every 2–3 days) but value was limited (see notes above)

Gonadotrophins

Follicle-stimulating hormone (FSH) and luteinising hormone (LH) together (as in human menopausal gonadotrophin), follicle-stimulating hormone alone (as in follicitropin), or choric gonadotrophin, are used in the treatment of infertility in women with proven hypopituitarism or who have not responded to clomifene, or in supernovulation treatment for assisted conception (such as in vitro fertilisation).

The gonadotrophins are also occasionally used in the treatment of hypogonadotropic hypogonadism and associated oligospermia. There is no justification for their use in primary gonadal failure.

Chorionic gonadotrophin has also been used in delayed puberty in the male to stimulate endogenous testosterone production, but has little advantage over testosterone (section 6.4.2).

CHORIONIC GONADOTROPIN

(Human Chorionic Gonadotrophin; HCG)

A preparation of a glycoprotein fraction secreted by the placenta and obtained from the urine of pregnant women having the action of the pituitary luteinising hormone

Indications see notes above

Cautions cardiac or renal impairment, asthma, epilepsy, migraine; prepubertal boys (risk of premature epiphyseal closure or precocious puberty)

Contra-indications androgen-dependent tumours

Side-effects oedema (particularly in males—reduce dose), headache, tiredness, mood changes, gynaecomastia, local reactions; may aggravate ovarian hyperstimulation, multiple pregnancy

Dose

• By subcutaneous or intramuscular injection, according to patient’s response

Choragon® (Ferring) Injection, powder for reconstitution, chorionic gonadotrophin. Net price 5000-unit amp (with solvent) = £3.26. For intramuscular injection

Pregnyl® (Organon) Injection, powder for reconstitution, chorionic gonadotrophin. Net price 1500-unit amp = £2.20; 5000-unit amp = £3.27 (both with solvent). For subcutaneous or intramuscular injection

CHORIOGONADOTROPIN ALFA

(Human chorionic gonadotropin)

Indications see notes above

Cautions rule out infertility caused by hypothyroidism, adrenocortical deficiency, hyperprolactinaemia, tumours of the pituitary or hypothalamus

Contra-indications ovarian enlargement or cyst (unless caused by polycystic ovarian disease); ectopic pregnancy in previous 3 months; active thromboembolic disorders; hypothyliamus, pituitary, ovarian, uterine or mammary malignancy

Side-effects nausea, vomiting, abdominal pain; headache, tiredness; injection-site reactions; ovarian hyperstimulation syndrome; rarely diarrhoea, depression, irritability, breast pain; ectopic pregnancy and ovarian torsion reported

Dose

• By subcutaneous injection, according to patient’s response

Ovitrelle® (Serono) Injection, choriogonadotropin alfa, net price 6500-unit/0.5 mL (250-micrograms/0.5 mL) prefilled syringe = £33.31
**FOLLITROPIN ALFA and BETA**

(Recombinant human follicle stimulating hormone)

**Indications**  see notes above

**Cautions**  see under Human Menopausal Gonadotrophins; acute porphyria (section 9.8.2)

**Contra-indications**  see under Human Menopausal Gonadotrophins

**Side-effects**  see under Human Menopausal Gonadotrophins

**Dose**

- **By subcutaneous or intramuscular injection,** according to patient’s response

---

**Follitropin alfa**

**Gonal-F®** (Serono)

Injection, powder for reconstitution, follitropin alfa. Net price 75-unit amp = £22.31; 450 units/0.75 mL multidose vial = £133.86; 1050 units/1.75 mL, multidose vial = £312.34 (all with solvent). For subcutaneous injection

Injection, prefilled pen, follitropin alfa 600 units/mL, net price 0.5 mL (300 units) = £97.08, 0.75 mL (450 units) = £145.62, 1.5 mL (900 units) = £291.24. For subcutaneous injection

**Follitropin alfa with lutropin alfa**

**Pergoveris®** (Serono)

Injection, powder for reconstitution, follitropin alfa 150 units (11 micrograms), lutropin alfa 75 units (3 micrograms), net price per vial (with solvent) = £60.29. For subcutaneous injection

**Electrolytes Na < 1 mmol/vial**

---

**Follitropin beta**

**Puregon®** (Organon)

Injection, follitropin beta 100 units/mL, net price 0.5-mL (50-unit) vial = £18.74; 200 units/mL, 0.5-mL (100-unit) vial = £37.48; 300 units/mL, 0.5-mL (150-unit) vial = £50.62; 400 units/mL, 0.5-mL (200-unit) vial = £67.49; 0.36-mL (300-unit) cartridge = £101.23, 0.72-mL (600-unit) cartridge = £202.47, 1.08-mL (900-unit) cartridge = £303.66. (cartridges for use with Puregon® pen). For subcutaneous (cartridges and vials) or intramuscular injection (vials)

**Excipients** may include neomycin and streptomycin

---

**HUMAN MENOPAUSAL GONADOTROPHINS**

**Indications**  see notes above

**Cautions**  rule out infertility caused by hypothyroidism, adrenocortical deficiency, hyperprolactinaemia, or tumours of the pituitary or hypothalamus

**Contra-indications**  ovarian cysts (not caused by polycystic ovarian disease); tumours of pituitary, hypothalamus, breast, uterus, ovaries, testes or prostate; undiagnosed vaginal bleeding; tumours of hypothalamus and pituitary; ovarian, uterine or mammary carcinoma

**Side-effects**  nausea, vomiting, abdominal and pelvic pain; headache, somnolence; injection-site reactions; ovarian hyperstimulation syndrome, ovarian cyst, breast pain, ectopic pregnancy; thromboembolism, adnexal torsion, and haemoperitoneum

**Dose**

- **By subcutaneous injection,** in conjunction with follicle-stimulating hormone, according to response

---

**LUTROPIN ALFA**

(Recombinant human luteinising hormone)

**Indications**  see notes above

**Cautions**  rule out infertility caused by hypothyroidism, adrenocortical deficiency, hyperprolactinaemia, or tumours of the pituitary or hypothalamus

**Contra-indications**  ovarian enlargement or cyst (unless caused by polycystic ovarian disease); undiagnosed vaginal bleeding; tumours of hypothalamus and pituitary; ovarian, uterine or mammary carcinoma

**Side-effects**  nausea, vomiting, abdominal and pelvic pain; headache, somnolence; injection-site reactions; ovarian hyperstimulation syndrome, ovarian cyst, breast pain, ectopic pregnancy; thromboembolism, adnexal torsion, and haemoperitoneum

**Dose**

- **By subcutaneous injection,** in conjunction with follicle-stimulating hormone, according to response

---

**Growth hormone**

Growth hormone is used to treat deficiency of the hormone in children and in adults (see NICE guidance below). In children it is used in Prader-Willi syndrome, Turner’s syndrome and in chronic renal insufficiency; growth hormone has also recently been licensed for use in short children considered small for gestational age at birth.
Growth hormone of human origin (HGH; somatropin) has been replaced by a growth hormone of human sequence, somatropin, produced using recombinant DNA technology.

### NICE guidance
**Somatropin in children with growth failure (May 2002)**

Treatment with somatropin is recommended for children with:
- proven growth-hormone deficiency;
- Turner’s syndrome;
- Prader-Willi syndrome;
- chronic renal insufficiency before puberty.

Treatment should be initiated and monitored by a paediatrician with expertise in managing growth-hormone disorders; treatment can be continued under a shared-care protocol by a general practitioner.

Treatment should be discontinued if the response is poor (i.e., an increase in growth velocity of less than 50% from baseline) in the first year of therapy. In children with chronic renal insufficiency, treatment should be stopped after renal transplantation and not restarted for at least a year.

**Somatropin for adults with growth hormone deficiency (August 2003)**

Somatropin is recommended in adults only if the following 3 criteria are fulfilled:
- Severe growth hormone deficiency, established by an appropriate method;
- Impaired quality of life, measured by means of a specific questionnaire;
- Already receiving treatment for another pituitary hormone deficiency.

Somatropin treatment should be discontinued if the quality of life has not improved sufficiently by 9 months. Severe growth hormone deficiency developing after linear growth is complete but before the age of 25 years should be treated with growth hormone; treatment should continue until adult peak bone mass has been achieved. Treatment for adult-onset growth hormone deficiency should be stopped only when the patient and the patient’s physician consider it appropriate.

Treatment with somatropin should be initiated and managed by a physician with expertise in growth hormone disorders; maintenance treatment can be prescribed in the community under a shared-care protocol.

**Mecasermin**, a human insulin-like growth factor-I (rIGF-I), is licensed to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency (section 6.7.4).

**SOMATROPIN**

**Synthetic Human Growth Hormone**

**Indications** see under Dose

**Cautions** diabetes mellitus (adjustment of antidiabetic therapy may be necessary), papilloedema (see under Side-effects), relative deficiencies of other pituitary hormones (notably hypothyroidism)—manufacturers recommend periodic thyroid function tests but limited evidence of clinical value), history of malignant disease, disorders of the ephipysis of the hip (monitor for limping), resolved intracranial hypertension (monitor closely), initiation of treatment close to puberty not recommended in child born small for gestational age; Silver-Russell syndrome; rotate subcutaneous injection sites to prevent lipoatrophy; breast-feeding (Appendix 5); **Interactions**: Appendix 1 (somatropin)

**Contra-indications** evidence of tumour activity (complete antitumour therapy and ensure intracranial lesions inactive before starting); not to be used after renal transplantation or for growth promotion in children with closed ephiphyses (or near closure in Prader-Willi syndrome); severe obesity or severe respiratory impairment in Prader-Willi syndrome; pregnancy (interrupt treatment if pregnancy occurs, Appendix 4)

**Side-effects** headache, fundoscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported); fluid retention (peripheral oedema), arthralgia, myalgia, carpal tunnel syndrome, paraesthesia, antibody formation, hypothyroidism, insulin resistance, hyperglycaemia, hypoglycaemia, reactions at injection site; leukaemia in children with growth hormone deficiency also reported

**Dose**
- Gonadal dysgenesis (Turner’s syndrome), by subcutaneous injection, 45–50 micrograms/kg daily or 1.4 mg/m daily
- Deficiency of growth hormone in children, by subcutaneous or intramuscular injection, 23–39 micrograms/kg daily or 0.7–1 mg/m daily
- Growth disturbance in short children born small for gestational age whose growth has not caught up by 4 years or later, by subcutaneous injection, 35 micrograms/kg daily or 1 mg/m daily
- Prader-Willi syndrome, by subcutaneous injection in children with growth velocity greater than 1 cm/year, in combination with energy-restricted diet, 35 micrograms/kg daily or 1 mg/m daily; max. 2.7 mg daily
- Chronic renal insufficiency in children (renal function decreased to less than 50%), by subcutaneous injection, 45–50 micrograms/kg daily or 1.4 mg/m daily (higher doses may be needed) adjusted if necessary after 6 months
- Adult growth hormone deficiency, by subcutaneous injection, initially 150–300 micrograms daily, gradually increased if required to max. 1 mg daily; use minimum effective dose (requirements may decrease with age)

**Note** Dose formerly expressed in units; somatropin 1 mg = 3 units

**Genotropin® (Pharmacia)**

**Injection**, two-compartment cartridge containing powder for reconstitution, somatropin (rbe) and diluent, net price 5.3-mg (16-unit) cartridge = £1122.87, 12-mg (36-unit) cartridge = £278.20. For use with Genotropin® Pen® device (available free of charge from clinics). For subcutaneous injection

**MiniQuick injection**, two-compartment single-dose syringe containing powder for reconstitution, somatropin (rbe) and diluent, net price 0.2-mg (0.6-unit)

**Genotropin®** (Pharmacia) **Pen®**
BNF 57 6.5.1 Hypothalamic and anterior pituitary hormones and anti-oestrogens

syringe = £4.64; 0.4-mg (1.2-unit) syringe = £9.27; 0.6-mg (1.8-unit) syringe = £13.91; 0.8-mg (2.4-unit) syringe = £18.55; 1-mg (3-unit) syringe = £23.18; 1.2-mg (3.6-unit) syringe = £27.82; 1.4-mg (4.2-unit) syringe = £32.46; 1.6-mg (4.8-unit) syringe = £37.09; 1.8-mg (5.4-unit) syringe = £41.73; 2-mg (6-unit) syringe = £46.37. For subcutaneous injection

Humatrope® (Lilly) (BNF

Injection, powder for reconstitution, somatropin (rbe), net price 6-mg (18-unit) cartridge = £137.25; 12-mg (36-unit) cartridge = £274.50; 24-mg (72-unit) cartridge = £549.00; all supplied with diluent. For subcutaneous or intramuscular injection; cartridges for subcutaneous injection

Norditropin® (Novo Nordisk) (BNF

SimplexXx injection, somatropin (epr) 3.3 mg (10 units)/mL, net price 1.5-mL (5-mg, 15-unit) cartridge = £115.90; 6.7 mg (20 units)/mL, 1.5-mL (10-mg, 30-unit) cartridge = £231.80; 10 mg (30 units)/mL, 1.5-mL (15-mg, 45-unit) cartridge = £347.70. For use with appropriate NordiPen® (Ferring) device (available free of charge from clinics). For subcutaneous injection

NutropinAQ® (Ipsen) (BNF

Injection, somatropin (rbe), net price 10 mg (30 units) 2-ml cartridge = £230.00. For use with NutropinAQ® Pen (Serono) device (available free of charge from clinics). For subcutaneous injection

Omnitrope® (Sandoz) ▼ (BNF

Injection, powder for reconstitution, somatropin (rbe), net price 5-mg (15-unit) vial (with diluent) = £91.33. For use with Omnitrope Pen L (Novo Nordisk) and Omnitrope Pen (Novo Nordisk) 10 (Serono) devices respectively. For subcutaneous injection

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p 2)

Note: Biosimilar medicine, see p. 1

Saizen® (Serono) (BNF

Injection, powder for reconstitution, somatropin (rnc), net price 1.33-mg (4-unit) vial (with diluent) = £29.28; 3.33-mg (10-unit) vial (with diluent) = £73.20. For subcutaneous or intramuscular injection

Click.easy®, powder for reconstitution, somatropin (rnc), net price 8-mg (24-unit) vial (in Click.easy® device with diluent) = £185.44. For use with One.click® (Ferring) autoinjector device or Cool.Click® (Sandoz) needle-free device (both available free of charge from clinics). For subcutaneous injection

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p 2)

Zomacton® (Ferring) (BNF

Injection, powder for reconstitution, somatropin (rbe), net price 4-mg (12-unit) vial (with diluent) = £81.32. For use with ZomaJet® 2 (Ferring) needle-free device or with Auto-Jector® (Ferring) (both available free of charge from clinics) or with needles and syringes. For subcutaneous injection

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p 2)

PEGVISOMANT

Indications see notes above

Caution liver disease (monitor liver enzymes every 4–6 weeks for 6 months or if symptoms of hepatitis develop); diabetes mellitus (adjustment of antidiabetic therapy may be necessary); possible increase in female fertility

Contra-indications pregnancy and breast-feeding

Side-effects diarrhea, constipation, nausea, vomiting, abdominal distension, dyspepsia, flatulence, elevated liver enzymes; hypertension; headache, asthenia, dizziness, drowsiness, tremor, sleep disturbances; influenza-like syndrome, weight gain, hyperglycaemia, hypoglycaemia; arthralgia, myalgia; injection-site reactions, sweating, pruritus, rash; fatigue; hypercholesterolaemia; less commonly thrombocytopenia, leucopenia, leucocytosis, bleeding tendency

Dose

• By subcutaneous injection, initially 80 mg, then 10 mg daily, increased in steps of 5 mg daily according to response; max. 30 mg daily; CHILD not recommended

Somavert® (Pfizer) ▼ (BNF

Injection, powder for reconstitution, pegvisomant, net price 10-mg vial = £50.00; 15-mg vial = £75.00; 20-mg vial = £100.00 (all with solvent)

Thyrotrophin

Thyrotrophin alfa is a recombinant form of thyrotrophin (thyroid stimulating hormone). It is licensed for use with or without radiodiode imaging, together with serum thyroglobulin testing, for the detection of thyroid remnants and thyroid cancer in post-thyroidectomy patients. It is also licensed to increase radioiodine uptake for the ablation of thyroid remnant tissue in suitable post-thyroidectomy patients.

THYROTROPIN ALFA

(Recombinant human thyroid stimulating hormone, rhTSH)

Indications see notes above and product literature

Caution presence of thyroglobulin autoantibodies may give false negative results

Contra-indications hypersensitivity to bovine or human thyrotrophin; pregnancy; breast-feeding

Side-effects nausea, vomiting; headache, dizziness, fatigue; less commonly asthenia, paraesthesia, back pain, influenza-like symptoms, rash, urticaria; rarely diarrhoea; very rarely palpitation, flushing, dyspnoea, pain at site of metastases, tremor, arthralgia, myalgia,
6 Endocrine system

Protirelin
By intravenous injection.

Dose
- By intramuscular injection into the gluteal muscle, 900 micrograms every 24 hours for 2 doses, consult product literature

Thyrogen® (Genzyme) (hosp.
Injection, powder for reconstitution, thyrotropin alfa 900 micrograms/vial, net price = £232.50

Hypothalamic hormones

Gonadorelin when injected intravenously in normal subjects leads to a rapid rise in plasma concentrations of both luteinising hormone (LH) and follicle-stimulating hormone (FSH). It has not proved to be very helpful, however, in distinguishing hypothalamic from pituitary lesions. Gonadorelin analogues are indicated in endometriosis and infertility (section 6.7.2) and in breast and prostate cancer (section 8.3.4).

Protirelin is a hypothalamic releasing hormone which stimulates the release of thyrotrophin from the pituitary. It is licensed for the diagnosis of mild hyperthyroidism or hypothyroidism, but its use has been superseded by immunoassays for thyroid-stimulating hormone.

GONADORELIN
(Gonadotrophin-releasing hormone; GnRH; LH–RH)

Indications see preparations below
Cautions pituitary adenoma
Side-effects rarely, nausea, headache, abdominal pain, increased menstrual bleeding; rarely, hypersensitivity reaction on repeated administration of large doses; irritation at injection site
Dose
- See under preparations

HRF® (Intrapharm) (hosp.
Injection, powder for reconstitution, gonadorelin. Net price 100-microgram vial (with diluent) = £13.72 (hosp. only)
Excipients include benzyl alcohol (avoid in neonates, see Excipients p. 2)
Dose for assessment of pituitary function (adults), by subcutaneous or intravenous injection, 100 micrograms

PROTIRELIN
(Thyrotrophin-releasing hormone; TRH)

Indications assessment of thyroid function and thyroid stimulating hormone reserve
Cautions severe hypopituitarism, myocardial ischaemia, bronchial asthma and obstructive airways disease, pregnancy, breast-feeding (Appendix 5)
Side-effects after rapid intravenous administration desire to micturate, flushing, dizziness, nausea, strange taste; transient increase in pulse rate and blood pressure; rarely bronchospasm
Dose
- By intravenous injection, 200 micrograms; CHILD under 12 years 1 microgram/kg
Protirelin (Cambridge) (hosp.
Injection, protirelin 100 micrograms/mL. Net price 2-ml amp = £14.43

Posterior pituitary hormones and antagonists

Diabetes insipidus Vasopressin (antidiuretic hormone, ADH) is used in the treatment of pituitary (‘cranial’) diabetes insipidus as is its analogue desmopressin. Dosage is tailored to produce a slight diuresis every 24 hours to avoid water intoxication. Treatment may be required for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus. Following a dose of 2 micrograms intramuscularly or 20 micrograms intranasally, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of cranial diabetes insipidus. Failure to respond occurs in nephrogenic diabetes insipidus.

In nephrogenic and partial pituitary diabetes insipidus benefit may be gained from the paradoxical antidiuretic effect of thiazides (section 2.2.1) e.g. chlorothalidone 100 mg twice daily reduced to maintenance dose of 50 mg daily.

Chlorpropamide (section 6.1.2.1) is also useful in partial pituitary diabetes insipidus, and probably acts by sensitising the renal tubules to the action of remaining endogenous vasopressin; it is given in doses of up to 350 mg daily in adults and 200 mg daily in children, care being taken to avoid hypoglycaemia. Carbamazepine (section 4.8.1) is also sometimes useful (in a dose of 200 mg once or twice daily) [unlicensed]; its mode of action may be similar to that of chlorpropamide.

Other uses Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand’s disease; it is also used to test fibrinolytic response. For a comment on use of desmopressin in nocturnal enuresis see section 7.4.2.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, prior to more definitive treatment and with variable results. Terlipressin, a derivative of vasopressin, is used similarly.

Oxytocin, another posterior pituitary hormone, is indicated in obstetrics (section 7.1.1).

VASOPRESSIN

Indications pituitary diabetes insipidus; bleeding from oesophageal varices
Cautions heart failure, hypertension, asthma, epilepsy, migraine or other conditions which might be aggra-

6.5.2 Posterior pituitary hormones and antagonists

Diabetes insipidus Vasopressin (antidiuretic hormone, ADH) is used in the treatment of pituitary (‘cranial’) diabetes insipidus as is its analogue desmopressin. Dosage is tailored to produce a slight diuresis every 24 hours to avoid water intoxication. Treatment may be required for a limited period only in diabetes insipidus following trauma or pituitary surgery.

Desmopressin is more potent and has a longer duration of action than vasopressin; unlike vasopressin it has no vasoconstrictor effect. It is given by mouth or intranasally for maintenance therapy, and by injection in the postoperative period or in unconscious patients. Desmopressin is also used in the differential diagnosis of diabetes insipidus. Following a dose of 2 micrograms intramuscularly or 20 micrograms intranasally, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of cranial diabetes insipidus. Failure to respond occurs in nephrogenic diabetes insipidus.

In nephrogenic and partial pituitary diabetes insipidus benefit may be gained from the paradoxical antidiuretic effect of thiazides (section 2.2.1) e.g. chlorothalidone 100 mg twice daily reduced to maintenance dose of 50 mg daily.

Chlorpropamide (section 6.1.2.1) is also useful in partial pituitary diabetes insipidus, and probably acts by sensitising the renal tubules to the action of remaining endogenous vasopressin; it is given in doses of up to 350 mg daily in adults and 200 mg daily in children, care being taken to avoid hypoglycaemia. Carbamazepine (section 4.8.1) is also sometimes useful (in a dose of 200 mg once or twice daily) [unlicensed]; its mode of action may be similar to that of chlorpropamide.

Other uses Desmopressin is also used to boost factor VIII concentration in mild to moderate haemophilia and in von Willebrand’s disease; it is also used to test fibrinolytic response. For a comment on use of desmopressin in nocturnal enuresis see section 7.4.2.

Vasopressin infusion is used to control variceal bleeding in portal hypertension, prior to more definitive treatment and with variable results. Terlipressin, a derivative of vasopressin, is used similarly.

Oxytocin, another posterior pituitary hormone, is indicated in obstetrics (section 7.1.1).
vated by water retention; renal impairment (see also Contra-indications); pregnancy (Appendix 4); avoid fluid overload

**Contra-indications** vascular disease (especially disease of coronary arteries) unless extreme caution, chronic nephritis (until reasonable blood nitrogen concentrations attained)

**Side-effects** fluid retention, pallor, tremor, sweating, vertigo, headache, nausea, vomiting, belching, abdominal cramps, desire to defaecate, hypersensitivity reactions (including anaphylaxis), constriction of coronary arteries (may cause anginal attacks and myocardial ischaemia), peripheral ischaemia and rarely gangrene

**Dose**
- **By subcutaneous or intramuscular injection**, diabetes insipidus, 5–20 units every four hours
- **By intravenous infusion**, initial control of variceal bleeding, 20 units over 15 minutes

**Synthetic vasopressin**

**Pitressin**<sup>(Goldshield)</sup> \( \text{AM} \)

Injection, argipressin (synthetic vasopressin)

20 units/mL. Net price 1-mL amp = £17.14 (hosp. only)

**DESMOPRESSIN**

**Indications** see under Dose

**Cautions** see under Vasopressin; less pressor activity, but still considerable caution in renal impairment (Appendix 3), in cardiovascular disease and in hypertension (not indicated for nocturnal enuresis or nocturia in these circumstances); elderly (avoid for nocturnal enuresis and nocturia in those over 65 years); also considerable caution in cystic fibrosis; in nocturia and nocturnal enuresis limit fluid intake to minimum from 1 hour before dose until 8 hours afterwards; in nocturia periodic blood pressure and weight checks needed to monitor for fluid overload; pregnancy (Appendix 4) interactions: Appendix 1 (desmopressin)

**Hyponatraemic convulsions** The CSM has advised that patients being treated for primary nocturnal enuresis should be warned to avoid fluid overload (including during swimming) and to stop taking desmopressin during an episode of vomiting or diarrhoea (until fluid balance normal). The risk of hyponatraemic convulsions can also be minimised by keeping to the recommended starting doses and by avoiding concomitant use of drugs which increase secretion of vasopressin (e.g. tricyclic antidepressants)

**Contra-indications** cardiac insufficiency and other conditions treated with diuretics; psychogenic polydipsia and polydipsia in alcohol dependence

**Side-effects** fluid retention, and hyponatraemia (in more serious cases with convulsions) on administration without restricting fluid intake; stomach pain, headache, nausea, vomiting, allergic reactions, and emotional disturbance in children also reported; epistaxis, nasal congestion, rhinitis with nasal spray

**Dose**
- **By mouth** (as desmopressin acetate)
  - Diabetes insipidus, treatment, \textit{ADULT} and \textit{CHILD} initially 300 micrograms daily (in 3 divided doses); maintenance, 300–600 micrograms daily in 3 divided doses; range 0.2–1.2 mg daily
  - Primary nocturnal enuresis (if urine concentrating ability normal), \textit{ADULT} (under 65 years) and \textit{CHILD} over 5 years (preferably over 7 years) 200 micrograms at bedtime, only increased to 400 micrograms if lower dose not effective (\textbf{important}: see also Cautions); withdraw for at least 1 week for reassessment after 3 months
  - Postoperative polyuria or polydipsia, adjust dose according to urine osmolality
    - **Sublingually** (as desmopressin base)
      - Diabetes insipidus, treatment, \textit{ADULT} and \textit{CHILD} initially 180 micrograms daily in 3 divided doses; range 120–720 micrograms daily
      - Polyuria or polydipsia after hypophysectomy, adjust dose according to urine osmolality
    - **Intranasally** (as desmopressin acetate)
      - Diabetes insipidus, diagnosis, \textit{ADULT} and \textit{CHILD} 20 micrograms (limit fluid intake to 500 mL from 1 hour before to 8 hours after administration)
      - Diabetes insipidus, treatment, \textit{ADULT} 10–40 micrograms daily (in 1–2 divided doses); \textit{CHILD} 5–20 micrograms daily; infants may require lower doses
      - Nocturia associated with multiple sclerosis (when other treatments have failed), \textit{ADULT} (under 65 years) 10–20 micrograms at bedtime (\textbf{important}: see also Cautions), dose not to be repeated within 24 hours
      - Renal function testing (empty bladder at time of administration and limit fluid intake to 500 mL from 1 hour before until 8 hours after administration), \textit{ADULT} 40 micrograms; \textit{INFANT} under 1 year 10 micrograms (restrict fluid intake to 50% at next 2 feeds to avoid fluid overload), \textit{CHILD} 1–15 years 20 micrograms
      - Mild to moderate haemophilia and von Willebrand’s disease, \textit{ADULT} 300 micrograms (one 150-microgram spray into each nostril) 30 minutes before surgery or when bleeding; may be repeated at intervals of 12 hours (or at intervals of at least 3 days if self-administered)
      - Fibrinolytic response testing, \textit{ADULT} 300 micrograms (one 150-microgram spray into each nostril); blood sampled after 1 hour for fibrinolytic activity
      - **By injection** (as desmopressin acetate)
        - Diabetes insipidus, diagnosis (subcutaneous or intramuscular), \textit{ADULT} and \textit{CHILD} 2 micrograms (limit fluid intake to 500 mL from 1 hour before to 8 hours after administration)
        - Diabetes insipidus, treatment (subcutaneous, intramuscular or intravenous), \textit{ADULT} 1–4 micrograms daily; \textit{INFANT} and \textit{CHILD} 400 nanograms
        - Renal function testing (empty bladder at time of administration and limit fluid intake to 500 mL from 1 hour before until 8 hours after administration) (subcutaneous or intramuscular), \textit{ADULT} and \textit{CHILD} 2 micrograms; \textit{INFANT} 400 nanograms (restrict fluid intake to 50% at next 2 feeds)
        - Mild to moderate haemophilia and von Willebrand’s disease, \textit{subcutaneous or intravenous}, \textit{ADULT} and \textit{CHILD} over 1 month 300 nanograms/kg as a single dose immediately before surgery or after trauma; may be repeated at intervals of 12 hours
        - Fibrinolytic response testing, (subcutaneous or intravenous), \textit{ADULT} and \textit{CHILD} 300 nanograms/kg; blood sampled after 20 minutes for fibrinolytic activity
        - Lumbar-puncture-associated headache, consult product literature
Desmopressin acetate (Non-proprietary) (Ferring)
Nasal spray, desmopressin acetate 10 micrograms/ metered spray, net price 6-mL unit (60 metered sprays) = £27.04. Counselling, fluid intake, see above
Brands include Presepinex
Note Children requiring dose of less than 10 micrograms should be given DDAVP intranasal solution

DDAVP® (Ferring) (Ferring)
Tablets, both scored, desmopressin acetate 100 micrograms, net price 90-tab pack = £45.48; 200 micrograms, 90-tab pack = £90.96. Counselling, fluid intake, see above
Sublingual tablets (DDAVP® Melt), desmopressin (as acetate) 60 micrograms, net price 100-tab pack = £50.53; 120 micrograms, 100-tab pack = £101.07; 240 micrograms, 100-tab pack = £202.14. Label: 26, counselling, fluid intake, see above
Intranasal solution, desmopressin acetate 100 micrograms/mL. Net price 2.5-mL dropper bottle and catheter = £9.72. Counselling, fluid intake, see above
Injection, desmopressin acetate 4 micrograms/mL. Net price 1-mL amp = £1.10

Desmotabs® (Ferring) (Ferring)
Tablets, scored, desmopressin acetate 200 micrograms, net price 30-tab pack = £30.34. Counselling, fluid intake, see above

DesmoMelt® (Ferring) (Ferring)
Sublingual tablets, desmopressin (as acetate) 120 micrograms, net price 30-tab pack = £30.34; 240 micrograms, 30-tab pack = £60.68. Label: 26, counselling, fluid intake, see above

Desmospray® (Ferring) (Ferring)
Nasal spray, desmopressin acetate 10 micrograms/ metered spray. Net price 6-mL unit (60 metered sprays) = £26.04. Counselling, fluid intake, see above
Note Children requiring dose of less than 10 micrograms should be given DDAVP intranasal solution

Octin® (Ferring) (Ferring)
Nasal spray, desmopressin acetate 150 micrograms/ metered spray, net price 2.5-mL unit (25 metered sprays) = £600.00. Counselling, fluid intake, see above
Injection, desmopressin acetate 15 micrograms/mL, net price 1-mL amp = £20.00

TERLIPRESSIN
Indications bleeding from oesophageal varices
Cautions see under Vasopressin
Contra-indications see under Vasopressin
Side-effects see under Vasopressin, but effects milder
Dose
• By intravenous injection, 2 mg followed by 1 or 2 mg every 4 to 6 hours until bleeding is controlled, for up to 72 hours

Glypressin® (Ferring) (Ferring)
Injection, terlipressin, powder for reconstitution. Net price 1-mg vial with 5 mL diluent = £19.44 (hosp. only)

Antidiuretic hormone antagonists
Demeclocycline (section 5.1.3) can be used in the treatment of hyponatraemia resulting from inappropriate secretion of antidiuretic hormone, if fluid restriction alone does not restore sodium concentration or is not tolerable. Demeclocycline is thought to act by directly blocking the renal tubular effect of antidiuretic hormone. Initially 0.9–1.2 g is given daily in divided doses, reduced to 600–900 mg daily for maintenance.

6.6 Drugs affecting bone metabolism

6.6.1 Calcitonin and parathyroid hormone

6.6.2 Bisphosphonates and other drugs affecting bone metabolism

See also calcium (section 9.5.1.1), phosphorus (section 9.5.2), vitamin D (section 9.6.4), and oestrogens in postmenopausal osteoporosis (section 6.4.1.1).

Osteoporosis
Osteoporosis occurs most commonly in postmenopausal women and in those taking long-term oral corticosteroids (glucocorticosteroids). Other risk factors for osteoporosis include low body weight, cigarette smoking, excess alcohol intake, lack of physical activity, family history of osteoporosis, and early menopause.

Those at risk of osteoporosis should maintain an adequate intake of calcium and vitamin D and any deficiency should be corrected by increasing dietary intake or taking supplements.

Elderly patients, especially those who are housebound or live in residential or nursing homes, are at increased risk of calcium and vitamin D deficiency and may benefit from supplements (section 9.5.1.1 and section 9.6.4). Reversible secondary causes of osteoporosis such as hyperthyroidism, hyperparathyroidism, osteomalacia or hypogonadism should be excluded, in both men and women, before treatment for osteoporosis is initiated.

Postmenopausal osteoporosis The bisphosphonates (alendronic acid, disodium etidronate, and risedronate, section 6.6.2) are effective for preventing postmenopausal osteoporosis. Hormone replacement therapy (HRT section 6.4.1.1) is an option where other therapies are contra-indicated, cannot be tolerated, or if there is a lack of response. The CSM has advised that HRT should not be considered first-line therapy for long-term prevention of osteoporosis in women over 50 years of age. HRT is of most benefit for the prophylaxis of postmenopausal osteoporosis if started early in menopause and continued for up to 5 years, but bone loss resumes (possibly at an accelerated rate) on stopping HRT. Calcitonin (section 6.6.1) may be considered for those at high risk of osteoporosis for whom a bisphosphonate is unsuitable. Women of Afro-Caribbean origin appear to be less susceptible to osteoporosis than those who are white or of Asian origin.
Postmenopausal osteoporosis may be treated with a bisphosphonate (section 6.6.2). The bisphosphonates (such as alendronate, etidronate, and risedronate) decrease the risk of vertebral fracture; alendronate and risedronate have also been shown to reduce non-vertebral fractures. If bisphosphonates are unsuitable calci-triol (section 9.6.4), calcitonin or strontium ranelate (section 6.6.2) may be considered. Calcitonin [unlicensed indication] may also be useful for pain relief for up to 3 months after a vertebral fracture if other analgesics are ineffective. Parathyroid hormone, and teriparatide (section 6.6.1) have been introduced for the treatment of postmenopausal osteoporosis.

Raloxifene (section 6.4.1.1) is licensed for the prophylaxis and treatment of vertebral fractures in postmeno-pausal women.

### NICE guidance

**Alendronate, etidronate, risedronate, raloxifene and strontium ranelate for the primary prevention of osteoporotic fragility fractures in postmenopausal women** (October 2008)

Alendronate is recommended as a treatment option for the primary prevention of osteoporotic fractures in the following susceptible postmenopausal women:

- Women over 70 years who have an independent risk factor for fracture (parental history of hip fracture, alcohol intake of 4 or more units per day, or rheumatoid arthritis) or an indicator of low bone mineral density (body mass index under 22 kg/m², ankylosing spondylitis, Crohn’s disease, prolonged immobility, untreated premature menopause, or rheumatoid arthritis) and confirmed osteoporosis
- Women aged 65–69 years who have an independent risk factor for fracture and confirmed osteoporosis
- Women under 65 years who have an independent risk factor for fracture and at least one additional indicator of low bone mineral density and confirmed osteoporosis

**Risedronate or etidronate** are recommended as alternatives for women:

- in whom alendronate is contra-indicated or not tolerated and
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance

**Strontium ranelate** or **raloxifene** are recommended as alternatives for women:

- in whom alendronate and either risedronate or etidronate are contra-indicated or not tolerated and
- who comply with particular combinations of bone mineral density measurement, age, and independent risk factors for fracture, as indicated in the full NICE guidance

**Teriparatide** is recommended as an alternative for women:

- in whom alendronate and either risedronate or etidronate are contra-indicated or not tolerated and
- who comply with particular combinations of bone mineral density measurement, age, and number of fractures, as indicated in the full NICE guidance

### Corticosteroid-induced osteoporosis

To reduce the risk of osteoporosis doses of oral corticosteroids should be as low as possible and courses of treatment as short as possible. The risk of osteoporosis may be related to cumulative dose of corticosteroids; even intermittent courses can therefore increase the risk. The greatest rate of bone loss occurs during the first 6–12 months of corticosteroid use and so early steps to prevent the development of osteoporosis are important. Long-term use of high-dose inhaled corticosteroids may also contribute to corticosteroid-induced osteoporosis (section 3.2).

Patients taking (or who are likely to take) an oral cortico-steroid for 3 months or longer should be assessed and where necessary given prophylactic treatment; those aged over 65 years are at greater risk. Patients taking oral corticosteroids who have sustained a low-trauma fracture should receive treatment for osteoporosis. The
therapeutic options for prophylaxis and treatment of corticosteroid-induced osteoporosis are the same:

- a bisphosphonate (section 6.6.2);
- calcitriol [unlicensed indication] (section 9.6.4);
- hormone replacement (HRT in women (section 6.4.1), testosterone in men [unlicensed indication] (section 6.4.2)).

### 6.6.1 Calcitonin and parathyroid hormone

Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homoeostasis. Calcitonin (salmon) (salcatonin, synthetic or recombinant salmon calcitonin) is used to lower the plasma-calcium concentration in some patients with hypercalcaemia (notably when associated with malignant disease). Calcitonin is licensed for treatment of Paget's disease of bone. It can also be used in the prevention and treatment of postmenopausal osteoporosis (see section 6.6).

Recombinant parathyroid hormone is used for the treatment of postmenopausal osteoporosis. Teriparatide (a recombinant fragment of parathyroid hormone) is used for the treatment of postmenopausal osteoporosis, osteoporosis in men at increased risk of fracture, and corticosteroid-induced osteoporosis. The Scottish Medicines Consortium, p. 3 has advised (February 2007) that parathyroid hormone (Preoact®) should be initiated by specialists experienced in the treatment of osteoporosis.

Cinacalcet (section 9.5.1.2) is licensed for the treatment of hypercalcaemia in parathyroid carcinoma.

### CALCITONIN (SALMON)/SALCATONIN

**Indications** see under Dose

**Cautions** history of allergy (skin test advised); renal impairment; heart failure; pregnancy (Appendix 4), breast-feeding (Appendix 5)

**Contra-indications** hypocalcaemia

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain; flushing; dizziness, headache, taste disturbances; musculoskeletal pain; with nasal spray nose and throat irritation, rhinitis, sinusitis and epistaxis; less commonly diuresis, oedema, cough, visual disturbances, injection-site reactions, rash, hypersensitivity reactions including pruritus

**Dose**

- Hypercalcaemia of malignancy (see also section 9.5.1.2), ADULT over 18 years, by subcutaneous or intramuscular injection, 100 units every 6–8 hours adjusted according to response; max. 400 units every 6–8 hours; in severe or emergency cases, by intravenous infusion, up to 10 units/kg over at least 6 hours
- Paget's disease of bone, ADULT over 18 years, by subcutaneous or intramuscular injection, 50 units 3 times weekly to 100 units daily adjusted according to response
- Postmenopausal osteoporosis to reduce risk of vertebral fractures, intranasally, 200 units (1 spray) into one nostril daily, with dietary calcium and vitamin D supplements (section 9.5.1.1 and section 9.6.4)
- Prevention of acute bone loss due to sudden immobility, ADULT over 18 years, by scubcutaneous or intramuscular injection, 100 units daily in 1–2 divided doses for 2–4 weeks, reduced to 50 units daily at start of mobilisation and continued until fully mobile

### PARATHYROID HORMONE

(Human recombinant parathyroid hormone)

**Indications** treatment of osteoporosis in postmenopausal women at high risk of fractures (to reduce the risk of vertebral fractures) (see also notes above)

**Cautions** monitor serum or urinary calcium concentration at 1, 3 and 6 months after initiation of treatment (consult product literature for guidance if serum calcium concentration raised); active or previous urolithiasis; concomitant cardiac glycosides; renal impairment (Appendix 3)

**Contra-indications** previous radiation therapy to skeleton, pre-existing hypercalcaemia, metabolic bone disease (including hyperparathyroidism and Paget's disease), unexplained raised levels of alkaline phosphatase; avoid in severe hepatic impairment; pregnancy; breast-feeding

**Side-effects** nausea, vomiting, dyspepsia, constipation, diarrhoea; palpitation; headache, dizziness, fatigue, asthenia; transient hypercalcaemia, hypercalciuria; muscle cramp, pain in extremities, back pain; injection-site reactions; less commonly abdominal pain, altered sense of smell, taste disturbance, anorexia, influenza, hyperuricaemia

**Dose**

- By subcutaneous injection, 100 micrograms daily, max. duration of treatment 24 months

**Preoact®** (Nycomed) ▼ (NVI)

**Injection**, dual-chamber cartridge containing powder for reconstitution, parathyroid hormone (rdna) and diluent, net price 1.61-mg (14-dose) cartridge = £130.20. For use with Preoact® pen device.

### TERIPARATIDE

**Indications** treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures; treatment of corticosteroid-induced osteoporosis; see also notes above

**Cautions** moderate renal impairment (avoid if severe)

**Contra-indications** pre-existing hypercalcaemia, skeletal malignancies or bone metastases, metabolic bone diseases, including Paget's disease and hyperparathyroidism, unexplained raised alkaline phosphatase, previous radiation therapy to the skeleton; pregnancy; breast-feeding

**Side-effects** gastro-intestinal disorders (including nausea, reflux and haemorrhoids); palpitation; dys-
Bisphosphonates

Bisphosphonates are adsorbed onto hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover. Bisphosphonates have an important role in the prophylaxis and treatment of osteoporosis and corticosteroid-induced osteoporosis; alendronic acid or risedronate sodium are considered the drugs of choice for these conditions, but disodium etidronate may be considered if these drugs are unsuitable or not tolerated (see also section 6.6).

Bisphosphonates are also used in the treatment of Paget’s disease, hypercalcaemia of malignancy (section 9.5.1.2), and in bone metastases in breast cancer (section 8.3.4.1). Disodium etidronate can impair bone mineralisation when used continuously or in high doses (such as in the treatment of Paget’s disease).

Osteonecrosis of the jaw Osteonecrosis of the jaw has been reported in patients receiving intravenous bisphosphonates and, rarely, in those taking oral bisphosphonates. Adequate oral hygiene should be maintained during and after treatment with bisphosphonates. Ideally in patients with concomitant risk factors (such as cancer, chemotherapy treatment, corticosteroid treatment, or poor oral hygiene), remedial dental work should be carried out before starting bisphosphonate treatment.

**ALENDRONIC ACID**

**Indications** see under Dose

**Cautions** upper gastro-intestinal disorders (dysphagia, symptomatic oesophageal disease, gastritis, duodenitis, or ulcers—see also under Contra-indications and Side-effects); history (within 1 year) of ulcers, active gastro-intestinal bleeding, or surgery of the upper gastro-intestinal tract; renal impairment (Appendix 3); correct disturbances of calcium and mineral metabolism (e.g. vitamin-D deficiency, hypocalcaemia) before starting and monitor serum-calcium concentration during treatment; consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); exclude other causes of osteoporosis; atypical stress fractures reported (discontinue unless benefits of continued treatment clearly outweigh risks); interactions: Appendix 1 (bisphosphonates)

**Contra-indications** abnormalities of oesophagus and other factors which delay emptying (e.g. stricture or achalasia), hypocalcaemia, pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** oesophageal reactions (see below), abdominal pain and distension, dyspepsia, regurgitation, melaena, diarrhoea or constipation, flatulence, musculoskeletal pain, headache; rarely rash, pruritus, erythema, photosensitivity, uveitis, scleritis, transient decrease in serum calcium and phosphate; nausea, vomiting, gastritis, peptic ulceration, hypersensitivity reactions (including urticaria and angioedema), and atypical stress fractures with long-term use also reported; myalgia, malaise, and fever at initiation of treatment; very rarely severe skin reactions (including Stevens-Johnson syndrome), osteonecrosis (see notes above)

**Oesophageal reactions** Severe oesophageal reactions (oesophagitis, oesophageal ulcers, oesophageal stricture and oesophageal erosions) have been reported; patients should be advised to stop taking the tablets and to seek medical attention if they develop symptoms of oesophageal irritation such as dysphagia, new or worsening heartburn, pain on swallowing or retrosternal pain

**Dose**

- Treatment of postmenopausal osteoporosis and osteoporosis in men, 10 mg daily or (in postmenopausal osteoporosis) 70 mg once weekly
- Prevention of postmenopausal osteoporosis, 5 mg daily
- Prevention and treatment of corticosteroid-induced osteoporosis, 5 mg daily (postmenopausal women not receiving hormone replacement therapy, 10 mg daily)

Counselling Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet

**Alendronic acid (Non-proprietary) Tablets, alendronic acid (as sodium alendronate)**

- 10 mg, net price 28-tab pack = £2.75. Counselling, administration

**Fosamax® (MSD) Tablets, alendronic acid (as sodium alendronate)**

- 10 mg, 28-tab pack = £23.12. Counselling, administration

**Alendronic Acid Once-Weekly (Non-proprietary) Tablets, alendronic acid (as sodium alendronate)**

- 70 mg, net price 4-tab pack = £3.66. Counselling, administration

**Fosamax® Once Weekly (MSD) Tablets, alendronic acid (as sodium alendronate)**

- 70 mg, net price 4-tab pack = £22.80. Counselling, administration

**With colecalciferol**

For caution, contra-indications, and side-effects of colecalciferol, see section 9.6.4

**Fosavance® (MSD)**

- 70 mg, colecalciferol 70 micrograms (2 800 units), net price 4-tab pack = £3.66. Counselling, administration

**Note** 3-ml prefilled pen intended for 28 doses

---

**Forsteo® (Lilly)**

- **Injection**, teriparatide 250 micrograms/mL, net price 3-mL prefilled pen = £271.88

---

BNF 57 6.6.2 Bisphosphonates and other drugs affecting bone metabolism 417
**6.6.2 Bisphosphonates and other drugs affecting bone metabolism**

**Didronel PMO**

Dose: treatment of postmenopausal osteoporosis in women at risk of vitamin D deficiency. 1 tablet once weekly.

Counselling: Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet.

**DISODIUM ETIDRONATE**

Indications: see under Dose.

Cautions: consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); renal impairment (avoid if creatinine clearance less than 20 mL/minute—Appendix 3); interactions: Appendix 1 (bisphosphonates).

Contra-indications: pregnancy (Appendix 4) and breast-feeding (Appendix 5); not indicated for osteoporosis in presence of hypercalcaemia or hypercalciuria or for osteomalacia.

Side-effects: nausea, diarrhoea or constipation, abdominal pain; increased bone pain in Paget’s disease, also increased risk of fractures with high doses in Paget’s disease (discontinue if fractures occur); rarely exacerbation of asthma, skin reactions (including angioedema, rash, urticaria and pruritus), transient hyperphosphataemia, headache, paraesthesia, peripheral neuropathy reported; blood disorders (including leucopenia, agranulocytosis and pancytopenia) also reported; very rarely osteonecrosis (see notes above).

Dose:

- Paget’s disease of bone, by mouth, 5 mg/kg as a single daily dose for up to 6 months; doses above 10 mg/kg daily for up to 3 months may be used with caution but doses above 20 mg/kg daily are not recommended; after interval of not less than 3 months may be repeated where evidence of reactivation—including biochemical indices (avoid premature retreatment).

Monitoring: Serum phosphate, serum alkaline phosphatase and (if possible) urinary hydroxyproline should be measured before starting and at intervals of 3 months—consult product literature for further details.

- Osteoporosis, see under Didronel PMO®

  Counselling: Avoid food for at least 2 hours before and after oral treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids.

Didronel® (Procter & Gamble Pharm.) Tablets, disodium etidronate 200 mg. Net price 60-tab pack = £20.68. Counselling, food and calcium (see above).

- With calcium carbonate

  For cautions and side-effects of calcium carbonate see section 9.5.1.1.

Didronel PMO® (Procter & Gamble Pharm.) Tablets, 14 white, disodium etidronate 400 mg; 76 pink, effervescent, calcium carbonate 1.25 g (Coact®). Net price per pack = £21.12. Label: 10, patient information leaflet, counselling, food and calcium (see above).

Dose: treatment of osteoporosis, prevention of bone loss in postmenopausal women (particularly if hormone replacement therapy inappropriate), and prevention and treatment of corticosteroid-induced osteoporosis, given in 90-day cycles. 1 Didronel tablet daily for 14 days, then 1 Coact tablet daily for 76 days.

**DISODIUM PAMIDRONATE**

Didronil pamidronate was formerly called aminoxypropyldenediphosphonate disodium (APD)

Indications: see under Dose.

Cautions: renal impairment (Appendix 3); assess renal function before each dose; ensure adequate hydration; hepatic impairment (Appendix 2); cardiac disease (especially in elderly); previous thyroid surgery (risk of hypocalcaemia); monitor serum electrolytes, calcium and phosphate—possibility of convulsions due to electrolyte changes; avoid concurrent use with other bisphosphonates; consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); interactions: Appendix 1 (bisphosphonates).

Driving: Patients should be warned against driving or operating machinery immediately after treatment (somnolence or dizziness can occur).

Contra-indications: pregnancy (Appendix 4); breast-feeding (Appendix 5).

Side-effects: hypophosphataemia, fever and influenza-like symptoms (sometimes accompanied by malaise, rigors, fatigue and flushes); nausea, vomiting, anorexia, abdominal pain, diarrhoea, constipation; symptomatic hypocalcaemia (paraesthesia, tetany), hypomagnesaemia, headache, insomnia, drowsiness; hypertension; anaemia, thrombocytopenia, lymphocytopenia; rash; arthralgia, myalgia, bone pain; rarely muscle cramps, dyspnoea, agitation, confusion, diziness, lethargy; leucopenia, hypotension, pruritus, hyperkalaemia or hypokalaemia, and hypernatraemia; osteonecrosis (see also notes above), isolated cases of seizures, hallucinations, haematuria, acute renal failure, deterioriation of renal disease, convulsions and other ocular symptoms; atrial fibrillation, and reactivation of herpes simplex and zoster also reported; also injection-site reactions.

Dose:

- By slow intravenous infusion (via cannula in a relatively large vein), see also Appendix 6

  Hypercalcaemia of malignancy, according to serum calcium concentration 15–60 mg in single infusion or in divided doses over 2–4 days; max. 90 mg per treatment course.

  Osteolytic lesions and bone pain in bone metastases associated with breast cancer or multiple myeloma, 90 mg every 4 weeks (or every 3 weeks to coincide with chemotherapy in breast cancer).

  Paget’s disease of bone, 30 mg once a week for 6 weeks (total dose 180 mg) or 30 mg in first week then 60 mg every other week (total dose 210 mg); max. total 360 mg (in divided doses of 60 mg) per treatment course; may be repeated every 6 months.

- CHILD not recommended.

Calcium and vitamin D supplements: Oral supplements are advised to minimise potential risk of hypocalcaemia for those with mainly lytic bone metastases or multiple myeloma at risk of calcium or vitamin D deficiency (e.g. through malabsorption or lack of exposure to sunlight) and in those with Paget’s disease.

Disodium pamidronate (Non-proprietary) Concentrate for intravenous infusion, disodium pamidronate 3 mg/mL, net price 5-mL vial = £27.50, 10-mL vial = £55.00; 6 mg/mL, 10-mL vial = £95.00; 9 mg/mL, 10-mL vial = £165.00.

Aredia Dry Powder® (Novantis) Injection, powder for reconstitution, disodium pamidronate, for use as an infusion. Net price 15-mg vial =
IBANDRONIC ACID

**Indications** see under Dose

**Cautions** consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); renal impairment (Appendix 3); monitor renal function and serum calcium, phosphate and magnesium; cardiac disease (avoid fluid overload); interactions: Appendix 1 (bisphosphonates)

**Contra-indications** pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Side-effects** hypocalcaemia, hypophosphataemia, influenza-like symptoms (including fever, chills, and muscle pain), bone pain; oesophageal reactions (see below), diarrhoea, nausea, vomiting, gastritis, abdominal pain, dyspepsia, pharyngitis; headache, asthenia, rash; rarely anaemia, hypersensitivity reactions (pruritus, bronchospasm and angioedema reported); urticaria; injection-site reactions; very rarely osteonecrosis (see notes above)

**Oesophageal reactions** Severe oesophageal reactions reported with all oral bisphosphonates; patients should be advised to stop tablets and seek medical attention for symptoms of oesophageal irritation such as dysphagia, pain on swallowing, retrosternal pain, or heartburn

**Dose**
- Reduction of bone damage in bone metastases in breast cancer, by mouth, 50 mg daily, or by intravenous infusion, 6 mg every 3–4 weeks
- Hypercalcaemia of malignancy by intravenous infusion, according to serum calcium concentration, 2–4 mg in single infusion
- Treatment of postmenopausal osteoporosis, by mouth, 150 mg once a month or by intravenous injection over 15–30 seconds, 3 mg every 3 months
- **CHILD** not recommended

**Counselling** Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk, also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising

**Bondronat** (Roche) ▼ (Procter & Gamble Pharm.)

- Tablets, f/c, ibandronic acid 50 mg, net price 28-tab pack = £195.00. Counselling, administration
- Concentrate for intravenous infusion, ibandronic acid 1 mg/mL, net price 2-ML amp = £94.86, 6-ML vial = £195.00

**Bonviva** (Roche) ▼ (Procter & Gamble Pharm.)

- Tablets, f/c, ibandronic acid 150 mg, net price 1-tab pack = £21.45, 3-tab pack = £64.35. Counselling, administration
- Injection, ibandronic acid 1 mg/mL, net price 3-ML prefilled syringe = £80.00

RISEDRONATE SODIUM

**Indications** see under Dose

**Cautions** oesophageal abnormalities and other factors which delay transit or emptying (e.g. stricture or achalasia—see also under Side-effects); renal impairment (Appendix 3); correct hypocalcaemia before starting, correct other disturbances of bone and mineral metabolism (e.g. vitamin-D deficiency) at onset of treatment; consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above).

**Interactions** Appendix 1 (bisphosphonates)

**Contra-indications** hypocalcaemia (see Cautions above), pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances (including abdominal pain, dyspepsia, nausea, diarrhoea, constipation); dizziness, headache; influenza-like symptoms, musculoskeletal pain; rarely oesophageal stricture, oesophagitis, oesophageal ulcer, dysphagia, gastritis, duodenitis, glossitis, peripheral oedema, weight loss, myasthenia, arthralgia, anæmia, bronchitis, sinusitis, rash, nocturia, amblyopia, corneal lesion, dry eye, tinnitus, iritis; very rarely hypersensitivity reactions including angioedema, osteonecrosis (see notes above)

**Dose**
- Paget’s disease of bone, 30 mg daily for 2 months; may be repeated if necessary after at least 2 months
- Treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, 5 mg daily or 35 mg once weekly
- Prevention of osteoporosis (including corticosteroid-induced osteoporosis) in postmenopausal women, 5 mg daily
- **CHILD** not recommended

**Counselling** Swallow tablets whole with full glass of water; on rising, take on an empty stomach at least 30 minutes before first food or drink of the day or, if taking at any other time of the day, avoid food and drink for at least 2 hours before or after risedronate (particularly avoid calcium-containing products e.g. milk, also avoid iron and mineral supplements and antacids); stand or sit upright for at least 30 minutes; do not take tablets at bedtime or before rising

**Actonel** (Procter & Gamble Pharm.)

- Tablets, f/c, risedronate sodium 5 mg (yellow), net price 28-tab pack = £19.10; 30 mg (white), 28-tab pack = £152.81. Counselling, administration, food and calcium (see above)

**Actonel Once a Week** (Procter & Gamble Pharm.)

- Tablets, f/c, risedronate sodium 35 mg (orange), net price 4-tab pack = £20.30. Counselling, administration, food and calcium (see above)

**With calcium carbonate and colecalciferol**

For cautions, contra-indications, and side-effects of calcium carbonate, see section 9.5.1.1 and of colecalciferol, see section 9.6.4

**Actonel® Combi** (Procter & Gamble Pharm.)

- Tablets, 4 orange, f/c, risedronate sodium 35 mg (Actonel Once a Week®).

**Granules**, 24 sachets, effervescent, lemon flavour, calcium carbonate 2.5 g (calcium 1 g or Ca 25 mmol) and colecalciferol 22 micrograms (880 units), net price per pack = £20.30. Counselling, administration, food and calcium (see above)

**Dose** treatment of postmenopausal osteoporosis to reduce risk of vertebral or hip fractures, given in weekly cycles, 1 Actonel Once a Week® tablet on the first day followed by 1 calcium and colecalciferol sachet daily for 6 days

**Counselling** Tablets should be swallowed whole with plenty of water while sitting or standing; to be taken on an empty stomach at least 30 minutes before breakfast (or another oral medicine); patient should stand or sit upright for at least 30 minutes after taking tablet. Granules should be stirred into a glass of water and after dissolution complete taken immediately
6.6.2 Bisphosphonates and other drugs affecting bone metabolism

**SODIUM CLODRONATE**

**Indications** see under Dose

**Cautions** monitor renal and hepatic function and white cell count; also monitor serum calcium and phosphate periodically; renal dysfunction reported in patients receiving concomitant NSAIDs; maintain adequate fluid intake during treatment; consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); interactions: Appendix 1 (bisphosphonates)

**Contra-indications** acute gastro-intestinal inflammatory conditions; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** nausea, diarrhoea; skin reactions; bronchospasm; very rarely osteonecrosis (see notes above)

**Dose**

- Osteolytic lesions, hypercalcaemia and bone pain associated with skeletal metastases in patients with breast cancer or multiple myeloma, by mouth, 1.6 g daily in single or 2 divided doses increased if necessary to a max. of 3.2 g daily
- Hypercalcaemia of malignancy, by slow intravenous infusion, 300 mg daily for max. 7–10 days or by single-dose infusion of 1.5 g

**Bonefos®** (Bayer)

Capsules, yellow, sodium clodronate 400 mg, net price 120-cap pack = £161.97. Counselling, food and calcium

Tablets, f/c, scored, sodium clodronate 800 mg, net price 60-tab pack = £169.62. Counselling, food and calcium

Concentrate (= intravenous solution), sodium clodronate 60 mg/mL, for dilution and use as infusion. Net price 5-mL amp = £12.82

**Clasteon®** (Beacon)

Capsules, blue/white, sodium clodronate 400 mg, net price 30-cap pack = £40.49, 120-cap pack = £161.97. Counselling, food and calcium

**Loron®** (Roche)

Loron 520 mg, f/c, scored, sodium clodronate 520 mg. Net price 60-tab pack = £161.99. Label: 10, patient information leaflet, counselling, food and calcium

**Dose** 2 tablets daily in single or two divided doses; may be increased to max. 4 tablets daily

**Side-effects** stomach pain, nausea, diarrhoea; rarely asthenia, dizziness, headache and skin reactions; very rarely osteonecrosis (see notes above)

**Dose**

- 400 mg daily as a single dose for 12 weeks; may be repeated if necessary after 6 months

**Counselling** Avoid food for 2 hours before and after treatment, particularly calcium-containing products e.g. milk; also avoid iron and mineral supplements and antacids; maintain adequate fluid intake

**TILUDRONIC ACID**

**Indications** Paget’s disease of bone

**Cautions** renal impairment (monitor renal function regularly, see under Contra-indications); correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting; avoid concomitant use of indomethacin; consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); interactions: Appendix 1 (bisphosphonates)

**Contra-indications** renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); juvenile Paget’s disease, pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** stomach pain, nausea, diarrhoea; rarely asthenia, dizziness, headache and skin reactions; very rarely osteonecrosis (see notes above)

**Dose**

- 400 mg daily as a single dose for 12 weeks; may be repeated if necessary after 6 months

**Counselling** Avoid food for 2 hours before and after treatment, particularly calcium-containing products e.g. milk; also avoid antacids

**Skelid®** (Sanofi-Synthelabo)

Tablets, tiludronic acid (as tiludronate disodium) 200 mg. Net price 28-tab pack = £99.00. Counselling, food and calcium

**ZOLEDRONIC ACID**

**Indications** see under Preparations

**Cautions** correct disturbances of calcium metabolism (e.g. vitamin D deficiency, hypocalcaemia) before starting; monitor serum electrolytes, calcium, phosphate and magnesium; assess renal function before each dose; ensure adequate hydration; renal impairment (Appendix 3); severe hepatic impairment (Appendix 2); cardiac disease (avoid fluid overload); consider preventive dental treatment before initiating bisphosphonate (risk of osteonecrosis of the jaw, see notes above); interactions: Appendix 1 (bisphosphonates)

**Contra-indications** pregnancy (Appendix 4), breast-feeding (Appendix 5)

**Side-effects** hypophosphataemia, anaemia, influenza-like symptoms including bone pain, myalgia, arthralgia, fever and rigors; gastro-intestinal disturbances; atrial fibrillation; headache, dizziness, conjunctivitis, renal impairment (rarely acute renal failure); less commonly anorexia, taste disturbance, dry mouth, stomatitis, chest pain, hypertension, hypotension, dyspnoea, cough, paraesthesia, tremor, anxiety, lethargy, sleep disturbance, blurred vision, weight gain, pruritus, rash, sweating, muscle cramps, haematuria, proteinuria, urinary frequency, hypersensitivity reactions (including angiooedema), asthenia, peripheral oedema, thrombocytopenia, leucopenia, hypomagnesaemia, hypokalaemia, also injection-site reactions; rarely bradycardia, confusion, hyperkalaemia, hypernatraemia, pancytopenia, osteonecrosis of the jaw (see also notes above); very rarely uveitis and episcleritis

**Dose**

- See under Preparations

**Aclasta®** (Novartis)

**Intravenous infusion**, zoledronic acid 50 micrograms/mL, net price 100-mL bottle = £283.74

**Dose** Treatment of Paget’s disease of bone, by intravenous infusion, 5 mg as a single dose over at least 15 minutes

**Note** At least 300 mg elemental calcium twice daily (with vitamin D, section 9.6.4) for at least 10 days is recommended following infusion

**Treatment of postmenopausal osteoporosis and osteoporosis in men, by intravenous infusion, 5 mg over at least 15 minutes once a year**

**Note** In patients with a recent low-trauma hip fracture, the dose should be given 2 or more weeks following hip fracture repair; before first infusion give 50 000–125 000 units of vitamin D (section 9.6.4)
Strontium ranelate

Strontium ranelate stimulates bone formation and reduces bone resorption. It is licensed for the treatment of postmenopausal osteoporosis. The Scottish Medicines Consortium has advised (July 2005) that strontium ranelate should be restricted to use when bisphosphonates are contra-indicated or not tolerated and then only in women aged over 75 years with a previous fracture and low bone mineral density or in other women at equivalent risk.

**Indications**
treatment of postmenopausal osteoporosis to reduce risk of vertebral and hip fractures

**Cautions**
predisposition to thromboembolism; interferes with colorimetric measurements of calcium in blood and urine; renal impairment (Appendix 3); interactions: Appendix 1 (strontium ranelate)

**Contra-indications**
pregnancy, breast-feeding

**Side-effects**
nausea, diarrhoea; venous thromboembolism; headache; dermatitis, eczema; very rarely vomiting, abdominal pain, stomatitis, and hypersensitivity reactions, including rash, pruritus, urticaria and angioedema—see Severe Allergic Reactions, below

**Dose**
- 2 g once daily in water, preferably at bedtime

**Counselling**
Avoid food for 2 hours before and after taking granules, particularly calcium-containing products e.g. milk; also preferably avoid concomitant antacids containing aluminium and magnesium hydroxides for 2 hours after taking granules

**Protelos** (Servier) ▼ (Yuk)
Granules, yellow, strontium ranelate, 2 g/sachet, net price 28-sachets = £25.60. Label: 5, 13, counselling, food and calcium

**Excipients** include aspartame (section 9.4.1)
Bromocriptine and cabergoline have been associated with pleuritis, pleural effusion, cardiac valvulopathy, pericardial effusion, constrictive pericarditis, and retroperitoneal, pleural, and pulmonary fibrosis (see Fibrotic Reactions).

**Fibrotic reactions**

The CSM (updated by MHRA/CHM July and October 2008) has advised that ergot-derived dopamine-receptor agonists, bromocriptine, cabergoline, lisuride [discontinued], and pergolide have been associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Exclude cardiac valvulopathy with echocardiography before starting treatment with these ergot derivatives for chronic endocrine disorders (excludes suppression of lactation) or Parkinson’s disease; it may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness. If long-term treatment is expected, then lung-function tests may also be helpful. Patients taking cabergoline or pergolide should be regularly monitored for cardiac fibrosis, by echocardiography (within 3–6 months of initiating treatment and subsequently at 6-12 month intervals).

**Sudden onset of sleep**

Excessive daytime sleepiness and sudden onset of sleep can occur with dopaminergic drugs. Patients starting treatment with these drugs should be warned of the possibility of these effects and of the need to exercise caution when driving or operating machinery. Patients who have suffered excessive sedation or sudden onset of sleep should refrain from driving or operating machines until those effects have stopped recurring.

**Suppression of lactation**

Although bromocriptine and cabergoline are licensed to suppress lactation, they are not recommended for routine suppression (or for the relief of symptoms of postpartum pain and engagement) that can be adequately treated with simple analgesics and breast support. If a dopamine-receptor agonist is required, cabergoline is preferred. Quinagolide is not licensed for the suppression of lactation.

**BROMOCRIPTINE**

**Indications**

see notes above and under Dose; parkinsonism (section 4.9.1)

**Cautions**

see notes above; also specialist evaluation—monitor for pituitary enlargement, particularly during pregnancy; monitor visual field to detect secondary field loss in macroprolactinoma; contraceptive advice if appropriate (oral contraceptives may increase prolactin concentration); avoid breast-feeding for about 5 days if lactation prevention fails; hepatic impairment (Appendix 2); interactions: Appendix 1 (bromocriptine)

**Contra-indications**

see notes above; also hypertension in postpartum women or in puerperium (see also below)

**Postpartum or puerperium** Should not be used postpartum or in puerperium in women with high blood pressure, coronary artery disease, or symptoms (or history) of serious mental disorder; monitor blood pressure carefully (especially during first few days) in postpartum women. Very rarely hypertension, myocardial infarction, seizures or stroke (both sometimes preceded by severe headache or visual disturbances), and mental disorders have been reported in postpartum women given bromocriptine for lactation suppression—caution with antihypertensive therapy and avoid other ergot alkaloids. Discontinue immediately if hypertension, unrelenting headache, or signs of CNS toxicity develop

**Side-effects**

see notes above; also drowsiness (see also Sudden Onset of Sleep, above), nasal congestion; *less commonly* vomiting, postural hypotension, fatigue, dizziness, dry mouth; also, particularly with *high doses*, confusion, psychomotor excitement, hallucinations, rarely diarrhoea, gastro-intestinal bleeding, gastric ulcer, abdominal pain, tachycardia, bradycardia, arrhythmia, insomnia, psychosis, visual disturbances, tinnitus; *very rarely* vasospasm of fingers and toes particularly in patients with Raynaud’s syndrome, and effects like neuroleptic malignant syndrome on withdrawal; urinary incontinence, leucopenia, thrombocytopenia, hyponatraemia, reversible hearing loss, increased libido, and hypersexuality also reported

**Dose**

- Prevention or suppression of lactation (but see notes above and under Cautions), 2.5 mg on day 1 (prevention) or daily for 2–3 days (suppression); then 2.5 mg twice daily for 14 days
- Hypogonadism, galactorrhoea, infertility, initially 1–1.25 mg at bedtime, increased gradually; usual dose 7.5 mg daily in divided doses, increased if necessary to max. 30 mg daily, usual dose in infertility without hyperprolactinaemia, 2.5 mg twice daily
- Acromegaly, initially 1–1.25 mg at bedtime, increase gradually to 5 mg every 6 hours
- Prolactinoma, initially 1–1.25 mg at bedtime; increased gradually to 5 mg every 6 hours (occasional patients may require up to 30 mg daily)
- **CHILD** under 15 years, not recommended

**Bromocriptine** (Non-proprietary)

Tablets, bromocriptine (as mesilate) 2.5 mg, net price 30-tab pack = £21.52. Label: 21, counselling, hypotensive reactions, driving, see notes above

**Parlodex** (Meda)

Tablets, both scored, bromocriptine (as mesilate) 1 mg, net price 100-tab pack = £9.90; 2.5 mg, 30-tab pack = £5.78. Label: 21, counselling, hypotensive reactions, driving, see notes above

**Capsules**, bromocriptine (as mesilate) 5 mg (blue/white), net price 100-cap pack = £37.57; 10 mg (white), 100-cap pack = £69.50. Label: 21, counselling, hypotensive reactions, driving, see notes above

**CABERGOLINE**

**Indications**

see notes above and under Dose

**Cautions**

see notes above; also severe hepatic impairment (Appendix 2); monthly pregnancy tests during the amenorrhoeic period; advise non-hormo-
nal contraception if pregnancy not desired (see also Contra-indications, below); interactions: Appendix 1 (cabergoline)

**Contra-indications** see notes above; history of puerperal psychosis; exclude pregnancy before starting and discontinue 1 month before intended conception (ovulatory cycles persist for 6 months)—discontinue if pregnancy occurs during treatment (specialist advice needed; Appendix 4); avoid breastfeeding if lactation prevention fails (Appendix 5); history of pulmonary, pericardial, or retroperitoneal fibrotic disorders (see Fibrotic Reactions in notes above); cardiac valvulopathy

**Side-effects** see notes above; also drowsiness (see also Sudden Onset of Sleep, above); dyspepsia, gastritis, epigastric and abdominal pain, angina, syncope, depression, confusion, hallucinations, breast pain; rarely vomiting, palpitation, epistaxis, digital vasospasm, hot flushes, transient hemianopia, muscle weakness; also reported cardiac valvulopathy, erythromelalgia

**Dose**
- Prevention of lactation (but see notes above and under Contra-indications), during first day postpartum, 1 mg as a single dose; suppression of established lactation (but see notes above) 250 micrograms every 12 hours for 2 days
- Hyperprolactinaemic disorders, 500 micrograms weekly (as a single dose or as 2 divided doses on separate days) increased at monthly intervals in steps of 500 micrograms until optimal therapeutic response (usually 1 mg weekly, range 0.25–2 mg weekly) with monthly monitoring of serum prolactin levels; reduce initial dose and increase more gradually if patient intolerant; over 1 mg weekly give as divided doses; up to 4.5 mg weekly has been used in hyperprolactinaemic patients
- Parkinsonism, section 4.9.1
- **CHILD** under 16 years, not recommended

**Cabergoline** (Non-proprietary) 
**Tablet**, scored, cabergoline 500 micrograms, net price 8-tab pack = £30.97. Label: 21, counselling, hypotensive reactions, driving, see notes above

**Note** Dispense in original container (contains desiccant)

**Dostinex** (Pharmacia) 
**Tablets**, scored, cabergoline 500 micrograms. Net price 8-tab pack = £30.04. Label: 21, counselling, hypotensive reactions, driving, see notes above

**Note** Dispense in original container (contains desiccant)

---

**6.7.2 Drugs affecting gonadotrophins**

Danazol inhibits pituitary gonadotrophins; it combines androgenic activity with anti-oestrogenic and anti-progestogenic activity. It is licensed for the treatment of endometriosis and for the relief of severe pain and tenderness in benign fibrocystic breast disease where other measures have proved unsatisfactory. It may also be effective in the long-term management of hereditary angioedema [unlicensed indication].

**Gestrinone** has general actions similar to those of danazol and is indicated for the treatment of endometriosis.

**Cetrorelix and ganirelix** are luteinising hormone releasing hormone antagonists, which inhibit the release of gonadotrophins (luteinising hormone and follicle-stimulating hormone). They are used in the treatment of infertility by assisted reproductive techniques.

---

**CETREOLIX**

**Indications** adjunct in the treatment of female infertility (under specialist supervision)

**Contra-indications** pregnancy, breast-feeding (Appendix 3), moderate renal impairment (Appendix 3), moderate hepatic impairment (Appendix 2)

**Side-effects** nausea, headache, injection site reactions; rarely hypersensitivity reactions

**Dose**
- By subcutaneous injection into the lower abdominal wall, either 250 micrograms in the morning, starting on day 5 or 6 of ovarian stimulation with gonadotrophins (or each evening starting on day 5 of ovarian stimulation); continue throughout administration of gonadotrophin including day of ovulation induction (or evening before ovulation induction)
- or 3 mg on day 7 of ovarian stimulation with gonadotrophins; if ovulation induction not possible on day 5 after 3-mg dose, additional 250 micrograms once daily until day of ovulation induction

**Cetrotide** (Serono) 
**Injection**, powder for reconstitution, cetrotrelax (as acetate), net price 250-micrograms vial = £24.00; 3-mg vial = £168.00 (both with solvent)
**DANAZOL**

**Indications** see notes above and under Dose

**Cautions** cardiac, hepatic, or renal impairment (avoid if severe), elderly, polycythaemia, epilepsy, diabetes mellitus, hypertension, migraine, lipoprotein disorder, history of thrombosis or thromboembolic disease; withdraw if virilisation (may be irreversible on continued use); non-hormonal contraceptive methods should be used, if appropriate; **interactions**: Appendix 1 (danazol)

**Contra-indications** pregnancy (Appendix 4), ensure that patients with amenorrhoea are not pregnant; breast-feeding (Appendix 5); severe hepatic, renal or cardiac impairment; thromboembolic disease; undiagnosed genital bleeding; androgen-dependent tumours; acute porphyria (section 9.8.2)

**Side-effects** nausea, dizziness, skin reactions including rashes, photosensitivity and exfoliative dermatitis, fever, backache, nervousness, mood changes, anxiety, changes in libido, vertigo, fatigue, epigastric and pleuritic pain, headache, weight gain; menstrual disturbances, vaginal dryness and irritation, flushing and reduction in breast size; musculo-skeletal spasm, joint pain and swelling, hair loss; androgenic effects including acne, oily skin, oedema, hirsutism, voice changes and rarely clitoral hypertrophy (see also Cautions); temporary alteration in lipoproteins and other metabolic changes, insulin resistance; thomboctic events; leucopenia, thrombocytopenia, eosinophilia, reversible erythrocytosis or polycythaemia reported; headache and visual disturbances may indicate benign intracranial hypertension; rarely cholesterol jaundice, pancreatitis, peliosis hepatis and benign hepatic adenomata

**Dose**

**Note** In women of child-bearing potential, treatment should start during menstruation, preferably on day 1

- Endometriosis, 200–800 mg daily in up to 4 divided doses, adjusted to achieve amenorrhoea, usually for 3–6 months
- Severe pain and tenderness in benign fibrocystic disease; nervousness, depression, change in appetite; weight gain, hirsutism, voice change; liver enzyme disturbances; headache; gastro-intestinal disturbances; change in libido, flushing, decrease in breast size; androgenic effects including acne, oily skin, oedema, hirsutism, voice changes and rarely clitoral hypertrophy (see also Cautions); temporary alteration in lipoproteins and other metabolic changes, insulin resistance; thrombotic events; leucopenia, thrombocytopenia, eosinophilia, reversible erythrocytosis or polycythaemia reported; headache and visual disturbances may indicate benign intracranial hypertension; rarely cholesterol jaundice, pancreatitis, peliosis hepatis and benign hepatic adenomata

**Danazol (Non-proprietary)**

- **Capsules**, danazol 100 mg, net price 28-cap pack = £16.54, 60-cap pack = £17.04; 200 mg, 56-cap pack = £67.61

**Danol** (Sanofi-Synthelabo)

- **Capsules**, danazol 100 mg (grey/white), net price 60-cap pack = £17.04; 200 mg (pink/white), 60-cap pack = £33.75

**GANIRELIX**

**Indications** adjunct in the treatment of female infertility (under specialist supervision)

**Contra-indications** pregnancy (Appendix 4), breast-feeding (Appendix 5); renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3); moderate hepatic impairment (Appendix 2)

**Side-effects** nausea, headache, malaise, injection-site reactions; **very rarely** hypersensitivity reactions including rash, facial oedema, and dyspnoea also reported

**Dose**

- By subcutaneous injection preferably into the upper leg (rotate injection sites to prevent lipatrophy), 250 micrograms in the morning (or each afternoon) starting on day 6 of ovarian stimulation with gonadotrophins; continue throughout administration of gonadotrophins including day of ovulation induction (if administering in afternoon, give last dose in afternoon before ovulation induction)

**Orgalutran** (Organon) (BNF)

**Injection**, ganirelix, 500 micrograms/mL, net price 0.5-mL prefilled syringe = £22.32

**GESTRINONE**

**Indications** endometriosis

**Cautions** cardiac dysfunction; renal impairment (avoid if creatinine clearance less than 10 mL/minute); **interactions**: Appendix 1 (gestrinone)

**Contra-indications** pregnancy (use non-hormonal method of contraception); breast-feeding (Appendix 5); severe cardiac or hepatic impairment; metabolic or vascular disorders associated with previous sex hormone treatment

**Side-effects** spotting; acne, oily skin, fluid retention, weight gain, hirsutism, voice change; liver enzyme disturbances; headache; gastro-intestinal disturbances; change in libido, flushing, decrease in breast size; nervousness, depression, change in appetite; muscle cramp

**Dose**

- 2.5 mg twice weekly starting on first day of cycle with second dose 3 days later, repeated on same two days preferably at same time each week; duration of treatment usually 6 months

**Missed doses** One missed dose—2.5 mg as soon as possible and maintain original sequence; two or more missed doses—discontinue, re-start on first day of new cycle (following negative pregnancy test)

**Dimetriose** (Sanofi-Aventis) (BNF)

- **Capsules**, gestrinone 2.5 mg, net price 8-cap pack = £103.91

**Gonadorelin analogues**

Administration of gonadorelin analogues produces an initial phase of stimulation; continued administration is followed by down-regulation of gonadotrophin-releasing hormone receptors, thereby reducing the release of gonadotrophins (follicle stimulating hormone and luteinising hormone) which in turn leads to inhibition of androgen and oestrogen production.

Gonadorelin analogues are used in the treatment of endometriosis, precocious puberty, infertility, anaemia due to uterine fibroids (together with iron supplementation), breast cancer (section 8.3.4.1), prostate cancer (section 8.3.4.2) and before intra-uterine surgery. Use of leuprorelin and triptorelin for 3 to 4 months before surgery reduces the uterine volume, fibroid size and associated bleeding. For women undergoing hysterectomy or myomectomy, a vaginal procedure is made more feasible following the use of a gonadorelin analogue.
Cautions  Non-hormonal, barrier methods of contraception should be used during entire treatment period with gonadorelin analogues; also use with caution in patients with metabolic bone disease because decrease in bone mineral density can occur.

Contra-indications  Gonadorelin analogues are contra-indicated for use longer than 6 months in the treatment of endometriosis (do not repeat), where there is undiagnosed vaginal bleeding, in pregnancy (Appendix 4; exclude pregnancy—also give first injection during menstruation or shortly afterwards for 1 month beforehand) and in breast-feeding.

Side-effects  Side-effects of the gonadorelin analogues related to the inhibition of oestrogen production include menopausal-like symptoms (e.g. hot flushes, increased sweating, vaginal dryness, dyspareunia and loss of libido) and a decrease in trabecular bone density; these effects can be reduced by hormone replacement (e.g. with an oestrogen and a progestogen or with tibolone). Side-effects of gonadorelin analogues also include headache (rarely migraine) and hypersensitivity reactions including urticaria, pruritus, rash, asthma and anaphylaxis; when treating urine fibroids, bleeding associated with fibroid degeneration can occur; spray formulations can cause irritation of the nasal mucosa including nose bleeds; local reactions at injection site can occur; other side-effects also reported with some gonadorelin analogues include palpatation, hypertension, ovarian cysts (may require withdrawal), changes in breast size, musculoskeletal pain or weakness, visual disturbances, paraesthesia, changes in scalp and body hair, oedema of the face and extremities, weight changes, and mood changes including depression.

BUSERELIN

Indications  see under Dose; prostate cancer (section 8.3.4.2)

Cautions  see notes above; polycystic ovarian disease; diabetes

Contra-indications  see notes above; hormone-dependent tumours

Side-effects  see notes above; initially withdrawal bleeding and subsequently breakthrough bleeding, leucorrhoea; nausea, vomiting, constipation, diarrhoea; anxiety, memory and concentration disturbances, sleep disturbances, nervousness, dizziness, drowsiness; breast tenderness, lactation; abdominal pain; fatigue; increased thirst, changes in appetite; acne, dry skin, splitting nails, dry eyes; altered blood lipids, leucopenia, thrombocytopenia; hearing disturbances; reduced glucose tolerance

Dose  
- Endometriosis, intranasally, 300 micrograms (one 150-microgram spray in each nostril) 3 times daily (starting on days 1 or 2 of menstruation); max. duration of treatment 6 months (do not repeat)
- Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under specialist supervision), by subcutaneous injection, 200–500 micrograms daily given as a single injection (occasionally up to 500 micrograms twice daily may be needed) starting in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually about 1–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

Intranasally, 150 micrograms (one spray in one nostril) 4 times daily during waking hours (occasionally up to 300 micrograms 4 times daily may be needed) starting in early follicular phase (day 1) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually about 2–3 weeks) then maintained during gonadotrophin administration (stopping gonadotrophin and buserelin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

Counselling  Avoid use of nasal decongestants before and for at least 30 minutes after treatment

Suprecur® (Aventis Pharma)  Nasal spray, buserelin (as acetate) 150 micrograms/metered spray. Net price 2 × 100-dose pack (with metered dose pumps) = £91.19. Counselling, nasal decongestants

Injection, buserelin (as acetate) 1mg/mL. Net price 5.5-mL vial = £28.64

GOSERELIN

Indications  see under Dose; prostate cancer (section 8.3.4.2); early and advanced breast cancer (section 8.3.4.1)

Cautions  see notes above; polycystic ovarian disease; diabetes

Contra-indications  see notes above; breast-feeding (Appendix 5)

Side-effects  see notes above; withdrawal bleeding

Dose  
- By subcutaneous injection into anterior abdominal wall (as Zoladex®)  Endometriosis, 3.6 mg every 28 days; max. duration of treatment 6 months (do not repeat)  
  - Endometrial thinning before intra-uterine surgery, 3.6 mg (may be repeated after 28 days if uterus is large or to allow flexible surgical timing)  
  - Before surgery in women who have anaemia due to uterine fibroids, 3.6 mg every 28 days (with supplementary iron); max. duration of treatment 3 months  

Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under specialist supervision), after exclusion of pregnancy, 3.6 mg to achieve pituitary down-regulation (usually 1–3 weeks) then gonadotrophin is administered (stopping gonadotrophin on administration of chorionic gonadotrophin at appropriate stage of follicular development)

Preparation  Section 8.3.4.2

LEUPRORELIN ACETATE

Indications  see under Dose; prostate cancer (section 8.3.4.2)

Cautions  see notes above; monitor liver function; family history of osteoporosis; chronic use of other drugs which reduce bone density including alcohol and tobacco; diabetes
Contra-indications see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects see notes above; breast tenderness; nausea, vomiting, diarrhoea, anorexia; fever, chills; sleep disturbances, dizziness, fatigue, leucopenia, thrombocytopenia, altered blood lipids, pulmonary embolism; spinal fracture, paralysis, hypotension and worsening of depression also reported

Dose
- By subcutaneous or intramuscular injection (as Prostapo SR)
  Endometriosis, 3.75 mg as a single dose in first 5 days of menstrual cycle then every month for max. 6 months (course not to be repeated)
  Endometrial thinning before intra-uterine surgery, 3.75 mg as a single dose (given between days 3 and 5 of menstrual cycle) 5–6 weeks before surgery
  Reduction of size of uterine fibroids and of associated bleeding before surgery, 3.75 mg as a single dose every month usually for 3–4 months (max. 6 months)
- By intramuscular injection (as Prostapo 3)
  Endometriosis, 11.25 mg as a single dose in first 5 days of menstrual cycle then every 3 months for max. 6 months (course not to be repeated)

Preparations
- Section 8.3.4.2

NAFARELIN

Indications see under Dose

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; acne

Dose
- Endometriosis, women over 18 years, 200 micrograms twice daily as one spray in one nostril in the morning and one spray in the other nostril in the evening (starting on days 2–4 of menstruation), max. duration of treatment 6 months (do not repeat)
- Pituitary desensitisation before induction of ovulation by gonadotrophins for in vitro fertilisation (under specialist supervision), 400 micrograms (one spray in each nostril) twice daily starting in early follicular phase (day 2) or, after exclusion of pregnancy, in midluteal phase (day 21) and continued until down-regulation achieved (usually within 4 weeks) then maintained (usually for 8–12 days) during gonadotrophin administration (stopping gonadotrophin and nafarelin on administration of chorionic gonadotrophin at follicular maturity); discontinue if down-regulation not achieved within 12 weeks

Counselling
- Avoid use of nasal decongestants before and for at least 30 minutes after treatment; repeat dose if sneezing occurs during or immediately after administration

Synarel (Pharmacia) (Ferring)
- Nasal spray, nafarelin (as acetate) 200 micrograms/metered spray. Net price 30-dose unit = £32.28; 60-dose unit = £55.66. Label: 10, patient information leaflet, counselling, see above

TRIPTORELIN

Indications endometriosis, precocious puberty, reduction in size of uterine fibroids; advanced prostate cancer (section 8.3.4.2)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; also gastro-intestinal disturbances; in precocious puberty, withdrawal bleeding may occur in the first month of treatment; asthenia

Dose
- See under preparations below

Decapeptyl SR (Ipsen) (Ferring)
- Injection, (powder for suspension), m/r, triptorelin (as acetate), net price 3-mg vial (with diluent) = £69.00
- Dose by intramuscular injection, endometriosis and reduction in size of uterine fibroids, 3 mg every 4 weeks starting during first 5 days of menstrual cycle, for uterine fibroids continue treatment for at least 3 months; max. duration of treatment 6 months (not to be repeated)
- Note Each vial includes an overage to allow accurate administration of 3-mg dose

Injection, (powder for suspension), m/r, triptorelin (as acetate), net price 11.25-mg vial (with diluent) = £207.00
- Dose by intramuscular injection, endometriosis, 11.25 mg every 3 months starting during first 5 days of menstrual cycle; max. duration of treatment 6 months (not to be repeated)
- Precocious puberty, 11.25 mg every 3 months; discontinue when bone maturation consistent with age of 12 years in girls or 13–14 years in boys
- Note Each vial includes an overage to allow accurate administration of 11.25-mg dose

Gonapeptyl Depot (Ferring)
- Injection, (powder for suspension), triptorelin (as acetate), net price 3.75-mg prefilled syringe (with prefilled syringe of vehicle) = £85.00
- Dose by subcutaneous or deep intramuscular injection, endometriosis and reduction in size of uterine fibroids, 3.75 mg every 4 weeks starting during first 5 days of menstrual cycle, max. duration of treatment 6 months (not to be repeated)
- Precocious puberty, body-weight over 30 kg, initially 3.75 mg every 2 weeks for 3 doses, then every 3–4 weeks; body-weight 20–30 kg, initially 2.5 mg every 2 weeks for 3 doses, then every 3–4 weeks; body-weight under 20 kg, initially 1.875 mg every 2 weeks for 3 doses, then every 3–4 weeks; discontinue when bone maturation consistent with age over 12 years in girls or over 13 years in boys

Breast pain (mastalgia)

Once any serious underlying cause for breast pain has been ruled out, most women will respond to reassurance and reduction in dietary fat; withdrawal of an oral contraceptive or of hormone replacement therapy may help to resolve the pain.

Mild, non-cyclical breast pain is treated with simple analgesics (section 4.7.1); moderate to severe pain, cyclical pain or symptoms that persist for longer than 6 months may require specific drug treatment.

Danazol (section 6.7.2) is licensed for the relief of severe pain and tenderness in benign fibrocystic breast disease which has not responded to other treatment.

Tamoxifen (section 8.3.4.1) may be a useful adjunct in the treatment of mastalgia [unlicensed indication] especially when symptoms can definitely be related to cyclic oestrogen production; it may be given on the days of the cycle when symptoms are predicted.

Treatment for breast pain should be reviewed after 6 months and continued if necessary. Symptoms recur in about 50% of women within 2 years of withdrawal of therapy but may be less severe.
Metyrapone and trilostane

Metyrapone is a competitive inhibitor of 11β-hydroxylase in the adrenal cortex; the resulting inhibition of cortisol (and to a lesser extent aldosterone) production leads to an increase in ACTH production which, in turn, leads to increased synthesis and release of cortisol precursors. It may be used as a test of anterior pituitary function.

Although most types of Cushing’s syndrome are treated surgically, that which occasionally accompanies carcinoma of the bronchus is not usually amenable to surgery. Metyrapone has been found helpful in controlling the symptoms of the disease; it is also used in other forms of Cushing’s syndrome to prepare the patient for surgery. The dosages used are either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed.

Trilostane reversibly inhibits 3β-hydroxysteroid dehydrogenase / delta 5-4 isomerase in the adrenal cortex; the resulting inhibition of the synthesis of mineralocorticoids and glucocorticoids may be useful in Cushing’s syndrome and primary hyperaldosteronism. Trilostane appears to be less effective than metyrapone for Cushing’s syndrome (where it is tailored to corticosteroid production). It also has a minor role in postmenopausal breast cancer that has relapsed following initial oestrogen antagonist therapy (corticosteroid replacement therapy is also required). Ketoconazole (section 5.2) is also used by specialists for the management of Cushing’s syndrome [unlicensed indication].

### METYRAPONE

**Indications** see notes above and under Dose (specialist supervision in hospital)

**Cautions** gross hypopituitarism (risk of precipitating acute adrenal failure); hypertension on long-term administration; hypothyroidism or hepatic impairment (delayed response); many drugs interfere with diagnostic estimation of steroids; avoid in acute porphyria (section 9.8.2)

**Driving** Drowsiness may affect the performance of skilled tasks (e.g. driving)

**Contra-indications** adrenocortical insufficiency (see Cautions); pregnancy (Appendix 4), breastfeeding (Appendix 5)

**Side-effects** occasional nausea, vomiting, dizziness, headache, hypotension, sedation; rarely abdominal pain, allergic skin reactions, hypoadrenalinism, hirsutism

**Dose**

- Differential diagnosis of ACTH-dependent Cushing’s syndrome, 750 mg every 4 hours for 6 doses; **CHILD** 15 mg/kg (minimum 250 mg) every 4 hours for 6 doses
- Management of Cushing’s syndrome, range 0.25–6 g daily, tailored to cortisol production; see notes above
- Resistant oedema due to increased aldosterone secretion in cirrhosis, nephrotic syndrome, and congestive heart failure (with glucocorticoid replacement therapy) 3 g daily in divided doses

### TRILOSTANE

**Indications** see notes above and under Dose (specialist supervision)

**Cautions** breast cancer (concurrent corticosteroid replacement therapy needed, see under Dose), adrenal cortical hyperfunction (tailored to cortisol and electrolytes, concurrent corticosteroid therapy may be needed, see under Dose); hepatic and renal impairment; **interactions**: Appendix 1 (trilostane)

**Contra-indications** pregnancy (use non-hormonal method of contraception; Appendix 4); breast-feeding; children

**Side-effects** flushing, tingling and swelling of mouth, rhinorrhea, nausea, vomiting, diarrhoea, and rashes reported; rarely granulocytopenia

**Dose**

- Adrenal cortical hyperfunction, 240 mg daily in divided doses for at least 3 days then tailored according to response with regular monitoring of plasma electrolytes and circulating corticosteroids (both mineralocorticoid and glucocorticoid replacement therapy may be needed); usual dose: 120–480 mg daily (may be increased to 960 mg)
- Postmenopausal breast cancer (with glucocorticoid replacement therapy) following relapse to initial oestrogen receptor antagonist therapy, initially 240 mg daily increased every 3 days in steps of 240 mg to a maintenance dose of 960 mg daily (720 mg daily if not tolerated)

### MECASERMIN

(Remcombinant human insulin-like growth factor-I; rhIGF-I)

**Indications** see notes above

**Cautions** correct hypothyroidism before initiating treatment; diabetes mellitus (adjustment of antidiabetic therapy may be necessary), monitor ECG before and on termination of treatment (and during treatment if ECG abnormal), papilloedema (see under Side-effects), monitor for disorders of the epiphysis of the hip (monitor for limping), monitor for signs of tonsillar hypertrophy (snoring, sleep apnoea, and chronic middle ear effusions); pregnancy (Appendix 4)

**Contra-indications** evidence of tumour activity (discontinue treatment), breast-feeding

Somatomedins are a group of polypeptide hormones structurally related to insulin and commonly known as insulin-like growth factors (IGFs). Mecasermin, a human insulin-like growth factor-I (rhIGF-I), is the principal mediator of the somatotropic effects of human growth hormone and is used to treat growth failure in children and adolescents with severe primary insulin-like growth factor-I deficiency.
Side-effects  headache, funduscopy for papilloedema recommended if severe or recurrent headache, visual problems, nausea and vomiting occur—if papilloedema confirmed consider benign intracranial hypertension (rare cases reported); cardiomegaly, ventricular hypertrophy, tachycardia; convulsions, sleep apnoea, night terrors, dizziness, nervousness; tonsillar hypertrophy (see Cautions above); hypoglycaemia (especially in first month, and in younger children), hyperglycaemia, gynaecomastia; arthralgia, myalgia; visual disturbance, impaired hearing; antibody formation; injection-site reactions (rotate site)

Dose  
- By subcutaneous injection, ADOLESCENT and CHILD over 2 years, initially 40 micrograms/kg twice daily for 1 week, if tolerated increase dose in steps of 40 micrograms/kg to max. 120 micrograms/kg twice daily; discontinue if no response within 1 year

Counselling  Dose should be administered just before or after food; do not increase dose if a dose is missed

Note Reduce dose if hypoglycaemia occurs despite adequate food intake; withhold injection if patient unable to eat

Increlex® (Ipsen)  Injection, mecasermin 10 mg/mL, net price 4-mL vial = £384.00. Counselling, administration

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2)
7 Obstetrics, gynaecology, and urinary-tract disorders

7.1 Drugs used in obstetrics

7.1.1 Prostaglandins and oxytocics

7.1.1.1 Ductus arteriosus

7.1.2 Mifepristone

7.1.3 Myometrial relaxants

7.2 Treatment of vaginal and vulval conditions

7.2.1 Preparations for vaginal and vulval changes

7.2.2 Vaginal and vulval infections

7.3 Contraceptives

7.3.1 Combined hormonal contraceptives

7.3.2 Progestogen-only contraceptives

7.3.2.1 Oral progestogen-only contraceptives

7.3.2.2 Parenteral progestogen-only contraceptives

7.3.2.3 Intra-uterine progestogen-only device

7.3.3 Spermicidal contraceptives

7.3.4 Contraceptive devices

7.3.5 Emergency contraception

7.4 Drugs for genito-urinary disorders

7.4.1 Drugs for urinary retention

7.4.2 Drugs for urinary frequency, enuresis, and incontinence

7.4.3 Drugs used in urological pain

7.4.4 Bladder instillations and urological surgery

7.4.5 Drugs for erectile dysfunction

For hormonal therapy of gynaecological disorders see section 6.4.1 (including HRT), section 6.5.1 and section 6.7.2.

Because of the complexity of dosage regimens in obstetrics, in all cases detailed specialist literature should be consulted.

7.1.1 Prostaglandins and oxytocics

Prostaglandins and oxytocics are used to induce abortion or induce or augment labour and to minimise blood loss from the placental site. They include oxytocin, carbetocin, ergometrine, and the prostaglandins. All induce uterine contractions with varying degrees of pain according to the strength of contractions induced.

Induction of abortion

Gemeprost, administered vaginally as pessaries is the preferred prostaglandin for the medical induction of late therapeutic abortion. Gemeprost ripens the cervix before surgical abortion, particularly in primigravida. The prostaglandin misoprostol (section 7.1.2) is given by mouth or by vaginal administration to induce medical abortion [unlicensed indication]; intravaginal use ripens the cervix before surgical abortion [unlicensed indication]. Extra-amniotic dinoprostone is rarely used nowadays.

Pre-treatment with mifepristone (section 7.1.2) can facilitate the process of medical abortion. It sensitises the uterus to subsequent administration of a prostaglandin and, therefore, abortion occurs in a shorter time and with a lower dose of prostaglandin.

Induction and augmentation of labour

Dinoprostone is available as vaginal tablets, pessaries and vaginal gels for the induction of labour. The intravenous solution is rarely used; it is associated with more side-effects.

Oxytocin (Synthocinon®) is administered by slow intravenous infusion, using an infusion pump, to induce or augment labour, usually in conjunction with amniotomy. Uterine activity must be monitored carefully and hyperstimulation avoided. Large doses of oxytocin may result in excessive fluid retention.

Misoprostol is given orally or vaginally for the induction of labour [unlicensed indication].
Prevention and treatment of haemorrhage

Bleeding due to incomplete abortion can be controlled with ergometrine and oxytocin (Syntometrine®) given intramuscularly; the dose is adjusted according to the patient’s condition and blood loss. This is commonly used before surgical evacuation of the uterus, particularly when surgery is delayed. Oxytocin and ergometrine combined are more effective in early pregnancy than either drug alone.

Active management of the third stage of labour reduces the risk of postpartum haemorrhage; ergometrine 500 micrograms with oxytocin 5 units (Syntometrine® 1 mL) is given by intramuscular injection on delivery of the anterior shoulder or, at the latest, immediately after the baby is delivered. Alternatively, oxytocin may be given alone by intramuscular injection [unlicensed], particularly if ergometrine is inappropriate (e.g. in pre-eclampsia); oxytocin alone causes less nausea, vomiting, and hypertension than when given with ergometrine.

In excessive uterine bleeding, any placental products remaining in the uterus should be removed. Oxytocics are drugs used to treat postpartum haemorrhage caused by uterine atony; treatment options are as follows:

- oxytocin 5–10 units by slow intravenous injection, followed in severe cases by intravenous infusion of oxytocin 5–30 units in 500 mL infusion fluid at a rate that controls uterine atony or
- ergometrine by intramuscular injection or
- ergometrine 250–500 micrograms by intravenous injection (use with caution—risk of hypertension) or
- ergometrine 500 micrograms with oxytocin 5 units (Syntometrine® 1 mL) by intramuscular injection

Carboprost has an important role in severe postpartum haemorrhage unresponsive to ergometrine and oxytocin.

Misoprostol [unlicensed] may be an alternative in postpartum haemorrhage unresponsive to ergometrine, oxytocin, and carboprost.

CARBETOCIN

**Indications** prevention of uterine atony after caesarean section

**Cautions** hypotension; cardiovascular disease (avoid if severe); migraine; asthma

**Contra-indications** pre-eclampsia and eclampsia; epilepsy; hepatic impairment; renal impairment

**Side-effects** nausea, vomiting, abdominal pain, metallic taste; flushing, hypotension, chest pain; dyspnoea; headache, tremor, dizziness; anaemia; back pain; pruritus; feeling of warmth, chills; tachycardia and sweating also reported

**Dose**

- By intravenous injection, a single dose of 100 micrograms, as soon as possible after delivery, preferably before removal of placenta

**Pabal® (Feringa)** ▼ [PA]

**Injection**, carbetocin 100 micrograms/mL, net price 1 mL amp = £18.00

CARBOPROST

**Indications** postpartum haemorrhage due to uterine atony in patients unresponsive to ergometrine and oxytocin

**Cautions** history of glaucoma or raised intra-ocular pressure, asthma, hypertension, hypotension, anaemia, jaundice, diabetes, epilepsy, uterine scars; excessive dosage may cause uterine rupture; interactions: Appendix 1 (prostaglandins)

**Contra-indications** untreated pelvic infection; cardiac, renal, pulmonary, or hepatic disease

**Side-effects** nausea, vomiting and diarrhoea, hyperthermia and flushing, bronchospasm; less frequent effects include raised blood pressure, dyspnoea, and pulmonary oedema; chills, headache, diaphoresis, dizziness; cardiovascular collapse also reported; erythema and pain at injection site reported

**Dose**

- By deep intramuscular injection, 250 micrograms repeated if necessary at intervals of 1½ hours (in severe cases the interval may be reduced but should not be less than 15 minutes); total dose should not exceed 2 mg (8 doses)

**Hembrate® (Pharmacia)** [PA]

**Injection**, carboprost as trometamol salt (tromethamine salt) 250 micrograms/mL, net price 1 mL amp = £18.20 (hosp. only)

DINOPROSTONE

**Indications** see notes above and under preparations below

**Cautions** history of asthma, glaucoma and raised intra-ocular pressure; hypertension; history of epilepsy; uterine scarring; monitor uterine activity and fetal status (particular care if history of uterine hypertony); uterine rupture; see also notes above; monitor for disseminated intravascular coagulation after parturition; risk factors for disseminated intravascular coagulation; effect of oxytocin enhanced (care needed in monitoring uterine activity when used in sequence); interactions: Appendix 1 (prostaglandins)

**Contra-indications** active cardiac, pulmonary, renal or hepatic disease; placenta praevia or unexplained vaginal bleeding during pregnancy, ruptured membranes, major cephalopelvic disproportion or fetal malpresentation, history of caesarean section or major uterine surgery, untreated pelvic infection, fetal distress, grand multiparas and multiple pregnancy, history of difficult or traumatic delivery; avoid extra-amniotic route in cervicitis or vaginitis

**Side-effects** nausea, vomiting, diarrhoea; other side-effects include uterine hypertonus, severe uterine contractions, pulmonary or amniotic fluid embolism, abruptio placenta, fetal distress, maternal hypertension, bronchospasm, rapid cervical dilation, fever, backache; uterine hypercontractility with or without fetal bradycardia, low Apgar scores; cardiac arrest, uterine rupture, stillbirth or neonatal death also reported; vaginal symptoms (warmth, irritation, pain); after intravenous administration—flushing, shivering, headache, dizziness, temporary pyrexia and raised white blood cell count; disseminated intravascular coagulation reported; also local tissue reaction and erythema after intravenous administration and possibility of infection after extra-amniotic administration
Ergometrine

- See under preparations, below

**Important** Do not confuse dose of Prostin E2 vaginal gel with that of Prostin E2 vaginal tablets—not bioequivalent.

**Propess** *(Ferring) (NH)*

**Pessaries** (within retrieval device), releasing dinoprostone approx. 10 mg over 24 hours; net price 1-pessary pack = £30.00

**Dose** by vagina, cervical ripening and induction of labour at term, 1 pessary (in retrieval device) inserted high into posterior fornix and removed when cervical ripening adequate; if oxytocin necessary, remove 30 minutes before oxytocin infusion; remove if cervical ripening inadequate after 24 doses (dose not to be repeated)

**Prostin E2** *(Pharmacia) (NH)*

**Intravenous solution** for dilution and use as an infusion, dinoprostone 1 mg/mL, net price 0.75-mL amp = £8.52; 10 mg/mL, 0.5-mL amp = £18.40 (both hosp. only; rarely used, consult product literature for dose and indications)

**Extra-amniotic solution** dinoprostone 10 mg/mL. Net price 0.5-mL amp (with diluent) = £18.40 (hosp. only; less commonly used nowadays, consult product literature for dose and indications)

**Vaginal gel,** dinoprostone 400 micrograms/mL, net price 2.5-mL (1 mg) = £13.28; 800 micrograms/mL, 2.5-mL (2 mg) = £13.28

**Dose** by vagina, induction of labour, inserted high into posterior fornix (avoid administration into cervical canal), 1 mg (unfavourable primigravida 2 mg), followed after 6 hours by 1–2 mg if required, max. gel 3 mg (unfavourable primigravida 4 mg)

**Vaginal tablets,** dinoprostone 3 mg. Net price 8-vaginal tab pack = £106.23

**Dose** by vagina, induction of labour, inserted high into posterior fornix, 3 mg, followed after 6–8 hours by 3 mg if labour is not established; max. 6 mg [vaginal tablets]

**Note** Prostin E2 Vaginal Gel and Vaginal Tablets are not bioequivalent

**ERGOMETRINE MALEATE**

**Indications** see notes above

**Cautions** cardiac disease; hypertension; multiple pregnancy; acute porphyria (section 9.8.2); hepatic impairment (avoid if severe; Appendix 2); renal impairment (avoid if severe; Appendix 3); interactions: Appendix 1 (ergot alkaloids)

**Contra-indications** induction of labour, first and second stages of labour, vascular disease, severe cardiac disease, sepsis, severe hypertension, eclampsia

**Side-effects** nausea, vomiting, headache, dizziness, tinnitus, abdominal pain, chest pain, palpitation, dyspnoea, bradycardia, transient hypertension, vasoconstriction, stroke, myocardial infarction and pulmonary oedema also reported

**Dose**

- See notes above

**Ergometrine** *(Non-proprietary) (NH)*

**Injection,** ergometrine maleate 500 micrograms/mL. Net price 1-mL amp = 60p

**With oxytocin**

**Syntometrine** *(Alliance) (NH)*

**Injection,** ergometrine maleate 500 micrograms, oxytocin 5 units/mL. Net price 1-mL amp = £1.31

**Dose** by intramuscular injection, 1 mL, by intravenous injection, no longer recommended

---

**GEMEPROST**

**Indications** see under Dose

**Cautions** obstructive airways disease, cardiovascular insufficiency, raised intra-ocular pressure, cervices or vaginitis; interactions: Appendix 1 (prostaglandins)

**Important** For warnings relating to use of gemeprost in a patient undergoing induction of abortion with mifepristone, see under Mifepristone and Note below

**Contra-indications** unexplained vaginal bleeding, uterine scarring, placenta praevia

**Side-effects** vaginal bleeding and uterine pain; nausea, vomiting, or diarrhoea; headache, muscle weakness, dizziness, flushing, chills, backache, dyspnoea, chest pain, palpitation and mild pyrexia; uterine rupture reported (most commonly in multi- parae or if history of uterine surgery or if given with intravenous oxytocics); also reported severe hypotension, coronary artery spasm and myocardial infarction

**Dose**

- By vagina, cervical ripening prior to first trimester surgical abortion, 1 mg inserted into posterior fornix 3 hours before surgery

- Second trimester abortion, 1 mg inserted into posterior fornix every 3 hours for max. of 5 administrations; second course may begin 24 hours after start of treatment (if treatment fails pregnancy should be terminated by another method)

- Second trimester intra-uterine death, 1 mg inserted into posterior fornix every 3 hours for max. of 5 administrations only; monitor for coagulopathy

**Note** If used in combination with mifepristone, carefully monitor blood pressure and pulse for 5 hours

**Gemeprost** *(Sanofi-Aventis) (NH)*

**Pessaries,** gemeprost 1 mg. Net price 5-pessary pack = £215.00

---

**OXYTOCIN**

**Indications** see under Dose and notes above

**Cautions** induction or enhancement of labour—presence of borderline cephalopelvic disproportion (avoid if significant), secondary uterine inertia, mild or moderate pregnancy-induced hypertension or cardiac disease, women over 35 years or with history of lower-uterine segment caesarean section (see also under Contra-indications below); risk factors for disseminated intravascular coagulation, monitor for disseminated intravascular coagulation after parturition; avoid large infusion volumes and restrict fluid intake by mouth (risk of hyponatraemia and water-intoxication—see also Appendix 6); effects enhanced by concomitant prostaglandins (very careful monitoring of uterine activity); caudal block anaesthesia (may enhance hypertensive effects of sympathomimetic vasopressors); see also interactions: Appendix 1 (oxytocin)

**Contra-indications** hypertonic uterine contractions, fetal distress; any condition where spontaneous labour or vaginal delivery inadvisable; avoid prolonged administration in oxytocin-resistant uterine inertia, severe pre-eclamptic toxemia, or severe cardiovascular disease

**Side-effects** nausea, vomiting; arrhythmia; headache; rarely disseminated intravascular coagulation, rash, and anaphylactoid reactions (with dyspnoea, hypertension, or shock); uterine spasm (may occur at low doses), uterine hyperstimulation (usually with exces-
sive doses—may cause fetal distress, asphyxia, and death, or may lead to hypertonicity, tetanic contractions, soft-tissue damage or uterine rupture; water intoxication and hyponatraemia associated with high doses with large infusion volumes of electrolyte-free fluid (see also under Dose below); placental abruption and amniotic fluid embolism also reported on overdose.

**Dose**
- Induction of labour for medical reasons or stimulation of labour in hypotonic uterine inertia, by intravenous infusion (not to be started for at least 6 hours after administration of vaginal prostaglandin), initially 0.001–0.004 units/minute, increased at intervals of at least 30 minutes until a maximum of 3–4 contractions occur every 10 minutes (0.01 units/minute is often adequate) up to max. 0.02 units/minute; max. 5 units in 1 day (may be repeated next day starting again at 0.001–0.004 units/minute).
- **Important** Careful monitoring of fetal heart rate and uterine motility essential for dose titration (avoid intravenous injection during labour); discontinue immediately in uterine hyperactivity or fetal distress.
- Caesarean section, by slow intravenous injection immediately after delivery, 5 units.
- Prevention of postpartum haemorrhage, after delivery of placenta, by slow intravenous injection, 5 units (if infusion used for induction or enhancement of labour, increase rate during third stage and for next few hours).
- **Important** Avoid rapid intravenous injection (may transiently reduce blood pressure).
- **Note** Can be given in a dose of 10 units by intramuscular injection [unlicensed route] instead of oxytocin with ergometrine (Syntometrine), see notes above.
- Treatment of postpartum haemorrhage, by slow intravenous injection, 5–10 units, followed if necessary by intravenous infusion, 0.02–0.04 units/minute or faster.
- **Important** Prolonged intravenous administration at high doses with large volume of fluid (as possible in inevitable or missed abortion or postpartum haemorrhage) may cause water intoxication with hyponatraemia. To avoid: use electrolyte-containing diluent (i.e. not glucose), increase oxytocin concentration to reduce fluid, restrict fluid intake by mouth; monitor fluid and electrolytes.
- **Note** Oxytocin doses in the BNF may differ from those in the product literature.

**Syntocinon** ([Alliance](https://www.alliancepharmaceuticals.com))
- **Injection**, oxytocin, net price 5 units/mL, 1-mL amp = 89p; 10 units/mL, 1-mL amp = £1.01
- **With ergometrine**
  - See **Syntometrine**®, p. 431

---

## 7.1.1 Ductus arteriosus

### Maintenance of patency

Alprostadil (prostaglandin E₁) is used to maintain patency of the ductus arteriosus in neonates with congenital heart defects, prior to corrective surgery in centres where intensive care is immediately available. See BNF for Children (section 2.14) for further advice on maintaining the patency of the ductus arteriosus.

### ALPROSTADIL

**Indications** congenital heart defects in neonates prior to corrective surgery; erectile dysfunction (section 7.4.5)

**Cautions** see notes above; history of haemorrhage, avoid in hyaline membrane disease, monitor arterial pressure; interactions: Appendix 1 (prostaglandins)

**Side-effects** apnoea (particularly in neonates under 2 kg), flushing, bradycardia, hypotension, tachycardia, cardiac arrest, oedema, diarrhoea, fever, convulsions, disseminated intravascular coagulation, hypokalaemia; cortical proliferation of long bones and weakening of the wall of the ductus arteriosus and of pulmonary artery may follow prolonged use; gastrointestinal obstruction reported

**Dose**
- By intravenous infusion, initially 10 nanograms/kg/minute, adjusted according to response in steps of 5–10 nanograms/kg/minute, max. 100 nanograms/kg/minute (but associated with increased side-effects)
- **Note** Alprostadil doses in BNF may differ from those in product literature.

**Prostin VR** ([Pharmacia](https://www.pharmacia.com))
- **Intravenous solution**, alprostadil 500 micrograms/mL in alcohol. For dilution and use as an infusion. Net price 1-mL amp = £7.519 (hosp. only)

### Closure of ductus arteriosus

**Indometacin** (indomethacin) is used to close a patent ductus arteriosus in premature babies, probably by inhibiting prostaglandin synthesis. See BNF for Children (section 2.14) for further advice on closure of the ductus arteriosus.

### INDOMETACIN

(Indomethacin)

**Indications** patent ductus arteriosus in premature babies (under specialist supervision in neonatal intensive care unit); uncomplicated premature labour [unlicensed indication] (section 7.1.3); rheumatoid disease (section 10.1.1)

**Cautions** may mask symptoms of infection; may reduce urine output by 50% or more (monitor carefully)—see also under Anuria or Oliguria, below) and precipitate renal impairment especially if extracellular volume depleted, heart failure, sepsis, or hepatic impairment, or if receiving nephrotoxic drugs; may induce hyponatraemia; monitor renal function and electrolytes; inhibition of platelet aggregation (monitor for bleeding); interactions: Appendix 1 (NSAIDs) Anuria or oliguria If anuria or marked oliguria (urinary output less than 0.6 mL/kg/hour) at time of scheduled second or third dose, delay until renal function returns to normal

**Contra-indications** untreated infection, bleeding (especially with active intracranial haemorrhage or gastro-intestinal bleeding); thrombocytopenia, coagulation defects, necrotising enterocolitis, renal impairment
**Side-effects** haemorrhagic, renal, gastro-intestinal (including necrotising enterocolitis), metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection

**Dose**

- **By intravenous injection**, over 20–30 minutes (using a suitable syringe driver), 3 doses at intervals of 12–24 hours (provided urine output remains adequate), **NEONATE under 48 hours**, 200 micrograms/kg then 100 micrograms/kg then 100 micrograms/kg; **NEONATE 2–7 days**, 200 micrograms/kg then 200 micrograms/kg then 200 micrograms/kg; **NEONATE over 7 days**, 200 micrograms/kg then 250 micrograms/kg then 250 micrograms/kg; solution prepared with 1–2 mL sodium chloride 0.9% or water for injections (not glucose and no preservatives)

If ductus arteriosus reopens a second course of 3 injections may be given 48 hours after first course

**Indocid PDA** (IDIS) **Injection**, powder for reconstitution, indometacin (as sodium trihydrate). Net price 3 × 1-mg vials = £43.50 (hosp. only)

### 7.1.2 Mifepristone

**Mifepristone**, an antiprogestogenic steroid, sensitises the myometrium to prostaglandin-induced contractions and ripens the cervix. For termination of pregnancy, a single dose of mifepristone is followed by administration of a prostaglandin (gemeprost or misoprostol [unlicensed]). Guidelines of the Royal College of Obstetricians and Gynaecologists (September 2004) include the following [unlicensed] regimens for inducing medical abortion:

- For gestation up to 9 weeks, mifepristone 200 mg by mouth followed 1–3 days later by misoprostol 800 micrograms vaginally; in women at more than 7 weeks gestation (49–63 days), if the abortion has not occurred 4 hours after misoprostol, a further dose of misoprostol 400 micrograms may be given vaginally or by mouth

- For gestation between 9 and 13 weeks, mifepristone 200 mg by mouth followed 36–48 hours later by misoprostol 800 micrograms vaginally followed if necessary by a maximum of 4 further doses at 3-hourly intervals of misoprostol 400 micrograms vaginally or by mouth

- For gestation between 15 and 24 weeks, mifepristone 200 mg by mouth followed 36–48 hours later by misoprostol 800 micrograms vaginally then a maximum of 4 further doses at 3-hourly intervals of misoprostol 400 micrograms by mouth

**Indications** see under dose

**Caution** asthma (avoid if severe and uncontrolled); haemorrhagic disorders and anticoagulant therapy; prosthetic heart valve or history of endocarditis (see section 5.1.2); risk factors for or existing cardiovascular disease; adrenal suppression (may require corticosteroid); **interactions**: Appendix 1 (mifepristone)

**Important** For warnings relating to use of gemeprost in a patient undergoing induction of abortion with mifepristone, see under Gemeprost

**Contra-indications** uncontrolled severe asthma; suspected ectopic pregnancy (use other specific means of termination); chronic adrenal failure; acute porphyria (section 9.8.2); hepatic impairment; renal impairment; breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal cramps; uterine contractions, vaginal bleeding (sometimes severe) may occur between administration of mifepristone and surgery (and rarely abortion may occur before surgery); less commonly hypersensitivity reactions including rash and urticaria; rarely hypotension, malaise, headache, fever, hot flushes, dizziness, and chills; infections (including toxic shock syndrome) also reported

**Dose**

- Medical termination of intra-uterine pregnancy of up to 49 days gestation, **by mouth**, mifepristone 600 mg as a single dose under medical supervision followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg **by vagina** or misoprostol 400 micrograms **by mouth** [unlicensed]; alternative regimen, mifepristone 200 mg **by mouth** as a single dose followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg **by vagina**; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion (if treatment fails essential that pregnancy be terminated by another method) and to assess vaginal bleeding

- Medical termination of intra-uterine pregnancy of 50–63 days gestation, **by mouth**, mifepristone 600 mg (200 mg also effective) as a single dose under medical supervision, followed 36–48 hours later (unless abortion already complete) by gemeprost 1 mg **by vagina**; observe for at least 3 hours (or until bleeding or pain at acceptable level); follow-up visit within 2 weeks to verify complete expulsion (if treatment fails essential that pregnancy be terminated by another method) and to assess vaginal bleeding

- Cervical ripening before mechanical cervical dilatation for termination of pregnancy of up to 84 days gestation, **by mouth**, mifepristone 200 mg as a single dose under medical supervision 36–48 hours before procedure

- Termination of pregnancy of 13–24 weeks gestation (in combination with a prostaglandin), **by mouth**, mifepristone 600 mg (200 mg may be effective) as a single dose under medical supervision followed 36–48 hours later by gemeprost 1 mg **by vagina** every 3 hours up to max. 5 mg or misoprostol (see above [unlicensed]); if abortion does not occur, 24 hours after start of treatment repeat course of gemeprost 1 mg **by vagina** up to max. 5 mg (if treatment fails pregnancy should be terminated by another method); follow-up visit after appropriate interval to assess vaginal bleeding recommended

**Note** Careful monitoring of blood pressure and pulse essential for 3 hours after administration of gemeprost pessary (risk of profound hypotension)

- Labour induction in fetal death **in utero** where prostaglandin or oxytocin inappropriate, **by mouth**, mifepristone 600 mg daily as a single dose for 2 days under medical supervision; if labour not started within 72 hours of first dose, another method should be used

**Mife glyne** (Exelgyn) **Tablets**, yellow, mifepristone 200 mg. Net price 3-tab pack = £41.83 (supplied to NHS hospitals and premises approved under Abortion Act 1967). Label: 10, patient information leaflet
7 Obstetrics, gynaecology, and urinary-tract disorders

7.1.3 Myometrial relaxants

Tocolytic drugs postpone premature labour and they are used with the aim of reducing harm to the child. However, there is no satisfactory evidence that the use of these drugs reduces mortality. The greatest benefit is gained by using the delay to administer corticosteroid therapy or to implement other measures which improve perinatal health (including transfer to a unit with neonatal intensive care facility).

The oxytocin receptor antagonist, atosiban, is licensed for the inhibition of uncomplicated premature labour between 24 and 33 weeks of gestation. Atosiban may be preferable to a beta agonist because it has fewer side-effects.

The dihydropyridine calcium-channel blocker nifedipine (section 2.6.2) also has fewer side-effects than a beta agonist. Nifedipine [unlicensed indication] can be given initially in a dose of 20 mg followed by 10–20 mg 3–4 times daily adjusted according to uterine activity.

A beta agonist (ritodrine, salbutamol or terbutaline) is used for inhibiting uncomplicated premature labour between 24 and 33 weeks of gestation and it may permit a delay in delivery of at least 48 hours. Prolonged therapy should be avoided since risk to the mother increases after 48 hours and there is a lack of evidence of benefit from further treatment; maintenance treatment is therefore not recommended.

Indometacin (indomethacin) (section 10.1.1), a cyclooxygenase inhibitor, also inhibits labour [unlicensed indication] and it can be useful in situations where a beta agonist is not appropriate; however, there are concerns about neonatal complications such as transient impairment of renal function and premature closure of ductus arteriosus.

**Atosiban**

**ATOSIBAN**

**Indications** uncomplicated premature labour (see notes above)

**Cautions** monitor blood loss after delivery; intra-uterine growth restriction; abnormal placental site; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** eclampsia and severe pre-eclampsia, intra-uterine infection, intra-uterine fetal death, antepartum haemorrhage (requiring immediate delivery), placenta praevia, abruptio placenta, intra-uterine growth restriction with abnormal fetal heart rate, premature rupture of membranes after 30 weeks’ gestation

**Side-effects** nausea, vomiting, tachycardia, hypotension, headache, dizziness, hot flushes, hyperglycaemia, injection-site reaction; less commonly pruritus, rash, fever, insomnia

**Dose**
- By intravenous injection, initially 6.75 mg over 1 minute, then by intravenous infusion 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours; max. duration of treatment 48 hours

**Tractocile® (Ferring)**

**Injection**, atosiban (as acetate) 7.5 mg/mL, net price 0.9-mL (6.75-mg) vial = £18.60

**Concentrate for intravenous infusion**, atosiban (as acetate) 7.5 mg/mL, net price 5-mL vial = £53.35

**Beta, agonists**

**Cautions** Beta agonists should be used with caution in patients with suspected cardiovascular disease (such patients should be assessed by a cardiologist before initiating therapy—see also Contra-indications, below), hypertension, mild to moderate pre-eclampsia, hyperthyroidism, and hypokalaemia (particular risk with potassium-depleting diuretics—see also CSM advice, p. 153). It is important to monitor pulse rate (should not exceed 140 beats per minute), ECG (discontinue treatment if signs of myocardial ischaemia develop), and the patient’s fluid and electrolyte status (avoid overhydration—discontinue drug immediately and initiate diuretic therapy if pulmonary oedema occurs). Beta agonists should also be used with caution in diabetes—monitor blood glucose (risk of hyperglycaemia and ketoacidosis, especially with intravenous beta agonists).

**Contra-indications** Beta agonists are contra-indicated in cardiac disease and in patients with significant risk factors for myocardial ischaemia; they should also be avoided in antepartum haemorrhage, intra-uterine infection, intra-uterine fetal death, placenta praevia, abruptio placenta, threatened miscarriage, cord compression, and eclampsia or severe pre-eclampsia.

**Side-effects** Side-effects of the beta agonists include nausea, vomiting, pulmonary oedema (see Cautions above and under Ritodrine dose), palpitation, tachycardia, arrhythmias, myocardial ischaemia, peripheral vasodilation, headache, tremor, hyperglycaemia, hypokalaemia (see Cautions), muscle cramps and tension, and hypersensitivity reactions (including angioedema, urticaria, rash, bronchospasm, hypotension, and collapse).

**RITODRINE HYDROCHLORIDE**

**Indications** uncomplicated premature labour (see notes above)

**Cautions** see notes above; **interactions**: Appendix 1 (sympathomimetics and sympathomimetics, beta )

**Contra-indications** see notes above

**Side-effects** see notes above; also reported flushing, sweating; salivary gland enlargement; leucopenia and agranulocytosis on prolonged administration (several weeks); liver function abnormalities (including increased transaminases and hepatitis)

**Dose**
- By intravenous infusion (important: minimum fluid volume, see below), initially 50 micrograms/minute, increased gradually according to response by 50 micrograms/minute every 10 minutes until contractions stop or maternal heart rate reaches 140 beats per minute; continue for 12–48 hours after contractions cease (usual rate 150–350 micrograms/minute); max. rate 350 micrograms/minute; or by intramuscular injection, 10 mg every 3–8 hours continued for 12–48 hours after contractions
by intravenous infusion  

**Dose**  
see notes above; also reported sleep disturbances and behavioural disturbances  

**Side-effects**  
see notes above  

**Contra-indications**  
see notes above; see also Oestrogens for HRT (section 6.4.1.1); pregnancy and breastfeeding  

**Cautions**  
complicated premature labour (see Indications).  

**Interactions:** Venusam (Alphapharm)  
10 mg, net price 90-tab pack = £30.40  

**Injection**, ritodrine hydrochloride 10 mg/mL, net price 5-mL amp = £3.55  

**SALBUTAMOL**  
(Albuterol)  

**Indications**  
uncomplicated premature labour (see notes above); asthma (section 3.1.1)  

**Cautions**  
see notes above; interactions: Appendix 1 (sympathomimetics, beta)  

**Contra-indications**  
see notes above  

**Side-effects**  
see notes above  

**Dose**  
- By intravenous infusion, initially 10 micrograms/minute, increased gradually according to response at 10-minute intervals until contractions diminish then increase rate slowly until contractions cease (max. rate 45 micrograms/minute); maintain rate for 1 hour after contractions have stopped, then gradually reduce by 50% every 6 hours; then by mouth (but see notes above), 4 mg every 6–8 hours  

**Preparations**  
Section 3.1.1.1  

**TERBUTALINE SULPHATE**  

**Indications**  
uncomplicated premature labour (see notes above); asthma (section 3.1.1)  

**Cautions**  
see notes above; interactions: Appendix 1 (sympathomimetics, beta)  

**Contra-indications**  
see notes above  

**Side-effects**  
see notes above; also reported sleep disturbances and behavioural disturbances  

**Dose**  
- By intravenous infusion, 5 micrograms/minute for 20 minutes, increased every 20 minutes in steps of 2.5 micrograms/minute until contractions have ceased (more than 10 micrograms/minute should seldom be given—20 micrograms/minute should not be exceeded), continue for 1 hour then decrease every 20 minutes in steps of 2.5 micrograms/minute to lowest dose that maintains suppression, continue at this level for 12 hours then by mouth (but see notes above), 5 mg every 8 hours for as long as is desirable to prolong pregnancy (or alternatively follow the intravenous infusion by subcutaneous injection) 250 micrograms every 6 hours for a few days then by mouth (as above)  

**Preparations**  
Section 3.1.1.1  

**OESTROGENS, TOPICAL**  

**Indications**  
see notes above  

**Cautions**  
see notes above; see also Oestrogens for HRT (section 6.4.1.1); interrupt treatment periodically to assess need for continued treatment  

**Contra-indications**  
see notes above; see also Oestrogens for HRT (section 6.4.1.1); pregnancy and breastfeeding  

**Side-effects**  
see notes above; see also Oestrogens for HRT (section 6.4.1.1); local irritation
Ortho-Gynest® (Janssen-Cilag) (Fr)

Intravaginal cream, estradiol 0.01%. Net price 80 g with applicator = £2.53
Excipients include arachis (peanut) oil
Condoms damages latex condoms and diaphragms
Dose insert 1 applicatorful daily, preferably in evening; reduced to 1 applicatorful twice a week; attempts to reduce or discontinue should be made at 3–6 month intervals with re-examination

Vaginal candidiasis almost invariably associated with vaginal infection
Candidal vulvitis
Fungal infections

Non-hormonal preparations for vaginal atrophy
Replens MD® and Sylik® are acidic, non-hormonal vaginal moisturisers; Replens MD® provides a high moisture content for up to 3 days.

Oral treatment of vaginal infection with oral fluconazole or itraconazole (section 5.2) is also effective; oral ketoconazole has been associated with fatal hepatotoxicity (see section 5.2 for CSM warning).

Vulvovaginal candidiasis in pregnancy Vulvovaginal candidiasis is common during pregnancy and can be treated with vaginal application of an imidazole (such as clotrimazole), and a topical imidazole cream for vulvitis. Pregnant women need a longer duration of treatment, usually about 7 days, to clear the infection. Oral antifungal treatment should be avoided during pregnancy.

Recurrent vulvovaginal candidiasis Recurrence of vulvovaginal candidiasis is particularly likely if there are predisposing factors such as antibacterial therapy, pregnancy, diabetes mellitus and possibly oral contraceptive use. Reservoirs of infection may also lead to recontamination and should be treated; these include other skin sites such as the digits, nail beds, and umbilicus as well as the gastro-intestinal tract and the bladder. The partner may also be the source of re-infection and, if symptomatic, should be treated with cream at the same time.

Treatment against candida may need to be extended for 6 months in recurrent vulvovaginal candidiasis. Some recommended regimens [all unlicensed] include:
- fluconazole (section 5.2) by mouth 100 mg (as a single dose) every week for 6 months
- clotrimazole vaginally 500-mg pessary (as a single dose) every week for 6 months
- itraconazole (section 5.2) by mouth 400 mg (as 2 divided doses on one day) every month for 6 months.
7.2.2 Vaginal and vulval infections

**Thrush Cream** (topical), clotrimazole 2%, net price 20 g = £3.99

- **Exipients** include benzyl alcohol, ceteareth 20, polysorbates
- **Condoms** damages latex condoms and diaphragms
- **Dose** apply to anogenital area 2–3 times daily

**Vaginal cream (10% VC®)** (Pharm), clotrimazole 10%. Net price 5-g applicator pack = £5.62

- **Exipients** include benzyl alcohol, ceteareth 20, polysorbates
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 5 g at night as a single dose; can be repeated once if necessary

**Note** Brands for sale to the public include Canesten Internal Cream

**Cream Combi**, clotrimazole 10% vaginal cream and 2% topical cream, net price 5-g vaginal cream (with applicator) and 10-g topical cream = £5.76

- **Exipients** include benzyl alcohol, ceteareth 20, polysorbates
- **Condoms** damages latex condoms and diaphragms
- **Dose** see under individual components

**Pessaries**, clotrimazole 100 mg, net price 6 pessaries with applicator = £3.63; 200 mg, 3 pessaries with applicator = £3.63

- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 200 mg for 3 nights or 100 mg for 6 nights; course can be repeated once if necessary

**Pessary**, clotrimazole 500 mg. Net price 1 with applicator = £3.25

- **Exipients** none as listed in section 13.1.3
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 1 pessary at night as a single dose; can be repeated once if necessary

**Combi**, clotrimazole 500-mg pessary and cream (topical) 2%. Net price 1 pessary and 10-g cream = £5.21

- **Condoms** damages latex condoms and diaphragms
- **Dose** see under individual components

**Ecostatin®** (Squibb)

- **Cream** (topical), econazole nitrate 1%. Net price 15 g = £1.49; 30 g = £2.75
- **Exipients** include butylated hydroxyanisole, fragrance
- **Condoms** damages latex condoms and diaphragms
- **Dose** apply to anogenital area twice daily

**Pessaries** (Pharm), econazole nitrate 150 mg. Net price 3 with applicator = £3.35

- **Exipients** none as listed in section 13.1.3
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 1 pessary for 3 nights; course can be repeated once if necessary

**Pessary (Ecostatin-1®)** (Pharm), econazole nitrate 150 mg, formulated for single-dose therapy. Net price 1 pessary with applicator = £3.35

- **Exipients** none as listed in section 13.1.3
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 1 pessary at night as a single dose; can be repeated once if necessary

**Twinpack** (Pharm), econazole nitrate 150-mg pessaries and cream 1%. Net price 3 pessaries and 15-g cream = £4.35

- **Condoms** damages latex condoms and diaphragms
- **Dose** see under individual components

**Gyno-Daktarin®** (Janssen-Cilag) (Pharm)

- **Intravaginal cream**, miconazole nitrate 2%. Net price 78 g with applicators = £4.60
- **Exipients** include butylated hydroxyanisole
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 5-g applicatorful once daily for 10–14 days or twice daily for 7 days; course can be repeated once if necessary; topical, apply to anogenital area twice daily

**Ovule (= vaginal capsule)** (Gyno-Daktarin 1®), miconazole nitrate 1.2 g in a fatty basis. Net price 1 ovule = £3.12

- **Exipients** include hydroxybenzazides (parabens)
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 1 ovule at night as a single dose; can be repeated once if necessary

**Gyno-Pevaryl®** (Janssen-Cilag) (Pharm)

- **Cream**, econazole nitrate 1%. Net price 15 g = £1.40; 30 g = £3.21
- **Exipients** none as listed in section 13.1.3
- **Condoms** damages latex condoms and diaphragms
- **Dose** insert 5-g applicatorful intravaginally and apply to vulva at night for at least 14 nights; course can be repeated once if necessary

**Pessaries**, econazole nitrate 150 mg. Net price 3 pessaries = £2.95

- **Exipients** none as listed in section 13.1.3
- **Condoms** damages latex condoms and diaphragms
- **Dose** ADULT and ADOLESCENT over 16 years, insert 1 pessary for 3 nights; course can be repeated once if necessary

**Pessary (Gyno-Pevaryl®)**, econazole nitrate 150 mg, formulated for single-dose therapy. Net price 1 pessary with applicator = £3.13

- **Exipients** none as listed in section 13.1.3
- **Condoms** damages latex condoms and diaphragms
- **Dose** ADULT and ADOLESCENT over 16 years, insert 1 pessary at night as a single dose; can be repeated once if necessary

**Nizoral®** (Janssen-Cilag) (Pharm)

- **Cream** (topical), ketoconazole 2%. Net price 30 g = £3.54
- **Exipients** include polysorbates, propylene glycol, stearyl alcohol
- **Condoms** effect on latex condoms and diaphragms not yet known
- **Dose** apply to anogenital area once or twice daily

**Other infections**

Vaginal preparations intended to restore normal acidity may prevent recurrence of vaginal infections and permit the re-establishment of the normal vaginal flora.

**Trichomonal infections** commonly involve the lower urinary tract as well as the genital system and need systemic treatment with metronidazole or tinidazole (section 5.1.11). **Bacterial infections** with Gram-negative organisms are particularly common in association with gynaecological operations and trauma. Metronidazole is effective against certain Gram-negative organisms, especially *Bacteroides* spp. and can be used prophylactically in gynaecological surgery.

Clindamycin cream and metronidazole gel are indicated for bacterial vaginosis. The antiviral drugs aciclovir, foscarnet, and valaciclovir can be used in the treatment of genital infection due to *herpes simplex* virus, the HSV type 2 being a major cause of genital ulceration. They have a beneficial effect on virus shedding and healing, generally giving relief from pain and other symptoms. See section 5.3.2.1 for systemic preparations, and section 13.10.3 for topical preparations.

**PREPARATIONS FOR OTHER VAGINAL INFECTIONS**

**Dalacin®** (Pharmacia) (Pharm)

- **Cream**, clindamycin 2% (as phosphate). Net price 40-g pack with 7 applicators = £10.86
- **Exipients** include benzy alcohol, ceteareth 20, polysorbates, propylene glycol
- **Condoms** damages latex condoms and diaphragms
Obstetrics, gynaecology, and urinary-tract disorders

1. See Department of Health Guidance (July 2004): Best of combined oral contraceptives include: most effective preparations for general use. Advantages progestogen ('combined oral contraceptives') are the Oral contraceptives containing an oestrogen and a progestogen in each active tablet are termed ‘monophasic’; those with varying amounts of the two hormones according to the stage of the cycle are termed ‘biphasic’ and ‘triphasic’. A transdermal patch containing an oestrogen with a progestogen is also available.

Choice The oestrogen content of combined oral contraceptives ranges from 20 to 40 micrograms. Generally a preparation with the lowest oestrogen and progestogen content which gives good cycle control and minimal side-effects in the individual woman is chosen.

- **Low strength preparations** (containing ethinylestradiol 20 micrograms) are particularly appropriate for women with risk factors for circulatory disease, provided a combined oral contraceptive is otherwise suitable. It is recommended that the combined oral contraceptive is not continued beyond 50 years of age since more suitable alternatives exist.
- **Standard strength preparations** (containing ethinylestradiol 30 or 35 micrograms or in 30–40 microgram phased preparations) are appropriate for standard use—but see Risk of Venous Thromboembolism below. Phased preparations are generally reserved for women who **either** do not have withdrawal bleeding or who have breakthrough bleeding with monophasic products.

The progestogens desogestrel, drospirenone, and gestodene (in combination with ethinylestradiol) may be considered for women who have side-effects (such as acne, headache, depression, weight gain, breast symptoms, and breakthrough bleeding) with other progestogens. However, women should be advised that desogestrel and gestodene have also been associated with an increased risk of **venous thromboembolism**. Drospirenone, a derivative of spironolactone, has anti-androgenic and anti-mineralocorticoid activity; it should be used with care if an increased plasma-potassium concentration might be hazardous. The progestogen nor-eldigestrom is combined with ethinylestradiol in a transdermal patch.

**Risk of venous thromboembolism** There is an increased risk of venous thromboembolic disease (particularly during the first year) in users of oral contraceptives but this risk is considerably smaller than that associated with pregnancy (about 60 cases of venous thromboembolic disease per 100 000 pregnancies). In all cases the risk of venous thromboembolism increases with age and in the presence of other risk factors for venous thromboembolism (e.g. obesity). The incidence of venous thromboembolism in healthy, non-pregnant women who are not taking an oral contraceptive is about 5–10 cases per 100 000 women per year. For those using combined oral contraceptives containing second-generation progestogens, e.g. levonorgestrel, this incidence is about 15 per 100 000 women per year of use. The risk of venous thromboembolism with transdermal patches may be slightly increased compared with combined oral contraceptives that contain levonorgestrel. Some studies have reported a greater risk of venous thromboembolism in women using combined oral contraceptives containing the third-generation progestogens desogestrel and gestodene; the incidence in these women is about 25 per

---

Side-effects Irritation, cervicitis and vaginitis; poorly absorbed into the blood—very low likelihood of systemic effects (section 5.1.6).

Dose Bacterial vaginosis, insert 5-g applicatorful at night for 3–7 nights.

**Zidoval** (3M) (see section 5.1.11 for systemic effects)

**Vaginal gel**, metronidazole 0.75%. Net price 40-g pack with 5 applicators = £4.31.

Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol.

Cautions Not recommended during menstruation; some absorption may occur, see section 5.1.11 for systemic effects.

Side-effects Local effects including irritation, candidiasis, abnormal discharge, pelvic discomfort.

Dose Bacterial vaginosis, insert 5-g applicatorful at night for 5 nights.

---

**7.3 Contraceptives**

| 7.3.1 Combined hormonal contraceptives |
| 7.3.2 Progestogen-only contraceptives |
| 7.3.3 Spermicidal contraceptives |
| 7.3.4 Contraceptive devices |
| 7.3.5 Emergency contraception |

The Fraser Guidelines should be followed when prescribing contraception for women under 16 years.

**Hormonal contraception** is the most effective method of fertility control, but has major and minor side-effects, especially for certain groups of women.

**Intra-uterine devices** are a highly effective method of contraception but may produce undesirable local side-effects. They are most suitable for older parous women, but less appropriate for younger nulliparous women and for those with an increased risk of pelvic inflammatory disease.

**Barrier methods** alone (condoms, diaphragms, and caps) are less effective but can be very reliable for well-motivated couples if used in conjunction with a spermicide. Occasionally sensitivity reactions occur. A female condom (Femidom®) is also available; it is prelubricated but does not contain a spermicide.

**7.3.1 Combined hormonal contraceptives**

Oral contraceptives containing an oestrogen and a progestogen (‘combined oral contraceptives’) are the most effective preparations for general use. Advantages of combined oral contraceptives include:

- Reliable and reversible;
- Reduced dysmenorrhea and menorrhagia;
- Reduced incidence of menopausal tension;
- Less symptomatic fibroids and functional ovarian cysts;
- Less benign breast disease;
- Reduced risk of ovarian and endometrial cancer;
- Reduced risk of pelvic inflammatory disease, which may be a risk with intra-uterine devices.

---

1. See Department of Health Guidance (July 2004): Best practice guidance for doctors and other health professionals on the provision of advice and treatment to young people under 16 on contraception, sexual and reproductive health. Available at www.dh.gov.uk
100 000 women per year of use. The absolute risk of venous thromboembolism in women using combined oral contraceptives containing these third-generation progestogens is very small and well below the risk associated with pregnancy. The incidence of venous thromboembolism in women using a combined oral contraceptive containing drospirenone is in the same range as that for users of combined oral contraceptives containing other progestogens, including levonorgestrel.

Provided that women are informed of the relative risks of venous thromboembolism and accept them, the choice of oral contraceptive is for the woman together with the prescriber jointly to make in light of her individual medical history and any contra-indications.

Travel

Women taking oral contraceptives, or using the patch, are at an increased risk of deep-vein thrombosis during travel involving long periods of immobility (over 5 hours). The risk may be reduced by appropriate exercise during the journey and possibly by wearing graduated compression hosiery.

Missed pill

The critical time for loss of contraceptive protection is when a pill is omitted at the beginning or end of a cycle (which lengthens the pill-free interval).

If a woman forgets to take a pill, it should be taken as soon as she remembers, and the next one taken at the normal time (even if this means taking 2 pills together). A missed pill is one that is 24 or more hours late. If a woman misses only one pill, she should take an active pill as soon as she remembers and then resume normal pill-taking. No additional precautions are necessary.

If a woman misses 2 or more pills (especially from the first 7 in a packet), she may not be protected. She should take an active pill as soon as she remembers and then resume normal pill-taking. In addition, she must either abstain from sex or use an additional method of contraception such as a condom for the next 7 days. If these 7 days run beyond the end of the packet, the next packet should be started at once, omitting the pill-free interval (or, in the case of everyday (ED) pills, omitting the 7 inactive tablets).

Emergency contraception (section 7.3.5) is recommended if 2 or more combined oral contraceptive tablets are missed from the first 7 tablets in a packet and unprotected intercourse has occurred since finishing the last packet.

Note

The Faculty of Sexual and Reproductive Healthcare offers 2 different types of missed pill advice depending on the ethinylestradiol content of the contraceptive pill. The missed pill information above offers the same advice regardless of the ethinylestradiol content of the contraceptive pill; it is a simplified, more cautious version of advice issued by The Faculty of Sexual and Reproductive Healthcare.

Delayed application or detached patch

If a patch is partly detached for less than 24 hours, reap ply to the same site or replace with a new patch immediately; no additional contraception is needed and the next patch should be applied on the usual change day. If a patch remains detached for more than 24 hours or if the user is not aware when the patch became detached then stop the current contraceptive cycle and start a new cycle by applying a new patch, giving a new ‘Day 1’; an additional non-hormonal contraceptive must be used concurrently for the first 7 days of the new cycle.

If application of a new patch at the start of a new cycle is delayed, contraceptive protection is lost. A new patch should be applied as soon as remembered giving a new ‘Day 1’; additional non-hormonal methods of contraception should be used for the first 7 days of the new cycle. If intercourse has occurred during this extended patch-free interval, a possibility of fertilisation should be considered. If application of a patch in the middle of the cycle is delayed (i.e. the patch is not changed on day 8 or day 15):

- for up to 48 hours, apply a new patch immediately; next patch change day remains the same and no additional contraception is required.
- for more than 48 hours, contraceptive protection may have been lost. Stop the current cycle and start a new 4-week cycle immediately by applying a new patch giving a new ‘Day 1’; additional non-hormonal contraception should be used for the first 7 days of the new cycle.

If the patch is not removed at the end of the cycle (day 22), remove it as soon as possible and start the next cycle on the usual ‘change day’, after day 28; no additional contraception is required.

Diarrhoea and vomiting

Vomiting and persistent, severe diarrhoea can interfere with the absorption of combined oral contraceptives. If vomiting occurs within 2 hours of taking a combined oral contraceptive another pill should be taken as soon as possible. In cases of persistent vomiting or severe diarrhoea lasting more than 24 hours, additional precautions should be used during and for 7 days after recovery (see also under Missed pill, above). If the vomiting and diarrhoea occurs during the last 7 tablets, the next pill-free interval should be omitted (in the case of ED tablets the inactive ones should be omitted).

Interactions

The effectiveness of both combined and progestogen-only oral contraceptives can be considerably reduced by interaction with drugs that induce hepatic enzyme activity (e.g. carbamazepine, griseofulvin, modafinil, nelfinavir, nevirapine, oxcarbazepine, phenytoin, phenobarbital, primidone, ritonavir, St John’s Wort, topiramate, and, above all, rifabutin and rifampicin). A condom together with a long-acting method, such as an injectable contraceptive, may be more suitable for patients with HIV infection or at risk of HIV infection; advice on the possibility of interaction with antiretroviral drugs should be sought from HIV specialists.

For a short course of an enzyme-inducing drug, the dose of combined oral contraceptives should be adjusted to provide ethinylestradiol 50 micrograms or more daily [unlicensed use]; furthermore, additional contraceptive precautions should be taken whilst taking the enzyme-inducing drug and for 4 weeks after stopping it.

Women requiring a long-term course of an enzyme-inducing drug should be encouraged to consider a contraceptive method that is unaffected by the interacting drug. In women unable to use an alternative method of contraception (for rifampicin and rifabutin see also below), a regimen of combined oral contraceptives should be taken which provides a daily intake of ethinylestradiol 50 micrograms or more [unlicensed use]; ‘tricycling’ (i.e. taking 3 or 4 packets of monophasic tablets without a break followed by a short tablet-free interval of 4 days) is recommended (but women should...
be warned of uncertainty about the effectiveness of this regimen. Rifampicin and rifabutin are such potent enzyme-inducing drugs that an alternative method of contraception (such as an IUD) is always recommended. Since enzyme activity does not return to normal for several weeks after stopping an enzyme-inducing drug, appropriate contraceptive measures are required for 4 to 8 weeks after stopping.

The effectiveness of contraceptive patches can also be reduced by drugs that induce hepatic enzyme activity. Additional contraceptive precautions are required whilst taking the enzyme-inducing drug and for 4 weeks after stopping. If concomitant administration runs beyond the 3 weeks of patch treatment, a new treatment cycle should be started immediately without a patch-free break. For women taking enzyme-inducing drugs over a long period, another method of contraception should be considered.

Some antibacterials that do not induce liver enzymes (e.g. amoxicillin, doxycycline) may reduce the efficacy of combined oral contraceptives by impairing the bacterial flora responsible for recycling ethinylenestradiol from the large bowel. Additional contraceptive precautions should be taken whilst taking a short course of an antibacterial drug that is not enzyme-inducing and for 7 days after stopping. If these 7 days run beyond the end of a packet the next packet should be started immediately without a break (in the case of ED tablets the inactive ones should be omitted). If the antibacterial course exceeds 3 weeks, the bacterial flora develop antibacterial resistance and additional precautions become unnecessary unless a new antibacterial is prescribed; additional precautions are also unnecessary if a woman starting a combined oral contraceptive has been on a course of antibacterial therapy for 3 weeks or more.

It is possible that some antibacterials affect the efficacy of contraceptive patches. Additional contraceptive precautions are recommended during concomitant use and for 7 days after discontinuation of an antibacterial that is not enzyme-inducing (except tetracycline). If concomitant administration runs beyond the 3 weeks of patch treatment, a new treatment cycle should be started immediately without a patch-free break. If the antibacterial course exceeds 3 weeks, additional precautions become unnecessary unless a new antibacterial is prescribed; additional precautions are also unnecessary if a woman starting a contraceptive patch has been on a course of antibacterial therapy for 3 weeks or more.

**Surgery** Oestrogen-containing contraceptives should preferably be discontinued (and adequate alternative contraceptive arrangements made) 4 weeks before major elective surgery and all surgery to the legs or surgery which involves prolonged immobilisation of a lower limb; they should normally be recommenced at the first menses occurring at least 2 weeks after full mobilisation. A depot injection of a progestogen-only contraceptive may be offered and the oestrogen-containing contraceptive restarted later—if preferred before the next injection would be due. When discontinuation of an oestrogen-containing contraceptive is not possible, e.g. after trauma or if a patient admitted for an elective procedure is still on an oestrogen-containing contraceptive, thromboprophylaxis (with heparin and graduated compression hosiery) is advised. These recommendations do not apply to minor surgery with short duration of anaesthesia, e.g. laparoscopic sterilisation or tooth extraction, or to women using oestrogen-free hormonal contraceptives (whether by mouth or by injection).

**Reason to stop immediately** Combined hormonal contraceptives or hormone replacement therapy (HRT) should be stopped (pending investigation and treatment), if any of the following occurs:

- sudden severe chest pain (even if not radiating to left arm);
- sudden breathlessness (or cough with blood-stained sputum);
- unexplained swelling or severe pain in calf of one leg;
- severe stomach pain;
- serious neurological effects including unusual severe, prolonged headache especially if first time or getting progressively worse or sudden partial or complete loss of vision or sudden disturbance of hearing or other perceptual disorders or dysphasia or bad fainting attack or collapse or first unexplained epileptic seizure or weakness, motor disturbances, very marked numbness suddenly affecting one side or one part of body;
- hepatitis, jaundice, liver enlargement;
- blood pressure above systolic 160 mmHg or diastolic 95 mmHg;
- prolonged immobility after surgery or leg injury;
- detection of a risk factor which contra-indicates treatment (see Cautions and Contra-indications under Combined Hormonal Contraceptives below or under Oestrogens for HRT (section 6.4.1.1)).

**COMBINED HORMONAL CONTRACEPTIVES**

**Indications** contraception; menstrual symptoms (section 6.4.1.2)

**Contra-indications**

- Use with caution if any of the following factors present but avoid if two or more factors present:
  - family history of venous thromboembolism in first-degree relative aged under 45 years (avoid contraceptive containing desogestrel or gestodene, or if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
  - obesity—body mass index above 30 kg/m² (avoid if body mass index above 30 kg/m²);
  - long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
  - history of superficial thrombophlebitis;
  - age over 35 years (avoid if over 50 years);
  - smoking.

**Risk factors for venous thromboembolism** See also notes above. Use with caution if any of the following factors present but avoid if two or more factors present:

- family history of venous thromboembolism in first-degree relative aged under 45 years (avoid contraceptive containing desogestrel or gestodene, or if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));
- obesity—body mass index above 30 kg/m² (avoid if body mass index above 30 kg/m²);
- long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);
- history of superficial thrombophlebitis;
- age over 35 years (avoid if over 50 years);
- smoking.

**Risk factors for arterial disease** Use with caution if any of the following factors present but avoid if two or more factors present:

- family history of arterial disease in first degree relative aged under 45 years (avoid if atherogenic lipid profile);
- diabetes mellitus (avoid if diabetes complications present);
- hypertension—blood pressure above systolic 140 mmHg or diastolic 90 mmHg (avoid if blood pressure above systolic 160 mmHg or diastolic 95 mmHg).
• smoking (avoid if smoking 40 or more cigarettes daily);
• age over 35 years (avoid if over 50 years);
• obesity (avoid if body mass index above 39 kg/m);
• migraine—see below.

Migraine Women should report any increase in headache frequency or onset of focal symptoms (discontinue immediately and refer urgently to neurology expert if focal neurological symptoms not typical of aura persist for more than 1 hour—see also Reason to stop immediately in notes above); contra-indicated in
• migraine with typical focal aura,
• severe migraine regularly lasting over 72 hours despite treatment,
• migraine treated with ergot derivatives; use with caution in
• migraine without focal aura,
• migraine controlled with SHT agonist (section 4.7.4.1).

Contra-indications see notes above; also pregnancy (Appendix 4); personal history of venous or arterial thrombosis, severe or multiple risk factors for arterial disease or for venous thromboembolism (see above), heart disease associated with pulmonary hypertension or risk of embolus; sclerosing treatment for varicose veins; migraine (but see above); transient cerebral ischaemic attacks without headaches; liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal); systemic lupus erythematosus; acute porphyria (section 9.8.2), liver tumour; gallstones; active trophoblastic disease (until return to normal of urine and plasma gonadotrophin concentration); history of haemolytic uraemic syndrome or history during pregnancy of pruritus, cholestasis jaundice, oedema, pemphigoid gestations; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable; undiagnosed vaginal bleeding; breast-feeding (until weaning or for 6 months after birth—Appendix 5)

Side-effects see notes above; also nausea, vomiting, abdominal cramps, changes in body-weight, liver impairment, hepatic tumours; fluid retention, thrombosis (more common when factor V Leiden present or in blood groups A, B, and AB; see also notes above), hypertension, changes in lipid metabolism; headache, depression, oedema, nervousness, irritability; changes in libido, breast tenderness, enlargement, and secretion; reduced menstrual loss, ‘spotting’ in early cycles, absence of withdrawal bleeding, amenorrhoea after discontinuation, changes in vaginal discharge, cervical erosion, contact lenses may irritate, visual disturbances; leg cramps; skin reactions, chloasma, photosensitivity; rarely gallstones and systemic lupus erythematosus

Breast cancer There is a small increase in the risk of having breast cancer diagnosed in women taking the combined oral contraceptive pill; this relative risk may be due to an earlier diagnosis. In users of combined oral contraceptive pills the cancers are more likely to be localised to the breast. The most important factor for diagnosing breast cancer appears to be the age at which the contraceptive is stopped rather than the duration of use; any increase in the rate of diagnosis diminishes gradually during the 10 years after stopping and disappears by 10 years.

Cervical cancer Use of combined oral contraceptives for 5 years or longer is associated with a small increased risk of cervical cancer; the risk diminishes after stopping and disappears by about 10 years. The risk of cervical cancer with transdermal patches is not yet known.

Note The possible small increase in the risk of breast cancer and cervical cancer should be weighed against the protective effect against cancers of the ovary and endometrium

Dose
• By mouth, each tablet should be taken at approximately same time each day; if delayed by longer than 24 hours contraceptive protection may be lost
• 21-day combined (monophasic) preparations, 1 tablet daily for 21 days; subsequent courses repeated after a 7-day interval (during which withdrawal bleeding occurs); first course usually started on day 1 of cycle—if starting on day 4 of cycle or later additional precautions (barrier methods) necessary during first 7 days

Every day (ED) combined (monophasic) preparations, 1 active tablet starting on day 1 of cycle (see also under preparations below)—if starting on day 4 of cycle or later additional precautions (barrier methods) necessary during first 7 days; withdrawal bleeding occurs when inactive tablets being taken; subsequent courses repeated without interval

Biphasic and triphasic preparations, see under individual preparations below

Changing to combined preparation containing different phases 21-day combined preparations: continue current pack until last tablet and start first tablet of new brand the next day. If a 7-day break is taken before starting new brand, additional precautions (barrier methods) should be used during first 7 days of taking the new brand.

Every Day (ED) combined preparations: start the new brand (first tablet of a 21-day preparation or the first active tablet of an ED preparation) the day after taking the last active tablet of previous brand (omitting the inactive tablets).

Changing from progestogen-only tablet Start on day 1 of menstruation or any day if amenorrhoea present and pregnancy has been excluded.

Secondary amenorrhoea (exclude pregnancy) Start any day, additional precautions (barrier methods) necessary during first 7 days.

After childbirth (not breast-feeding) Start 3 weeks after birth (increased risk of thrombosis if started earlier); later than 3 weeks postpartum additional precautions (barrier methods) necessary for first 7 days.

Not recommended if woman breast-feeding—oral progestogen-only contraceptive preferred.

After abortion or miscarriage Start same day.

• By transdermal application, apply first patch on day 1 of cycle, change patch on days 8 and 15; remove third patch on day 22 and apply new patch after 7-day patch-free interval to start subsequent contraceptive cycle.

Note If first patch applied later than day 1, additional precaution (abstinence or barrier methods) should be used for the next 7 days

Changing from combined oral contraception Apply patch on the first day of withdrawal bleeding; if no withdrawal bleeding within 5 days of taking last active tablet, rule out pregnancy before applying first patch. Unless patch is applied on first day of withdrawal bleeding, additional precautions (barrier methods) should be used concurrently for first 7 days

Changing from progestogen-only method From an implant, apply first patch on the day implant removed; from an injection, apply first patch when next injection due; from oral progestogen, first patch may be started on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days.

After childbirth (not breast-feeding) Start 4 weeks after birth; if started later than 4 weeks after birth additional precautions (barrier methods) should be used for first 7 days

After abortion or miscarriage Before 20 weeks’ gestation—oral progestogen-only contraceptive preferred. After 20 weeks’ gestation start on day 21 after abortion or on the first day of first spontaneous menstruation; additional precautions (barrier methods) should be used for first 7 days after applying the patch
### Low strength (oral)

**Ethinylestradiol with Norethisterone**

*Loestrin 20° (Galén)*

- **Tablets**, blue, norethisterone acetate 1 mg, ethinylestradiol 20 micrograms. Net price 3 × 21-tab pack = £7.20
- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

**Ethinylestradiol with Desogestrel**

- **See Risk of Venous Thromboembolism in notes above before prescribing**

*Mericon° (Organon)*

- **Tablets**, desogestrel 150 micrograms, ethinylestradiol 20 micrograms. Net price 3 × 21-tab pack = £7.97
- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

**Ethinylestradiol with Drospirenone**

*Yaz° (Bayer)*

- **Tablets**, 1/5 c, pink, drospirenone 3 mg, ethinylestradiol 20 micrograms, white inactive tablets. Net price 3 × 28-tab (4 are inactive) pack = £19.80
- **Cautions** use with care if increased plasma-potassium concentration might be hazardous; renal impairment (Appendix 3)
- **Dose** 1 tablet daily for 28 days starting on day 1 of cycle with active tablet (withdrawal bleeding begins when inactive tablets being taken), subsequent courses repeated without interval; for starting routines see also under Dose above

**Ethinylestradiol with Gestodene**

- **See Risk of Venous Thromboembolism in notes above before prescribing**

*Femodette° (Schering Health)*

- **Tablets**, s/c, gestodene 75 micrograms, ethinylestradiol 20 micrograms, net price 3 × 21-tab pack = £9.45
- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

*Sunya 20/75° (Stragen)*

- **Tablets**, s/c, gestodene 75 micrograms, ethinylestradiol 20 micrograms, net price 3 × 21-tab pack = £6.62
- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

**Low strength (transdermal)**

**Ethinylestradiol with Norelgestromin**

*Eva° (Janssen-Cilag)*

- **Patches**, self-adhesive (releasing ethinylestradiol approx. 20 micrograms/24 hours and norelgestromin approx. 150 micrograms/24 hours); net price 9-patch pack = £16.26. Counselling, administration
- **Dose** 1 patch to be applied once weekly for three weeks, followed by a 7-day patch-free interval; subsequent courses repeated after 7-day patch-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above
- **Note** Adhesives or bandages should not be used to hold patch in place. If patch no longer sticky do not reapply but use a new patch.

*The Scottish Medicines Consortium has advised (September 2003) that Eva patches should be restricted for use in women who are likely to comply poorly with combined oral contraceptives*

**Standard strength**

**Ethinylestradiol with Levonorgestrel**

*Logynon° (Schering Health)*

- **6 light brown tablets**, ethinylestradiol 30 micrograms, levonorgestrel 50 micrograms;
- **5 white tablets**, ethinylestradiol 40 micrograms, levonorgestrel 75 micrograms;
- **10 ochre tablets**, ethinylestradiol 30 micrograms, levonorgestrel 125 micrograms.
- **Net price** 3 × 21-tab pack = £4.12
- **Dose** 1 tablet daily for 21 days, starting with light brown tablet marked 1 on day 1 of cycle; repeat after 7-day tablet-free interval

*Logynon ED° (Schering Health)*

- **6 light brown tablets**, ethinylestradiol 30 micrograms, levonorgestrel 50 micrograms;
- **5 white tablets**, ethinylestradiol 40 micrograms, levonorgestrel 75 micrograms;
- **10 ochre tablets**, ethinylestradiol 30 micrograms, levonorgestrel 125 micrograms;
- **7 white, inactive tablets**.
- **Net price** 3 × 28-tab pack = £4.12
- **Dose** 1 tablet daily for 28 days, starting on day 1 of cycle with active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval, for starting routines see under Dose above

*Microgynon 30° (Schering Health)*

- **Tablets**, s/c, levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £2.99
- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

*Microgynon 30 ED° (Schering Health)*

- **Tablets**, beige, levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms, white inactive tablets. Net price 3 × 28-tab (7 are inactive) pack = £2.69
- **Dose** 1 tablet daily for 28 days starting on day 1 of cycle with active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval, for starting routines see also under Dose above

*Ovranette° (Wyeth)*

- **Tablets**, levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £2.29
- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

**Ethinylestradiol with Norethisterone**

*BiNovum° (Janssen-Cilag)*

- **7 white tablets**, ethinylestradiol 35 micrograms, norethisterone 500 micrograms;
- **14 peach tablets**, ethinylestradiol 35 micrograms, norethisterone 1mg.
- **Net price** 3 × 21-tab pack = £2.08
- **Dose** 1 tablet daily for 21 days, starting with white tablet on day 1 of cycle; repeat after 7-day tablet-free interval

*Brevino° (Pharmacia)*

- **Dose** 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above
7.3.2 Progestogen-only contraceptives

Loestrin 30® (Galén) (FW)
Tablets, pale green, norethisterone acetate 1.5 mg, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £3.90
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Norimin® (Pharmacia) (FW)
Tablets, norethisterone 1 mg, ethinylestradiol 35 micrograms. Net price 3 × 21-tab pack = £2.28
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Ovysmen® (Janssen-Cilag) (FW)
Tablets, norethisterone 500 micrograms, ethinylestradiol 35 micrograms. Net price 3 × 21-tab pack = £1.58
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Synphase® (Pharmacia) (FW)
7 blue tablets, ethinylestradiol 35 micrograms, norethisterone 500 micrograms;
9 white tablets, ethinylestradiol 35 micrograms, norethisterone 1 mg;
5 blue tablets, ethinylestradiol 35 micrograms, norethisterone 500 micrograms.
Net price 21-tab pack = £1.20
Dose 1 tablet daily for 21 days, starting with blue tablet marked 1 on day 1 of cycle; repeat after 7-day tablet-free interval

TriNovum® (Janssen-Cilag) (FW)
7 white tablets, ethinylestradiol 35 micrograms, norethisterone 500 micrograms;
7 light peach tablets, ethinylestradiol 35 micrograms, norethisterone 750 micrograms;
7 peach tablets, ethinylestradiol 35 micrograms, norethisterone 1 mg.
Net price 3 × 21-tab pack = £2.89
Dose 1 tablet daily for 21 days, starting with white tablet on day 1 of cycle; repeat after 7-day tablet-free interval

Ethinylestradiol with Norgestimate
Cilest® (Janssen-Cilag) (FW)
Tablets, blue, norgestimate 250 micrograms, ethinylestradiol 35 micrograms. Net price 3 × 21-tab pack = £5.97, 6 × 21-tab pack = £11.94
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Ethinylestradiol with Desogestrel
See Risk of Venous Thromboembolism in notes above before prescribing

Marvelon® (Organon) (FW)
Tablets, desogestrel 150 micrograms, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £6.70
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Ethinylestradiol with Drospirenone
Yasmin® (Bayer) (FW)
Tablets, f/c, yellow, drospirenone 3 mg, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £14.70

Caution use with care if increased plasma-potassium concentration might be hazardous; renal impairment (Appendix 3)
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Note The Scottish Medicines Consortium has advised (March 2003) that Yasmin is not recommended

Ethinylestradiol with Gestodene
See Risk of Venous Thromboembolism in notes above before prescribing

Femodone® (Schering Health) (FW)
Tablets, s/c, gestodene 75 micrograms, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £7.18
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Femodone® ED (Schering Health) (FW)
Tablets, s/c, gestodene 75 micrograms, ethinylestradiol 30 micrograms. Net price 3 × 28-tab (7 are inactive) pack = £7.18
Dose 1 tablet daily for 28 days, starting on day 1 of cycle with active tablet (withdrawal bleeding occurs when inactive tablets being taken); subsequent courses repeated without interval; for starting routines see under Dose above

Katya 30/75® (Stragen) (FW)
Tablets, s/c, gestodene 75 micrograms, ethinylestradiol 30 micrograms. Net price 3 × 21-tab pack = £5.03
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Triadene® (Schering Health) (FW)
6 beige tablets, ethinylestradiol 30 micrograms, gestodene 50 micrograms;
5 dark brown tablets, ethinylestradiol 40 micrograms, gestodene 70 micrograms;
10 white tablets, ethinylestradiol 30 micrograms, gestodene 100 micrograms.
Net price 3 × 21-tab pack = £9.54
Dose 1 tablet daily for 21 days, starting with beige tablet marked ‘start’ on day 1 of cycle; repeat after 7-day tablet-free interval

Mestranol with Norethisterone
Norinyl®-1 (Pharmacia) (FW)
Tablets, norethisterone 1 mg, mestranol 50 micrograms. Net price 3 × 21-tab pack = £2.19
Dose 1 tablet daily for 21 days; subsequent courses repeated after 7-day tablet-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above

Ethinylestradiol with cyproterone acetate
See Co-cyprindiol (section 13.6.2)
past history or predisposition to venous thrombosis), but have a higher failure rate than combined preparations. They are suitable for older women, for heavy smokers, and for those with hypertension, valvular heart disease, diabetes mellitus, and migraine. Menstrual irregularities (oligomenorrhoea, menorrhagia) are more common but tend to resolve on long-term treatment.

**Interactions** Effectiveness of oral progestogen-only preparations is not affected by antibacterials that do not induce liver enzymes. The efficacy of oral progestogen-only preparations is, however, reduced by enzyme-inducing drugs and an additional or alternative contraceptive method is recommended during treatment with an enzyme-inducing drug and for at least 4 weeks afterwards—see p. 439 and Appendix 1 (progestogens).

**Surgery** All progestogen-only contraceptives (including those given by injection) are suitable for use as an alternative to combined oral contraceptives before major elective surgery, before all surgery to the legs, or before surgery which involves prolonged immobilisation of a lower limb.

**Starting routine** One tablet daily, on a continuous basis, starting on day 1 of cycle and taken at the same time each day (if delayed by longer than 3 hours contraceptive protection may be lost). Additional contraceptive precautions are not necessary when initiating treatment.

**Changing from a combined oral contraceptive** Start on the day following completion of the combined oral contraceptive course without a break (or in the case of ED tablets omitting the inactive ones).

**After childbirth** Start any time after 3 weeks postpartum (increased risk of breakthrough bleeding if started earlier)—lactation is not affected.

**Missed pill** The following advice is now recommended by family planning organisations: ‘If you forget a pill, take it as soon as you remember and carry on with the next pill at the right time. If the pill was more than 3 hours (12 hours for Cerazette®) overdue you are not protected. Continue normal pill-taking but you must also use another method, such as the condom, for the next 2 days.’

The Faculty of Sexual and Reproductive Healthcare recommends emergency contraception (see p. 448) if one or more progestogen-only contraceptive tablets are missed or taken more than 3 hours (12 hours for Cerazette®) late and unprotected intercourse has occurred before 2 further tablets have been correctly taken.

**Diarrhoea and vomiting** Vomiting and persistent, severe diarrhoea can interfere with the absorption of oral progestogen-only contraceptives. If vomiting occurs within 2 hours of taking an oral progestogen-only contraceptive, another pill should be taken as soon as possible. If a replacement pill is not taken within 3 hours (12 hours for Cerazette®) of the normal time for taking the progestogen-only pill, or in cases of persistent vomiting or very severe diarrhoea, additional precautions should be used during illness and for 2 days after recovery (see also under Missed pill above).

---

**ORAL PROGESTOGEN-ONLY CONTRACEPTIVES**

*(Progestogen-only pill, ‘POP’)*

**Indications** contraception

**Cautions** arterial disease; sex-steroid dependent cancer; past ectopic pregnancy; malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration); functional ovarian cysts; active liver disease; recurrent cholestatic jaundice; history of jaundice in pregnancy; interactions: see notes above and Appendix 1 (progestogens)

**Other conditions** The product literature advises caution in patients with history of thromboembolism, hypertension, diabetes mellitus and migraine; evidence for caution in these conditions is unsatisfactory

**Contra-indications** pregnancy; undiagnosed vaginal bleeding; severe arterial disease; liver tumour; acute porphyria (section 9.8.2); history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable

**Side-effects** menstrual irregularities (see also notes above); nausea, vomiting, headache, dizziness, breast discomfort, depression, skin disorders, disturbance of appetite, weight changes, changes in libido

**Breast cancer** There is a small increase in the risk of having breast cancer diagnosed in women using, or who have recently used, a progestogen-only contraceptive pill; this relative risk may be due to an earlier diagnosis. The most important risk factor appears to be the age at which the contraceptive is stopped rather than the duration of use; the risk disappears gradually during the 10 years after stopping and there is no excess risk by 10 years. The CSM has advised that a possible small increase in the risk of breast cancer should be weighed against the benefits

**Dose**

- 1 tablet daily at same time each day, starting on day 1 of cycle then continuously; if administration delayed for 3 hours (12 hours for Cerazette®) or more it should be regarded as a ‘missed pill’, see notes above

**Cerazette®** *(Pharmacia)*

- Tablets, 1/c, desogestrel 75 micrograms. Net price 3 × 28-tab pack = £8.85
- The Scottish Medicines Consortium has advised (September 2003) that Cerazette® should be restricted for use in women who cannot tolerate oestrogen-containing contraceptives or in whom these preparations are contra-indicated

**Femulen®** *(Pharmacia)*

- Tablets, etynodiol diacetate 500 micrograms. Net price 3 × 28-tab pack = £3.31

**Micronor®** *(Janssen-Cilag)*

- Tablets, norethisterone 350 micrograms. Net price 3 × 28-tab pack = £1.76

**Noriday®** *(Pharmacia)*

- Tablets, norethisterone 350 micrograms. Net price 3 × 28-tab pack = £2.10

---

**7.3.2.2 Parenteral progestogen-only contraceptives**

Medroxyprogesterone acetate *(Depo-Provera®)* is a long-acting progestogen given by intramuscular injection; it is as effective as the combined oral preparations
but because of its prolonged action it should never be given without full counselling backed by the patient information leaflet. It may be used as a short-term or long-term contraceptive for women who have been counselled about the likelihood of menstrual disturbance and the potential for a delay in return to full fertility. Delayed return of fertility and irregular cycles may occur after discontinuation of treatment but there is no evidence of permanent infertility. Heavy bleeding has been reported in patients given medroxyprogesterone acetate in the immediate puerperium (the first dose is best delayed until 6 weeks after birth). If the woman is not breast-feeding, the first injection may be given within 5 days postpartum (she should be warned that the risk of heavy or prolonged bleeding may be increased).

Reduction in bone mineral density and, rarely, osteoporosis and osteoporotic fractures have also been reported with medroxyprogesterone acetate. The reduction in bone mineral density occurs in the first 2–3 years of use and then stabilises. See also CSM advice below.

**CSM advice**

The CSM has advised that:

- in adolescents, medroxyprogesterone acetate (Depo-Provera®) be used only when other methods of contraception are inappropriate;
- in all women, benefits of using medroxyprogesterone acetate beyond 2 years should be evaluated against risks;
- in women with risk factors for osteoporosis a method of contraception other than medroxyprogesterone acetate should be considered.

Norethisterone enantate (Noristerat®) is a long-acting progestogen given as an oily injection which provides contraception for 8 weeks; it is used as short-term interim contraception e.g. before vasectomy becomes effective.

An etonogestrel-releasing implant (Implanon®), consisting of a single flexible rod, is also available; the rod is inserted subdermally into the lower surface of the upper arm and it provides effective contraception for up to 3 years. The manufacturer advises that in heavier women, blood etonogestrel concentrations are lower and therefore the implant may not provide effective contraception during the third year; they advise that earlier replacement should be considered in such patients—however evidence to support this recommendation is lacking. Local reactions such as bruising and itching can occur at the insertion site. The contraceptive effect of Implanon® is rapidly reversed on removal of the implant. The doctor or nurse administering (or removing) the implant should be fully trained in the technique and should provide full counselling reinforced by the patient information leaflet.

The cautions, contra-indications, and side-effects of oral progestogen-only contraceptives apply to parenteral progestogen-only contraceptives, except that parenteral preparations reliably inhibit ovulation and therefore protect against ectopic pregnancy and functional ovarian cysts.

**Interactions**

Effectiveness of parenteral progestogen-only contraceptives is not affected by antibacterials that do not induce liver enzymes. However, effectiveness of norethisterone and etonogestrel (but not medroxyprogesterone acetate) may be reduced by enzyme-inducing drugs; additional contraceptive precautions should be taken whilst taking the enzyme-inducing drug and for 4 weeks after stopping it or an alternative contraceptive method should be considered if long-term use of the enzyme-inducing drug is contemplated.

**Parentreral Progestogen-Only Contraceptives**

**Indications**

Contraception, see also notes above and under preparations (roles vary according to preparations)

**Cautions**

see notes above and under preparations; possible risk of breast cancer, see oral progestogen-only contraceptives (section 7.3.2.1); history during pregnancy of pruritus or of deterioration of osteoporosis, disturbances of lipid metabolism; interactions: see notes above and Appendix 1 (progestogens)

**Counselling**

Full counselling backed by patient information leaflet required before administration

**Contra-indications**

see notes above; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal contraceptive methods unacceptable

**Side-effects**

see notes above; injection-site reactions

**Cervical cancer**

Use of injectable progestogen-only contraceptives may be associated with a small increased risk of cervical cancer, similar to that seen with combined oral contraceptives, see p. 440. The risk of cervical cancer with other progestogen-only contraceptives is not yet known.

**Dose**

- See under preparations

### Injectable preparations

**Depo-Provera®** *(Pfizer)*

**Injection** (aqueous suspension), medroxyprogesterone acetate 150 mg/mL, net price 1-mL prefilled syringe = £6.01, 1-mL vial = £6.01. Counselling, see patient information leaflet

**Dose** by deep intramuscular injection, 150 mg within first 5 days of cycle or within first 5 days after parturition (delay until 6 weeks after parturition if breast-feeding); for long-term contraception, repeated every 12 weeks (if interval greater than 12 weeks and 5 days, rule out pregnancy before next injection and advise patient to use additional contraceptive measures (e.g. barrier) for 14 days after the injection)

**Noristerat®** *(Schering Health)*

**Injection** (oily), norethisterone enantate 200 mg/mL, net price 1-mL amp = £3.59. Counselling, see patient information leaflet

**Dose** by deep intramuscular injection given very slowly into gluteal muscle, short-term contraception, 200 mg within first 5 days of cycle or immediately after parturition (duration 8 weeks); may be repeated once after 8 weeks (withhold breast-feeding for neonates with severe or persistent jaundice requiring medical treatment)

### Implants

**Implanon®** *(Organon)*

**Implant**, containing etonogestrel 68 mg in each flexible rod, net price = £81.00. Counselling, see patient information leaflet

**Dose** by subcutaneous implantation, no previous hormonal contraception. 1 implant inserted during first 5 days of cycle; parturition or abortion in second trimester, 1 implant inserted between days 21–28 after delivery or abortion (if inserted after 28 days additional precautions necessary for next 7 days); abortion in first trimester, 1 implant inserted immediately, changing from other contraceptive, consult product literature; remove within 3 years of insertion
The progestogen-only intra-uterine system, Mirena®, releases levonorgestrel directly into the uterine cavity. It is licensed for use as a contraceptive, for the treatment of primary menorrhagia and for the prevention of endometrial hyperplasia during oestrogen replacement therapy. This may therefore be a contraceptive method of choice for women who have excessively heavy menses.

The effects of the progestogen-only intra-uterine system are mainly local and hormonal including prevention of endometrial proliferation, thickening of cervical mucus, and suppression of ovulation in some women (in some cycles). In addition to the progestogenic activity, the intra-uterine system itself may contribute slightly to the contraceptive effect. Return of fertility after removal is rapid and appears to be complete.

Advantages of the progestogen-only intra-uterine system over copper intra-uterine devices are that there may be an improvement in any dysmenorrhoea and a reduction in blood loss; there is also evidence that the frequency of pelvic inflammatory disease may be reduced (particularly in the youngest age groups who are most at risk).

In primary menorrhagia, menstrual bleeding is reduced significantly within 3–6 months of inserting the progestogen-only intra-uterine system, probably because it prevents endometrial proliferation. Another treatment should be considered if menorrhagia does not improve within this time (section 6.4.1.2).

Cautions and contra-indications Generally the cautions and contra-indications for the progestogen-only intra-uterine system are as for standard intra-uterine devices (section 7.3.4), but the risk of ectopic pregnancy is considerably smaller. Although the progestogen-only intra-uterine system produces little systemic progestogenic activity, it is usually avoided for 5 years after any evidence of breast cancer. However, the system can be considered for a woman in long-term remission from breast cancer who has menorrhagia and requires effective contraception. Since levonorgestrel is released close to the site of the main contraceptive action (on cervical mucus and endometrium) progestogenic side-effects and interactions are less likely; in particular, enzyme-inducing drugs are unlikely to significantly reduce the contraceptive effect of the progestogen-only intra-uterine system and additional contraceptive precautions are not required.

Side-effects Initially, changes in the pattern and duration of menstrual bleeding (spotting or prolonged bleeding) are common; endometrial disorders should be ruled out before insertion and the patient should be fully counselled (and provided with a patient information leaflet). Improvement in progestogenic side-effects, such as mastalgia and mood changes, and in the bleeding pattern usually occurs a few months after insertion and bleeding may often become very light or absent. Functional ovarian cysts (usually asymptomatic) can occur and usually resolve spontaneously (ultrasound monitoring recommended).
**7.3.4 Contraceptive devices**

**Intra-uterine devices**

The intra-uterine device (IUD) is suitable for older parous women and as a second-line contraceptive in young nulliparous women who should be carefully screened because they have an increased background risk of pelvic inflammatory disease.

Smaller devices have been introduced to minimise side-effects; these consist of a plastic carrier wound with copper wire or fitted with copper bands; some also have a central core of silver to prevent fragmentation of the copper. Fertility declines with age and therefore a copper intra-uterine device which is fitted in a woman over the age of 40, may remain in the uterus until menopause. The intra-uterine device Gyne-T 380® (Janssen-Cilag) is no longer available, but some women may have the device in place until 2009. The intra-uterine devices Multiload® Cu250 and Multiload® Cu250 Short (Organon) have been discontinued, but some women may have the devices in place until 2011.

A frameless, copper-bearing intra-uterine device (GyneFix®) is also available. It consists of a knotted, polypropylene thread with 6 copper sleeves; the device is anchored in the uterus by inserting the knot into the uterine fundus. The healthcare professional inserting (or removing) the device should be fully trained in the technique and should provide full counselling backed by the patient information leaflet.

The timing and technique of fitting an intra-uterine device are critical for its subsequent performance and call for proper training and experience. Devices should not be fitted during the heavy days of the period; they are best fitted after the end of menstruation and before the calculated time of implantation. The main excess risk of infection occurs in the first 20 days after insertion and is believed to be related to existing carriage of a sexually transmitted disease. Women are considered to be at a higher risk of sexually transmitted diseases if:

- they are under 25 years old or
- they are over 25 years old and
  - have a new partner or
  - have had more than one partner in the past year or
  - their regular partner has other partners.

In these women, pre-insertion screening (for chlamydia and, depending on sexual history, *Neisseria gonorrhoeae*) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appropriate prophylactic antibacterial cover should be given. The woman should be advised to attend as an emergency if she experiences sustained pain during the next 20 days.

An intra-uterine device should not be removed in mid-cycle unless an additional contraceptive was used for the previous 7 days. If removal is essential post-coital contraception should be considered. If an intra-uterine device fails and the woman wishes to continue to full-term the device should be removed in the first trimester if possible.

**Indications**

see notes above

**Cautions**

see notes above; also anaemia, menorrhagia (progestogen intra-uterine system might be preferable, section 7.3.2.3), endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, diabetes, fertility problems, nulliparity and young age, severely scarred uterus (including after endometrial resection) or severe cervical stenosis; valvular heart disease or history of endocarditis (Table 2, section 5.1); drug- or disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression); epilepsy (risk of seizure at time of insertion); increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion, 6–8 weeks after then annually but counsel women to see doctor promptly in case of significant symptoms, especially pain; anticoagulant therapy (avoid if possible); remove if pregnancy occurs; if pregnancy occurs, increased likelihood that it may be ectopic

**Contra-indications**

pregnancy, severe anaemia, recent sexually transmitted infection (if not fully investigated and treated), unexplained uterine bleeding, distorted or small uterine cavity, genital malignancy, active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration), pelvic inflammatory disease, established or marked immunosuppression; copper devices: copper allergy, Wilson’s disease, medical diathery

**Side-effects**

uterine or cervical perforation, displacement, expulsion; pelvic infection may be exacerbated, menorrhagia, dysmenorrhoea, allergy; on insertion: pain (alleviated by NSAID such as ibuprofen 30 minutes before insertion) and bleeding, occasionally epileptic seizure and vasovagal attack

**Flexi-T 300 (FP)**

Intra-uterine device, copper wire, surface area approx. 300 mm wound on vertical stem of T-shaped plastic carrier, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £9.47.

For uterine length over 5 cm; replacement every 5 years (see also notes above)

**Flexi-T + 380 (FP)**

Intra-uterine device, copper wire, surface area approx. 380 mm wound on vertical stem of T-shaped plastic carrier with copper sleeve on each arm, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £10.06.

For uterine length over 6 cm; replacement every 5 years (see also notes above)

**GyneFix (FP)**

Intra-uterine device, 6 copper sleeves with surface area of 330 mm on polypropylene thread, net price = £26.64.

Suitable for all uterine sizes; replacement every 5 years

**Load 375 (Durbin)**

Intra-uterine device, copper wire, surface area approx. 375 mm, wound on vertical stem of U-shaped plastic carrier, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.48.

For uterine length over 7 cm; replacement every 5 years (see also notes above)

**Mini TT 380 Slimline (Durbin)**

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeves fitted flush on to distal portion of each horizontal arm, total surface area

---

**Intra-uterine contraceptive devices**

**Indications**

see notes above

**Cautions**

see notes above; also anaemia, menorrhagia (progestogen intra-uterine system might be preferable, section 7.3.2.3), endometriosis, severe primary dysmenorrhoea, history of pelvic inflammatory disease, diabetes, fertility problems, nulliparity and young age, severely scarred uterus (including after endometrial resection) or severe cervical stenosis; valvular heart disease or history of endocarditis (Table 2, section 5.1); drug- or disease-induced immunosuppression (risk of infection—avoid if marked immunosuppression); epilepsy (risk of seizure at time of insertion); increased risk of expulsion if inserted before uterine involution; gynaecological examination before insertion, 6–8 weeks after then annually but counsel women to see doctor promptly in case of significant symptoms, especially pain; anticoagulant therapy (avoid if possible); remove if pregnancy occurs; if pregnancy occurs, increased likelihood that it may be ectopic

**Contra-indications**

pregnancy, severe anaemia, recent sexually transmitted infection (if not fully investigated and treated), unexplained uterine bleeding, distorted or small uterine cavity, genital malignancy, active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration), pelvic inflammatory disease, established or marked immunosuppression; copper devices: copper allergy, Wilson’s disease, medical diathery

**Side-effects**

uterine or cervical perforation, displacement, expulsion; pelvic infection may be exacerbated, menorrhagia, dysmenorrhoea, allergy; on insertion: pain (alleviated by NSAID such as ibuprofen 30 minutes before insertion) and bleeding, occasionally epileptic seizure and vasovagal attack

**Flexi-T 300 (FP)**

Intra-uterine device, copper wire, surface area approx. 300 mm wound on vertical stem of T-shaped plastic carrier, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £9.47.

For uterine length over 5 cm; replacement every 5 years (see also notes above)

**Flexi-T + 380 (FP)**

Intra-uterine device, copper wire, surface area approx. 380 mm wound on vertical stem of T-shaped plastic carrier with copper sleeve on each arm, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £10.06.

For uterine length over 6 cm; replacement every 5 years (see also notes above)

**GyneFix (FP)**

Intra-uterine device, 6 copper sleeves with surface area of 330 mm on polypropylene thread, net price = £26.64.

Suitable for all uterine sizes; replacement every 5 years

**Load 375 (Durbin)**

Intra-uterine device, copper wire, surface area approx. 375 mm, wound on vertical stem of U-shaped plastic carrier, impregnated with barium sulphate for radio-opacity, monofilament thread attached to base of vertical stem; preloaded in inserter, net price = £8.48.

For uterine length over 7 cm; replacement every 5 years (see also notes above)

**Mini TT 380 Slimline (Durbin)**

Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper sleeves fitted flush on to distal portion of each horizontal arm, total surface area
T Obsetrics, gynaecology, and urinary-tract disorders

Type A Diaphragm with Flat Metal Spring
Silicone Contraceptive Pessary
Type C Contraceptive Pessary
Type B Contraceptive Pessary
Other contraceptive devices

TT 380 Slimline (Durbin)
Intra-uterine device, copper wire wound on vertical stem of T-shaped plastic carrier, impregnated with barium sulphate for radio-opacity, threads attached to base of vertical stem, net price = £10.29
For uterine length 6.5–9 cm, replacement every 10 years (see notes above)

Silicone contraceptive caps
Silicone Contraceptive Pessary
Other contraceptive devices

Fertility (Ovulation) Thermometer (Zeal)
Mercury in glass thermometer, range 35 to 39°C (graduated in 0.1°C), net price = £1.94
For monitoring ovulation for the fertility awareness method of contraception

Hormonal methods
Hormonal emergency contraception involves the use of levonorgestrel. It is effective if taken within 72 hours (3 days) of unprotected intercourse; taking the dose as soon as possible increases efficacy. Levonorgestrel may also be used between 72 and 120 hours after unprotected intercourse [unlicensed use] but efficacy decreases with time. Hormonal emergency contraception is less effective than insertion of an intra-uterine device (see below).

If vomiting occurs within 2 hours of taking levonorgestrel, a replacement dose should be given. If an antiemetic is required domperidone is preferred.

When prescribing hormonal emergency contraception the doctor should explain:
• that the next period may be early or late;
• that a barrier method of contraception needs to be used until the next period;
• the need to return promptly if any lower abdominal pain occurs because this could signify an ectopic pregnancy (and also in 3 to 4 weeks if the subsequent menstrual bleed is abnormally light, heavy or brief, or is absent, or if she is otherwise concerned).

Intra-uterine pregnancy despite treatment: see Appendix 4 (levonorgestrel).

Interactions The effectiveness of hormonal emergency contraception is reduced by enzyme-inducing drugs; a copper intra-uterine device can be offered instead or the dose of levonorgestrel should be increased to a total of 3 mg taken as a single dose [unlicensed dose—advise women accordingly]. There is no need to increase the dose for emergency contraception if the patient is taking antibacterials that are not enzyme inducers.
**LEVONORGESTREL**

**Indications** emergency contraception

**Cautions** see notes above; past ectopic pregnancy; severe malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration); pregnancy (see notes above and Appendix 4); breast-feeding (Appendix 5); interactions: see notes above and Appendix 1 (progestogens)

**Contra-indications** acute porphyria (section 9.8.2)

**Side-effects** menstrual irregularities (see also notes above), nausea, low abdominal pain, fatigue, headache, dizziness, breast tenderness, vomiting

**Dose**
- 1.5 mg as a single dose as soon as possible after coitus (preferably within 12 hours but no later than after 72 hours)

1. **Levonelle® One Step** (Schering Health)
   Tablets, levonorgestrel 1.5 mg, net price 1-tab pack = £13.83

1. Can be sold to women over 16 years; when supplying emergency contraception to the public, pharmacists should refer to guidance issued by the Royal Pharmaceutical Society of Great Britain

**Levonelle® 1500** (Schering Health)

Tablets, levonorgestrel 1.5 mg, net price 1-tab pack = £5.11

**Intra-uterine device**

Insertion of an intra-uterine device is more effective than the hormonal methods of emergency contraception. A copper intra-uterine contraceptive device (section 7.3.4) can be inserted up to 120 hours (5 days) after unprotected intercourse; sexually transmitted diseases should be tested for and insertion of the device should usually be covered by antibacterial prophylaxis (e.g. azithromycin 1 g as a single dose). If intercourse has occurred more than 5 days previously, the device can still be inserted up to 5 days after the earliest likely calculated ovulation (i.e. within the minimum period before implantation).

**7.4 Drugs for genito-urinary disorders**

**7.4.1 Drugs for urinary retention**

**Acute retention** is painful and is treated by catheterisation.

**Chronic retention** is painless and often long-standing. Catheterisation is unnecessary unless there is deterioration of renal function. After the cause has initially been established and treated, drugs may be required to increase detrusor muscle tone.

**Benign prostatic hyperplasia** is treated either surgically or medically with alpha-blockers (see below). Dutasteride and finasteride (section 6.4.2) are alternatives to alpha-blockers, particularly in men with a significantly enlarged prostate.

**Alpha-blockers**

The selective alpha-blockers, _alfuzosin, doxazosin, indoramin, prazosin, tamsulosin_ and _terazosin_ relax smooth muscle in benign prostatic hyperplasia producing an increase in urinary flow-rate and an improvement in obstructive symptoms.

**Cautions** Since selective alpha-blockers reduce blood pressure, patients receiving antihypertensive treatment may require reduced dosage and specialist supervision. Caution may be required in the elderly and in patients with hepatic impairment (Appendix 2) and renal impairment (Appendix 3). For interactions see Appendix 1 (alpha-blockers).

**Contra-indications** Alpha-blockers should be avoided in patients with a history of postural hypotension and micturition syncope.

**Side-effects** Side-effects of selective alpha-blockers include drowsiness, hypotension (notably postural hypotension), syncope, asthenia, depression, headache, dry mouth, gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, constipation), oedema, blurred vision, rhinitis, erectile disorders (including priapism), tachycardia, and palpitations. Hypersensitivity reactions including rash, pruritus and angioedema have also been reported.

**ALFUZOSIN HYDROCHLORIDE**

**Indications** see notes above

**Cautions** see notes above

**Contra-indications** see notes above; severe hepatic impairment

**Side-effects** see notes above; also flushes and chest pain

**Dose**
- 2.5 mg 3 times daily, max. 10 mg daily; **ELDERLY** initially 2.5 mg twice daily

**First dose effect** First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely

For drugs used in the treatment of urinary-tract infections see section 5.1.13.
Alfuzosin hydrochloride (Non-proprietary) [PH1]
Tablets, I/c, alfuzosin hydrochloride 2.5 mg, net price 60-tab pack = £21.20. Label: 3, counselling, see dose above

Xatral® (Sanofi-Synthelabo) [PH1]
Tablets, I/c, alfuzosin hydrochloride 2.5 mg, net price 60-tab pack = £21.20. Label: 3, counselling, see dose above

Modulated release
Besavar® XL (Winthrop) [PH1]
Tablets, m/r, yellow/white, alfuzosin hydrochloride 10 mg, net price 30-tab pack = £13.28. Label: 3, 21, 25, counselling, see above
Dose benign prostatic hyperplasia 10 mg once daily
Acute urinary retention associated with benign prostatic hyperplasia in men over 65 years, 10 mg once daily for 2–3 days during catheterisation and for one day after removal; max. 4 days

Xatral® XL (Sanofi-Synthelabo) [PH1]
Tablets, m/r, yellow/white, alfuzosin hydrochloride 10 mg, net price 10-tab pack = £4.42, 30-tab pack = £13.28. Label: 3, 21, 25, counselling, see above
Dose benign prostatic hyperplasia 10 mg once daily
Acute urinary retention associated with benign prostatic hyperplasia in men over 65 years, 10 mg once daily for 2–3 days during catheterisation and for one day after removal; max. 4 days

DOXAZOSIN
Indications see notes above and section 2.5.4
Cautions see notes above and section 2.5.4
Contra-indications see notes above
Side-effects see notes above and section 2.5.4
Dose
● Initially 1 mg daily; dose may be doubled at intervals of 1–2 weeks according to response, up to max. 8 mg daily; usual maintenance 2–4 mg daily

INDORAMIN
Indications see notes above and section 2.5.4
Cautions see notes above and section 2.5.4
Contra-indications see notes above
Side-effects see notes above and section 2.5.4
Dose
● 20 mg twice daily; increased if necessary by 20 mg every 2 weeks to max. 100 mg daily in divided doses; ELDERY, 20 mg at night may be adequate

Doralese® (Chemidex) [PH1]
Tablets, yellow, I/c, indoramin 20 mg, net price 60-tab pack = £25.85. Label: 2

PRAZOSIN
Indications see notes above and section 2.5.4
Cautions see notes above and section 2.5.4
Contra-indications see notes above and section 2.5.4
Side-effects see notes above and section 2.5.4; also paraesthesia, arthralgia, epistaxis, nervousness, dyspnœa, hallucinations, and alopecia
Dose
● Initially 500 micrograms twice daily for 3–7 days, subsequently adjusted according to response; usual maintenance (and max.) 2 mg twice daily; ELDERY initiate with lowest possible dose
First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely

Preparations
Section 2.5.4

TAMSULOSIN HYDROCHLORIDE
Indications see notes above
Cautions see notes above; also cataract surgery (risk of intra-operative floppy iris syndrome)
Contra-indications see notes above; severe hepatic impairment
Side-effects see notes above
Dose
● 400 micrograms daily as a single dose
Tamsulosin hydrochloride (Non-proprietary) [PH1]
Capsules, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-cap pack = £6.11. Label: 25
Brands include Bazetham MR, Contiflo XL, Diffundox XL, Omnic MR, Stronazon MR, Tabphyn MR
Flomaxtra® XL (Astellas) [PH1]
Tablets, m/r, tamsulosin hydrochloride 400 micrograms. Net price 30-tab pack = £17.55. Label: 25

TERAZOSIN
Indications see notes above and section 2.5.4
Cautions see notes above and section 2.5.4
Contra-indications see notes above
Side-effects see notes above and section 2.5.4; also weight gain, paraesthesia, dyspnœa, thrombocytopenia, nervousness, decreased libido, back pain and pain in extremities
Dose
● Initially 1 mg at bedtime; if necessary dose may be doubled at intervals of 1–2 weeks according to response, up to max. 10 mg once daily; usual maintenance 5–10 mg daily
First dose effect First dose may cause collapse due to hypotensive effect (therefore should be taken on retiring to bed). Patient should be warned to lie down if symptoms such as dizziness, fatigue or sweating develop, and to remain lying down until they abate completely
Terazosin (Non-proprietary) [PH1]
Tablets, terazosin (as hydrochloride) 2 mg, net price 28-tab pack = £2.27; 5 mg, 28-tab pack = £2.85; 10 mg, 28-tab pack = £7.71. Label: 3, counselling, see dose above
Hytrin® (Ampidipharm) [PH1]
Tablets, terazosin (as hydrochloride) 2 mg (yellow) net price, 28-tab pack = £4.57; 5 mg (tan), 28-tab pack = £8.57; 10 mg (blue), 28-tab pack = £17.14; starter pack (for benign prostatic hyperplasia) of 7 × 1-mg tab with 14 × 2-mg tab and 7 × 5-mg tab = £10.97. Label: 3, counselling, see dose above

Parasympathomimetics
The parasympathomimetic bethanechol increases detrusor muscle contraction. However, it has only a
limited role in the relief of urinary retention; its use has been superseded by catheterisation.

Distigmine inhibits the breakdown of acetylcholine. It may help patients with an upper motor neurone neurogenic bladder.

## BETHANECHOL CHLORIDE

### Indications

Urinary retention, but see notes above

### Cautions

Autonomic neuropathy (use lower initial dose); interactions: Appendix 1 (parasympathomimetics)

### Contra-indications

Peptic ulcer; intestinal or urinary obstruction; conditions where increased motility of the urinary or gastro-intestinal tract could be harmful; cardiovascular disorders (including recent myocardial infarction, bradycardia, and heart block); hypotension; obstructive airways disease; epilepsy; parkinsonism; hyperthyroidism; pregnancy (Appendix 4); breastfeeding

### Side-effects

Nausea, vomiting, diarrhoea, abdominal pain, increased salivation, eructation; flushing, hypertension, bradycardia; bronchoconstriction, rhinorrhea; headache; increased lacrimation; increased sweating

### Dose

- 10–25 mg 3–4 times daily half an hour before food

**Myotonic®** (Glenwood) Tablets, scored, bethanechol chloride 10 mg, net price 20 = £1.01; 25 mg, 20 = £1.30. Label: 22

## DISTIGMINE BROMIDE

### Indications

Postoperative urinary retention (see notes above); neurogenic bladder; myasthenia gravis (section 10.2.1)

### Cautions

Peptic ulcer; conditions where increased motility of the urinary or gastro-intestinal tract could be harmful; oesophagitis; cardiovascular disease; bronchospasm; epilepsy; parkinsonism; pregnancy (Appendix 4); breastfeeding; interactions: Appendix 1 (parasympathomimetics)

### Contra-indications

Intestinal or urinary obstruction; severe circulatory insufficiency; asthma

### Side-effects

Abdominal pain, diarrhoea, increased salivation; bradycardia, AV block, hypotension; dyspnoea; muscle twitching; increased lacrimation, miosis; increased sweating

### Dose

- Urinary retention, 5 mg daily, half an hour before breakfast
- Neurogenic bladder, 5 mg daily or on alternate days, half an hour before breakfast

**Ucbretid®** (Rhône-Poulenc Rorer) Tablets, scored, distigmine bromide 5 mg, net price 30-tab pack = £14.22. Label: 22

## Drugs for urinary frequency, enuresis, and incontinence

### Urinary incontinence

Incontinence in adults which arises from detrusor instability is managed by combining drug therapy with conservative methods for managing urge incontinence such as pelvic floor exercises and bladder training; stress incontinence is generally managed by non-drug methods. Duloxetine, an inhibitor of serotonin and noradrenaline re-uptake can be added and is licensed for the treatment of moderate to severe stress incontinence in women; it may be more effective when used as an adjunct to pelvic floor exercises.

Involuntary detrusor contractions cause urgency and urge incontinence, usually with frequency and nocturia. Antimuscarinic drugs reduce these contractions and increase bladder capacity. Oxybutynin also has a direct relaxant effect on urinary smooth muscle. Side-effects limit the use of oxybutynin but they may be reduced by starting at a lower dose. A modified-release preparation of oxybutynin is effective and has fewer side-effects; a transdermal patch is also available. The efficacy and side-effects of tolterodine are comparable to those of modified-release oxybutynin. Flavoxate has less marked side-effects but it is also less effective. Darifenacin, fesoterodine, propiverine, solifenacin, and trospium are newer antimuscarinic drugs licensed for urinary frequency, urgency, and incontinence. The need for continued antimuscarinic drug therapy should be reviewed after 3–6 months.

The **Scottish Medicines Consortium** (p. 3) has advised (June 2008) that fesoterodine (Toviaz®) is accepted for restricted use within NHS Scotland as a second-line treatment for overactive bladder syndrome.

Propantheline and tricyclic antidepressants were used for urge incontinence but they are little used now because of their side-effects. The use of imipramine is limited by its potential to cause cardiac side-effects.

Purified bovine collagen implant (Contigen®, Bard) is indicated for **urinary incontinence** caused by intrinsic sphincter deficiency (poor or non-functioning bladder outlet mechanism). The implant should be inserted only by surgeons or physicians trained in the technique for injection of the implant.

### Cautions

Antimuscarinic drugs should be used with caution in the elderly (especially if frail), in those with autonomic neuropathy, and in those susceptible to angle-closure glaucoma. They should also be used with caution in hiatus hernia with reflux oesophagitis, hepatic impairment (Appendix 2), and renal impairment (Appendix 3). Antimuscarinics can worsen hyperthyroidism, coronary artery disease, congestive heart failure, hypertension, prostatic hyperplasia, arrhythmias, and tachycardia. For interactions see Appendix 1 (antimuscarinics).

### Contra-indications

Antimuscarinic drugs should be avoided in patients with myasthenia gravis, significant bladder outflow obstruction or urinary retention, severe...
ulcerative colitis, toxic megacolon, and in gastro-intestinal obstruction or intestinal atony.

**Side-effects** Side-effects of antimuscarinic drugs include dry mouth, gastro-intestinal disturbances including constipation, flatulence, taste disturbances, blurred vision, dry eyes, drowsiness, dizziness, fatigue, difficulty in micturition (less commonly urinary retention), palpitation, and skin reactions (including dry skin, rash, and photosensitivity); also headache, diarrhoea, angioedema, arrhythmias, and tachycardia. Central nervous system stimulation, such as restlessness, disorientation, hallucination, and convulsion may occur; children are at higher risk of these effects. Antimuscarinic drugs can reduce sweating, leading to heat sensations and fainting in hot environments or in patients with fever, and very rarely may precipitate angle-closure glaucoma.

**DARIFENACIN**

**Indications** urinary frequency, urgency, and incontinence

**Cautions** see notes above; breast-feeding (Appendix 5)

**Contra-indications** see notes above; pregnancy (Appendix 4)

**Side-effects** see notes above; also less commonly ulcerative stomatitis, oedema, hypertension, dysphonia, cough, rhinitis, weakness, insomnia, impotence, and vaginitis

**Dose**

- **ADULT** over 18 years, 7.5 mg once daily, increased if necessary after 2 weeks to 15 mg once daily

**Emselex**

- **Novatis** ▼ *(Novartis)*

**Tablets** m/r, darifenacin (as hydrobromide) 7.5 mg (white), net price 28-tab pack = £26.13; 15 mg (peach), 28-tab pack = £26.13. Label: 3, 25

**Note** The Scottish Medicines Consortium has advised (May 2007) that darifenacin (**Emselex**) is accepted for restricted use as a second-line drug for the symptomatic treatment of urge incontinence, urinary frequency, and urgency in patients with overactive bladder syndrome

**DULOXETINE**

**Indications** moderate to severe stress urinary incontinence in women; major depressive disorder (section 4.3.4); diabetic neuropathy (section 4.3.4); generalised anxiety disorder (section 4.3.4)

**Cautions** elderly; cardiac disease; hypertension (avoid if uncontrolled); history of mania; history of seizures; raised intra-ocular pressure, susceptibility to angle-closure glaucoma; bleeding disorders or concomitant use of drugs that increase risk of bleeding; interactions: Appendix 1 (duloxetine)

**Withdrawal** Nausea, vomiting, headache, anxiety, dizziness, paraesthesia, sleep disturbances, and tremor are the most common features of abrupt withdrawal or marked reduction of the dose; dose should be reduced over at least 1–2 weeks

**Contra-indications** hepatic impairment; renal impairment (avoid if creatinine clearance less than 30 mL/minute); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, dyspepsia, constipation, diarrhoea, abdominal pain, weight changes, decreased appetite, flatulence, dry mouth; palpitation, hot flush; insomnia, abnormal dreams, paraesthesia, drowsiness, anxiety, headache, dizziness, fatigue, weakness, tremor, nervousness, anorexia; sexual dysfunction; visual disturbances; sweating, pruritus; less commonly gastritis, haliotosis, hepatitis, bruxism, tachycardia, hypertension, postural hypotension, syncope, raised cholesterol, vertigo, taste disturbance, cold extremities, impaired temperature regulation, impaired attention, movement disorders, muscle twitching, musculoskeletal pain, thirst, stomatitis, hypothroidism, urinary disorders, and photosensitivity; rarely mania and angle-closure glaucoma; also reported supraventricular arrhythmia, chest pain, hallucinations, suicidal behaviour (see Suicidal Behaviour and Antidepressant Therapy, p. 206), seizures, hypersensitivity reactions including urticaria, angioedema, rash (including Stevens-Johnson syndrome) and anaphylaxis, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 206)

**Dose**

- **ADULT** over 18 years, 40 mg twice daily, assess for benefit and tolerability after 2–4 weeks

**Note** Initial dose of 20 mg twice daily for 2 weeks can minimise side-effects

**Yentreve**

- **Lilly** ▼ *(Pfizer)*

**Capsules** duloxetine (as hydrochloride) 20 mg (blue), net price 28-cap pack = £15.40, 56-cap pack = £30.80; 40 mg (orange/blue), 56-cap pack = £30.80. Label: 2

**Cymbalta**

- **Lilly** ▼ *(BMS)*

**Section 4.3.4 (major depressive episode, generalised anxiety disorder, and diabetic neuropathy)**

**FESOTERODINE**

**Indications** urinary frequency, urgency, and urge incontinence

**Cautions** see notes above; gastro-oesophageal reflux

**Contra-indications** see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see notes above; also insomnia; less commonly nasal dryness, pharyngolaryngeal pain, cough, and vertigo

**Dose**

- **ADULT** over 18 years, 4 mg once daily, increased if necessary to max. 8 mg once daily; assess for benefit after 8 weeks

**Note** Max. 4 mg daily with concomitant atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, or telithromycin; in patients with hepatic or renal impairment, consult product literature before concomitant use of amphotericin, aprepitant, atazanavir, clarithromycin, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, nelfinavir, ritonavir, saquinavir, telithromycin, verapamil, or grapefruit juice

**Toviaz**

- **Pfizer** ▼ *(Pfizer)*

**Tablets** m/r, ti, f/c, fesoterodine fumarate 4 mg (light blue), net price 28-tab pack = £29.03; 8 mg (blue), 28-tab pack = £29.03. Label: 3, 25

**FLAVOXATE HYDROCHLORIDE**

**Indications** urinary frequency and incontinence, dysuria, urgency; bladder spasms due to catheterisation, cystoscopy, or surgery

**Cautions** see notes above; pregnancy (Appendix 4), breast-feeding (Appendix 5)

**Contra-indications** see notes above; gastro-intestinal haemorrhage

**Side-effects** see notes above; also vertigo, eosinophilia, leucopenia, urticaria, erythema, and pruritus
Dose
- ADULT and ADOLESCENT over 12 years, 200 mg 3 times daily

Urispas 200® (Recordati) Tablets, f/c, flavoxate hydrochloride 200 mg, net price 90-tab pack = £11.87

**OXIBUTYNIN HYDROCHLORIDE**

**Indications** urinary frequency, urgency and incontinence, neurogenic bladder instability, and nocturnal enuresis associated with overactive bladder

**Cautions** see notes above; pregnancy (Appendix 4); acute porphyria (section 9.8.2)

**Contra-indications** see notes above; breast-feeding (Appendix 5)

**Side-effects** see notes above; also less commonly anorexia, facial flushing; rarely night terrors; application site reactions with patches

**Dose**
- ADULT and CHILD over 12 years, initially 5 mg 2–3 times daily, increased if necessary to max. 5 mg 4 times daily; ELDERLY initially 2.5–3 mg twice daily, increased to 5 mg twice daily according to response and tolerance; CHILD 5–12 years, neurogenic bladder instability, 2.5–3 mg twice daily, increased to 5 mg 2–3 times daily; CHILD under 5 years, see BNF for Children; CHILD 7–18 years, nocturnal enuresis associated with overactive bladder, 2.5–3 mg twice daily increased to 5 mg 2–3 times daily (last dose before bedtime)

**Oxybutynin Hydrochloride** (Non-proprietary) Tablets, oxybutynin hydrochloride 2.5 mg, net price 56-tab pack = £7.24; 3 mg, 56-tab pack = £9.15; 5 mg, 56-tab pack = £10.21, 84-tab pack = £2.96. Label: 3

**Cystrin®** (Sanofi-Synthelabo) Tablets, oxybutynin hydrochloride 3 mg, net price 56-tab pack = £9.15; 5 mg (scored), 84-tab pack = £22.88. Label: 3

**Ditropan®** (Sanofi-Synthelabo) Tablets, both blue, scored, oxybutynin hydrochloride 2.5 mg, net price 84-tab pack = £6.86; 5 mg, 84-tab pack = £13.34. Label: 3

**Elixir** oxybutynin hydrochloride 2.5 mg/5 mL. Net price 150-mL pack = £5.74. Label: 3

**Modified release**

**Lyrinel XL** (Janssen-Cilag) Tablets, m/r, oxybutynin hydrochloride 5 mg (yellow), net price 30-tab pack = £11.48; 10 mg (pink), 30-tab pack = £22.95. Label: 3, 25

**Dose** Initially 5 mg once daily, adjusted according to response in steps of 5 mg at weekly intervals; max. 20 mg once daily; CHILD over 6 years, neurogenic bladder instability; initially 5 mg once daily, adjusted according to response in steps of 5 mg at weekly intervals; max. 15 mg once daily

**Note** Patients taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of Lyrinel XL

**Transdermal preparations**

**Kentera®** (Recordati) Patches, self-adhesive, oxybutynin 36 mg (releasing oxybutynin approx. 3.9 mg/24 hours), net price 8-patch pack = £27.20. Label: 3, counselling, administration

**Dose** ADULT over 18 years, urinary frequency, urgency and incontinence, apply 1 patch twice weekly to clean, dry, unbroken skin on abdomen, hip or buttock, remove after every 3–4 days and site replacement patch on a different area (avoid using same area for 7 days)

**Note** The Scottish Medicines Consortium has advised (July 2005) that Kentera should be restricted for use in patients who benefit from oral oxybutynin but cannot tolerate its side-effects

**PROPANTHELINE BROMIDE**

**Indications** adult enuresis

**Cautions** see notes above; ulcerative colitis, pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above; also facial flushing

**Dose**
- Initially 15 mg 3 times daily at least one hour before food and 30 mg at bedtime, subsequently adjusted according to response (max. 120 mg daily)

**Preparations**
Section 1.2

**PROPIVERINE HYDROCHLORIDE**

**Indications** urinary frequency, urgency and incontinence; neurogenic bladder instability

**Cautions** see notes above

**Contra-indications** see notes above; moderate to severe hepatic impairment; pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** see notes above

**Dose**
- 15 mg 1–3 times daily, increased if necessary to max. 15 mg 4 times daily; CHILD not recommended

**Detrnorm®** (Amdipharm) Tablets, pink, s/c, propiverine hydrochloride 15 mg, net price 56-tab pack = £24.45. Label: 3

**Modified release**

**Detrnorm® XL** (Amdipharm) Capsules, orange/white, m/r, propiverine hydrochloride 30 mg, net price 28-cap pack = £24.45. Label: 3, 25

**Dose** urinary frequency, urgency, and incontinence, 30 mg once daily; CHILD not recommended

**SOLIFENACIN SUCCINATE**

**Indications** urinary frequency, urgency and urge incontinence

**Cautions** see notes above; neurogenic bladder disorder; pregnancy (Appendix 4)

**Contra-indications** see notes above; severe hepatic impairment (Appendix 2); haemodialysis; breast-feeding (Appendix 5)

**Side-effects** see notes above; also gastro-oesophageal reflux; oedema

**Dose**
- 5 mg daily, increased if necessary to 10 mg once daily; CHILD not recommended

**Note** Max. 5 mg daily with concomitant itraconazole, ketoconazole, nelfinavir or ritonavir

**Vesicare®** (Astellas) Tablets, f/c, solifenacin succinate 5 mg (yellow), net price 30-tab pack = £27.62; 10 mg (pink), 30-tab pack = £35.91. Label: 3
7 Obstetrics, gynaecology, and urinary-tract disorders

7.4.3 Drugs used in urological pain

TOLTERODINE TARTRATE

**Indications** urinary frequency, urgency and incontinence

**Cautions** see notes above; history of QT-interval prolongation; concomitant use with other drugs known to prolong QT interval

**Contra-indications** see notes above; pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** see notes above; also chest pain, peripheral oedema; sinusitis, bronchitis; paraesthesia, fatigue, vertigo, weight gain; flushing also reported

**Dose**
- **ADULT** over 18 years, 2 mg twice daily; reduce to 1 mg twice daily if necessary to minimise side-effects

<table>
<thead>
<tr>
<th><strong>Detrusitol®</strong> (Pharmacia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablets</strong>, 1/c, tolterodine tartrate 1 mg, net price 56-tab pack = £29.03; 2 mg, 56-tab pack = £30.56. Label: 3</td>
</tr>
</tbody>
</table>

**Modified release**

<table>
<thead>
<tr>
<th><strong>Detrusitol® XL</strong> (Pharmacia)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Capsules</strong>, blue, m/r, tolterodine tartrate 4 mg, net price 28-cap pack = £29.03. Label: 3, 25</td>
</tr>
</tbody>
</table>

**Dose** **ADULT** over 18 years, 4 mg once daily (dose form not appropriate for hepatic impairment or if creatinine clearance less than 30 mL/minute)

TROSPUIM CHLORIDE

**Indications** urinary frequency, urgency and incontinence

**Cautions** see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above; also chest pain, dyspnoea, rash and asthenia

**Dose**
- 20 mg twice daily before food; **CHILD** not recommended

<table>
<thead>
<tr>
<th><strong>Regurin®</strong> (Galen)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tablets</strong>, brown, f/c, trospium chloride 20 mg, net price 60-tab pack = £26.00. Label: 23</td>
</tr>
</tbody>
</table>

Nocturnal enuresis

Nocturnal enuresis is a common occurrence in young children but persists in as many as 5% by 10 years of age. Treatment is not appropriate in children under 5 years and it is usually not needed in those aged under 7 years and in cases where the child and parents are not anxious about the bedwetting; however, children over 10 years usually require prompt treatment. An enuresis alarm should be first-line treatment for well-motivated children aged over 7 years because it may achieve a more sustained reduction of enuresis than use of drugs. Use of an alarm may be combined with drug therapy if either method alone is unsuccessful.

Drug therapy is not usually appropriate for children under 7 years of age; it can be used when alternative measures have failed, preferably on a short-term basis, to cover periods away from home for example. The possible side-effects of the various drugs should be borne in mind when they are prescribed.

Desmopressin (section 6.5.2), an analogue of vasopressin, is used for nocturnal enuresis; it is given by oral or by sublingual administration. Particular care is needed to avoid fluid overload. Treatment should not be continued for longer than 3 months without stopping for 1 week for full re-assessment. Desmopressin should not be given intranasally for nocturnal enuresis due to an increased incidence of side-effects.

Tricyclics (section 4.3.1) such as amitriptyline, imipramine, and less often nortriptyline can be used, but behavioural disturbances can occur and relapse is common after withdrawal. Treatment should not normally exceed 3 months unless a full physical examination is made and the child is fully re-assessed; toxicity following overdosage with tricyclics is of particular concern.

DRUGS USED IN UROLOGICAL PAIN

Alkalisation of urine

Alkalisation of urine can be undertaken with potassium citrate. The alkalinising action may relieve the discomfort of cystitis caused by lower urinary tract infections. Sodium bicarbonate is used as a urinary alkalinising agent in some metabolic and renal disorders (section 9.2.1.3).

POTASSIUM CITRATE

**Indications** relief of discomfort in mild urinary-tract infections; alkalinisation of urine

**Cautions** renal impairment (avoid if creatinine clearance less than 10 mL/minute); Appendix 3), cardiac disease; elderly; **interactions**: Appendix 1 (potassium salts)

**Side-effects** hyperkalaemia on prolonged high dosage, mild diuresis

**Potassium Citrate Mixture BP**

(Potassium Citrate Oral Solution)

**Oral solution**, potassium citrate 30%, citric acid monohydrate 5% in a suitable vehicle with a lemon flavour. Extemporaneous preparations should be recently prepared according to the following formula: potassium citrate 3 g, citric acid monohydrate 500 mg, syrup 2.5 mL, quillaia tincture 0.1 mL, lemon spirit 0.05 mL, double-strength chloroform water 3 mL, water to 10 mL. Contains about 28 mmol K+/10 mL.

**Dose** 10 mL 3 times daily well diluted with water

**Proprietary brands of potassium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections**

**SODIUM BICARBONATE**

**Indications** relief of discomfort in mild urinary-tract infections; alkalinisation of urine
Mycotic infections. 50 micrograms/mL (section 5.2) may be of value in continuous bladder irrigation with amphotericin, considered as a mechanical irrigant. Sodium chloride solution 0.9% (section 8.1.1) is used for recurrent superficial bladder infections (section 8.1.2), and mitomycin (section 8.1.2), and thiotepa (section 8.1.2) is also used for some papillary tumours.

Instillation of epirubicin (section 8.1.2) is used for treatment and prophylaxis of certain forms of superficial bladder cancer; instillation of doxorubicin (section 8.1.2) is also used for some papillary tumours.

Instillation of BCG (Bacillus Calmette-Guérin), a live attenuated strain derived from Mycobacterium bovis (section 8.2.4), is licensed for the treatment of primary or recurrent bladder carcinoma in-situ and for the prevention of recurrence following transurethral resection.

Interstitial cystitis Dimethyl sulfoxide (dimethyl sulfoxide) may be used for symptomatic relief in patients with interstitial cystitis (Hunner’s ulcer). 50 mL of a 50% solution (Rimso-50®—available on named-patient basis from Britannia) is instilled into the bladder, retained for 15 minutes, and voided by the patient. Treatment is repeated at intervals of 2 weeks. Bladder spasm and hypersensitivity reactions may occur and long-term use requires ophthalmic, renal, and hepatic assessment at intervals of 6 months. Interactions: see Appendix 1 (dimethyl sulfoxide).

SODIUM CITRATE

Indications relief of discomfort in mild urinary-tract infections

Cautions renal impairment; cardiac disease; hypertension; pregnancy; patients on a sodium-restricted diet; elderly

Side-effects mild diuresis

Note Proprietary brands of sodium citrate are on sale to the public for the relief of discomfort in mild urinary-tract infections

Other preparations for urinary disorders

A terpene mixture (Rowatinex®) is claimed to be of benefit in urolithiasis for the expulsion of calculi.

Rowatinex® (Rowa), yellow, e/c, anethol 4 mg, borneol 10 mg, camphene 15 mg, cineole 3 mg, fenchone 4 mg, pinene 31 mg. Net price 50 = £7.35. Label: 25

Dose 1–2 capsules 3–4 times daily before food. CHILD not recommended

BNF 57 7.4.4 Bladder instillations and urological surgery

Bladder infection Various solutions are available as irrigations or washouts.

Aqueous chlorhexidine (section 13.11.2) can be used in the management of common infections of the bladder but it is ineffective against most Pseudomonas spp. Solutions containing chlorhexidine 1 in 5000 (0.02%) are used but they may irritate the mucosa and cause burning and haematuria (in which case they should be discontinued); sterile sodium chloride solution 0.9% (physiological saline) is usually adequate and is preferred as a mechanical irrigant.

Continuous bladder irrigation with amphotericin 50 micrograms/mL (section 5.2) may be of value in mycotic infections.

Dissolution of blood clots Clot retention is usually treated by irrigation with sterile sodium chloride solution 0.9% but sterile sodium citrate solution for bladder irrigation 3% may also be helpful.

Bladder cancer Bladder instillations of doxorubicin (section 8.1.2), mitomycin (section 8.1.2), and thiotepa (section 8.1.1) are used for recurrent superficial bladder tumours. Such instillations reduce systemic side-effects; adverse effects on the bladder (e.g. micturition disorders and reduction in bladder capacity) may occur.

Interleukin-2 therapy Interferon-α is licensed for the treatment of recurrent superficial bladder cancer and for prophylaxis of recurrent bladder carcinoma following transurethral resection.
Drugs for erectile dysfunction

7.4.5 Drugs for erectile dysfunction

Reasons for failure to produce a satisfactory erection include psychogenic, vascular, neurogenic, and endocrine abnormalities; impotence can also be drug-induced. Intracavernosal injection or urethral application of vasoactive drugs under careful medical supervision is used for both diagnostic and therapeutic purposes.

Erectile disorders may also be treated with drugs given for both diagnostic and therapeutic purposes.

Intracavernosal injection or urethral application of vasoactive drugs under careful medical supervision is used for both diagnostic and therapeutic purposes.

Priapism

If priapism occurs with alprostadil, treatment should not be delayed more than 6 hours and is as follows:

Initial therapy by penile aspiration—using aseptic technique—should not be delayed more than 6 hours and is as follows:

1. If aspiration is unsuccessful a second 19–21 gauge butterfly needle can be inserted into the opposite corpus cavernosum and sterile physiological saline introduced through the first needle and drained through the second.

2. If aspiration and lavage of corpora are unsuccessful, cautious intracavernosal injection of a sympathomimetic (section 2.7.2) with action on alpha-adrenergic receptors, continuously monitoring blood pressure and pulse (extreme caution: coronary heart disease, hypertension, cerebral ischaemia or if taking antidepressant) as follows:

   - intracavernosal injections of phenylephrine 100–200 micrograms (0.5–1 mL of a 200 microgram/mL solution) every 5–10 minutes; max. total dose 100 micrograms [unlicensed indication] [important: if suitable strength of adrenaline not available may be specially prepared by diluting 0.1 mL of the phenylephrine 1% (10 mg/mL) injection (section 2.7.2) to 5 mL with sodium chloride 0.9%]; alternatively

   - intracavernosal injections of adrenaline 10–20 micrograms (0.5–1 mL of a 20 microgram/mL solution) every 5–10 minutes; max. total dose 100 micrograms [unlicensed indication] [important: if suitable strength of adrenaline not available may be specially prepared by diluting 0.1 mL of the adrenaline 1 in 1000 (1 mg/mL, section 3.4.3) injection to 5 mL with sodium chloride 0.9%]; alternatively

   - intracavernosal injection of metaraminol (caution: has been associated with fatal hypertensive crises); metaraminol 1 mg (0.1 mL of 10 mg/mL metaraminol injection, section 2.7.2) is diluted to 50 mL with sodium chloride injection 0.9% and given carefully by slow injection into the corpora in 5 mL injections every 15 minutes [unlicensed indication].

   If necessary the sympathomimetic injections can be followed by further aspiration of blood through the same butterfly needle. If sympathomimetics unsuccessful, urgent surgical referral for management (possibly including shunt procedure).

Prescribing on the NHS

Drug treatments for erectile dysfunction may only be prescribed on the NHS under certain circumstances (see individual preparations). The Department of Health (England) has recommended that treatment should also be available from specialist services (commissioned by Health Authorities and Primary Care Groups, and operating under local agreement) when the condition is causing severe distress; specialist centres should use form FP10(HP) or form HBP in Scotland or form WP10HP in Wales and endorse them ‘SLS’ if the treatment is to be dispensed in the community. The following criteria should be considered when assessing distress:

- significant disruption to normal social and occupational activities;
- a marked effect on mood, behaviour, social and environmental awareness;
- a marked effect on interpersonal relationships.

Alprostadil

Alprostadil (prostaglandin E1) is given by intracavernosal injection or intraurethral application for the management of erectile dysfunction (after exclusion of treatable medical causes); it is also used as a diagnostic test.

**ALPROSTADIL**

**Indications** erectile dysfunction (including aid to diagnosis); neonatal congenital heart defects (section 7.1.1.1)

**Cautions** priapism—patients should be instructed to report any erection lasting 4 hours or longer—for management, see section 7.4.5; anatomical deformations of penis (painful erection more likely)—follow up regularly to detect signs of penile fibrosis (consider discontinuation if angulation, cavernosal fibrosis or Peyronie’s disease develop); interactions: Appendix 1 (prostaglandins)

**CATHETER PATENCY SOLUTIONS**

Chlorhexidine 0.02%

Brands include Uriflex C®, 100-mL sachets = £2.40; Uro-Tainer Chlorhexidine®, 100-mL sachets = £2.60

Sodium chloride 0.9%

Brands include OptiFlo S®, 50- and 100-mL sachets = £3.20; Uriflex S®, 100-mL sachet = £2.40; Uriflex SP®, with integral drug additive port, 100-mL sachet = £2.40; Uro-Tainer Sodium Chloride®, 50- and 100-mL sachets = £3.23; Uro-Tainer M®, with integral drug additive port, 50- and 100-mL sachets = £2.90

Solution G

Citric acid 3.23%, magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01%. Brands include OptiFlo G®, 50- and 100-mL sachets = £3.40; Uriflex G®, 100-mL sachet = £2.40; Uro-Tainer® Twin Suby G, 2 x 30-mL = £4.42

Solution R

Citric acid 6%, gluconolactone 0.6%, magnesium carbonate 2.8%, disodium edetate 0.01%. Brands include OptiFlo R®, 50- and 100-mL sachets = £3.40; Uriflex R®, 100-mL sachet = £2.40; Uro-Tainer® Twin Solutio R, 2 x 30-mL = £4.42

**7.4.5 Drugs for erectile dysfunction**
Contra-indications predisposition to prolonged erection (as in sickle cell anaemia, multiple myeloma or leukaemia); not for use with other agents for erectile dysfunction, in patients with penile implants or when sexual activity medically inadvisable; urethral application also contra-indicated in urethral stricture, severe hypospadias, severe curvature, balanitis, urethritis

Side-effects hypotension, hypertension; dizziness, headache; penile pain, other localised pain (buttocks, leg, testicular, abdominal); influenza-like syndrome; urethral burning, urethral bleeding; injection site reactions including penile fibrosis, penile oedema, penile rash, haematoma, haemosiderin deposits; less commonly nausea, dry mouth, vasodilatation, syncope, suprapubcentricular extrasyosyle, rapid pulse, asthenia, leg cramps, pelvic pain, scrotal or testicular oedema, scrotal erythema, testicular thickening, micturition difficulties, haematuria, mydriasis, and sweating; local reactions including penile warmth, pruritus, irritation, penile numbness or sensitivity, balanitis, phimosis, priapism (see section 7.4.5 and under Cautions), abnormal ejaculation; rarely vertigo, urinary-tract infection, and hypersensitivity reactions (including rash, erythema, urticaria, and anaphylaxis)

Dose
- See under preparations below

Intracavernosal injection

Caverject® (Pharmacia) Injection, powder for reconstitution, alprostadil, net price 5-microgram vial = £7.73; 10-microgram vial = £9.24; 20-microgram vial = £11.94; 40-microgram vial = £21.58 (all with diluent-filled syringe, needles and swabs)

Caverject® Dual Chamber, double-cylinder cartridges (containing alprostadil and diluent), net price 10-microgram cartridge (for doses 2.5–10 micrograms) = £7.35; 20-microgram cartridge (for doses 5–20 micrograms) = £9.50 (both with needles)

Dose by direct intracavernosal injection, ADULT over 18 years, erectile dysfunction, first dose 2.5 micrograms, second dose 5 micrograms (if some response to first dose) or 7.5 micrograms (if no response to first dose), increasing in steps of 5–10 micrograms to obtain dose suitable for producing erection lasting not more than 1 hour (neurological dysfunction, first dose 1.25 micrograms, second dose 2.5 micrograms, third dose 5 micrograms, increasing in steps of 5–10 micrograms to obtain suitable dose), if no response to dose then next higher dose can be given within 1 hour, if there is a response the next dose should not be given for at least 24 hours; usual dose 5–20 micrograms; max. 40 micrograms; max. frequency of injection not more than 2–3 times per week with at least 24 hour interval between injections; reduce dose if erection lasts longer than 2 hours

Note The first dose must be given by medically trained personnel; self-administration may only be undertaken after proper training

Urethral application

Counselling If partner pregnant barrier contraception should be used

MUSE® (Meda) Urethral application, alprostadil, net price 125-microgram single-use applicator = £9.89; 250-microgram single-use applicator = £10.76; 500-microgram single-use applicator = £10.76, 1-mg single-use applicator = £11.01 (all strengths also available in packs of 6 applicators)

Condoms no evidence of harm to latex condoms and diaphragms

Dose by direct urethral application, ADULT over 18 years, erectile dysfunction, initially 250 micrograms adjusted according to response (usual range 0.125–1 mg); max. 2 doses in 24 hours and 7 doses in 7 days

Note During initiation of treatment MUSE® should be used under medical supervision, self-administration may only be undertaken after proper training

Aid to diagnosis, 500 micrograms as a single dose

Phosphodiesterase type-5 inhibitors

Sildenafil, tadalafil and vardenafil are phosphodiesterase type-5 inhibitors licensed for the treatment of erectile dysfunction; they are not recommended for use with other treatments for erectile dysfunction. The patient should be assessed appropriately before prescribing sildenafil, tadalafil or vardenafil. Since these drugs are given by mouth there is a potential for drug interactions.

Cautions Sildenafil, tadalafil, and vardenafil should be used with caution in cardiovascular disease, left ventricular outflow obstruction, anatomical deformation of the penis (e.g. angulation, cavernosal fibrosis, Peyronie’s disease), and in those with a predisposition to priapism (e.g. in sickle-cell disease, multiple myeloma, or leukaemia).

Contra-indications Sildenafil, tadalafil, and vardenafil are contra-indicated in patients receiving nitrates, in patients in whom vasodilatation or sexual activity are inadvisable, or in patients with a previous history of non-arteritic anterior ischaemic optic neuropathy. In the absence of information, manufacturers contra-indicate these drugs in hypotension (avoid if systolic blood pressure below 90 mmHg), recent stroke, unstable angina, and myocardial infarction.

Side-effects The side-effects of sildenafil, tadalafil, and vardenafil include dyspepsia, nausea, vomiting,
headache (including migraine), flushing, dizziness, myalgia, back pain, visual disturbances (non-arteritic anterior ischaemic optic neuropathy has been reported—stop drug if sudden visual impairment occurs), and nasal congestion. Less common side-effects include painful red eyes, palpitation, hypotension, hypertension, epistaxis. Other side-effects reported rarely include syncope, hypersensitivity reactions (including rash, facial oedema, and Stevens-Johnson syndrome), and priapism. Serious cardiovascular events (including arrhythmia, unstable angina, and myocardial infarction), sudden hearing loss (discontinue drug and seek medical advice), and retinal vascular occlusion have also been reported.

**SILDENAFIL**

**Indications** erectile dysfunction; pulmonary hypertension (section 2.5.1)

**Cautions** see notes above; also hepatic impairment (Appendix 2—avoid if severe); renal impairment (Appendix 3); bleeding disorders or active peptic ulceration; **interactions:** Appendix 1 (sildenafil)

**Contra-indications** see notes above; also hereditary degenerative retinal disorders

**Side-effects** see notes above

**Dose**

- **ADULT** over 18 years initially 50 mg approx. 1 hour before sexual activity, subsequent doses adjusted according to response to 25–100 mg as a single dose as needed; max. 1 dose in 24 hours (max. single dose 100 mg)

**Note** Onset of effect may be delayed if taken with food

1 **Viagra** (Pfizer)  
Tablets, all blue, f/c, sildenafil (as citrate), 25 mg, net price 4-tab pack = £16.59, 8-tab pack = £33.19; 50 mg, 4-tab pack = £19.34, 8-tab pack = £38.67; 100 mg, 4-tab pack = £23.50, 8-tab pack = £46.99

**Revatio** (Pfizer) ▼
Section 2.5.1 (pulmonary hypertension)

**TADALAFIL**

**Indications** erectile dysfunction

**Cautions** see notes above; also hepatic impairment (Appendix 2); renal impairment (Appendix 3); **interactions:** Appendix 1 (tadalafil)

**Contra-indications** see notes above; also moderate heart failure, uncontrolled arrhythmias, uncontrolled hypertension

**Side-effects** see notes above; also increased sweating and abdominal pain reported

1 except to treat erectile dysfunction in men who:

- have diabetes, multiple sclerosis, Parkinson’s disease, poliomyelitis, prostate cancer, severe pelvic injury, single gene neurological disease, spina bifida, or spinal cord injury;
- are receiving dialysis for renal failure;
- have had radical pelvic surgery, prostatectomy (including transurethral resection of the prostate), or kidney transplant;
- were receiving Caverject, Erecnos, MUSE, Viagra, or Voidal for erectile dysfunction, at the expense of the NHS, on 14 September 1998;
- are suffering severe distress as a result of impotence (prescribed in specialist centres only, see notes above).

The prescription must be endorsed ‘SLS’.

**Dose**

- **ADULT** over 18 years, initially 10 mg at least 30 minutes before sexual activity, subsequent doses adjusted according to response to 20 mg as a single dose; max. 1 dose in 24 hours (but daily use not recommended)

**Note** Effect may persist for longer than 24 hours

1 **Cialis** (Lilly)  
Tablets, f/c, tadalafil 10 mg (light yellow), net price 4-tab pack = £24.99; 20 mg (yellow), 4-tab pack = £24.99; 8-tab pack = £49.97

**VARDENAFIL**

**Indications** erectile dysfunction

**Cautions** see notes above; also hepatic impairment (Appendix 2—avoid if severe); renal impairment (Appendix 3); bleeding disorders or active peptic ulceration; susceptibility to prolongation of QT interval (including concomitant use of drugs which prolong QT interval); **interactions:** Appendix 1 (vardenafil)

**Contra-indications** see notes above; also hereditary degenerative retinal disorders

**Side-effects** see notes above; also less commonly drowsiness, dyspnoea, increased lacrimation, photosensitivity; rarely anxiety, seizures, transient amnesia, hypertonia, and raised intra-ocular pressure

**Dose**

- **ADULT** over 18 years, initially 10 mg (elderly) and patients on alpha-blocker therapy 5 mg approx. 25–60 minutes before sexual activity, subsequent doses adjusted according to response up to max. 20 mg as a single dose; max. 1 dose in 24 hours

**Note** Onset of effect may be delayed if taken with high-fat meal

1 **Levitra** (Bayer)  
Tablets, all orange, f/c, vardenafil (as hydrochloride trihydrate) 5 mg, net price 4-tab pack = £16.58, 8-tab pack = £33.19; 10 mg, 4-tab pack = £22.24, 8-tab pack = £44.47; 20 mg, 4-tab pack = £23.50, 8-tab pack = £46.99

**Papaverine and phentolamine**

Although not licensed the smooth muscle relaxant papaverine has also been given by intracavernosal injection for erectile dysfunction. Patients with neurological or psychogenic impotence are more sensitive to the effect of papaverine than those with vascular abnormalities. Phentolamine is added if the response is inadequate [unlicensed indication].

Persistence of the erection for longer than 4 hours is an emergency, see advice in section 7.4.5.
8 Malignant disease and immunosuppression

8.1 Cytotoxic drugs

8.1.1 Alkylating drugs
8.1.2 Anthracyclines and other cytotoxic antibiotics
8.1.3 Antimetabolites
8.1.4 Vinca alkaloids and etoposide
8.1.5 Other antineoplastic drugs

8.2 Drugs affecting the immune response

8.2.1 Antiproliferative immunosuppressants
8.2.2 Corticosteroids and other immunosuppressants
8.2.3 Rituximab and alemtuzumab
8.2.4 Other immunomodulating drugs

8.3 Sex hormones and hormone antagonists in malignant disease

8.3.1 Oestrogens
8.3.2 Progestogens
8.3.3 Androgens
8.3.4 Hormone antagonists
8.3.4.1 Breast cancer
8.3.4.2 Prostate cancer and gonadorelin analogues
8.3.4.3 Somatostatin analogues

The chemotherapy of cancer is complex and should be confined to specialists in oncology. Cytotoxic drugs have both anti-cancer activity and the potential to damage normal tissue. Chemotherapy may be given with a curative intent or it may aim to prolong life or to palliate symptoms. In an increasing number of cases chemotherapy may be combined with radiotherapy or surgery or both as either neoadjuvant treatment (initial chemotherapy aimed at shrinking the primary tumour, thereby rendering local therapy less destructive or more effective) or as adjuvant treatment (which follows definitive treatment of the primary disease, when the risk of sub-clinical metastatic disease is known to be high). All chemotherapy drugs cause side-effects and a balance has to be struck between likely benefit and acceptable toxicity.

Guidelines for handling cytotoxic drugs:
1. Trained personnel should reconstitute cytotoxics;
2. Reconstitution should be carried out in designated areas;
3. Protective clothing (including gloves, gowns, and masks) should be worn;
4. The eyes should be protected and means of first aid should be specified;
5. Pregnant staff should avoid exposure to cytotoxic drugs (all females of child-bearing age should be informed of the reproductive hazard);
6. Use local procedures for dealing with spillages and safe disposal of waste material, including syringes, containers, and absorbent material;
7. Staff exposure to cytotoxic drugs should be monitored.
Cytotoxic drugs fall into a number of classes, each with characteristic antitumour activity, sites of action, and toxicity. A knowledge of sites of metabolism and excretion is important because impaired drug handling as a result of disease is not uncommon and may result in enhanced toxicity.

**Side-effects of cytotoxic drugs**

Side-effects common to most cytotoxic drugs are discussed below whilst side-effects characteristic of a particular drug or class of drugs (e.g. neurotoxicity with vinca alkaloids) are mentioned in the appropriate sections. Manufacturers’ product literature should be consulted for full details of side-effects associated with individual drugs.

**Extravasation of intravenous drugs**

A number of cytotoxic drugs will cause severe local tissue necrosis if leakage into the extravascular compartment occurs. To reduce the risk of extravasation injury it is recommended that cytotoxic drugs are administered by appropriately trained staff. For information on the prevention and management of extravasation injury, see section 10.3.

**Oral mucositis**

A sore mouth is a common complication of cancer chemotherapy; it is most often associated with fluorouracil, methotrexate, and the anthracyclines. It is best to prevent the complication. Good oral hygiene (rinsing the mouth frequently and effective brushing of the teeth with a soft brush 2–3 times daily) is probably beneficial. For fluorouracil, sucking ice chips during short infusions of the drug is also helpful.

Once a sore mouth has developed, treatment is much less effective. Saline mouthwashes should be used but there is no good evidence to support the use of anti-septic or anti-inflammatory mouthwashes. In general, mucositis is self-limiting but with poor oral hygiene it can be a focus for blood-borne infection.

**Tumour lysis syndrome**

Tumour lysis syndrome can occur as a result of massive cell breakdown following treatment of cancer sensitive to the chemotherapy. Features include hyperkalaemia, hyperuricaemia (see below), and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow.

**Hyperuricaemia**

Hyperuricaemia, which may be present in high-grade lymphoma and leukaemia, can be markedly worsened by chemotherapy and is associated with acute renal failure. Allopurinol (section 10.1.4) should be started 24 hours before treating such tumours and patients should be adequately hydrated. The dose of mercaptopurine or azathioprine should be reduced if allopurinol needs to be given concomitantly (see Appendix 1).

**Rasburicase**

Rasburicase (section 10.1.4), a recombinant urate oxidase, is licensed for hyperuricaemia in patients with haematological malignancy, for details, see p. 575. It rapidly reduces plasma uric acid and may be of particular value in reducing complications following treatment of leukaemias or bulky lymphomas.

**Nausea and vomiting**

Nausea and vomiting cause considerable distress to many patients who receive chemotherapy and, to a lesser extent, abdominal radiotherapy; it may lead to refusal of further treatment. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment), or anticipatory (occurring prior to subsequent doses). Delayed and anticipatory symptoms are more difficult to control than acute symptoms and require different management.

Patients vary in their susceptibility to drug-induced nausea and vomiting; those affected more often include women, patients under 50 years of age, anxious patients, and those who experience motion sickness. Susceptibility also increases with repeated exposure to the cytotoxic drug.

Drugs may be divided according to their emetogenic potential and some examples are given below, but the symptoms vary according to the dose, to other drugs administered and to individual susceptibility.

**Mildly emetogenic treatment**—fluorouracil, etoposide, methotrexate (less than 100 mg/m²), the vinca alkaloids, and abdominal radiotherapy.

**Moderately emetogenic treatment**—the taxanes, doxorubicin, intermediate and low doses of cyclophosphamide, mitoxantrone (mitozantrone), and high doses of methotrexate (0.1–1.2 g/m²).

**Highly emetogenic treatment**—cisplatin, dacarbazine, and high doses of cyclophosphamide.

**Prevention of acute symptoms**

For patients at low risk of emesis, pretreatment with domperidone or, in adults over 20 years, with metoclopramide, continued for up to 24 hours after chemotherapy, is often effective (section 4.6). If metoclopramide or domperidone are not sufficiently effective, additional drugs such as dexamethasone (6–10 mg by mouth) or lorazepam (1–2 mg by mouth) may be used.
For patients at high risk of emesis or when other treatment is inadequate, a specific (5HT) serotonin antagonist (section 4.6), usually given by mouth, is often highly effective, particularly when used with dexamethasone; adding the neurokinin receptor antagonist, aprepitant (section 4.6) can improve control of cisplatin-related nausea and vomiting.

Prevention of delayed symptoms. Dexamethasone, given by mouth, is the drug of choice for preventing delayed symptoms; it is used alone or with metoclopramide or prochlorperazine. The 5HT antagonists may be less effective for delayed symptoms.

Prevention of anticipatory symptoms. Good symptom control is the best way to prevent anticipatory symptoms. Lorazepam can be helpful for its amnesic, sedative, and anxiolytic effects.

Bone-marrow suppression All cytotoxic drugs except vincristine and bleomycin cause bone-marrow depression. This commonly occurs 7 to 10 days after administration, but is delayed for certain drugs, such as Carmustine, lomustine, and melphalan. Peripheral blood counts must be checked before each treatment, and doses should be reduced or therapy delayed if bone-marrow has not recovered.

Fever in a neutropenic patient (neutrophil count less than 1.0 × 10⁹/litre) requires immediate broad-spectrum antibacterial therapy. Patients at low risk (those receiving chemotherapy for solid tumours, lymphoma or chronic leukaemia) can be treated with oral ciprofloxacin with or without co-amoxiclav (initially in hospital). All other patients should receive parenteral broad-spectrum antibacterial therapy. Appropriate bacteriological investigations should be conducted as soon as possible.

In selected patients, the duration and the severity of neutropenia can be reduced by the use of recombinant human granulocyte-colony stimulating factors, section 9.1.6.

Symptomatic anaemia is usually treated with red blood cell transfusions. For guidance on the use of erythropoietins in patients with cancer, see MHLRA/CHM advice (p. 509) and NICE guidance (p. 510).

Alopecia Reversible hair loss is a common complication, although it varies in degree between drugs and individual patients. No pharmacological methods of preventing this are available.

Reproductive function Most cytotoxic drugs are teratogenic and should not be administered during pregnancy, especially during the first trimester.

Contraceptive advice should be offered where appropriate before cytotoxic therapy begins (and should cover the duration of contraception required after therapy has ended). Regimens that do not contain an alkylating drug may have less effect on fertility, but those with an alkylating drug carry the risk of causing permanent male sterility (there is no effect on potency). Pre-treatment counselling and consideration of sperm storage may be appropriate. Women are less severely affected, though the span of reproductive life may be shortened by the onset of a premature menopause. No increase in fetal abnormalities or abortion-rate has been recorded in patients who remain fertile after cytotoxic chemotherapy.

Thromboembolism Venous thromboembolism can be a complication of cancer itself, but chemotherapy can also increase the risk.

Drugs for cytotoxic-induced side-effects

Anthracrycline side-effects

Anthracrycline-induced cardiotoxicity The anthracrycline cytotoxic drugs are associated with dose-related, cumulative, and potentially life-threatening cardiotoxic side-effects.

Dexrazoxane, an iron chelator, is licensed for the prevention of chronic cumulative cardiotoxicity caused by doxorubicin or epirubicin treatment in advanced or metastatic cancer patients who have previously received anthracycline therapy. Patients receiving dexrazoxane should still be monitored for cardiac toxicity. The myelosuppressive effects of dexrazoxane may be additive to those of chemotherapy.

Anthracrycline extravasation Dexrazoxane is licensed for the treatment of anthracycline extravasation. The first dose should be given as soon as possible and within six hours after the injury. For further information on the prevention and management of extravasation injury, see section 10.3.

Local guidelines for the management of extravasation should be followed or specialist advice sought.

---

**DEXRAZOXANE**

**Indications** see notes above and under preparations

**Cautions** monitor full blood count; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** pregnancy (Appendix 4); breastfeeding

**Side-effects** nausea, vomiting, dyspepsia, abdominal pain, diarrhoea, stomatitis, dry mouth, anorexia; dyspnoea; dizziness, syncope, asthenia, paraesthesia, tremor, fatigue, drowsiness; pyrexia; vaginal haemorrhage; myalgia; bone-marrow suppression; conjunctivitis; alopecia, pruritus; peripheral oedema; injection-site reactions including phlebitis

**Dose**

- See under preparations

**Cardoxane® (Novartis) ▼ (FIN)

Intravenous infusion, powder for reconstitution, dexrazoxane (as hydrochloride), net price 500-mg vial = £156.57

Dose prevention of anthracycline-induced cardiotoxicity, ADULT over 18 years, by intravenous infusion (30 minutes prior to anthracycline administration), 20 times the doxorubicin-equivalent dose or 10 times the epirubicin-equivalent dose

**Savene® (TopoTarget) ▼ (FIN)

Intravenous infusion, powder for reconstitution, dexrazoxane (as hydrochloride), net price 10 x 500-mg vials (with diluent) = £6750.00

Dose anthracycline extravasation, ADULT over 18 years, by intravenous infusion, 1 g/m² (max. 2 g) daily for 2 days, then 500 mg/m² for 1 day

Note Local coolants such as ice packs should be removed at least 15 minutes before administration
Chemotherapy-induced mucositis and myelosuppression

Folinic acid (given as calcium folinate) is used to counteract the folate-antagonist action of methotrexate and thus speed recovery from methotrexate-induced mucositis or myelosuppression (‘folic acid rescue’).

Folinic acid is also used in the management of methotrexate overdose, together with other measures to maintain fluid and electrolyte balance, and to manage possible renal failure.

Folinic acid does not counteract the antibacterial activity of folate antagonists such as trimethoprim.

When folinic acid and fluorouracil are used together in metastatic colorectal cancer the response-rate improves compared to that with fluorouracil alone.

The calcium salt of levofolinic acid, a single isomer of folinic acid, is also used for rescue therapy following methotrexate administration, for cases of methotrexate overdose, and for use with fluorouracil for colorectal cancer. The dose of calcium levofolinate is generally half that of calcium folinate.

The disodium salt of folinic acid is also licensed for rescue therapy following methotrexate therapy and for use with fluorouracil for colorectal cancer.

Palifermin, a human keratinocyte growth factor, is licensed for the management of oral mucositis in patients with haematological malignancies receiving myeloablative therapy with autologous haematopoietic stem-cell support.

CALCIUM FOLINATE
(Calcium leucovorin)

Indications see notes above

Cautions avoid simultaneous administration of methotrexate; not indicated for pernicious anaemia or other megaloblastic anaemias due to vitamin B deficiency; pregnancy (Appendix 4) and breast-feeding (Appendix 5); interactions: Appendix 1 (folic acid);

Side-effects hypersensitivity reactions; rarely pyrexia after parenteral use

Dose

Note Doses expressed as folinic acid

• Prevention of methotrexate-induced adverse effects, usually started 24 hours after start of methotrexate infusion, by intramuscular injection, or by intravenous injection, or by intravenous infusion, 15 mg, repeated every 6 hours for 24 hours (may be continued by mouth); consult local treatment protocol for further information.

• Suspected methotrexate overdosage, by intravenous injection or by intravenous infusion (at a max. rate of 160 mg/minute), initial dose equal to or exceeding dose of methotrexate; consult poisons information service (p. 27) for advice on continuing management.

• Adjunct to fluorouracil in colorectal cancer, consult product literature

Calcium Folinate (Non-proprietary) [TA]

Tablets, scored, folinic acid (as calcium salt) 15 mg, net price 10-tab pack = £39.20, 30-tab pack = £85.74. Brands include Referolinon

Note Not all strengths and pack sizes are available from all manufacturers

Injection, folinic acid (as calcium salt) 3 mg/mL, net price 1-mL amp = £4.00, 10-mL amp = £4.62; 7.5 mg/mL, net price 2-mL amp = £7.80; 10 mg/mL, net price 5-mL vial = £19.41, 10-mL vial = £35.09, 30-mL vial = £94.69, 35-mL vial = £90.98

Note Not all strengths and pack sizes are available from all manufacturers

CALCIUM LEVOFOLINATE
(Calcium levoleucovorin)

Indications see notes above

Cautions see Calcium Folinate

Side-effects see Calcium Folinate

Dose

Note Doses expressed as levofolic acid

• Prevention of methotrexate-induced adverse effects, usually started 24 hours after beginning of methotrexate infusion, by intramuscular injection, or by intravenous injection or by intravenous infusion, usually 7.5 mg every 6 hours for 10 doses

• Suspected methotrexate overdosage, by intravenous injection or by intravenous infusion (at a max. rate of 160 mg/minute), initial dose at least 50% of the dose of methotrexate; consult poisons information service (p. 27) for advice on continuing management.

• Adjunct to fluorouracil in colorectal cancer, consult product literature

Isovorin® (Wyeth) ▼ [TA]

Injection, levofolic acid (as calcium salt) 10 mg/mL, net price 2.5-mL vial = £12.09, 5-mL vial = £26.00, 17.5-mL vial = £84.63

DISODIUM FOLINATE

Indications see notes above

Cautions see Calcium Folinate

Side-effects see Calcium Folinate

Dose

• As an antidote to methotrexate, see Calcium Folinate

• Adjunct to fluorouracil in colorectal cancer, consult product literature

Sodiofolin® (Medac) ▼ [TA]

Injection, folinic acid (as disodium salt) 50 mg/mL, net price 2-mL vial = £35.09, 8-mL vial = £126.25, 18-mL vial = £284.07

PALIFERMIN

Indications see notes above

Cautions pregnancy (Appendix 4)

Contra-indications breast-feeding

Side-effects taste disturbance, thickening and discoloration of tongue; fever; oedema; arthralgia; rash, pruritus, erythema

Dose

• By intravenous injection, 60 micrograms/kg once daily for 3 doses (third dose given 24–48 hours before myeloablative therapy) then 3 further doses at least 24 hours after myeloablative therapy, starting on same day as (but after) stem-cell infusion; CHILD not recommended
Kepivance® (Amgen) ▼ (PaF)
Injection, powder for reconstitution, palifermin, net price 6.25-mg vial = £544.24

Urothelial toxicity

Haemorrhagic cystitis is a common manifestation of urothelial toxicity which occurs with the oxazaphosphorines, cyclophosphamide and ifosfamide; it is caused by the metabolite acrolein. Mesna reacts specifically with this metabolite in the urinary tract, preventing toxicity. Mesna is used routinely (preferably by mouth) in patients receiving ifosfamide, and in patients receiving cyclophosphamide by the intravenous route at a high dose (e.g. more than 2 g) or in those who experienced urothelial toxicity when given cyclophosphamide previously.

MESNA
Indications see notes above
Contra-indications hypersensitivity to thiol-containing compounds
Side-effects nausea, vomiting, colic, diarrhoea, fatigue, headache, limb and joint pains, depression, irritability, rash, hypotension and tachycardia; rarely hypersensitivity reactions (more common in patients with auto-immune disorders)
Dose
Note Doses calculated according to oxazaphosphorine (cyclophosphamide or ifosfamide) treatment—for details consult product literature
• By mouth, dose is given 2 hours before oxazaphosphorine treatment and repeated 2 and 6 hours after treatment
• By intravenous injection, dose is given with oxazaphosphorine treatment and repeated 4 and 8 hours after treatment

Uromitexan® (Baxter) ▼ (PaF)
Tablets, t/c, mesna 400 mg, net price 10-tab pack = £23.20; 600 mg, 10-tab pack = £30.10
Injection, mesna 100 mg/mL. Net price 4-mL amp = £1.95; 10-mL amp = £4.38
Note For oral administration contents of ampoule are taken in a flavoured drink such as orange juice or cola which may be stored in a refrigerator for up to 24 hours in a sealed container

8.1.1 Alkylating drugs

Extensive experience is available with these drugs, which are among the most widely used in cancer chemotherapy. They act by damaging DNA, thus interfering with cell replication. In addition to the side-effects common to many cytotoxic drugs (section 8.1), there are two problems associated with prolonged usage. Firstly, gametogenesis is often severely affected (section 8.1). Secondly, prolonged use of these drugs, particularly when combined with extensive irradiation, is associated with a marked increase in the incidence of acute non-lymphocytic leukaemia.

Cyclophosphamide is used for the treatment of chronic lymphocytic leukaemia, the lymphomas, soft-tissue and osteogenic sarcoma, and solid tumours. It is given by mouth or intravenously; it is inactive until metabolised by the liver. A urinary metabolite of cyclophosphamide, acrolein, can cause haemorrhagic cystitis; this is a rare but serious complication; increased fluid intake for 24–48 hours after intravenous injection, can prevent this complication. When high-dose therapy (e.g. more than 2 g intravenously) is used or when the patient is considered to be at high risk of cystitis (e.g. because of pelvic irradiation) mesna (given initially intravenously then by mouth) can also help prevent cystitis—see under Urothelial Toxicity (section 8.1).

Ifosfamide is related to cyclophosphamide and is given intravenously; mesna (section 8.1) is routinely given with it to reduce urothelial toxicity.

Chlorambucil is used to treat chronic lymphocytic leukaemia, non-Hodgkin’s lymphoma, Hodgkin’s disease, and Waldenstrom’s macroglobulinaemia. It is given by mouth. Side-effects, apart from bone-marrow suppression, are uncommon. However, patients occasionally develop severe widespread rashes which can progress to Stevens-Johnson syndrome or to toxic epidermal necrolysis. If a rash occurs further chlorambucil is contra-indicated and cyclophosphamide is substituted.

Melphalan is licensed for the treatment of multiple myeloma, advanced ovarian adenocarcinoma, advanced breast cancer, childhood neuroblastoma, and polycythæmia vera. Melphalan is also licensed for regional arterial perfusion in localised malignant melanoma of the extremities and localised soft-tissue sarcoma of the extremities. Intestinal pneumonitis and life-threatening pulmonary fibrosis are associated with melphalan.

Busulfan (busulphan) is given by mouth to treat chronic myeloid leukaemia. Busulfan given by mouth or intravenously, followed by cyclophosphamide, is also licensed as conditioning treatment before haematopoietic stem-cell transplantation in adults and children. Frequent blood tests are necessary because excessive myelosuppression may result in irreversible bone-marrow aplasia. Rarely, progressive pulmonary fibrosis is associated with busulfan. Skin hyperpigmentation is a common side-effect of oral therapy.

Lomustine is a lipid-soluble nitrosourea and is given by mouth. It is used mainly to treat Hodgkin’s disease resistant to conventional therapy, malignant melanoma and certain solid tumours. Bone-marrow toxicity is delayed, and the drug is therefore given at intervals of 4 to 6 weeks. Permanent bone-marrow damage can occur with prolonged use. Nausea and vomiting are common and moderately severe.

Carmustine given intravenously has similar activity to lomustine; it is given to patients with multiple myeloma, non-Hodgkin’s lymphomas, and brain tumours. Cumulative renal damage and delayed pulmonary fibrosis may occur with intravenous use. Carmustine implants are licensed for intralesional use in adults for the treatment of recurrent glioblastoma multiforme as an adjunct to surgery. Carmustine implants are also licensed for high-grade malignant glioma as adjunctive treatment to surgery and radiotherapy.

NICE guidance (carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma)
See p. 476

Estramustine is a combination of an oestrogen and chlormethine used predominantly in prostate cancer. It is given by mouth and has both an antimitotic effect
and (by reducing testosterone concentration) a hormonal effect.

**Tresolusfan** is given by mouth or by intravenous or intraperitoneal administration and is used to treat ovarian cancer. Skin pigmentation is a common side-effect and allergic alveolitis, pulmonary fibrosis and haemorrhagic cystitis occur rarely.

**Thiotepa** is usually used as an intracavitary drug for the treatment of malignant effusions or bladder cancer (section 7.4.4). It is also occasionally used to treat breast cancer, but requires parenteral administration.

**Mitobronitol** is occasionally used to treat chronic myeloid leukaemia; it is available on a named-patient basis from specialist importing companies, see p. 939.

---

**BUSULFAN**

(Busulphan)

**Indications** see notes above

**Cautions** see section 8.1 and notes above; monitor cardiac function; previous radiation therapy; avoid in acute porphyria (section 9.8.2); hepatic impairment (Appendix 2); interactions: Appendix 1 (busulfan)

**Contra-indications** pregnancy (Appendix 4); breastfeeding

**Side-effects** see section 8.1 and notes above; also hepatotoxicity (including hepatic veno-occlusive disease, hyperbilirubinaemia, jaundice and fibrosis), cardiac tamponade in thalassaemia; pneumonia; skin hyperpigmentation

**Dose**

• Chronic myeloid leukaemia, induction of remission, by mouth, 80 micrograms/kg daily (max. 4 mg); maintenance, usually 0.5–2 mg daily

• Conditioning treatment before haematopoietic stem-cell transplantation, by mouth or by intravenous infusion, consult product literature

**Busilvex**

(Fabre) ▼ PH

Concentrate for intravenous infusion, busulfan 6 mg/mL, net price 10-mL vial = £201.25

**Mylegran**

(GSK) ▼ PH

Tablets, f/c, busulfan 2 mg, net price 25-tab pack = £5.20

---

**CARMUSTINE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above

**Contra-indications** pregnancy (Appendix 4), breast-feeding

**Side-effects** see section 8.1 and notes above; irritant to tissues

**Glialdel**

(Link) ▼ PH

Implant, Carmustine 7.7 mg, net price = £650.38

---

**CHLORAMBUCIL**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; history of epilepsy and children with nephrotic syndrome (increased risk of seizures); hepatic impairment (Appendix 2); avoid in acute porphyria (section 9.8.2)

**Contra-indications** pregnancy (Appendix 4), breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**

• Hodgkin’s disease, used alone, 200 micrograms/kg daily for 4–8 weeks

• Non-Hodgkin’s lymphoma, used alone, initially 100–200 micrograms/kg daily for 4–8 weeks then dose reduced or given intermittently

• Chronic lymphocytic leukaemia, initially 150 micrograms/kg daily until leucocyte count sufficiently reduced; maintenance (started 4 weeks after end of first course) 100 micrograms/kg daily

• Waldenstrom’s macroglobulinaemia, 6–12 mg daily until leucopenia occurs, then reduce to 2–8 mg daily

**Leukeran**

(GSK) ▼ PH

Tablets, f/c, brown, chlorambucil 2 mg, net price 25-tab pack = £8.36

---

**CYCLOPHOSPHAMIDE**

**Indications** see notes above; rheumatoid arthritis (section 10.1.3)

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); renal impairment (Appendix 3); avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (cyclophosphamide)

**Contra-indications** haemorrhagic cystitis; pregnancy (Appendix 4), breast-feeding (Appendix 5)

**Side-effects** see section 8.1 and notes above; also anorexia; cardiotoxicity at high doses; interstitial pulmonary fibrosis; inappropriate secretion of aldosterone; disturbances of carbohydrate metabolism; urothelial toxicity; pigmentation of palms, nails, and soles

**Cyclophosphamide**

(Non-proprietary) ▼ PH

Tablets, s/c, cyclophosphamide (anhydrous) 50 mg, net price 20 = £2.49. Label: 27

**Injection**, powder for reconstitution, cyclophosphamide, net price 500-mg vial = £2.88; 1-g vial = £5.04

**Endoxana**

(Baxter) ▼ PH

Tablets, s/c, cyclophosphamide 50 mg, net price 100-tab pack = £12.00. Label: 23, 25, 27

**Injection**, powder for reconstitution, cyclophosphamide. Net price 200-mg vial = £1.86; 500-mg vial = £3.54; 1-g vial = £6.18

---

**ESTRAMUSTINE PHOSPHATE**

**Indications** prostate cancer

**Cautions** see section 8.1; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** peptic ulceration, cardiac disease

**Side-effects** see section 8.1; also gynaecomastia, altered liver function, cardiovascular disorders (angina and rare reports of myocardial infarction)

**Dose**

• 0.14–1.4 g daily in divided doses (usual initial dose 560 mg daily)

**Counselling** Each dose should be taken not less than 1 hour before or 2 hours after meals and should not be taken with dairy products

**Estracyt**

(Pharmacia) ▼ PH

Capsules, estramustine phosphate 140 mg (as disodium salt). Net price 100-cap pack = £171.28. Label: 23, counselling, see above
### Anthracyclines and Other Cytotoxic Antibiotics

**8.1.2** Anthracyclines and other cytotoxic antibiotics

**Indications** see notes above

**Cautions** see section 8.1 and notes above; achieve satisfactory electrolyte balance and renal function before each course (risk of tubular dysfunction, Fanconi's syndrome or diabetes insipidus if renal toxicity not treated promptly); renal impairment (avoid if serum creatinine concentration greater than 120 micromol/litre; Appendix 3); **interactions:** Appendix 1 (ifosfamide)

**Contra-indications** myelosuppression; urinary-tract obstruction; acute infection (including urinary-tract infection); urothelial damage; hepatic impairment; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above; also drowsiness, confusion, disorientation, restlessness, psychosis; urothelial toxicity, renal toxicity (see Cautions, above)

**Mitoxana** (Baxter) **Injection**, powder for reconstitution. Ifosfamide. Net price 1-g vial = £27.03; 2-g vial = £45.49 (hospital only)

**MELPHALAN**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; renal impairment; coeliac disease; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**
- Used alone, 120–130 mg/m body-surface every 6–8 weeks
- Lomustine (Medac) **Injection**, blue/clear, lomustine 40 mg. Net price 20-cap pack = £396.19
- **Note** The brand name CCNU has been used for lomustine capsules

**THIOTEPA**

**Indications** see notes above and section 7.4.4

**Cautions** see section 8.1; **interactions:** Appendix 1 (thiotepa)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1

**Thiotepa** (Goldshield) **Injection**, powder for reconstitution. Thiotepa, net price 15-mg vial = £5.20

**TREOSULFAN**

**Indications** see notes above

**Cautions** see section 8.1

**Contra-indications** pregnancy; breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**
- Consult product literature
  - **Treasulfan** (Medac) **Injection**, treosulfan 250 mg. Net price 20 = £77.34 Label: 25
- **Injection**, powder for reconstitution. Treosulfan. Net price 1 g = £39.44; 5 g = £152.41 (both in infusion bottle with transfer needle)

**8.1.2 Anthracyclines and other cytotoxic antibiotics**

Drugs in this group are widely used. Many cytotoxic antibiotics act as radiomimetics and simultaneous use of radiotherapy should be avoided as it may result in markedly enhanced toxicity.

Daunorubicin, doxorubicin, epirubicin and idarubicin are anthracycline antibiotics. Mitoxantrone (mitozantrone) is an anthracycline derivative.

Doxorubicin is used to treat the acute leukaemias, Hodgkin's and non-Hodgkin's lymphomas, paediatric malignancies and some solid tumours. It is given by injection into a fast-running infusion, commonly at 21-day intervals. Extravasation can cause severe tissue necrosis. Doxorubicin is largely excreted in the bile and an elevated bilirubin concentration is an indication for reducing the dose. Supraventricular tachycardia related to drug administration is an uncommon complication. Higher cumulative doses are associated with cardiomyopathy and it is usual to limit total cumulative doses to 450 mg/m because symptomatic and potentially fatal heart failure is common above this dose. Patients with cardiac disease, hypertension, the elderly, and those who have received myocardial irradiation should be treated cautiously. Cardiac monitoring may assist in determining safe dosage. Some evidence suggests that weekly low-dose administration may be less cardiotoxic. Doxorubicin is also given by bladder instillation for the treatment of transitional cell carcinoma, papillary bladder tumours and carcinoma in situ.

Liposomal formulations of doxorubicin for intravenous use are also available. They may reduce the incidence of cardiotoxicity and lower the potential for local necrosis, but infusion reactions, sometimes severe, may occur. Hand-foot syndrome (painful, macular reddening skin eruptions) occurs commonly with liposomal doxorubicin and may be dose limiting. It can occur after 2–3

**IFOSFAMIDE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; ensure satisfactory electrolyte balance and renal function before each course (risk of tubular dysfunction, Fanconi's syndrome or diabetes insipidus if renal toxicity not treated promptly); renal impairment (avoid if serum creatinine concentration greater than 120 micromol/litre; Appendix 3); **interactions:** Appendix 1 (ifosfamide)

**Contra-indications** myelosuppression; urinary-tract obstruction; acute infection (including urinary-tract infection); urothelial damage; hepatic impairment; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above; also drowsiness, confusion, disorientation, restlessness, psychosis; urothelial toxicity, renal toxicity (see Cautions, above)

**Mitoxana** (Baxter) **Injection**, powder for reconstitution. Ifosfamide. Net price 1-g vial = £27.03; 2-g vial = £45.49 (hospital only)

**LOMUSTINE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above

**Contra-indications** severe renal impairment; coeliac disease; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**
- Used alone, 120–130 mg/m body-surface every 6–8 weeks
- Lomustine (Medac) **Injection**, blue/clear, lomustine 40 mg. Net price 20-cap pack = £396.19
- **Note** The brand name CCNU has been used for lomustine capsules

**MELPHALAN**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; renal impairment (Appendix 3); **interactions:** Appendix 1 (melphalan)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**
- By mouth, multiple myeloma, dose may vary according to regimen; typical dose 150 micrograms/kg daily for 4 days, repeated every 6 weeks
- Ovarian adenocarcinoma, 200 micrograms/kg daily for 5 days, repeated every 4–8 weeks
- Advanced breast cancer, 150 micrograms/kg daily for 5 days, repeated every 6 weeks
- Polycythaemia vera, initially, 6–10 mg daily reduced after 5–7 days to 2–4 mg daily until satisfactory response then further reduce to 2–6 mg per week
- **By intravenous injection or infusion and regional arterial perfusion, consult product literature**

**Alkeran®** (GSK) **Injection**, powder for reconstitution. Melphalan 50 mg (as hydrochloride). Net price 50-mg vial (with solvent-diluent) = £27.61

**TREOSULFAN**

**Indications** see notes above

**Cautions** see section 8.1

**Contra-indications** pregnancy; breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**
- Consult product literature
  - **Treasulfan** (Medac) **Injection**, treosulfan 250 mg. Net price 20 = £77.34 Label: 25
- **Injection**, powder for reconstitution. Treosulfan. Net price 1 g = £39.44; 5 g = £152.41 (both in infusion bottle with transfer needle)
Malignant disease and immunosuppression

8.1.2 Anthracyclines and other cytotoxic antibiotics

Mitoxantrone (mitoxantrone) is structurally related to doxorubicin, and clinical trials suggest that it is as effective in the treatment of metastatic breast cancer. A maximum cumulative dose of 0.9–1 g/m² is recommended to help avoid cardiotoxicity. Like doxorubicin it is given intravenously and by bladder instillation.

Idarubicin has general properties similar to those of doxorubicin; it is mostly used in the treatment of haematological malignancies. Idarubicin is given intravenously and may also be given by mouth.

Daunorubicin also has general properties similar to those of doxorubicin. It should be given by intravenous infusion and is indicated for acute leukaemias. A liposomal formulation for intravenous use is licensed for AIDS-related Kaposi's sarcoma.

Use with trastuzumab

Concomitant use of anthracyclines with trastuzumab (section 8.1.5) is associated with cardiotoxicity; for details, see p. 485.

Bleomycin is given intravenously or intramuscularly to treat metastatic germ cell cancer and, in some regimens, non-Hodgkin's lymphoma and adult non-lymphocytic leukaemia. It is given intravenously and is well tolerated but myelosuppression and dose-related cardiotoxicity occur; cardiac examinations are recommended after a cumulative dose of 160 mg/m².

Bleomycin is given intravenously or intramuscularly to treat metastatic germ cell cancer and, in some regimens, non-Hodgkin's lymphoma. It causes little bone-marrow suppression but dermatological toxicity is common and increased pigmentation particularly affecting the flexures and subcutaneous sclerotic plaques may occur. Mucositis is also relatively common and an association with Raynaud's phenomenon is reported. Hypersensitivity reactions manifest by chills and fevers commonly occur a few hours after drug administration and may be prevented by simultaneous administration of a corticosteroid, for example hydrocortisone intravenously. The principal problem associated with the use of bleomycin is progressive pulmonary fibrosis. This is dose-related, occurring more commonly at cumulative doses greater than 300 000 units (see Bleomycin, below) and in the elderly. Basal lung crepitations or suspicious chest X-ray changes are an indication to stop therapy with this drug. Patients who have received extensive treatment with bleomycin (e.g. cumulative dose more than 100 000 units—see Bleomycin below) may be at risk of developing respiratory failure if a general anaesthetic is given with high inspired oxygen concentrations. Anaesthetists should be warned of this.

Bleomycin is principally used to treat paediatric cancers; it is given intravenously. Its side-effects are similar to those of doxorubicin, except that cardiac toxicity is not a problem.

Mitomycin is given intravenously to treat upper gastrointestinal and breast cancers and by bladder instillation for superficial bladder tumours. It causes delayed bone-marrow toxicity and therefore it is usually administered at 6-weekly intervals. Prolonged use may result in permanent bone-marrow damage. It may also cause lung fibrosis and renal damage.

Dactinomycin is principally used to treat paediatric cancers; it is given intravenously. Its side-effects are similar to those of doxorubicin, except that cardiac toxicity is not a problem.

Mitomycin is given intravenously to treat upper gastrointestinal and breast cancers and by bladder instillation for superficial bladder tumours. It causes delayed bone-marrow toxicity and therefore it is usually administered at 6-weekly intervals. Prolonged use may result in permanent bone-marrow damage. It may also cause lung fibrosis and renal damage.

Dactinomycin is principally used to treat paediatric cancers; it is given intravenously. Its side-effects are similar to those of doxorubicin, except that cardiac toxicity is not a problem.

Mitomycin is given intravenously to treat upper gastrointestinal and breast cancers and by bladder instillation for superficial bladder tumours. It causes delayed bone-marrow toxicity and therefore it is usually administered at 6-weekly intervals. Prolonged use may result in permanent bone-marrow damage. It may also cause lung fibrosis and renal damage.

DACTINOMYCIN

(Actinomycin D)

Indications see notes above
Caution see section 8.1 and notes above; caution in handling—irritant to tissues
Contra-indications pregnancy (Appendix 4); breastfeeding
Side-effects see section 8.1 and notes above

Cosmegen Lyovac® (Ovation) Injection, powder for reconstitution, dactinomycin, net price 500-microgram vial = £6.75

DAUNORUBICIN

Indications see notes above
Caution see section 8.1 and notes above; renal impairment (Appendix 3); caution in handling—irritant to tissues
Contra-indications pregnancy (Appendix 4); breastfeeding
Side-effects see section 8.1 and notes above

Daunorubicin (Non-proprietary) Injection, powder for reconstitution, daunorubicin (as hydrochloride), net price 20-mg vial = £44.76

Note The brand name Cerubidin was formerly used.

Lipid formulation DaunoXome® (Diatos) Concentrate for intravenous infusion, daunorubicin encapsulated in liposomes. For dilution before use. Net price 50-mg vial = £137.67

For advanced AIDS-related Kaposi’s sarcoma.
DOXORUBICIN HYDROCHLORIDE

**Indications** see notes above and section 7.4.4

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); caution in handling—irritant to tissues; interactions: Appendix 1 (doxorubicin)

**Contra-indications** see notes above; severe hepatic impairment; severe myocardial insufficiency, recent myocardial infarction, severe arrhythmias; previous treatment with maximum cumulative doses of doxorubicin or other anthracyclines; intravascular use in urinary infections, bladder inflammation, and in urethral stenosis with catheterisation difficulties; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Pharmorubicin** (Non-proprietary) (Pharmacia)

**Injection** powder for reconstitution, doxorubicin hydrochloride, net price 10-mg vial = £18.72; 50-mg vial = £96.86

**Note** The brand name Adriamycin was formerly used

**Mitoxantrone** (Mitoxantrone)

**Injection** powder for reconstitution, mitoxantrone hydrochloride, net price 5-mg vial = £20.60; 25-mL vial = £102.00, 100-mL vial = £412.00

**Lipid formulation**

**Caelyx** (Scherering-Plough) ▼ (Wyeth)

Concentrate for intravenous infusion, pegylated doxorubicin hydrochloride 2 mg/mL, encapsulated in liposomes. For dilution before use. Net price 10-mL vial = £382.51, 25-mL vial = £813.49

For AIDS-related Kaposi’s sarcoma in patients with low CD4 count and extensive mucocutaneous or visceral disease, for advanced ovarian cancer when platinum-based chemotherapy has failed, for progressive multiple myeloma (in combination with bortezomib) in patients who have received at least one prior therapy and who have undergone or are unsuitable for bone-marrow transplantation, and as monotherapy for metastatic breast cancer in patients with increased cardiac risk

**Myocet** (Zeneus) ▼ (Wyeth)

**Injection** powder for reconstitution, doxorubicin hydrochloride (as doxorubicin–citrate complex) encapsulated in liposomes, net price 50-mg vial (with vials of liposomes and buffer) = £64.50

For use with cyclophosphamide for metastatic breast cancer in patients with increased cardiac risk

**EPIRUBICIN HYDROCHLORIDE**

**Indications** see notes above and section 7.4.4

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); caution in handling—irritant to tissues; interactions: Appendix 1 (epirubicin)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Pharmorubicin** Rapid Dissolution (Pharmacia) (Pharmacia)

**Injection** powder for reconstitution, epirubicin hydrochloride, net price 50-mg vial = £96.54

**Pharmorubicin** Solution for Injection (Pharmacia) (Pharmacia)

**Injection** epirubicin hydrochloride 2 mg/mL, net price 5-mL vial = £19.31, 25-mL vial = £96.54, 100-mL vial = £386.16

**IDARUBICIN HYDROCHLORIDE**

**Indications** advanced breast cancer after failure of first-line chemotherapy (not including anthracyclines); acute leukaemias—see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); caution in handling—irritant to tissues

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**

- **By mouth**, acute non-lymphocytic leukaemia, monotherapy, 30 mg/m³ daily for 3 days or in combination therapy, 15–30 mg/m³ daily for 3 days

- **Advanced breast cancer**, monotherapy, 45 mg/m³ as a single dose or 15 mg/m³ daily for 3 consecutive days; repeat every 3–4 weeks

**Note** Max. cumulative dose by mouth (for all indications) 400 mg/m³

- **By intravenous administration**, consult product literature

**Zavedos** (Pharmacia) (Wyeth)

**Capsules** idarubicin hydrochloride, 5 mg (red), net price 1-cap pack = £34.56; 10 mg (red/white), 1-cap pack = £69.12; 25 mg (white), 1-cap pack = £172.90. Label: 25

**Injection** powder for reconstitution, idarubicin hydrochloride, net price 5-mg vial = £87.36; 10-mg vial = £174.72

**MITOMYCIN**

**Indications** see notes above and section 7.4.4

**Cautions** see section 8.1 and notes above; caution in handling—irritant to tissues

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Mitomycin C Kyowa** (Kyowa Hakko) (Kyowa Hakko)

**Injection** powder for reconstitution, mitomycin. Net price 2-mg vial = £5.88; 10-mg vial = £19.37; 20-mg vial = £36.94; 40-mg vial = £73.88 (hosp. only)

**MITOXANTRONE** (Mitozantrone)

**Indications** see notes above

**Cautions** see section 8.1 and notes above; intrathecal administration not recommended

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Mitoxantrone** (Non-proprietary) (Wyeth)

Concentrate for intravenous infusion, mitoxantrone (as hydrochloride) 2 mg/mL, net price 10-mL vial = £100.00

**Onkotrone** (Baxter) (Wyeth)

Concentrate for intravenous infusion, mitoxantrone (as hydrochloride) 2 mg/mL, net price 10-mL vial = £121.85, 12.5-mL vial = £152.33, 15-mL vial = £203.04
8.1.3 Antimetabolites

Antimetabolites are incorporated into new nuclear material or combine irreversibly with vital cellular enzymes, preventing normal cellular division.

**Methotrexate** inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines. It is given by mouth, intravenously, intramuscularly, or intrathecally.

Methotrexate is used as maintenance therapy for childhood acute lymphoblastic leukaemia, and as a therapy for established meningeal cancer or lymphoma. Methotrexate causes myelosuppression, mucositis, and rarely pneumonitis. It is contra-indicated in significant renal impairment because it is excreted primarily by the kidney. It is also contra-indicated in patients with severe hepatic impairment. It should also be avoided in the presence of significant pleural effusion or ascites because it can accumulate in these fluids, and its subsequent return to the circulation may cause myelosuppression. Systemic toxicity may follow intrathecal administration and blood counts should be carefully monitored.

Folinic acid (section 8.1) following methotrexate administration helps to prevent methotrexate-induced mucositis or myelosuppression.

**Capecitabine**, which is metabolised to fluorouracil, is given by mouth. It is licensed for adjuvant treatment of advanced colon cancer following surgery, for monotherapy or combination therapy of metastatic colorectal cancer, and for first-line treatment of advanced gastric cancer in combination with a platinum-based regimen. Capecitabine is also licensed for second-line treatment of locally advanced or metastatic breast cancer either in combination with docetaxel (where previous therapy included an anthracycline) or alone (after failure of a taxane and anthracycline regimen or where further anthracycline treatment is not indicated).

**NICE guidance**

Capecitabine and oxaliplatin in the adjuvant treatment of stage III (Dukes’ C) colon cancer (April 2006)

Capecitabine alone or oxaliplatin combined with fluorouracil and folinic acid are options for adjuvant treatment following surgery for stage III (Dukes’ C) colon cancer.

**NICE guidance**

Capecitabine and tegafur with uracil for metastatic colorectal cancer (May 2003)

Capecitabine or tegafur with uracil (in combination with folinic acid) is an option for the first-line treatment of metastatic colorectal cancer.

**Fludarabine** is licensed for the initial treatment of advanced B-cell chronic lymphocytic leukaemia (CLL) or after first-line treatment in patients with sufficient bone-marrow reserves; it is given by mouth, by intravenous injection, or by intravenous infusion. Fludarabine is well tolerated but it does cause myelosuppression, which may be cumulative. Immunosuppression is also common (see panel on cladribine and fludarabine below) and co-trimoxazole is often used to prevent pneumocystis infection. Immune-mediated haemolytic anaemia, thrombocytopenia, and neutropenia are less common side-effects.

The Scottish Medicines Consortium has advised (October 2006) that fludarabine is accepted for restricted use for the treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves. First-line treatment should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease-related symptoms or evidence of progressive disease.

**NICE guidance**

Fludarabine monotherapy for the first-line treatment of chronic lymphocytic leukaemia (February 2007)

Fludarabine monotherapy, is not recommended for the first-line treatment of chronic lymphocytic leukaemia.

**Cytarabine** acts by interfering with pyrimidine synthesis. It is given subcutaneously, intravenously, or intrathecally. Its predominant use is in the induction of remission of acute myeloblastic leukaemia. It is a potent myelosuppressant and requires careful haematological monitoring. A liposomal formulation of cytarabine for intrathecal use is licensed for lymphomatous meningitis.

**Cladribine** is given by intravenous infusion for the treatment of hairy cell leukaemia. It is also given for chronic lymphocytic leukaemia in patients who have failed to respond to standard regimens containing an alkylating agent. Cladribine produces severe myelosuppression, with neutropenia, anaemia, and thrombocytopenia; haemolytic anaemia has also been reported. High doses of cladribine have been associated with acute renal failure and severe neurotoxicity.
**Cladribine** and **fludarabine** have a potent and prolonged immunosuppressive effect. Patients treated with cladribine or fludarabine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in those at risk. To prevent potentially fatal transfusion-related graft-versus-host reaction, only irradiated blood products should be administered. Prescribers should consult specialist literature when using highly immunosuppressive drugs.

**Clofarabine** is licensed for the treatment of acute lymphoblastic leukaemia in patients aged 1 to 21 years who have relapsed or are refractory after receiving at least two previous regimens. It is given by intravenous infusion.

**Nelarabine** is licensed for the treatment of T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma in patients who have relapsed or who are refractory after receiving at least two previous regimens. It is given by intravenous infusion. Neurotoxicity is common with nelarabine and close monitoring for neurological adverse events is strongly recommended—discontinue if neurotoxicity occurs.

The Scottish Medicines Consortium (p. 3) has advised (March 2008) that nelarabine (Atriasene®) is accepted for restricted use within NHS Scotland, within the licensed indication, for the treatment of T-cell acute lymphoblastic leukaemia and T-cell lymphoblastic lymphoma when used to bridge to stem cell transplantation.

**Gemcitabine** is used intravenously, it is given alone for palliative treatment or with cisplatin as first-line treatment for locally advanced or metastatic non-small cell lung cancer. It is also used in the treatment of locally advanced or metastatic pancreatic cancer (see NICE guidance below). Combined with cisplatin, gemcitabine is also licensed for the treatment of advanced bladder cancer. Combined with paclitaxel, gemcitabine is also licensed for the treatment of metastatic breast cancer which has relapsed after previous chemotherapy including an anthracycline (see NICE guidance below). Gemcitabine is generally well tolerated but it can cause mild gastro-intestinal side-effects and rashes; renal impairment, pulmonary toxicity and influenza-like symptoms have also been reported. Haemolytic uraemic syndrome has been reported rarely and gemcitabine should be discontinued if signs of microangiopathic haemolytic anaemia occur.

The Scottish Medicines Consortium has advised (November 2006) that gemcitabine is accepted for restricted use for the treatment of metastatic breast cancer, which has relapsed following previous chemotherapy including an anthracycline (unless contra-indicated).

**Fluorouracil** is usually given intravenously because absorption following oral administration is unpredictable. It is used to treat a number of solid tumours, including gastro-intestinal tract cancers and breast cancer. It is commonly used with folic acid in advanced colorectal cancer. It may also be used topically for certain malignant and pre-malignant skin lesions. Toxicity is unusual, but may include myelosuppression, mucositis, and rarely a cerebellar syndrome. On prolonged infusion, a desquamative hand-foot syndrome may occur.

**Pemetrexed** inhibits thymidylate transferase and other folate-dependent enzymes. It is licensed for use with cisplatin for the treatment of unresectable malignant pleural mesothelioma which has not previously been treated with chemotherapy (see NICE guidance, below). Pemetrexed is also licensed for use with cisplatin for the first-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology, and as monotherapy for its second-line treatment (but see NICE guidance, below). Pemetrexed is given by intravenous infusion. Common adverse effects include myelosuppression, gastro-intestinal toxicity, and skin disorders.

The Scottish Medicines Consortium (p. 3) has advised (July 2005) that pemetrexed (Alimta®) in combination with cisplatin is accepted for restricted use within NHS Scotland for the treatment of chemotherapy-naive patients with stage III/IV unresectable malignant pleural mesothelioma.

The Scottish Medicines Consortium (p. 3) has advised (August 2008) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland as monotherapy for the second-line treatment of locally advanced or metastatic non-small cell lung cancer without predominantly squamous cell histology, and as monotherapy for its second-line treatment (but see NICE guidance, below). Pemetrexed is given by intravenous infusion. Common adverse effects include myelosuppression, gastro-intestinal toxicity, and skin disorders.

**Gemcitabine for the treatment of pancreatic cancer (May 2001)**

Gemcitabine is an option for first-line chemotherapy for patients with advanced or metastatic adenocarcinoma of the pancreas and a Karnofsky score of at least 50 [Karnofsky score is a measure of the ability to perform ordinary tasks]. Gemcitabine is not recommended for patients who can have potentially curative surgery. There is insufficient evidence about its use for second-line treatment of pancreatic adenocarcinoma.

**Fluorouracil** is usually given intravenously because absorption following oral administration is unpredictable. It is used to treat a number of solid tumours, including gastro-intestinal tract cancers and breast cancer. It is commonly used with folic acid in advanced colorectal cancer. It may also be used topically for certain malignant and pre-malignant skin lesions. Toxicity is unusual, but may include myelosuppression, mucositis, and rarely a cerebellar syndrome. On prolonged infusion, a desquamative hand-foot syndrome may occur.

**Pemetrexed** inhibits thymidylate transferase and other folate-dependent enzymes. It is licensed for use with cisplatin for the treatment of unresectable malignant pleural mesothelioma which has not previously been treated with chemotherapy (see NICE guidance, below). Pemetrexed is also licensed for use with cisplatin for the first-line treatment of locally advanced or metastatic non-small cell lung cancer other than predominantly squamous cell histology, and as monotherapy for its second-line treatment (but see NICE guidance, below). Pemetrexed is given by intravenous infusion. Common adverse effects include myelosuppression, gastro-intestinal toxicity, and skin disorders.

The Scottish Medicines Consortium (p. 3) has advised (July 2005) that pemetrexed (Alimta®) in combination with cisplatin is accepted for restricted use within NHS Scotland for the treatment of chemotherapy-naive patients with stage III/IV unresectable malignant pleural mesothelioma.

The Scottish Medicines Consortium (p. 3) has advised (August 2008) that pemetrexed (Alimta®) is accepted for restricted use within NHS Scotland as monotherapy for the second-line treatment of locally advanced or metastatic non-small cell lung cancer without predominantly squamous cell histology, and as monotherapy for its second-line treatment (but see NICE guidance, below). Pemetrexed is given by intravenous infusion. Common adverse effects include myelosuppression, gastro-intestinal toxicity, and skin disorders.

**Gemcitabine for the treatment of metastatic breast cancer (January 2007)**

Gemcitabine, in combination with paclitaxel, is an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate.
8 Malignant disease and immunosuppression

**mercaptopurine** is used as maintenance therapy for the acute leukaemias and in the management of ulcerative colitis and Crohn's disease (section 1.5.3). Azathioprine, which is metabolised to mercaptopurine, is generally used as an immunosuppressant (section 8.2.1 and section 10.1.3). The dose of both drugs should be reduced if the patient is receiving allopurinol since it interferes with their metabolism.

**Tegafur** (in combination with uracil) is given by mouth, together with calcium folinate, in the management of metastatic colorectal cancer. Tegafur is a produg of fluorouracil; uracil inhibits the degradation of fluorouracil. Tegafur (with uracil) has been shown to be of similar efficacy as a combination of fluorouracil and folinic acid for metastatic colorectal cancer. For NICE guidance on capecitabine and tegafur with uracil for metastatic colorectal cancer, see above.

**Tygocin** (thioguanine) is given by mouth for the treatment of acute leukaemias and chronic myeloid leukaemia. It can be given at various stages of treatment in short-term cycles. Long-term therapy is no longer recommended because of the high risk of liver toxicity; treatment with thioguanine should be discontinued if liver toxicity develops.

**NICE guidance**

**Pemetrexed for the treatment of non-small cell lung cancer (August 2007)**

Pemetrexed is not recommended for the treatment of locally advanced or metastatic non-small cell lung cancer.

Patients currently receiving pemetrexed should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Raltitrexed, a thymidylate synthase inhibitor, is given intravenously for palliation of advanced colorectal cancer when fluorouracil and folinic acid cannot be used. It is probably of similar efficacy to fluorouracil. Raltitrexed is generally well tolerated, but can cause marked myelosuppression and gastro-intestinal side-effects.

**NICE guidance**

**irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer**

See p. 478

**CAPECITABINE**

**Indications** see notes above

Cautions see section 8.1: history of significant cardiovascular disease, arrhythmias; monitor plasma-calcium concentration; diabetes mellitus; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); interactions: Appendix 1 (fluorouracil)

Contra-indications hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding

Side-effects see section 8.1 and notes above; hand-foot (desquamative) syndrome; diarrhoea

Dose

- Stage III colon cancer, adjuvant following surgery, ADULT over 18 years 1.25 g/m twice daily for 14 days, followed by a 7-day interval, given as 3-week cycles for a total of 8 cycles
- Metastatic colorectal cancer, monotherapy, ADULT over 18 years 1.25 g/m twice daily for 14 days; subsequent courses repeated after a 7-day interval
- Metastatic colorectal cancer, in combination therapy, ADULT over 18 years 0.8–1 g/m twice daily for 14 days, subsequent courses repeated after a 7-day interval or 625 mg/m twice daily given continuously
- Advanced gastric cancer, in combination with a platinum-based regimen, ADULT over 18 years 0.8–1 g/m twice daily for 14 days, subsequent courses repeated after a 7-day interval or 625 mg/m twice daily given continuously
- Locally advanced or metastatic breast cancer, monotherapy or in combination with docetaxel, ADULT over 18 years 1.25 g/m twice daily for 14 days; subsequent courses repeated after a 7-day interval

Note Adjust dose according to tolerability—consult product literature

Xeloda® (Roche) ▼ £165.00 Tablets, 500 mg, net price 60-tab pack = £44.47; 500 mg, 120-tab pack = £295.06. Label: 21

**CLOFARABINE**

Indications see notes above

Cautions see section 8.1 and notes above; use irradiated blood only; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

Contra-indications pregnancy (Appendix 4); breast-feeding

Side-effects see section 8.1 and notes above; also constipation, diarrhoea, abdominal pain, flatulence; oedema, tachycardia, cough, dyspnoea; dizziness, insomnia, anxiety, headache; chills, asthenia, malaise; myalgia, arthralgia; sweating, rash, pruritus, and purpura

Leustat® (Janssen-Cilag) ▼ Concentrate for intravenous infusion, cladribine 1 mg/mL. For dilution and use as an infusion, net price 10-mL vial = £169.53

For hairy cell leukaemia and for B-cell chronic lymphocytic leukaemia in patients who have failed to respond to standard regimens containing an alkylating agent

Litak® (Lipomed) ▼ Injection (for subcutaneous use only—no dilution required), cladribine 2 mg/mL, net price 5-mL vial = £165.00

For hairy cell leukaemia

**EVOTRA** (Bioenvision) ▼ £1200.00 Concentrate for intravenous infusion, clofarabine 1 mg/mL, net price 20-mL vial = Electrolytes Na 3.08 mmol/vial

**CLADRIBINE**

Indications see notes above

Cautions see section 8.1 and notes above; use irradiated blood only; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

Contra-indications pregnancy (Appendix 4); breast-feeding

Side-effects see section 8.1; also jaundice; tachycardia, flushing, hypotension, pericardial effusion, haematemesis; dyspnoea, cough; anxiety, agitation, dizziness, drowsiness, headache, paraesthesia, peripheral neuropathy, restlesslessness; rash, pruritus, sweating

**CAPECITABINE**

Indications see notes above

Cautions see section 8.1; history of significant cardiovascular disease, arrhythmias; monitor plasma-calcium concentration; diabetes mellitus; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); interactions: Appendix 1 (fluorouracil)

Contra-indications hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding

Side-effects see section 8.1 and notes above; hand-foot (desquamative) syndrome; diarrhoea

Dose

- Stage III colon cancer, adjuvant following surgery, ADULT over 18 years 1.25 g/m twice daily for 14 days, followed by a 7-day interval, given as 3-week cycles for a total of 8 cycles
- Metastatic colorectal cancer, monotherapy, ADULT over 18 years 1.25 g/m twice daily for 14 days; subsequent courses repeated after a 7-day interval
**FLUDARABINE PHOSPHATE**

**Indications**  see notes above

**Cautions** see section 8.1 and notes above; monitor for signs of haemolysis; monitor for neurological toxicity; worsening of existing and increased susceptibility to skin cancer; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); interactions: Appendix 1 (fludarabine)

**Contra-indications** haemolytic anaemia, pregnancy (Appendix 4); breast-feeding

**Side-effects**  see section 8.1 and notes above; also local irritation with topical preparation

**Dose**
- By mouth, maintenance 15 mg/kg weekly; max. in one day 1 g
- By intravenous injection or infusion, consult product literature

**FLUOROURACIL**

**Indications**  see notes above; pre-malignant and malignant skin lesions (section 13.8.1)

**Cautions** see section 8.1 and notes above; caution in handling—irritant to tissues; hepatic impairment (Appendix 2); interactions: Appendix 1 (fluorouracil)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects**  see section 8.1 and notes above; also local irritation with topical preparation

**Dose**
- By mouth, maintenance 15 mg/kg weekly; max. in one day 1 g
- By intravenous injection or infusion, consult product literature

**GEMCITABINE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects**  see section 8.1 and notes above

**MERCAPTOPURINE**

**Indications** acute leukaemias and chronic myeloid leukaemia; inflammatory bowel disease [unlicensed indication] (section 1.5.3)

**Cautions** see section 8.1 and notes above; monitor liver function—hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (mercaptopurine)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects**  see section 8.1 and notes above; also hepatotoxicity; rarely intestinal ulceration, pancreatitis

**Dose**
- Initially 2.5 mg/kg daily

**METHOTREXATE**

**Indications** see notes above and under Dose; Crohn's disease [unlicensed indication] (section 1.5.3); rheumatoid arthritis (section 10.1.3); psoriasis (section 13.5.3)

**Cautions** see section 8.1, notes above and section 10.1.3; hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3); interactions: Appendix 1 (methotrexate)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects**  see section 8.1, notes above and section 10.1.3
8.1.3 Antimetabolites

**Dose**

- By mouth, leukaemia in children (maintenance), 15 mg/m weekly in combination with other drugs

**Important**

Note that the above dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:

- the patient is carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath).

- By intravenous injection or infusion, or by intramuscular injection, or intrathecal administration, consult product literature

**Methotrexate** (Non-proprietary)

**Injection**, methotrexate (as sodium salt) 2.5 mg/mL, net price 2-mL vial = £2.62; 25 mg/mL, 2-mL vial = £6.22, 20-mL vial = £25.07

**Injection**, methotrexate 100 mg/mL (not for intrathecal use), net price 10-mL vial = £78.33, 50-mL vial = £380.07

**Oral preparations** Section 10.1.3

**NELARABINE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; previous or concurrent intrathecal chemotherapy or craniospinal irradiation (increased risk of neurotoxicity)

**Driving** May affect performance of skilled tasks (e.g. driving)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1; also abdominal pain, constipation, taste disturbance, anorexia, diarrhea, hypotension, oedema; pleural effusion, wheezing, dyspnoea, cough; confusion, seizures, amnesia, drowsiness, peripheral neurological disorders, hypoaesthesia, paraesthesia, ataxia, demyelination, tremor, dizziness, headache, asthenia, fatigue; pyrexia; electrolyte disturbances; blurred vision; muscle weakness, myalgia, arthralgia; benign and malignant tumours also reported

**Atriance** (GSK) ▼ (Novartis)

**Intravenous infusion**, nedarabine 5 mg/mL, net price 50-mL vial = £222.00

**Electrolytes** Na 3.75 mmol/vial

**PEMETREXED**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; history of cardiovascular disease; diabetes; prophylactic folic acid and vitamin B supplementation required (consult product literature); renal impairment (avoid if creatinine clearance less than 45 mL/minute; Appendix 3)

**Contra-indications** pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see section 8.1 and notes above; also dehydration, hepatitis, colitis, myocardial infarction, transient ischaemic attack, interstitial pneumonitis, and acute renal failure also reported

**Alimta** (Lilly) ▼

**Injection**, powder for reconstitution, pemetrexed 500 mg (as disodium), net price 500-mg vial = £800.00

**RALTITREXED**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); renal impairment (avoid if creatinine clearance less than 25 mL/minute; Appendix 3)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Tomudex** (AstraZeneca) ▼

**Injection**, powder for reconstitution, raltitrexed. Net price 2-mg vial = £121.86

**TEGAFUR WITH URACIL**

**Indications** see notes above

**Cautions** see section 8.1; cardiac disease; renal impairment; hepatic impairment (avoid if severe—Appendix 2); interactions: Appendix 1 (fluorouracil)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**

- **ADULT**, tegafur 300 mg/m (with uracil 672 mg/m ) daily in 3 divided doses for 28 days; subsequent courses repeated after 7-day interval; for dose adjustment due to toxicity, consult product literature

**Uftoral** (Merck Serono) ▼

**Capsules**, tegafur 100 mg, uracil 224 mg, net price 36-cap pack = £96.12, 120-cap pack = £320.40. Label: 23

**TIOGUANINE** (Thioguanine)

**Indications** see notes above

**Cautions** see section 8.1 and notes above; monitor liver function weekly; hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (tioguanine)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Dose**

- **100–200 mg/m daily**

**Lanvis** (GSK) ▼

**Tablets**, yellow, scored, thioguanine 40 mg. Net price 25-tab pack = £45.41
8.1.4 Vinca alkaloids and etoposide

The vinca alkaloids, vinblastine, vincristine, and vindesine, are used to treat a variety of cancers including leukaemias, lymphomas, and some solid tumours (e.g. breast and lung cancer). Vinorelbine is a semi-synthetic vinca alkaloid, it is given intravenously or orally for the treatment of advanced breast cancer (see also NICE guidance below) and for advanced non-small cell lung cancer.

Neurotoxicity, usually as peripheral or autonomic neuropathy, occurs with all vinca alkaloids and is a limiting side-effect of vincristine; it occurs less often with vindesine, vinblastine, and vinorelbine. Patients with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; ototoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced. Motor weakness can also occur, and increasing motor weakness calls for discontinuation of these drugs. Recovery from neurotoxic effects is usually slow but complete.

Myelosuppression is the dose-limiting side-effect of vinblastine, vindesine, and vinorelbine; vincristine causes negligible myelosuppression. The vinca alkaloids may cause reversible alopecia. They cause severe local irritation and care must be taken to avoid extravasation.

The Scottish Medicines Consortium (p. 3) has advised (May 2005 and August 2007) that vinorelbine capsules (Navelbine®) are accepted for restricted use within NHS Scotland for treatment of advanced non-small cell lung cancer and advanced breast cancer within the licensed indications, as an alternative to the intravenous formulation of vinorelbine.

NICE guidance

Vinorelbine for advanced breast cancer (December 2002)

Vinorelbine monotherapy is an option for the second-line (or subsequent) treatment of advanced breast cancer where anthracycline-based regimens have failed or are unsuitable. Vinorelbine monotherapy is not recommended as first-line treatment for advanced breast cancer. Insufficient information is available to recommend the routine use of vinorelbine in combination with other therapies for advanced breast cancer.

Etoposide may be given orally or by slow intravenous infusion, the oral dose being double the intravenous dose. A preparation containing etoposide phosphate can be given by intravenous injection or infusion. Etoposide is usually given daily for 3–5 days and courses should not be repeated more frequently than at intervals of 21 days. It has particularly useful activity in small cell carcinoma of the bronchus, the lymphomas, and testicular cancer. Toxic effects include alopecia, myelosuppression, nausea, and vomiting.

### ETOPOSIDE

**Indications** see notes above

**Cautions** see section 8.1 and notes above; renal impairment (Appendix 3); interactions: Appendix 1 (etoposide)

**Contra-indications** see section 8.1 and notes above; severe hepatic impairment; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above; irritant to tissues

- By mouth, 120–240 mg/m² daily for 5 days
- By intravenous infusion, consult product literature

**Etoposide (Non-proprietary)**

Concentrate for intravenous infusion, etoposide 20 mg/mL, net price 5-mL vial = £12.15, 10-mL vial = £29.00. 25-mL vial = £60.75

Brands include: Etoposin

**Etopophos®** (Bristol-Myers Squibb)

Injection, powder for reconstitution, etoposide (as phosphate), net price 100-mg vial = £27.78 (hosp. only)

**Vepesid®** (Bristol-Myers Squibb)

Capsules, both pink, etoposide 50 mg, net price 20 = £105.97; 100 mg, 10-cap pack = £92.60 (hosp. only). Label: 23

### VINBLASTINE SULPHATE

**Indications** see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); caution in handling; interactions: Appendix 1 (vinblastine)

**Contra-indications** see section 8.1 and notes above; pregnancy (Appendix 4); breast-feeding

**Important** Intrathecal injection contra-indicated

**Side-effects** see section 8.1 and notes above; irritant to tissues

**Vinblastine (Non-proprietary)**

Injection, vinblastine sulphate 1 mg/mL. Net price 10-mL vial = £13.09

**Velbe®** (Genus)

Injection, powder for reconstitution, vinblastine sulphate. Net price 10-mg amp = £14.15

### VINCristine sulphate

**Indications** see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); neuromuscular disease; caution in handling; interactions: Appendix 1 (vincristine)

**Contra-indications** see section 8.1 and notes above; pregnancy (Appendix 4); breast-feeding

**Important** Intrathecal injection contra-indicated

**Side-effects** see section 8.1 and notes above; irritant to tissues

**Vincristine (Non-proprietary)**

Injection, vincristine sulphate 1 mg/mL. Net price 1-mL vial = £10.92; 2-mL vial = £21.17; 5-mL vial = £44.16

**Oncovin®** (Genus)

Injection, vincristine sulphate 1 mg/mL. Net price 1-mL vial = £14.18; 2-mL vial = £28.05
8.1.5 Other antineoplastic drugs

**VINDESINE SULPHATE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); neuromuscular disease; caution in handling

**Contra-indications** see section 8.1 and notes above; pregnancy (Appendix 4); breast-feeding

**Important** Intrathecal injection contra-indicated

**Side-effects** see section 8.1 and notes above; irritant to tissues

**Eldisine** (Genus) 5-mL vial = £139.98

Injection, powder for reconstitution, vindesine sulphate, net price 5-mg vial = £78.30 (hosp. only)

**VINORELBINE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); caution in handling

**Contra-indications** see section 8.1 and notes above; pregnancy (Appendix 4); breast-feeding

**Important** Intrathecal injection contra-indicated

**Side-effects** see section 8.1 and notes above; irritant to tissues

**Dose**
- By mouth, 60 mg/m² once weekly for 3 weeks, increased if tolerated to 80 mg/m² once weekly; max. 160 mg once weekly
- By intravenous injection or infusion, consult product literature

**Vinorelbine** (Non-proprietary) 5-mL vial = £153.98

Concentrate for intravenous infusion, vinorelbine (as tartrate) 10 mg/mL, net price 1-mL vial = £32.95, 5-mL vial = £153.98

**Navelbine** (Fabre) 5-mL vial = £170.98

Concentrate for intravenous infusion, vinorelbine (as tartrate) 10 mg/mL. Net price 1-mL vial = £29.75; 5-mL vial = £139.98

Capsules 5-mg vial = £43.98; 30 mg (pink), 1-cap pack = £65.98. Label: 21, 25

**Bevacizumab**

Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor. It is licensed for the treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy (but see NICE guidance below). It is also licensed for first-line treatment of metastatic breast cancer in combination with paclitaxel and for advanced or metastatic renal cell carcinoma in combination with interferon alfa-2a. Bevacizumab, in combination with platinum-based chemotherapy, is licensed for first-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. Bevacizumab is given by intravenous infusion.

The Scottish Medicines Consortium (p. 3) has advised (February 2008 and May 2008) that bevacizumab (Avastin®) is not recommended for use within NHS Scotland for the treatment of advanced or metastatic renal cell carcinoma or for metastatic carcinoma of the colon or rectum, within the licensed indications.

**AMSACRINE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; reduce dose in renal or hepatic impairment; also caution in handling—irritant to skin and tissues

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Amsidine** (Goldshield) 13.5-mL diluent vial = £54.08 (hosp. only)

Concentrate for intravenous infusion, amsacrine 5 mg (as lactate)/mL, when reconstituted by mixing two solutions. Net price 1.5-mL (75-mg) amp with 13.5-mL diluent vial = £54.08 (hosp. only)

**Note** Use glass apparatus for reconstitution

**Arsenic trioxide**

Arsenic trioxide is licensed for acute promyelocytic leukaemia in patients who have relapsed or failed to respond to previous treatment with a retinoid and chemotherapy.

**ARSENIC TRIOXIDE**

**Indications** see notes above

**Cautions** see section 8.1; correct electrolyte abnormalities before treatment; ECG required before and during treatment—consult product literature; avoid concomitant administration with drugs causing QT interval prolongation, hypokalaemia, and hypomagnesaemia; previous treatment with anthracyclines (increased risk of QT interval prolongation); renal impairment (Appendix 3)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1; leucocyte activation syndrome (requires immediate treatment—consult product literature); hyperglycaemia, hypokalaemia, leucocytosis, QT interval prolongation, atrial fibrillation, atrial flutter, haemorrhage, dyspnoea, pleuritic pain, musculoskeletal pain, paraesthesia, fatigue

**Trisenox** (Cephalon) 13.5-mL diluent vial = £54.08 (hosp. only)

Concentrate for intravenous infusion, arsenic trioxide 1 mg/mL, net price 10-mL amp = £250.90

**Amsacrine**

Amsacrine has an action and toxic effects similar to those of doxorubicin (section 8.1.2) and is given intravenously. It is occasionally used in acute myeloid leukaemia. Side-effects include myelosuppression and mucositis; electrolytes should be monitored as fatal arrhythmias have occurred in association with hypokalaemia.

**Side-effects** see notes above; leucocyte activation syndrome (requires immediate treatment—consult product literature); hyperglycaemia, hypokalaemia, leucocytosis, QT interval prolongation, atrial fibrillation, atrial flutter, haemorrhage, dyspnoea, pleuritic pain, musculoskeletal pain, paraesthesia, fatigue

**Important** Intrathecal injection contra-indicated

**Capsules** vinorelbine (as tartrate) 20 mg (brown), net price 1-cap pack = £43.98; 30 mg (pink), 1-cap pack = £65.98. Label: 21, 25

**Side-effects** see section 8.1; correct electrolyte abnormalities before treatment; ECG required before and during treatment—consult product literature; avoid concomitant administration with drugs causing QT interval prolongation—irritant to skin and tissues

**Important** Intrathecal injection contra-indicated

**Bevacizumab**

Bevacizumab is a monoclonal antibody that inhibits vascular endothelial growth factor. It is licensed for the treatment of metastatic colorectal cancer in combination with fluoropyrimidine-based chemotherapy (but see NICE guidance below). It is also licensed for first-line treatment of metastatic breast cancer in combination with paclitaxel and for advanced or metastatic renal cell carcinoma in combination with interferon alfa-2a. Bevacizumab, in combination with platinum-based chemotherapy, is licensed for first-line treatment of unresectable advanced, metastatic or recurrent non-small cell lung cancer other than predominantly squamous cell histology. Bevacizumab is given by intravenous infusion.

The Scottish Medicines Consortium (p. 3) has advised (February 2008 and May 2008) that bevacizumab (Avastin®) is not recommended for use within NHS Scotland for the treatment of advanced or metastatic renal cell carcinoma or for metastatic carcinoma of the colon or rectum, within the licensed indications.
NICE guidance
Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer (January 2007)
- Bevacizumab in combination with fluorouracil plus folinic acid, with or without irinotecan, is not recommended for the first-line treatment of metastatic colorectal cancer;
- Cetuximab in combination with irinotecan is not recommended for the second-line or subsequent treatment of metastatic colorectal cancer after the failure of an irinotecan-containing chemotherapy regimen;
- Patients currently receiving bevacizumab or cetuximab should have the option to continue therapy until they and their consultants consider it appropriate to stop.

BEVACIZUMAB
Indications see notes above
Cautions see section 8.1; intra-abdominal inflammation (risk of gastro-intestinal perforation); increased risk of fistulas (discontinue permanently if tracheoesophageal or grade 4 fistula develops); withhold treatment for elective surgery and avoid for at least 28 days after major surgery or until wound fully healed; history of hypertension (increased risk of proteinuria—discontinue if nephrotic syndrome); uncontrolled hypertension; monitor blood pressure; history of arterial thromboembolism; history of cardiovascular disease (increased risk of cardiovascular events especially in the elderly); monitor for congestive heart failure; increased risk of haemorrhage (especially in the elderly); monitor for reversible posterior leucoencephalopathy syndrome (presenting as seizures, headache, altered mental status, visual disturbance or cortical blindness, with or without hypertension)
Contra-indications pregnancy (Appendix 4); breast-feeding (Appendix 5); untreated CNS metastases
Side-effects see section 8.1; gastro-intestinal perforation, intestinal obstruction, abdominal pain, diarrhoea, constipation, taste disturbances; mucocutaneous bleeding, haemorrhage, hypoxia, arterial thromboembolism, congestive heart failure, syncope, supraventricular tachycardia, hypertension (see also Cautions); dyspnoea, rhinitis; anorexia, drowsiness, headache, peripheral neuropathy; anemia, lethargy; pyrexia; proteinuria; dehydration; eye disorders; fistulas; pulmonary hypertension, impaired wound healing, hand-foot syndrome, exfoliative dermatitis, dry skin, and skin discoloration also reported
Avastin® (Roche) ▼ £924.40
Concentrate for intravenous infusion, bevacizumab 25 mg/mL, net price 4-ml (100-mg) vial = £242.66, 16-ml (400-mg) vial = £924.40

Bexarotene
Bexarotene is an agonist at the retinoid X receptor, which is involved in the regulation of cell differentiation and proliferation. It is associated with little myelosuppression or immunosuppression. Bexarotene can cause regression of cutaneous T-cell lymphoma. The main adverse effects are hyperlipidaemia, hypothyroidism, leucopenia, headache, rash, and pruritus.
The Scottish Medicines Consortium has advised (November 2002) that bexarotene is recommended for restricted use as a second-line treatment for patients with advanced cutaneous T-cell lymphoma.

BEXAROTENE
Indications skin manifestations of cutaneous T-cell lymphoma refractory to previous systemic treatment
Cautions see section 8.1 and notes above; hyperlipidaemia (avoid if uncontrolled), hypothyroidism (avoid if uncontrolled); hypersensitivity to retinoids; interactions: Appendix 1 (bexarotene)
Contra-indications see section 8.1 and notes above; history of pancreatitis, hypervitaminosis A, hepatic impairment; pregnancy (Appendix 4); breast-feeding
Side-effects see section 8.1 and notes above
Dose
- Initially 300 mg/m² daily as a single dose with a meal; adjust dose according to response
Targettin® (Zeneus) £937.50
Capsules, bexarotene 75 mg in a liquid suspension, net price 100-cap pack = £937.50

Bortezomib
Bortezomib, a proteasome inhibitor, is licensed as monotherapy for the treatment of multiple myeloma which has progressed despite the use of at least one therapy, and where the patient has already had, or is unable to have, bone-marrow transplantation. It is also licensed for use in combination with melphalan and prednisolone for the treatment of previously untreated multiple myeloma in patients who are not eligible for high-dose chemotherapy with bone marrow transplant. Bortezomib is given by intravenous injection.
The Scottish Medicines Consortium (p. 3) has advised (July 2007) that bortezomib (Velcade®) is not recommended for use within NHS Scotland for multiple myeloma within the licensed indication.

NICE guidance
Bortezomib monotherapy for relapsed multiple myeloma (October 2007)
Bortezomib monotherapy is an option for the treatment of progressive multiple myeloma in patients who are at first relapse having received one prior therapy and who have undergone, or are unsuitable for, bone-marrow transplantation, under the following circumstances:
- the response to bortezomib is measured using serum M protein after a maximum of four cycles of treatment, and treatment is continued only in patients who have a reduction in serum M protein of 50% or more (where serum M protein is not measurable, an appropriate alternative biochemical measure of response should be used) and
- the manufacturer rebates the full cost of bortezomib if there is an inadequate response (as defined above) after four cycles of treatment.
Patients currently receiving bortezomib monotherapy who do not meet the above criteria should have the option to continue therapy until they and their clinicians consider it appropriate to stop.

8.1.5 Other antineoplastic drugs
Cetuximab

Cetuximab is licensed, in combination with irinotecan, for the treatment of metastatic colorectal cancer in patients with tumours expressing epidermal growth factor receptor in whom previous chemotherapy, that has included irinotecan, has failed (but see NICE guidance under Bevacizumab on p. 474). Cetuximab is also licensed, in combination with radiotherapy, for the treatment of locally advanced squamous cell cancer of the head and neck.

Cetuximab is given by intravenous infusion. Patients must receive an antihistamine before the first infusion; an antihistamine is also recommended before subsequent infusions of cetuximab. Resuscitation facilities should be available and treatment should be initiated by a specialist.

Erbitux® (Merck) ▼ (F Hoffman-La Roche)

Intravenous infusion, cetuximab 5 mg/mL, net price
20-mL vial = £159.02, 100-mL vial = £795.10

Crisantaspase

Crisantaspase is the enzyme asparaginase produced by Erwinia chrysanthemi. It is given intramuscularly, intravenously, or subcutaneously almost exclusively in acute lymphoblastic leukaemia. Facilities for the management of anaphylaxis should be available. Side-effects also include nausea, vomiting, fever, pancreatitis, CNS depression, neurotoxicity, liver function changes, coagulation disorders, and blood lipid changes; careful monitoring is therefore necessary and the urine is tested for glucose because of a risk of hyperglycaemia.

Dacarbazine and temozolomide

Dacarbazine is used to treat metastatic melanoma and, in combination therapy, soft tissue sarcomas. It is also a component of a commonly used combination for Hodgkin’s disease (ABVD—doxorubicin [previously Adriamycin®], bleomycin, vinblastine, and dacarbazine). It is given intravenously. The predominant side-effects are myelosuppression and severe nausea and vomiting.

Temozolomide is structurally related to dacarbazine. It is given by mouth and is licensed for the initial treatment of glioblastoma multiforme (in combination with radiotherapy) and for second-line treatment of malignant glioma.

NICE guidance

Temozolomide for the treatment of recurrent malignant glioma (brain cancer) (April 2001)

Temozolomide may be considered for the treatment of recurrent malignant glioma, which has not responded to first-line chemotherapy.

Carmustine implants and temozolomide

Carmustine implants and temozolomide for the treatment of newly diagnosed high-grade glioma (June 2007)

Temozolomide is an option for the treatment of newly diagnosed glioblastoma multiforme in patients with a WHO performance status of 0 or 1. Carmustine implants are an option for the treatment of newly diagnosed high-grade (Grade 3 or 4) glioma only for patients in whom at least 90% of the tumour has been resected. Carmustine implants should only be used within specialist centres.
Mitotane

Mitotane is licensed for the symptomatic treatment of advanced or inoperable adrenocortical carcinoma. It selectively inhibits the activity of the adrenal cortex, necessitating corticosteroid replacement therapy (section 6.3.1); the dose of glucocorticoid should be increased in case of shock, trauma, or infection. Gastro-intestinal side-effects such as anorexia, nausea, and vomiting, and endocrine side-effects, such as hypogonadism and thyroid disorders, are very common with mitotane; neurotoxicity occurs in many patients.

Malignant disease and immunosuppression

Panitumumab

Panitumumab is a monoclonal antibody that binds to the epidermal growth factor receptor (EGFR). It is indicated as monotherapy for the treatment of EGFR expressing metastatic colorectal cancer with non-mutated KRAS gene after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Panitumumab is given by intravenous infusion. The Scottish Medicines Consortium (p. 3) has advised (May 2008) that panitumumab (Vectibix®) is not recommended for use within NHS Scotland for colorectal cancer.
8.1.5 Other antineoplastic drugs

**PANITUMUMAB**

**Indications** see notes above

**Cautions** monitor for dermatological reactions (may require temporary or permanent discontinuation—consult product literature); pulmonary disease—discontinue if pneumonitis or lung infiltrates occur; monitor for hypomagnesaemia and hypocalcaemia

**Contra-indications** interstitial pulmonary disease; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see section 8.1; also infusion-related reactions: diarrhoea, dry mouth and nose; dyspnoea, cough; fatigue, headache; hypomagnesaemia, hypocalcaemia, hypokalaemia, dehydration; ocular disorders (including conjunctivitis, increased lacrimation, dry eyes, ocular hyperaemia); skin reactions (including rash, erythema, pruritus, dry skin, and exfoliation), mucosal inflammation, hypertrichosis, and nail disorders

**Vectibix** (Amgen) ▼ (HII)

Concentrate for intravenous infusion, panitumumab 20 mg/mL, net price 5-mL vial = £299.00, 20-mL vial = £1196.00

**Electrolytes** Na 0.75 mmol/vial

**PENTOSTATIN**

**Pentostatin** is highly active in hairy cell leukaemia. It is given intravenously on alternate weeks and is capable of inducing prolonged complete remission. It is potentially toxic, causing myelosuppression, immunosuppression and a number of other side-effects which may be severe. Its use is probably best confined to specialist centres.

**Indications** see notes above

**Cautions** see section 8.1 and notes above; interactions: Appendix 1 (pentostatin)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Nipent** (Hospira) ▼ (HII)

Injection, powder for reconstitution, pentostatin. Net price 10-mg vial = £863.78

**Platinum compounds**

**Carboplatin** is widely used in the treatment of advanced ovarian cancer and lung cancer (particularly the small cell type). It is given intravenously. The dose of carboplatin is determined according to renal function rather than body surface area. Carboplatin can be given on an outpatient basis and is better tolerated than cisplatin; nausea and vomiting are reduced in severity and nephrotoxicity, neurotoxicity, and ototoxicity are much less of a problem than with cisplatin. It is, however, more myelosuppressive than cisplatin.

**Cisplatin** is used alone or in combination for the treatment of testicular, lung, cervical, bladder, head and neck, and ovarian cancer (but carboplatin is preferred for ovarian cancer). It is given intravenously. Cisplatin requires intensive intravenous hydration and treatment may be complicated by severe nausea and vomiting. Cisplatin is toxic, causing nephrotoxicity (monitoring of renal function is essential), ototoxicity, peripheral neuropathy, hypomagnesaemia and myelosuppression. It is, however, increasingly given in a day-care setting.

**Oxaliplatin** is licensed in combination with fluorouracil and folinic acid, for the treatment of metastatic colorectal cancer and as adjuvant treatment of colon cancer after resection of the primary tumour; it is given by intravenous infusion. Neurotoxic side-effects (including sensory peripheral neuropathy) are dose limiting. Other side-effects include gastro-intestinal disturbances, ototoxicity, and myelosuppression. Manufacturers advise renal function monitoring in moderate impairment.

**NICE guidance**

Irinotecan, oxaliplatin, and raltitrexed for advanced colorectal cancer (August 2005)

A combination of fluorouracil and folinic acid with either irinotecan or oxaliplatin are options for first-line treatment for advanced colorectal cancer. Irinotecan alone or fluorouracil and folinic acid with oxaliplatin are options for patients who require further treatment subsequently. Raltitrexed is not recommended for the treatment of advanced colorectal cancer. Its use should be confined to clinical studies.

**NICE guidance**

Paclitaxel for ovarian cancer (January 2003)

*Either* paclitaxel in combination with a platinum compound (cisplatin or carboplatin) or a platinum compound alone are alternatives for the first-line treatment of ovarian cancer (usually following surgery).

**NICE guidance**

Paclitaxel, pegylated liposomal doxorubicin, and topotecan for second-line or subsequent treatment of advanced ovarian cancer (May 2005)

Paclitaxel, combined with a platinum compound (carboplatin or cisplatin), is an option for advanced cancer that relapses 6 months or more after completing initial platinum-based chemotherapy. Paclitaxel alone is an option for advanced ovarian cancer that does not respond to, or relapses within 6 months of completing initial platinum-based chemotherapy. Pegylated liposomal doxorubicin is an option for advanced ovarian cancer that does not respond to, or relapses within 12 months of completing initial platinum-based chemotherapy. Paclitaxel alone or pegylated liposomal doxorubicin are options for advanced ovarian cancer in patients who are allergic to platinum compounds. Topotecan alone is an option only for advanced ovarian cancer that does not respond to, or relapses within 6 months of completing initial platinum-based chemotherapy or in those allergic to platinum compounds and for whom paclitaxel alone or pegylated liposomal doxorubicin are inappropriate.
CARBOPLATIN

**Indications** see notes above

**Cautions** see section 8.1 and notes above; renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3); interactions: Appendix 1 (platinum compounds)

**Contra-indications** see section 8.1; acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Carboplatin** (Non-proprietary)

**Injection**, carboplatin 10 mg/mL, net price 5-mL vial = £22.04, 15-mL vial = £56.29, 45-mL vial = £168.85, 60-mL vial = £244.88

Paraplatin® (Bristol-Myers Squibb) (MW)

Concentrate for intravenous infusion, carboplatin 10 mg/mL, net price 5-mL vial = £21.26, 60-mL vial = £244.88

CISPLATIN

**Indications** see notes above

**Cautions** see section 8.1 and notes above; interactions: Appendix 1 (platinum compounds)

**Contra-indications** see section 8.1; peripheral neuropathy with functional impairment; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Cisplatin** (Non-proprietary) (MW)

**Injection**, cisplatin 1 mg/mL, net price 10-mL vial = £5.85, 50-mL vial = £24.50, 100-mL vial = £50.22

**Injection**, powder for reconstitution, cisplatin, net price 50-mg vial = £17.00

OXALIPLATIN

**Indications** metastatic colorectal cancer in combination with fluorouracil and folinic acid; colon cancer—see notes above

**Cautions** see section 8.1 and notes above; interactions: Appendix 1 (platinum compounds)

**Contra-indications** see section 8.1; peripheral neuropathy with functional impairment; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Oxaliplatin** (Non-proprietary) (MW)

**Injection**, powder for reconstitution, oxaliplatin, net price 50-mg vial = £156.75, 100-mg vial = £313.50

**Injection**, oxaliplatin 5 mg/mL, net price 10-mL vial = £165.00, 20-mL vial = £330.00

Porfimer sodium and temoporfin

Porfimer sodium and temoporfin are used in the photodynamic treatment of various tumours. The drugs accumulate in malignant tissue and are activated by laser light to produce a cytotoxic effect. Porfimer sodium is licensed for photodynamic therapy of non-small cell lung cancer and obstructing oesophageal cancer. Temoporfin is licensed for photodynamic therapy of advanced head and neck cancer.

The Scottish Medicines Consortium has advised (May 2004) that temoporfin is not recommended for the palliative treatment of advanced head and neck cancer.

PORFIMER SODIUM

**Indications** non-small cell lung cancer; oesophageal cancer; see notes above

**Cautions** see section 8.1; avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 30 days

**Contra-indications** see section 8.1; severe hepatic impairment; tracheo-oesophageal or broncho-oesophageal fistula; acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see section 8.1; photosensitivity (see Cautions above—sunscreens offer no protection), constipation

**Photofrin®** (Sinclair) (MW)

**Injection**, powder for reconstitution, porfimer sodium, net price 15-mg vial = £154.00, 75-mg vial = £770.00

TEMOPORFIN

**Indications** advanced head and neck squamous cell carcinoma refractory to, or unsuitable for, other treatments

**Cautions** see section 8.1; avoid exposure of skin and eyes to direct sunlight or bright indoor light for at least 15 days after administration; avoid prolonged exposure of injection site arm to direct sunlight for 6 months after administration, if extravasation occurs protect area from light for at least 3 months; interactions: Appendix 1 (temoporfin)

**Contra-indications** see section 8.1; acute porphyria (section 9.8.2) or other diseases exacerbated by light; elective surgery or ophthalmic slit-lamp examination for 30 days after administration; concomitant photosensitising treatment; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see section 8.1; also constipation, dysphagia; haemorrhage, oedema; giddiness, trismus, facial pain; injection site pain, blistering, scarring, erythema, skin necrosis, hyperpigmentation, photosensitivity (see Cautions above; sunscreens ineffective)

**Foscan®** (Biolitec) (MW)

**Injection**, temoporfin 4 mg/mL, net price 5-mL vial = £440.00

Procarbazine

Procarbazine is most often used in Hodgkin’s disease. It is given by mouth. Toxic effects include nausea, myelosuppression, and a hypersensitivity rash preventing further use of this drug. It is a mild monoamine-oxidase inhibitor and dietary restriction is rarely considered necessary. Alcohol ingestion may cause a disulfiram-like reaction.

**Procarbazine** (Sanofi-Aventis)

Concentrate for intravenous infusion, procarbazine, net price 20-mg vial = £22.04, 15-mL vial = £56.29, 45-mL vial = £168.85, 60-mL vial = £220.00

Foscarbin

Foscarbin is recommended for the palliative treatment of advanced head and neck cancer.
8 Malignant disease and immunosuppression

8.1.5 Other antineoplastic drugs

if creatinine clearance less than 10 mL/minute; Appendix 3; Interactions: Appendix 1 (procarbazine)

Contra-indications pregnancy (Appendix 4); breast-feeding

Side-effects see section 8.1 and notes above

Dose

- Used alone, initially 50 mg daily, increased by 50 mg to 250–300 mg daily in divided doses; mainte-
nance (on remission) 50–150 mg daily to cumulative total of at least 6 g

Procarbazine (Cambridge) (NH)
Capsules, ivory, procarbazine (as hydrochloride)
50 mg, net price 50-cap pack = £181.04. Label: 4

Protein kinase inhibitors

Dasatinib, erlotinib, imatinib, lapatinib, nilotinib, sorafenib, sunitinib, and temsirolimus are protein kinase inhibi-
tors.

Dasatinib, a tyrosine kinase inhibitor, is licensed for the treatment of chronic myeloid leukaemia in those who have resistance to or intolerance of previous therapy, including imatinib. It is also licensed for acute lympho-
blastic leukaemia in those who have resistance to or intolerance of previous therapy.

The Scottish Medicines Consortium (p. 3) has advised (April 2007) that dasatinib (Sprycel®) is accepted for restricted use within NHS Scotland, within the licensed indication, for the treatment of chronic myeloid leuk-
aemia in patients who are in the chronic phase of the disease.

Erlotinib, a tyrosine kinase inhibitor, is licensed in combination with gemcitabine for the treatment of metastatic pancreatic cancer. It is also licensed for the treatment of locally advanced or metastatic non-small cell lung cancer after failure of previous chemotherapy.

The Scottish Medicines Consortium (p. 3) has advised (June 2006) that erlotinib (Tarceva®) is accepted for restricted use for the treatment of locally advanced or metastatic non-small cell lung cancer, after failure of at least one chemotherapy regimen. Erlotinib is restricted to use in patients who would otherwise be eligible for treatment with docetaxel monotherapy.

Imatinib, a tyrosine kinase inhibitor, is licensed for the treatment of newly diagnosed chronic myeloid leuk-
aemia where bone marrow transplantation is not con-
sidered first-line treatment, and for chronic myeloid leukaemia in chronic phase after failure of interferon alfa, or in accelerated phase, or in blast crisis (see NICE guidance below). It is also licensed for c-kit (CD117)-
positive unrectatable or metastatic malignant gastro-
intestinal stromal tumours (GIST). Imatinib is licensed for the treatment of newly diagnosed acute lympho-
blastic leukaemia in combination with other chemother-
apy, and as monotherapy for relapsed or refractory acute lymphoblastic leukaemia. Imatinib is also licensed for the treatment of unrectatable dermatofibrosarcoma protubersan and for patients with recurrent or meta-
static dermatofibrosarcoma protuberas who cannot
have surgery.

Imatinib is also licensed for the treatment of myelodys-
plastic/myeloproliferative diseases associated with pla-
telet-derived growth factor receptor gene rearrange-
ment and for the treatment of advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia.

The Scottish Medicines Consortium (p. 3) has advised (March 2002) that imatinib (Glivec®) should be used for chronic myeloid leukaemia only under specialist supervision in accordance with British Society of Haematology guidelines (November 2001).

NICE guidance

Imatinib for chronic myeloid leukaemia
(October 2003)

Imatinib is recommended as first-line treatment for Philadelphia-chromosome-positive chronic myeloid leukaemia in the chronic phase and as an option for patients presenting in the accelerated phase or with blast crisis, provided that imatinib has not been used previously.

Where imatinib has failed to stop disease progres-
sion from chronic phase to accelerated phase or to
blast crisis, continued use is recommended only as part of further clinical study.

Lapatinib, a tyrosine kinase inhibitor, is licensed in combination with capecitabine for the treatment of advanced or metastatic breast cancer in patients with tumours that overexpress human epidermal growth factor receptor-2 (HER2). It is indicated for patients who have had previous treatment with an anthracycline, a taxane, and trastuzumab.

Nilotinib, a tyrosine kinase inhibitor, is licensed for the treatment of chronic myeloid leukaemia in those who have resistance to or intolerance of previous therapy, including imatinib.

The Scottish Medicines Consortium (p. 3) has advised (February 2008) that nilotinib (Tasigna®) is accepted for restricted use within NHS Scotland for the treatment of chronic-phase chronic myeloid leukaemia in adults resistant to or intolerant of at least one previous therapy, including imatinib.

Sorafenib, an inhibitor of multiple kinases, is licensed for the treatment of advanced renal cell carcinoma when treatment with interferon alfa or interleukin-2 has failed or is contra-indicated. It is also licensed for the treatment of hepatocellular carcinoma.

The Scottish Medicines Consortium (p. 3) has advised (October 2006) that sorafenib (Nexavar®) is not recommended for use within NHS Scotland for the treatment of advanced renal cell carcinoma.

Sunitinib, a tyrosine kinase inhibitor, is licensed for the treatment of advanced or metastatic renal cell carci-
noma. It is also licensed for the treatment of unrectatable or metastatic malignant gastro-intestinal stromal tumours (GIST) after failure of imatinib.

The Scottish Medicines Consortium (p. 3) has advised (June 2007) that sunitinib (Sutent®) is not recommended for use within NHS Scotland for the treatment of advanced or metastatic renal cell carcinoma.

Temsirolimus is a protein kinase inhibitor licensed for the first-line treatment of advanced renal cell carci-
noma. Hypersensitivity reactions occur commonly with temsirolimus, usually during administration of the first dose. Symptoms include flushing, chest pain, dys-
pnoea, apnoea, hypotension, loss of consciousness, and anaphylaxis. Where possible, patients should receive an intravenous dose of antihistamine 30 minutes before
starting the temsirolimus infusion. The infusion may have to be stopped temporarily for the treatment of infusion-related effects—consult product literature for appropriate management. If adverse reactions are not managed with dose delays, a dose reduction should be considered—consult product literature.

### DASATINIB

**Indications** see notes above

**Cautions** see section 8.1; susceptibility to QT-interval prolongation; hypokalaemia; hypomagnesaemia; hepatic impairment (Appendix 2); pregnancy (Appendix 4 and section 8.1); **interactions**: Appendix 1 (dasatinib)

**Contra-indications** breast-feeding

**Side-effects** see section 8.1; also diarrhoea, anorexia, weight gain, abdominal pain, taste disturbance, constipation, dyspepsia, colitis, gastritis, arrhythmias, congestive cardiac failure, chest pain, flushing, haemorrhage (including gastro-intestinal and CNS haemorrhage), palpitation; dyspnoea, cough, oedema (including pleural effusion); depression, dizziness, headache, insomnia, neuropathy; influenza-like symptoms; musculoskeletal pain; visual disturbances; acne, dry skin, sweating, pruritus, urticaria; *less commonly* pancreatitis, hepatitis, cholestasis, hypertension, hypotension, transient ischaemic attack, thrombophlebitis, syncope, pulmonary hypertension, asthma, convulsions, amnesia, tremor, drowsiness, vertigo, gynaecomastia, irregular menstruation, urinary frequency, proteinuria, hypocalcaemia, rhabdomyolysis, tinnitus, hypersensitivity reactions (including dermatitis, photosensitivity), pigmentation and nail disorders

**Dose**
- Chronic phase chronic myeloid leukaemia, **ADULT** over 18 years 100 mg once daily, increased if necessary to max. 140 mg once daily
- Accelerated and blast phase chronic myeloid leukaemia, **ADULT** over 18 years 70 mg twice daily, increased if necessary to max. 100 mg twice daily
- Acute lymphoblastic leukaemia, **ADULT** over 18 years 70 mg twice daily increased if necessary to max. 100 mg twice daily

*Sprycel*® (Bristol-Myers Squibb) ▼ (©)

**Tablets** 7.5 mg, net price 56-tab pack = £1216.43; 50 mg, 56-tab pack = £2432.85; 70 mg, 56-tab pack = £2432.85. Label: 25

### ERLOTINIB

**Indications** see notes above

**Cautions** see section 8.1; pre-existing liver disease or concomitant use with hepatotoxic drugs—monitor liver function; hepatic impairment (Appendix 2); **interactions**: Appendix 1 (erlotinib)

**Contra-indications** renal impairment (avoid if creatinine clearance less than 15 mL/minute; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see section 8.1; diarrhoea, abdominal pain, dyspepsia, flatulence; anorexia, depression, headache; fatigue, rigor; conjunctivitis; rash, pruritus, dry skin; *less commonly* intestinal life disease—discontinue if unexplained symptoms such as dyspnoea, cough or fever occur; *rarely* hepatic failure

**Dose**
- Non-small cell lung cancer, 150 mg once daily
- Pancreatic cancer, 100 mg once daily in combination with gemcitabine

**Tarceva®** (Roche) ▼ (©)

**Tablets** 125 mg, white-yellow, erlotinib (as hydrochloride) 25 mg, net price 30-tab pack = £378.33; 100 mg, 30-tab pack = £1324.14; 150 mg, 30-tab pack = £1631.53. Label: 23

### IMATINIB

**Indications** see notes above

**Cautions** see section 8.1; cardiac disease; monitor for fluid retention; monitor liver function; hepatic impairment (Appendix 2); renal impairment (Appendix 3); **interactions**: Appendix 1 (imatinib)

**Contra-indications** pregnancy (Appendix 4 and section 8.1); breast-feeding

**Side-effects** see section 8.1; also abdominal pain, appetite changes, constipation, diarrhoea, flatulence, gastro-oesophageal reflux, taste disturbance, weight changes, dry mouth, oedema (including pulmonary oedema, pleural effusion, and ascites), flushing, haemorrhage; cough, dyspnoea; dizziness, headache, insomnia, hypoaesthesia, paraesthesia, fatigue; influenza-like symptoms; cramps, arthralgia, visual disturbances, increased lacrimation, conjunctivitis, dry eyes; epistaxis; dry skin, sweating, rash, pruritus, photosensitivity; *less commonly* gastric ulceration, pancreatitis, hepatic dysfunction (*rarely* hepatic failure, hepatic necrosis), dysphagia, heart failure, tachycardia, palpitation, syncope, hypertension, hypotension, cold extremities, cough, acute respiratory failure, depression, drowsiness, anxiety, peripheral neuropathy, tremor, migraine, impaired memory, vertigo, gynaecomastia, menorrhagia, irregular menstruation, sexual dysfunction, electrolyte disturbances, renal failure, urinary frequency, gout, tinnitus, hearing loss; skin hyperpigmentation; *rarely* intestinal obstruction, gastro-intestinal perforation, inflammatory bowel disease, arrhythmia, atrial fibrillation, myocardial infarction, angina, pulmonary fibrosis, pulmonary hypertension, increased intracranial pressure, convulsions, confusion, haemolytic anaemia, aseptic necrosis of bone, cataract, glaucoma, angioedema, exfoliative dermatitis, and Stevens-Johnson syndrome

**Dose**
- Chronic phase chronic myeloid leukaemia, **ADULT** over 18 years 100–400 mg once daily, increased if necessary to max. 800 mg daily (in 2 divided doses); **CHILD** (chronic and advanced phase) 2–18 years 340 mg/m² (max. 800 mg) daily (in 2 divided doses), increased to 570 mg/m² (max. 800 mg) daily if necessary (consult product literature)
- Accelerated and blast crisis chronic myeloid leukaemia, **ADULT** 600 mg once daily, increased if necessary to max. 800 mg daily (in 2 divided doses)
- Acute lymphoblastic leukaemia, **ADULT** 600 mg once daily
- Gastro-intestinal stromal tumours, **ADULT** 400 mg once daily
- Dermatofibrosarcoma protuberans, **ADULT** 800 mg daily in 2 divided doses
- Myelodysplastic/myeloproliferative diseases, **ADULT** 400 mg once daily
- Advanced hypereosinophilic syndrome and chronic eosinophilic leukaemia, **ADULT** 100–400 mg once daily
Glivec® (Novartis) ▼ (Novartis)
Tablets, f/c, imatinib (as mesilate) 100 mg (yellow-brown, scored), net price 60-tab pack = £802.04; 400 mg (yellow), 30-tab pack = £1604.08. Label: 21, 27

Counselling Tablets may be dispersed in water or apple juice

LAPATINIB

Indications see notes above

Cautions see section 8.1; low gastric pH (reduced absorption); monitor left ventricular function; monitor for pulmonary toxicity; monitor liver function before treatment and at monthly intervals; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4 and section 8.1); interactions: Appendix 1 (lapatinib)

Contra-indications breast-feeding

Side-effects see section 8.1; anorexia, diarrhoea (treat promptly); decreased left ventricular ejection fraction; fatigue; rash; hyperbilirubinaemia, hepatotoxicity; less commonly interstitial lung disease

Dose

• ADULT over 18 years, 1.25 g once daily as a single dose

Counselling Always take at the same time in relation to food: either one hour before or one hour after food

Tyverb® (GSK) ▼ (Novartis)
Tablets, yellow, f/c, lapatinib 250 mg, net price 70-tab pack = £804.30. Counselling, administration

NILOTINIB

Indications see notes above

Cautions see section 8.1; history of pancreatitis; susceptibility to QT-interval prolongation (including electrolyte disturbances, concomitant use of drugs that prolong QT interval); hepatic impairment (Appendix 2); pregnancy (Appendix 4 and section 8.1); interactions: Appendix 1 (nilotinib)

Contra-indications breast-feeding (Appendix 5)

Side-effects see section 8.1; also abdominal pain, constipation, diarrhoea, dyspepsia, flatulence, anorexia, weight changes; palpitation, QT-interval prolongation, hypertension, oedema, flushing; dyspepsia, cough, dysphonia; headache, fatigue, asthenia, dizziness, paraesthesia, insomnia, vertigo; hypomagnesaemia, hyperkalaemia, blood glucose changes; bone pain, arthralgia, muscle spasm; urticaria, erythema, hyperhidrosis, dry skin, rash, pruritus; less commonly interstitial lung disease

Dose

• ADULT over 18 years, 400 mg twice daily

Sorafenib

Indications see notes above

Cautions major surgical procedures; cardiac ischaemia; hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (sorafenib)

Contra-indications breast-feeding

Side-effects see section 8.1; also diarrhoea, constipation, dyspepsia, dysphagia, anorexia, hypertension, haemorrhage, flushing, hoarseness, fatigue, asthenia, depression, peripheral neuropathy, fever, erectile dysfunction, hypophosphataemia, arthralgia, myalgia, tinnitus, rash, pruritus, erythema, dry skin, desquamation, acne, hand-foot skin reaction; less commonly reversible posterior leucoencephalopathy, myocardial infarction, congestive heart failure, hypertensive crisis, and gastrointestinal perforations

Dose

• ADULT over 18 years, 400 mg twice daily

Nexavar® (Bayer) ▼ (Novartis)
Tablets, f/c, red, sorafenib (as tosylate) 200 mg, net price 112-tab pack = £2504.60. Label: 23

SUNITINIB

Indications see notes above

Cautions see section 8.1; cardiovascular disease—discontinue if congestive heart failure develops; susceptibility to QT-interval prolongation; hypertension; increased risk of bleeding; monitor for hypothyroidism; pregnancy (Appendix 4 and section 8.1); interactions: Appendix 1 (sunitinib)

Contra-indications breast-feeding

Side-effects see section 8.1; also abdominal pain, anorexia, taste disturbance, dehydration, hypertension, oedema; dyspepsia; fatigue, dizziness, head-ache, paraesthesia, hypothyroidism; arthralgia, myalgia; increased lacrimation; epistaxis; skin, hair, and urine discoloration, hand-foot syndrome, dry skin, and rash; gastro-intestinal perforation, pancreatitis, hepatic failure, and seizures reported

Dose

• 50 mg daily for 4 weeks, followed by a 2-week treatment-free period to complete 6-week cycle; adjust dose in steps of 12.5 mg according to tolerability; dose range 25–75 mg daily

Sutent® (Pfizer) ▼ (Pfizer)
Capsules, sunitinib (as malate) 12.5 mg (orange), net price 28-caps pack = £784.70; 25 mg (caramel), 28-caps pack = £1569.40; 50 mg (caramel/orange), 28-caps pack = £3138.80. Label: 14

TEMSIROLIMUS

Indications see notes above

Cautions see notes above; monitor respiratory function; monitor blood lipids; hepatic impairment (avoid if severe; Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (temsirolimus)

Contra-indications pregnancy (Appendix 4); breast-feeding

Side-effects see section 8.1; also abdominal pain, diarrhoea, anorexia, taste disturbance; hypertension, oedema, thrombophlebitis; cough, dyspnoea, chest
pain, interstitial lung disease, hypersensitivity reactions (see notes above); asthenia; increased susceptibility to infection (including urinary-tract infection and pneumonia), pyrexia; hyperglycaemia; renal failure; hypophosphataemia, hypokalaemia, hyper-cholesterolaemia, hyperlipidaemia; arthralgia; eye disorders; rhinitis, epistaxis; skin disorders (including rash and acne), folliculitis, impaired wound healing; less commonly intestinal perforation and intracerebral bleeding.

**Dose**

- By intravenous infusion (over 30–60 minutes), **ADULT over 18 years, 25 mg once weekly**

**Torisel®** (Wyeth) ▼ (Rx)

Concentrate for intravenous infusion, temsirolimus 25 mg/mL, net price 1.2-mL amp (with diluent) = £620.00

Excipients include propylene glycol and ethanol.

---

**Taxanes**

**Paclitaxel** is a member of the taxane group of drugs. It is given by intravenous infusion. Paclitaxel given with carboplatin or cisplatin is used for the treatment of ovarian cancer (see NICE guidance p. 478); the combination is also considered appropriate for women whose ovarian cancer is initially considered inoperable. Paclitaxel is also used in the secondary treatment of metastatic breast cancer (see NICE guidance below). There is limited evidence to support its use in non-small cell lung cancer. Routine premedication with a corticosteroid, an antihistamine and a histamine H₁-receptor antagonist is recommended to prevent severe hypersensitivity reactions; hypersensitivity reactions may occur rarely despite premedication, although more commonly only bradycardia or asymptomatic hypotension occur. Other side-effects of paclitaxel include myelosuppression, peripheral neuropathy, and cardiac conduction defects with arrhythmias (which are nearly always asymptomatic). It also causes alopecia and muscle pain; nausea and vomiting is mild to moderate.

**Docetaxel** is licensed for use in locally advanced or metastatic breast cancer and non-small cell lung cancer resistant to other cytotoxic drugs (see NICE guidance on breast cancer, below) or for initial chemotherapy in combination with other cytotoxic drugs. It is also licensed for hormone-resistant prostate cancer, for use with other cytotoxic drugs for gastric adenocarcinoma and head and neck cancer, and for adjuvant treatment of operable node-positive breast cancer. Its side-effects are similar to those of paclitaxel but persistent fluid retention (commonly as leg oedema that worsens during treatment) can be resistant to treatment; hypersensitivity reactions also occur. Dexamethasone by mouth is recommended for reducing fluid retention and hypersensitivity reactions.

The *Scottish Medicines Consortium* (p. 3) has advised that docetaxel (*Taxotere®*) in combination with cisplatin and 5-fluorouracil is accepted for restricted use within NHS Scotland for the induction treatment of patients with unresectable (May 2007) and resectable (June 2008) locally advanced squamous cell carcinoma of the head and neck.

---

### NICE guidance

**Docetaxel for the adjuvant treatment of early node-positive breast cancer (September 2006)**

Docetaxel, in combination with doxorubicin and cyclophosphamide, is an option for the adjuvant treatment of women with early node-positive breast cancer.

**Docetaxel for the adjuvant treatment of early node-positive breast cancer (September 2006)**

Docetaxel is not recommended for the adjuvant treatment of early node-positive breast cancer.

**Taxanes for the treatment of breast cancer (September 2001)**

Both docetaxel and paclitaxel are options for the treatment of advanced breast cancer where initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate. See p. 478.

**Docetaxel for the treatment of hormone-refractory metastatic prostate cancer (June 2006)**

Docetaxel is an option for hormone-refractory metastatic prostate cancer and a Karnofsky score of at least 60% [Karnofsky score is a measure of the ability to perform ordinary tasks].

### DOCETAXEL

**Indications** adjuvant treatment of operable node-positive breast cancer, in combination with doxorubicin and cyclophosphamide; with doxorubicin for initial chemotherapy of locally advanced or metastatic breast cancer; monotherapy for locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline or an alkylating drug has failed; with capecitabine for locally advanced or metastatic breast cancer where cytotoxic chemotherapy with an anthracycline has failed; with trastuzumab for initial chemotherapy of metastatic breast cancer which overexpresses human epidermal growth factor-2; locally advanced or metastatic non-small cell lung cancer where first-line chemotherapy has failed; with cisplatin for unresectable, locally advanced or metastatic non-small cell lung cancer; with prednisolone for hormone-refractory metastatic prostate cancer; with cisplatin and fluorouracil for initial treatment of metastatic gastric adenocarcinoma, including adenocarcinoma of the gastro-oesophageal junction; with cisplatin and fluorouracil for induction treatment of advanced squamous cell cancer of the head and neck.
locally advanced squamous cell carcinoma of the head and neck

**Cautions** see section 8.1 and notes above; hepatic impairment (Appendix 2); interactions: Appendix 1 (docetaxel)

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Taxotere** (Sanofi-Aventis) (UK)
Concentrate for intravenous infusion, docetaxel 40 mg/mL. Net price 0.5-mL vial = £162.75, 2-mL vial = £354.75 (both with diluent) (hosp. only)

**PACLITAXEL**

**Indications** ovarian cancer (advanced or residual disease following laparotomy) in combination with cisplatin; metastatic ovarian cancer where platinum-containing therapy has failed; locally advanced or metastatic breast cancer (in combination with other cytotoxics or alone if other cytotoxics have failed or are inappropriate); adjuvant treatment of node-positive breast cancer following treatment with anthracycline and cyclophosphamide; non-small cell lung cancer (in combination with cisplatin) when surgery or radiotherapy not appropriate; advanced AIDS-related Kaposi’s sarcoma where liposomal anthracycline therapy has failed

**Cautions** see section 8.1 and notes above; interactions: Appendix 1 (paclitaxel)

**Contra-indications** see section 8.1 and notes above; severe hepatic impairment; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Paclitaxel** (Non-proprietary) (UK)
Concentrate for intravenous infusion, paclitaxel 6 mg/mL, net price 5-mL vial = £111.41, 16.7-mL vial = £333.91, 25-mL vial = £500.86, 50-mL vial = £1001.72
Excipients include polyoxyl castor oil (risk of anaphylaxis, see Excipients, p. 2)

**Taxol** (Bristol-Myers Squibb) (UK)
Concentrate for intravenous infusion, paclitaxel 6 mg/mL, net price 5-mL vial = £116.05, 16.7-mL vial = £347.82, 25-mL vial = £521.73, 50-mL vial = £1043.46 (hosp. only)
Excipients include polyoxyl castor oil (risk of anaphylaxis, see Excipients, p. 2)

**Topoisomerase I inhibitors**

Irinotecan and topotecan inhibit topoisomerase I, an enzyme involved in DNA replication.

**Irinotecan** is licensed for metastatic colorectal cancer in combination with fluorouracil and folinic acid or as monotherapy when treatment containing fluorouracil has failed. It is also licensed in combination with cetuximab for the treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer after failure of chemotherapy that has included irinotecan. Irinotecan is also licensed in combination with 5-fluorouracil, folinic acid and bevacizumab for the first-line treatment of metastatic carcinoma of the colon or rectum. Irinotecan is given by intravenous infusion.

**IRINOTECAN HYDROCHLORIDE**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; raised plasma-bilirubin concentration (see under Contra-indications and Appendix 2)

**Contra-indications** see section 8.1 and notes above; also chronic inflammatory bowel disease, bowel obstruction; plasma-bilirubin concentration greater than 3 times the upper limit of reference range; renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above; also acute cholinergic syndrome (with early diarrhoea) and delayed diarrhoea (consult product literature), interstitial pulmonary disease

**Campto** (Pfizer) (UK)
Concentrate for intravenous infusion, irinotecan hydrochloride 20 mg/mL, net price 2-mL vial = £130.00; 5-mL vial = £290.00

**TOPOTECAN**

**Indications** see notes above

**Cautions** see section 8.1 and notes above; renal impairment (avoid infusion if creatinine clearance less than 20 mL/minute; avoid oral route if creatinine clearance less than 60 mL/minute; Appendix 3)

**Contra-indications** see section 8.1 and notes above; severe hepatic impairment; pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Hycamtin** (GSK) (UK)
Capsules, topotecan (as hydrochloride) 250 micrograms (white), net price 10-cap pack = £75.00; 1 mg (pink), 10-cap pack = £300.00

Intravenous infusion, powder for reconstitution, topotecan (as hydrochloride), net price 1-mg vial = £97.65; 4-mg vial = £290.62

**NICE guidance (irinotecan, oxaliplatin and raltitrexed for advanced colorectal cancer)**
See p. 478

**NICE guidance (paclitaxel, pegylated liposomal doxorubicin and topotecan for second-line or subsequent treatment of advanced ovarian cancer)**
See p. 478

**Topotecan** is given by intravenous infusion or orally in metastatic ovarian cancer when first-line or subsequent therapy has failed.

In addition to dose-limiting myelosuppression, side-effects of irinotecan and topotecan include gastrointestinal effects (delayed diarrhoea requiring prompt treatment may follow irinotecan treatment), asthenia, alopecia, and anorexia.

The Scottish Medicines Consortium has advised (November 2007) that topotecan is accepted for restricted use in combination with cisplatin for treatment of recurrent carcinoma of the cervix after radiotherapy and for stage IVB disease; it is restricted to patients who are cisplatin-naive.

**Topoisomerase I inhibitors**

Irinotecan and topotecan inhibit topoisomerase I, an enzyme involved in DNA replication.

**Irinotecan** is licensed for metastatic colorectal cancer in combination with fluorouracil and folinic acid or as monotherapy when treatment containing fluorouracil has failed. It is also licensed in combination with cetuximab for the treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer after failure of chemotherapy that has included irinotecan. Irinotecan is also licensed in combination with 5-fluorouracil, folinic acid and bevacizumab for the first-line treatment of metastatic carcinoma of the colon or rectum. Irinotecan is given by intravenous infusion.

**Contra-indications** pregnancy (Appendix 4); breast-feeding

**Side-effects** see section 8.1 and notes above

**Taxotere** (Sanofi-Aventis) (UK)
Concentrate for intravenous infusion, docetaxel 40 mg/mL. Net price 0.5-mL vial = £162.75, 2-mL vial = £354.75 (both with diluent) (hosp. only)
Trabectedin

Trabectedin is licensed for the treatment of advanced soft tissue sarcoma when treatment with anthracyclines and ifosfamide has failed or is contra-indicated.

Trabectedin is given by intravenous infusion. Dexamethasone by intravenous infusion should be given concomitantly for its antiemetic and hepatoprotective effects.

The Scottish Medicines Consortium (p. 3) has advised (January 2008) that trabectedin (Yondelis®) is not recommended for use within NHS Scotland for the treatment of advanced soft tissue sarcoma.

TRABECTEDIN

Indications see notes above

Cautions see section 8.1 and notes above; measure creatine phosphokinase, renal function and hepatic function before starting (consult product literature); monitor haematological and hepatic parameters weekly during first 2 cycles and at least once between treatments in subsequent cycles; concomitant use with hepatotoxic drugs (avoid alcohol); hepatic impairment (Appendix 2)

Contra-indications raised bilirubin; renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects see section 8.1; also abdominal pain, constipation, diarrhoea, dyspepsia, taste disturbance, hepatobiliary disorders; hypotension, oedema, flushing; dyspnoea, cough; headache, insomnia, peripheral neuropathy, paraesthesia, dizziness, anorexia, asthenia, fatigue; pyrexia; hypokalaemia, dehydration, increased blood creatine phosphokinase; myalgia, arthralgia, back pain

Yondelis® (Pharma Mar) ▼ (Ph)

Injection, powder for reconstitution, trabectedin, net price 250-microgram vial = £263.00; 1-mg vial = £1366.00

Trastuzumab

Trastuzumab is licensed for the treatment of early breast cancer which overexpresses human epidermal growth factor receptor-2 (HER2) (see NICE guidance, below).

Trastuzumab is also licensed, in combination with paclitaxel or docetaxel, for metastatic breast cancer in patients with HER2-positive tumours who have not received chemotherapy for metastatic breast cancer and in whom anthracycline treatment is inappropriate.

Trastuzumab is also licensed, in combination with an aromatase inhibitor, for metastatic breast cancer in postmenopausal patients with hormone-receptor positive HER2-positive tumours not previously treated with trastuzumab.

Trastuzumab is also licensed as monotherapy for metastatic breast cancer in patients with tumours that overexpress HER2 who have received at least 2 chemotherapy regimens including, where appropriate, an anthracycline and a taxane; women with oestrogen-receptor-positive breast cancer should also have received hormonal therapy.

Trastuzumab is given by intravenous infusion. Resuscitation facilities should be available and treatment should be initiated by a specialist.

NICE guidance

Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer (August 2006)

Trastuzumab is an option for women with early-stage HER2-positive breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant), and radiotherapy (if appropriate).

Use with anthracyclines Concomitant use of trastuzumab with anthracyclines (section 8.1.2) is associated with cardiotoxicity. The use of anthracyclines even after stopping trastuzumab can increase the risk of cardiotoxicity and if possible should be avoided for up to 24 weeks. If an anthracycline needs to be used, cardiac function should be monitored closely.

TRASTUZUMAB

Indications see notes above and product literature

Cautions see section 8.1 and notes above; symptomatic heart failure, history of hypertension, coronary artery disease, uncontrolled arrhythmias; pregnancy (Appendix 4)

Cardiotoxicity Monitor cardiac function before and during treatment—for details of monitoring and managing cardiotoxicity, consult product literature

Contra-indications see section 8.1 and notes above; severe dyspnoea at rest; breast-feeding (Appendix 5)

Side-effects infusion-related side-effects including chills, fever, hypersensitivity reactions such as anaphylaxis, urticaria, and angioedema; gastrointestinal symptoms; cardiotoxicity (see also above), chest pain, hypotension; pulmonary events (possibly delayed onset); headache, taste disturbance, anxiety, malaise, depression, insomnia, drowsiness, dizziness, paraesthesia, tremor, asthenia, peripheral neuropathy, hypotonia; mastitis, urinary-tract infection; leukopenia, ecchymosis, oedema, weight loss; arthralgia, myalgia, arthritis, bone pain, leg cramps; rash, pruritus, sweating, dry skin, alopecia, acne, nail disorders

Herceptin® (Roche) ▼ (Vain)

Intravenous infusion, powder for reconstitution, trastuzumab, net price 150-mg vial = £407.40

Tretinoin

Tretinoin is licensed for the induction of remission in acute promyelocytic leukaemia. It is used in previously untreated patients as well as in those who have relapsed after standard chemotherapy or who are refractory to it.

TRETINOIN

Note Tretinoin is the acid form of vitamin A

Indications see notes above; acne (section 13.6.1); photodamage (section 13.8.1)
Malignant disease and immunosuppression

Immunomodulators may be used to initiate treatment both. Specialist management is required and other drug (azathioprine or mycophenolate mofetil), (ciclosporin or tacrolimus), corticosteroid combined with a calcineurin inhibitor organ transplant patients are usually maintained on a chronic inflammatory and autoimmune diseases. Solid organ transplant recipients and to treat a variety of immunosuppressants are used to suppress rejection in renal, hepatic or cardiac transplanta-

Bioavailability

Different formulations of the same immunosuppres-
sant may vary in bioavailability and to avoid reduced effect or excessive side-effects, it is important not to change formulation except on the advice of a transplant specialist.

Impaired immune responsiveness

Modification of tissue reactions caused by corticosteroids and other immunosuppressants may result in the rapid spread of infection. Corticosteroids may suppress clinical signs of infection and allow diseases such as septicaemia or tuberculosis to reach an advanced stage before being recognised—important: for advice on measles and chickenpox (varicella) exposure, see Immunoglobulins (section 14.5). For advice on the use of live vaccines in individuals with impaired immune response, see section 14.1. For general comments and warnings relating to corticosteroids and immunosuppressants, see section 6.3.2 (under Prednisolone).

Pregnancy

Transplant patients immunosuppressed with azathioprine should not discontinue it on becoming pregnant; there is no evidence that azathioprine is teratogenic. However, there have been reports of premature birth and low birth-weight following exposure to azathioprine, particularly in combination with corticosteroids. Spontaneous abortion has been reported following maternal or paternal exposure. There is less experience of ciclosporin in pregnancy but it does not appear to be any more harmful than azathioprine. The use of these drugs during pregnancy needs to be supervised in specialist units. Manufacturers contra-indicate the use of tacrolimus and mycophenolate in pregnancy (Appendix 4).

8.2 Drugs affecting the immune response

8.2.1 Antiproliferative immunosuppressants

Azathioprine is widely used for transplant recipients and it is also used to treat a number of auto-immune conditions, usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced when allopurinol is given concurrently.

Blood tests and monitoring for signs of myelosuppres-

Mycophenolate mofetil is metabolised to mycophene-

nolic acid which has a more selective mode of action than azathioprine. It is licensed for the prophylaxis of acute rejection in renal, hepatic or cardiac transplanta-

tion when used in combination with ciclosporin and corticosteroids. There is evidence that compared with similar regimens incorporating azathioprine, mycophenolate mofetil reduces the risk of acute rejection epi-

8.2.2 Corticosteroids and other immunosuppressants

8.2.3 Rituximab and alemtuzumab

8.2.4 Other immunomodulating drugs

Immunosuppressant therapy

Immunosuppressants are used to suppress rejection in organ transplant recipients and to treat a variety of chronic inflammatory and autoimmune diseases. Solid organ transplant patients are usually maintained on a corticosteroid combined with a calcineurin inhibitor (ciclosporin or tacrolimus), or with an antiproliferative drug (azathioprine or mycophenolate mofetil), or with both. Specialist management is required and other immunomodulators may be used to initiate treatment or to treat rejection.

8.2.1 Antiproliferative immunosuppressants

Azathioprine is widely used for transplant recipients and it is also used to treat a number of auto-immune conditions, usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced when allopurinol is given concurrently.

Blood tests and monitoring for signs of myelosuppression are essential in long-term treatment with azathioprine. The enzyme thiopurine methyltransferase (TPMT) metabolises azathioprine; the risk of myelosuppression is increased in those with a low activity of the enzyme, particularly in the very few individuals who are homozygous for low TPMT activity.

Mycophenolate mofetil is metabolised to mycophenolic acid which has a more selective mode of action than azathioprine. It is licensed for the prophylaxis of acute rejection in renal, hepatic or cardiac transplantation when used in combination with ciclosporin and corticosteroids. There is evidence that compared with similar regimens incorporating azathioprine, mycophenolate mofetil reduces the risk of acute rejection epi-
AZATHIOPRINE

Indications  see notes above; inflammatory bowel disease [unlicensed indication] (section 1.5.3); rheumatoid arthritis (section 10.1.3)

Cautions  monitor for toxicity throughout treatment; monitor full blood count weekly (more frequently with higher doses or if hepatic or renal impairment) for first 4 weeks (manufacturer advises weekly monitoring for 8 weeks but evidence of practical value unsatisfactory), thereafter reduce frequency of monitoring to at least every 3 months; hepatic impairment (Appendix 2); renal impairment (Appendix 3); reduce dose in elderly; pregnancy (see section 8.2)—treatment should not generally be initiated during pregnancy; breast-feeding (Appendix 5); interactions: Appendix 1 (azathioprine)

Bone marrow suppression  Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection

Contra-indications  hypersensitivity to azathioprine or mercaptopurine

Side-effects  hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis—calling for immediate withdrawal); dose-related bone marrow suppression (see also Cautions); liver impairment, cholestatic jaundice, hair loss and increased susceptibility to infections and colitis in patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, hepatic veno-occlusive disease

Dose  • By mouth, or (if oral administration not possible— intravenous solution very irritating, see below) by intravenous injection over at least 1 minute (followed by 50 mL sodium chloride intravenous infusion), or by intravenous infusion

Autoimmune conditions, 1–3 mg/kg daily, adjusted according to response (consider withdrawal if no improvement in 3 months)

Suppression of transplant rejection, initially up to 5 mg/kg then 1–4 mg/kg daily according to response

Note  Intravenous injection is alkaline and very irritant, see below)

Bone marrow suppression (including bone marrow suppression e.g. inexplicable bruising or bleeding, infection)

Bone marrow suppression Patients should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding

Contra-indications pregnancy (exclude before starting and avoid for 6 weeks after discontinuation) (Appendix 4); breast-feeding (Appendix 5)

Side-effects gastro-intestinal disturbances (including diarrhoea, vomiting, and abdominal pain), gastrointestinal ulceration and bleeding, abnormal liver function tests, hepatitis, jaundice, pancreatitis; oedema, tachycardia, hypertension, hypotension, vasodilatation; cough, dyspnoea; insomnia, agitation, tremor, dizziness, headache; influenza-like syndrome, infections (viral, bacterial, and fungal); hyperglycaemia; renal impairment; increased risk of malignancies, particularly of the skin; blood disorders (including leucopenia, anaemia, thrombocytopenia, pancytopenia), disturbances of electrolytes and blood lipids; arthralgia; alopecia, acne, and rash; progressive multifocal leuкоencephalopathy reported

Dose  • Renal transplantation, by mouth, 1 g twice daily starting within 72 hours of transplantation or by intravenous infusion, 1 g twice daily starting within 24 hours of transplantation for max. 14 days (then transfer to oral therapy); child and adolescent 2–18 years, by mouth 600 mg/m² twice daily (max. 2 g daily)

Note  Tablets and capsules not appropriate for dose titration in children with body surface area less than 1.25 m²

• Cardiac transplantation, by mouth, 1.5 g twice daily starting within 5 days of transplantation

• Hepatic transplantation, by intravenous infusion, 1 g twice daily starting within 24 hours of transplantation for 4 days (up to max. 14 days), then by mouth, 1.5 g twice daily as soon as is tolerated

CellCept® (Roche) Capsules, blue/brown, mycophenolate mofetil

250 mg, net price 100-cap pack = £87.33

Tablets, lavender, mycophenolate mofetil 500 mg, net price 50-tab pack = £87.33

Cautions  full blood counts every week for 4 weeks then twice a month for 2 months then every month in the first year (consider interrupting treatment if neutropenia develops); elderly (increased risk of infection, gastrointestinal haemorrhage and pulmonary oedema); children (higher incidence of side-effects may call for temporary reduction of dose or interruption); active serious gastrointestinal disease (risk of haemorrhage, ulceration and perforation); delayed graft function; increased susceptibility to skin cancer (avoid exposure to strong sunlight); interactions: Appendix 1 (mycophenolate)

Malignant disease and immunosuppression

Notes  patients also receiving corticosteroids; nausea; rarely pancreatitis, pneumonitis, hepatic veno-occlusive disease
**8.2.2 Corticosteroids and other immunosuppressants**

**Prednisolone** (section 6.3.2) is widely used in oncology. It has a marked antitumour effect in acute lymphoblastic leukaemia, Hodgkin’s disease, and the non-Hodgkin lymphomas. It has a role in the palliation of symptomatic end-stage malignant disease when it may enhance appetite and produce a sense of well-being (see also Prescribing in Palliative Care, p. 17).

The corticosteroids are also powerful immunosuppressants. They are used to prevent organ transplant rejection, and in high dose to treat rejection episodes.

**Ciclosporin** (cyclosporin), a calcineurin inhibitor, is a potent immunosuppressant which is virtually non-competitive but markedly nephrotoxic. It has an important role in organ and tissue transplantation, for prevention of graft rejection following bone marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, and for prophylaxis and treatment of graft-versus-host disease.

**Sirolimus** is recommended as a component of immunosuppressive regimen only if intolerance necessitates the withdrawal of a calcineurin inhibitor. These recommendations may not be consistent with the marketing authorisation of some of the products.

**Antithymocyte immunoglobulin (rabbit)**

**Indications** see notes above

**Cautions** see notes above; monitor blood count; pregnancy (Appendix 4)

**Contra-indications** infection; breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, dysphagia, diarrhoea; hypotension; infusion-related reactions (including cytokine release syndrome and anaphylaxis, see notes above), serum sickness; fever, shivering, increased susceptibility to infection; increased susceptibility to malignancy; lymphopenia, neutropenia, thrombocytopenia; myalgia; pruritus, rash

**Dose**
- Heart transplantation, by intravenous infusion over at least 6 hours, 1–2.5 mg/kg daily for 3–5 days
- Renal transplantation, by intravenous infusion over at least 6 hours, 1–1.5 mg/kg daily for 3–9 days
- Corticosteroid-resistant renal graft rejection, by intravenous infusion over at least 6 hours, 1.5 mg/kg daily for 7–14 days

**Note** To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight.

**Thymoglobulin®** (Genzyme) ▼ Intravenous infusion, powder for reconstitution, rabbit anti-human thymocyte immunoglobulin, net price 25-mg vial = £168.18

**Basiliximab**

**Indications** see notes above

**Contra-indications** pregnancy (Appendix 4) and breast-feeding

**Side-effects** rarely severe hypersensitivity reactions; cytokine release syndrome also reported; for side-effects, see notes above; monitor blood count; infection; breast-feeding (Appendix 5)

**Dose**
- Renal transplantation, by intravenous infusion over at least 6 hours, 1 mg/kg daily for 4 days
- Intravenous infusion over at least 6 hours, 1.5 mg/kg daily for 7–14 days

**Note** To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight.

**Mycophenolic acid**

**Myfortic®** (Novartis) Tablets, e/c, mycophenolic acid (as mycophenolate sodium) 180 mg (green), net price 120-tab pack = £99.71; 360 mg (orange), 120-tab pack = £199.41.

**Label:** 25

**Dose** renal transplantation, 720 mg twice daily starting within 72 hours of transplantation

**Equivalence to mycophenolate mofetil** Mycophenolic acid 720 mg is approximately equivalent to mycophenolate mofetil 1 g but avoid unnecessary switching because of pharmacokinetic differences.

**Sirolimus** is a potent non-calcineurin inhibiting immunosuppressant licensed for renal transplantation. It can cause hyperlipidaemia.

**Basiliximab** is a monoclonal antibody that prevents T-lymphocyte proliferation; it is used for prophylaxis of acute rejection in allogeneic renal transplantation. It is given with ciclosporin and corticosteroid immunosuppressive regimens; its use should be confined to specialist centres.

**Antithymocyte immunoglobulin (rabbit)** is licensed for the prophylaxis of organ rejection in renal and heart allograft recipients and for the treatment of corticosteroid-resistant allograft rejection in renal transplantation. Tolerability may be increased by pretreatment with an intravenous corticosteroid and antihistamine; an antipyretic drug such as paracetamol may also be beneficial.

**Tacrolimus** is a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects, but the incidence of neurotoxicity appears to be greater; cardiomyopathy has also been reported. Disturbance of glucose metabolism also appears to be significant; hypertrichosis appears to be less of a problem than with ciclosporin.

**Mycophenolate mofetil** [mycophenolic acid also chemically related to ciclosporin it has a similar mode of action and side-effects, but the incidence of neurotoxicity appears to be greater; cardiomyopathy has also been reported. Disturbance of glucose metabolism also appears to be significant; hypertrichosis appears to be less of a problem than with ciclosporin.]

**Corticosteroid-resistant renal graft rejection, either basiliximab or daclizumab [discontinued] are options for combining with a calcineurin inhibitor. For each individual, ciclosporin or tacrolimus is chosen as the calcineurin inhibitor on the basis of side-effects. Mycophenolate mofetil [mycophenolic acid also available but not licensed for use in children, see above] is recommended as part of an immunosuppressive regimen only if:

- the calcineurin inhibitor is not tolerated, particularly if nephrotoxicity endangers the transplanted kidney, or
- there is very high risk of nephrotoxicity from the calcineurin inhibitor, requiring a reduction in the dose of the calcineurin inhibitor or its avoidance.

Sirolimus is recommended as a component of immunosuppressive regimen only if intolerance necessitates the withdrawal of a calcineurin inhibitor.
effects of regimen see under Ciclosporin (below) and Prednisolone (section 6.3.2).

**Dose**
- By intravenous injection or by intravenous infusion, 20 mg within 2 hours before transplant surgery and 20 mg 4 days after surgery; withhold second dose if severe hypersensitivity or graft loss occurs; CHILD and ADOLESCENT 1–17 years, body-weight under 35 kg, 10 mg within 2 hours before transplant surgery and 10 mg 4 days after surgery; body-weight over 35 kg, adult dose

Simulect® (Novartis) Injection, powder for reconstitution, basiliximab, net price 10-mg vial = £758.69, 20-mg vial = £842.38 (both with water for injections). For intravenous infusion

---

**CICLOSPORIN**

(Cyclosporin)

**Indications** see notes above, and under Dose; severe acute ulcerative colitis [unlicensed indication] (section 1.5.3); rheumatoid arthritis (section 10.1.3); atopic dermatitis and psoriasis (section 13.5.3).

**Cautions** monitor kidney function—dose dependent on renal function (dosage adjustment based on bilirubin increase in serum creatinine and urea during first few weeks may necessitate dose reduction in transplant patients (exclude rejection if kidney transplant) or discontinuation in non-transplant patients; monitor liver function (dosage adjustment based on bilirubin and liver enzymes may be needed); monitor blood pressure—discontinue if hypertension develops that cannot be controlled by antihypertensives; hyperuricaemia; monitor serum potassium especially in renal dysfunction (risk of hyperkalaemia); monitor serum magnesium; measure blood lipids before treatment and thereafter as appropriate; pregnancy (see p. 486) and breast-feeding (Appendix 5); acute porphyria (section 9.8.2); use with tacrolimus specifically contra-indicated; for patients other than transplant recipients, preferably avoid other immunosuppressants (increased risk of infection and malignancies, including lymphoma and skin cancer); avoid excessive exposure to UV light, including sunlight; interactions: Appendix 1 (ciclosporin); Additional cautions in nephrotic syndrome Contra-indicated in uncontrolled hypertension, uncontrolled infections, and malignancy; reduce dose by 25–50% if serum creatinine more than 30% above baseline on more than one measurement; in renal impairment initially 2.5 mg/kg daily; in long-term management, perform renal biopsies at yearly intervals; Additional cautions Atopic Dermatitis and Psoriasis, section 13.5.3; Rheumatoid Arthritis, section 10.1.3.

**Side-effects** gastro-intestinal disturbances, gingival hyperplasia, hepatic dysfunction, anorexia, hypertension; tremor, headache, paraesthesia, fatigue; renal dysfunction (renal structural changes on long-term administration, see also under Cautions), hyperuricaemia, hyperkalaemia, hypomagnesaemia, hyperlipaemia; muscle cramps, myalgia; hypertrichosis; less commonly oedema, weight gain, encaphalopathy or demyelination especially in liver transplant patients, anaemia, thrombocytopenia, rash; rarely pancreatitis, motor polyneuropathy, menstrual disturbances, gynaecomastia, microangiopathic haemolytic anaemia, haemolytic uraemic syndrome, hyperglaemia, muscle weakness, myopathy; visual disturbances secondary to benign intracranial hypertension (discontinue), also anaphylaxis reported with infusion.

---

**Dose**
- Organ transplantation, used alone, ADULT and CHILD over 3 months 10–15 mg/kg by mouth 4–12 hours before transplantation followed by 10–15 mg/kg daily for 1–2 weeks postoperatively then reduced gradually to 2–6 mg/kg daily for maintenance (dose should be adjusted according to blood-ciclosporin concentration and renal function); dose lower if given concomitantly with other immunosuppressant therapy (e.g. corticosteroids); if necessary one-third corresponding oral dose can be given by intravenous infusion over 2–6 hours.

- Bone-marrow transplantation, prevention and treatment of graft-versus-host disease, ADULT and CHILD over 3 months 3–5 mg/kg daily by intravenous infusion over 2–6 hours from day before transplantation to 2 weeks postoperatively (or 12.5–15 mg/kg daily by mouth) then 12.5 mg/kg daily by mouth for 3–6 months then tailed off (may take up to a year after transplantation).

- Nephrotic syndrome, by mouth, 5 mg/kg daily in 2 divided doses; CHILD 6 mg/kg daily in 2 divided doses; maintenance treatment reduce to lowest effective dose according to proteinuria and serum creatinine measurements; discontinue after 3 months if no improvement in glomerulonephritis or glomerulosclerosis (after 6 months in membranous glomerulonephritis).

**Conversion** Any conversion between brands should be undertaken very carefully and the manufacturer contacted for further information. Currently only Neoral remains available for oral use; Sandimmune capsules and oral solution and SangCya oral solution are available on named-patient basis only for patients who cannot be transferred to another brand of oral ciclosporin.

Because of differences in bioavailability, the brand of oral ciclosporin to be dispensed should be specified by the prescriber.

**Neoral®** (Novartis) capsules, ciclosporin 10 mg (yellow/white), net price 60-cap pack = £18.98; 25 mg (blue/grey), 30-cap pack = £19.10; 50 mg (yellow/white), 30-cap pack = £37.40; 100 mg (blue/grey), 30-cap pack = £70.99.

Counselling, administration
- Oral solution, yellow, sugar-free, ciclosporin 100 mg/mL, net price 50 mL = £106.37.

Counselling, administration
- Counselling Total daily dose should be taken in 2 divided doses. Avoid grapefruit or grapefruit juice for 1 hour before dose.

Mix solution with orange juice (or squash) or apple juice (to improve taste) or with water immediately before taking and rinse mouth for 3–6 hours then tapered off (may take up to a year after transplantation).

**Sandimmune** (Novartis) Concentrate for intravenous infusion (oily), ciclosporin 50 mg/mL. To be diluted before use. Net price 1-mL amp = £1.94; 5-mL amp = £9.17

Excipients include polysorbate castor oil (risk of anaphylaxis, see Excipients, p 2).

**Note** Observe patients for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter.

---

**SIROLIMUS**

**Indications** prophylaxis of organ rejection in kidney allograft recipients (initially in combination with ciclosporin and corticosteroid, then with corticosteroid only); see also under Dose

**Cautions** monitor kidney function when given with ciclosporin; Afro-Caribbean patients may require...
Malignant disease and other immunosuppressants

Contra-indications

hypoalbuminemia (section 13.5.3)

rejection resistant to conventional immunosuppressive regimes used)

When changing between oral solution and tablets, measurement of serum 'trough' blood-sirolimus concentration after 1–2 weeks is recommended

Note

expectoration, renal failure, pulmonary hypertension, pleural effusion, pericardial effusion, pancreatitis, pulmonary embolism, rare bleeding, disseminated intravascular coagulation, sepsis, severe atopic eczema (section 13.5.3)

Driving

MHRA/CHM advice (December 2008)

Prograf and Advagraf (tacrolimus): serious medication errors

It is important to note the correct use of these medicines:

- Prograf is an immediate-release formulation that is taken twice daily, once in the morning and once in the evening.
- Advagraf is a prolonged-release formulation that is taken once daily in the morning.

Prograf and Advagraf are not interchangeable; switching between Prograf and Advagraf requires careful therapeutic monitoring. Substitution should be made only under the close supervision of a transplant specialist.

Prograf® (Astellas)  
Capsules, tacrolimus 500 micrograms (yellow), net price 50-cap pack = £65.69; 1 mg (white), 50-cap pack = £85.22, 100-cap pack = £170.43; 5 mg (greyish-red), 50-cap pack = £314.84. Label: 23, counselling, driving

Concentrate for intravenous infusion, tacrolimus 5 mg/mL. To be diluted before use. Net price 1-mL amp = £62.05

Excipients include polysorbate 80 (risk of anaphylaxis, see Excipients, p. 2)

Dose

Liver transplantation, starting 12 hours after transplantation, requires a prolonged-release formulation that is taken once daily in the morning.

Prograf and Advagraf are not interchangeable; switching between Prograf and Advagraf requires careful therapeutic monitoring. Substitution should be made only under the close supervision of a transplant specialist.

TACROLIMUS

Indications

prophylaxis of organ rejection in liver, kidney, and heart allograft recipients and allograft rejection resistant to conventional immunosuppressive regimes, see also notes above: moderate to severe atopic eczema (section 13.5.3)

Cautions

see under Ciclosporin; also monitor ECG (important: also echocardiography, see CSM warning below), visual status, blood glucose, haematological and neurological parameters and whole blood 'trough' concentrations of tacrolimus (especially during episodes of diarrhoea); hepatic impairment (Appendix 2); interactions: Appendix 1 (tacrolimus)

Driving May affect performance of skilled tasks (e.g. driving)

Contra-indications

hypersensitivity to macrolides; pregnancy (exclude before starting—if contraception needed non-hormonal methods should be used, Appendix 4); breast-feeding (Appendix 5); avoid concurrent administration with ciclosporin (care if patient has previously received ciclosporin)

Side-effects

gastro-intestinal disturbances including dyspepsia, and inflammatory and ulcerative disorders; hepatic dysfunction, jaundice, bile-duct and gall-bladder abnormalities; hypertension (less frequently hypotension), tachycardia, angina, arrhythmias, thromboembolic and ischaemic events, rarely myocardial hypertrophy, cardiomyopathy (important: see CSM warning below), dyspnoea, pleural effusion, tremor, headache, insomnia, paraesthesia, confusion, depression, dizziness, anxiety, convulsions, incoordination, encephalopathy, psychosis, visual and hearing abnormalities; haematological effects including anaemia, leucocytosis, leucopenia, thrombocytopenia, pancytopenia, coagulation disorders; altered acid-base balance and glucose metabolism, electrolyte disturbances including hyperkalaemia (less frequently hypokalaemia); altered renal function including increased serum creatinine; hypophosphataemia, hypercalcemia, hyperuricaemia; muscle cramps, arthralgia; pruritus, alopecia, rash, sweating, acne, photosensitivity; susceptibility to lymphoma and other malignancies particularly of the skin, less commonly ascites, pancreatitis, atelectasis, kidney damage and renal failure, myasthenia, hirsutism; rarely Stevens-Johnson syndrome

CSM Warning

Cardiomyopathy has been reported in children given tacrolimus after transplantation. Patients should be monitored carefully by echocardiography for trophic changes; dose reduction or discontinuation should be considered if these occur

Dose

See under preparations

MHRA/CHM advice (December 2008)

Prograf and Advagraf (tacrolimus): serious medication errors

It is important to note the correct use of these medicines:

- Prograf is an immediate-release formulation that is taken twice daily, once in the morning and once in the evening.
- Advagraf is a prolonged-release formulation that is taken once daily in the morning.

Prograf and Advagraf are not interchangeable; switching between Prograf and Advagraf requires careful therapeutic monitoring. Substitution should be made only under the close supervision of a transplant specialist.

TACROLIMUS

Indications

prophylaxis of organ rejection in liver, kidney, and heart allograft recipients and allograft rejection resistant to conventional immunosuppressive regimes, see also notes above: moderate to severe atopic eczema (section 13.5.3)

Cautions

see under Ciclosporin; also monitor ECG (important: also echocardiography, see CSM warning below), visual status, blood glucose, haematological and neurological parameters and whole blood 'trough' concentrations of tacrolimus (especially during episodes of diarrhoea); hepatic impairment (Appendix 2); interactions: Appendix 1 (tacrolimus)

Driving May affect performance of skilled tasks (e.g. driving)

Contra-indications

hypersensitivity to macrolides; pregnancy (exclude before starting—if contraception needed non-hormonal methods should be used, Appendix 4); breast-feeding (Appendix 5); avoid concurrent administration with ciclosporin (care if patient has previously received ciclosporin)

Side-effects

gastro-intestinal disturbances including dyspepsia, and inflammatory and ulcerative disorders; hepatic dysfunction, jaundice, bile-duct and gall-bladder abnormalities; hypertension (less frequently hypotension), tachycardia, angina, arrhythmias, thromboembolic and ischaemic events, rarely myocardial hypertrophy, cardiomyopathy (important: see CSM warning below), dyspnoea, pleural effusion, tremor, headache, insomnia, paraesthesia, confusion, depression, dizziness, anxiety, convulsions, incoordination, encephalopathy, psychosis, visual and hearing abnormalities; haematological effects including anaemia, leucocytosis, leucopenia, thrombocytopenia, pancytopenia, coagulation disorders; altered acid-base balance and glucose metabolism, electrolyte disturbances including hyperkalaemia (less frequently hypokalaemia); altered renal function including increased serum creatinine; hypophosphataemia, hypercalcemia, hyperuricaemia; muscle cramps, arthralgia; pruritus, alopecia, rash, sweating, acne, photosensitivity; susceptibility to lymphoma and other malignancies particularly of the skin, less commonly ascites, pancreatitis, atelectasis, kidney damage and renal failure, myasthenia, hirsutism; rarely Stevens-Johnson syndrome

CSM Warning

Cardiomyopathy has been reported in children given tacrolimus after transplantation. Patients should be monitored carefully by echocardiography for trophic changes; dose reduction or discontinuation should be considered if these occur

Dose

See under preparations

MHRA/CHM advice (December 2008)

Prograf and Advagraf (tacrolimus): serious medication errors

It is important to note the correct use of these medicines:

- Prograf is an immediate-release formulation that is taken twice daily, once in the morning and once in the evening.
- Advagraf is a prolonged-release formulation that is taken once daily in the morning.

Prograf and Advagraf are not interchangeable; switching between Prograf and Advagraf requires careful therapeutic monitoring. Substitution should be made only under the close supervision of a transplant specialist.
of a specialist. See section 10.1.3 for the role of rituximab in rheumatoid arthritis.

Rituximab should be used with caution in patients receiving cardiotoxic chemotherapy or with a history of cardiovascular disease because exacerbation of angina, arrhythmia, and heart failure have been reported. Transient hypotension occurs frequently during infusion and antihypertensives may need to be withheld for 12 hours before infusion. Patients should be monitored for neurological deficits; if progressive multifocal leucoencephalopathy is suspected, suspend treatment until excluded.

Infusion-related side-effects (including cytokine release syndrome) are reported commonly with rituximab and occur predominantly during the first infusion; they include fever and chills, nausea and vomiting, allergic reactions (such as rash, pruritus, angioedema, bronchospasm and dyspnoea), flushing and tumour pain. Patients should be given an analgesic and an antihistamine before each dose of rituximab to reduce these effects. Premedication with a corticosteroid should also be considered. The infusion may have to be stopped temporarily and the infusion-related effects treated—consult product literature for appropriate management. Evidence of pulmonary infiltration and features of tumour lysis syndrome should be sought if infusion-related effects occur.

Fatalities following severe cytokine release syndrome (characterised by severe dyspnoea) and associated with features of tumour lysis syndrome have occurred 1–2 hours after infusion of rituximab. Patients with a high tumour burden as well as those with pulmonary insufficiency or infiltration are at increased risk and should be monitored very closely (and a slower rate of infusion considered).

### NICE guidance

**Rituximab for the treatment of follicular lymphoma (September 2006)**

Rituximab, in combination with cyclophosphamide, vincristine, and prednisolone is an option for the treatment of symptomatic stage III and IV follicular lymphoma in previously untreated patients.
NICE guidance

Rituximab for aggressive non-Hodgkin’s lymphoma (September 2003)

Rituximab, in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone, is recommended for first-line treatment of CD20-positive diffuse large-B-cell lymphoma at clinical stage II, III or IV. The use of rituximab for localised (stage I) disease should be limited to clinical trials.

Alemtuzumab, another monoclonal antibody that causes lysis of B lymphocytes, is licensed for use in patients with chronic lymphocytic leukaemia for whom fludarabine treatment is not appropriate. In common with rituximab, it causes infusion-related side-effects including cytokine release syndrome (see above) and premedication with an analgesic, an antihistamine, and a corticosteroid is recommended.

8.2.4 Other immunomodulating drugs

Interferon alfa

Interferon alfa has shown some antitumour effect in certain lymphomas and solid tumours. Interferon alfa preparations are also used in the treatment of chronic hepatitis B, and chronic hepatitis C ideally in combination with ribavirin (section 5.3.3). Side-effects are dose-related, but commonly include anorexia, nausea, influenza-like symptoms, and lethargy. Ocular side-effects and depression (including suicidal behaviour) have also been reported. Myelosuppression may occur, particularly affecting granulocyte counts. Cardiovascular problems (hypotension, hypertension, and arrhythmias), nephrotoxicity and hepatotoxicity have been reported. Hypertriglyceridaemia, sometimes severe, has been observed; monitoring of lipid concentration is recommended. Other side-effects include hypersensitivity reactions, thyroid abnormalities, hyperglycaemia, alopecia, psoriasiform rash, confusion, coma and seizures (usually with high doses in the elderly).

Polyethylene glycol-conjugated (‘pegylated’) derivatives of interferon alfa (peginterferon alfa-2a and peginterferon alfa-2b) are available; pegylation increases the persistence of the interferon in the blood. The peginterferons are licensed for the treatment of chronic hepatitis C, ideally in combination with ribavirin (see section 5.3.3). Peginterferon alfa-2a is also licensed for the treatment of chronic hepatitis B.

NICE guidance (adefovir dipivoxil and peginterferon alfa-2a for chronic hepatitis B)
See p. 348

NICE guidance (peginterferon alfa, interferon alfa, and ribavirin for chronic hepatitis C)
See p. 348

Interferon alfa

Indications see under preparations

Cautions consult product literature; interactions:
Appendix 1 (interferons)

Contra-indications consult product literature; avoid injections containing benzyl alcohol in neonates (see under preparations below); pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects see notes above and consult product literature

Dose
Consult product literature

INTRON A® (Schering-Plough) (Roche)

Injection, interferon alfa-2b (rbe) 10 million units/mL, net price 1-mL vial = £43.17, 2.5-mL vial = £108.00.
For subcutaneous injection or intravenous infusion
Injection pen, interferon alfa-2b (rbe), net price 15 million units/mL, 1.5-mL cartridge = £77.76; 25 million units/mL, 1.5-mL cartridge = £129.60; 50 million units/mL, 1.5-mL cartridge = £259.20. For subcutaneous injection

Note Each 1.5-mL multidose cartridge delivers 6 doses of 0.2 mL i.e. a total of 1.2 mL.
For chronic myelogenous leukaemia (as monotherapy or in combination with cytarabine), hairy cell leukaemia, follicular lymphoma, lymph or liver metastases of carcinoid tumour, chronic hepatitis B, chronic hepatitis C, adjunct to surgery in malignant melanoma and maintenance of remission in multiple myeloma

Roferon-A® (Roche) (Roche)

Injection, interferon alfa-2a (rbe). Net price 6 million units/mL, 0.5-mL (3 million-unit) prefilled syringe = £15.07; 9 million units/mL, 0.5-mL (4.5 million-unit) prefilled syringe = £22.60; 12 million units/mL, 0.5-mL (6 million-unit) prefilled syringe = £30.12; 18 mil-
lion units/mL, 0.5-mL (9 million-unit) prefilled syringe = £45.19; 36 million units/mL, 0.5-mL (18 million-unit) prefilled syringe = £90.39; 30 million units/mL, 0.6-mL (18 million-unit) cartridge = £90.39, for use with Roferon pen device. For subcutaneous injection (cartridges, vials, and prefilled syringes) and intra-muscular injection (cartridges and vials) Excipients include benzenyl alcohol (avoid in neonates, see Excipients, p. 2)

For AIDS-related Kaposi’s sarcoma, hairy cell leukaemia, chronic myelogenous leukaemia, recurrent or metastatic renal cell carcinoma, progressive cutaneous T-cell lymphoma, chronic hepatitis B and chronic hepatitis C, follicular non-Hodgkin’s lymphoma, adjunct to surgery in malignant melanoma

PEGINTERFERON ALFA

Indications see under preparations
Cautions consult product literature; interactions: Appendix 1 (interferons)
Contra-indications consult product literature
Side-effects see notes above and consult product literature

Dose
• Consult product literature

Pegasys® (Roche) \(\text{INF}\)
Injection, peginterferon alfa-2a, net price 135-microgram prefilled syringe = £114.39, 180-microgram prefilled syringe = £132.06. For subcutaneous injection
Combined with ribavirin for chronic hepatitis C, as monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated (see section 5.3.3), as monotherapy for chronic hepatitis B

ViraferonPeg® (Schering-Plough) \(\text{INF}\)
Injection, powder for reconstitution, peginterferon alfa-2b (rbe), net price 50-microgram vial = £82.78, 80-microgram vial = £100.44, 100-microgram vial = £125.55, 120-microgram vial = £150.66, 150-microgram vial = £188.33 (all with injection equipment and water for injections). For subcutaneous injection
Combined with ribavirin for chronic hepatitis C, as monotherapy for chronic hepatitis C if ribavirin not tolerated or contra-indicated (see section 5.3.3)

Interferon beta

Interferon beta is licensed for use in patients with relapsing, remitting multiple sclerosis (characterised by at least two attacks of neurological dysfunction over the previous 2 or 3 years, followed by complete or incomplete recovery) who are able to walk unaided. Not all patients respond and a deterioration in the bouts has been observed in some. It is also licensed for use in patients with a single demyelinating event with an active inflammatory process, if it is severe enough to require treatment with an intravenous corticosteroid, and they are at high risk of developing multiple sclerosis. Interferon beta-1b is also licensed for use in patients with secondary progressive multiple sclerosis but its role in this condition has not been confirmed.

Interferon beta should not be used in those with severe depressive illness (or suicidal ideation), or in decompensated liver disease. Caution is advised in those with severe hepatic or renal impairment or a history of cardiac disorders, depressive disorders (avoid in severe depression or in those with suicidal ideation), seizures, or severe myelosupression. Patients should be monitored for signs of hepatic injury. Side-effects reported most frequently include irritation at injection site (including inflammation, hypersensitivity, necrosis) and influenza-like symptoms (fever, chills, myalgia, or malaise) but these decrease over time; nausea and vomiting occur occasionally. Other side-effects include hypersensitivity reactions (including anaphylaxis and urticaria), blood disorders, menstrual disorders, mood and personality changes, suicide attempts, confusion and convulsions; alopecia, hepatitis, and thyroid dysfunction have been reported rarely with interferon beta-1b.

NICE guidance

Interferon beta and glatiramer acetate for multiple sclerosis (January 2002)

Interferon beta and glatiramer acetate are not recommended for the treatment of multiple sclerosis in the NHS in England and Wales. Patients who are currently receiving interferon beta or glatiramer acetate for multiple sclerosis, whether as routine therapy or as part of a clinical trial, should have the option to continue treatment until they and their consultant consider it appropriate to stop, having regard to the established criteria for withdrawal from treatment.

Provision of disease-modifying therapies for multiple sclerosis

The Department of Health, the National Assembly for Wales, the Scottish Executive, the Northern Ireland Department of Health, Social Services & Public Safety, and the manufacturers have reached agreement on a risk-sharing scheme for the NHS supply of interferon beta and glatiramer acetate for multiple sclerosis. Health Service Circular (HSC 2002/004) explains how patients can participate in the scheme. It is available on the Department of Health website (www.dh.gov.uk).

INTERFERON BETA

Indications see notes above and under preparations
Cautions see notes above and consult product literature
Contra-indications see notes above and consult product literature
Side-effects see notes above and consult product literature

Dose
• Consult product literature

Interferon beta-1a

Avonex® (Biogen) \(\text{INF}\)
Injection, interferon beta-1a 60 micrograms (12 million units)/mL, net price 0.5-mL (30-microgram, 6 million-unit) prefilled syringe = £163.50. For intra-muscular injection
8 Malignant disease and immunosuppression

Injection, powder for reconstitution, interferon beta-1a, net price 30-microgram (6 million-unit) vial with diluent = £163.50. For intramuscular injection

For relapsing, remitting multiple sclerosis or for a single demyelinating event with an active inflammatory process (if it is severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

Rebif® (Serono) \[\text{Bacillus Calmette-Guérin}\]

Injection, interferon beta-1a, net price 22-microgram (6 million-unit) prefilled syringe = £48.16; 44-microgram (12 million-unit) prefilled syringe = £57.32; starter pack of 6 x 8.8-microgram (2.4 million-unit) prefilled syringes with 6 x 22–microgram (6 million-unit) prefilled syringes = £586.19. For subcutaneous injection

For relapsing, remitting multiple sclerosis

Interferon beta-1b

Betaloven® (Schering Health) \[\text{Bacillus Calmette-Guérin}\]

Injection, powder for reconstitution, interferon beta-1b. Net price 300-microgram (9.6 million-unit) vial with diluent = £39.78. For subcutaneous injection

Note An autoinjector device (Betatject Light) is available from Schering Health

For relapsing, remitting multiple sclerosis, for secondary progressive multiple sclerosis with active disease, or for a single demyelinating event with an active inflammatory process (if severe enough to require intravenous corticosteroid and patient at high risk of developing multiple sclerosis)

Aldesleukin

Aldesleukin (recombinant interleukin-2) is licensed for metastatic renal cell carcinoma; it is usually given by subcutaneous injection. It is now rarely given by intravenous infusion because of an association with a capillary leak syndrome, which can cause pulmonary oedema and hypotension. Aldesleukin produces tumour shrinkage in a small proportion of patients, but it has not been shown to increase survival. Bone-marrow, hepatic, renal, thyroid, and CNS toxicity is common. It is for use in specialist units only. Interactions: Appendix 1 (aldesleukin)

Proleukin® (Novartis) \[\text{Bacillus Calmette-Guérin}\]

Injection, powder for reconstitution, aldesleukin. Net price 18.5-milligram vial = £72.60. For subcutaneous injection

Injection, powder for reconstitution, aldesleukin. Net price 18-milligram vial = £112.00. For intravenous infusion but see notes above

For metastatic renal cell carcinoma, excluding patients in whom all three of the following prognostic factors are present: performance status of Eastern Co-operative Oncology Group of 1 or greater, more than one organ with metastatic disease sites, and a period of less than 24 months between initial diagnosis of primary tumour and date of evaluation of treatment.

BCG bladder instillation

BCG (Bacillus Calmette-Guérin) is a live attenuated strain derived from Mycobacterium bovis. It is licensed as a bladder instillation for the treatment of primary or recurrent bladder carcinoma and for the prevention of recurrence following transurethral resection.

Bacillus Calmette-Guérin

Indications see notes above; BCG immunisation (section 14.4)

Cautions screen for active tuberculosis (contra-indicated if tuberculosis confirmed); traumatic catheterisation or urethral or bladder injury (delay administration until mucosal damage healed)

Contra-indications impaired immune response, HIV infection, urinary-tract infection, severe haematuria, tuberculosis, fever of unknown origin; pregnancy and breast-feeding

Side-effects cystitis, dysuria, urinary frequency, haematuria, malaise, fever, influenza-like syndrome; also systemic BCG infection (with fatalities)—consult product literature; rarely hypersensitivity reactions (such as arthralgia and rash), orchitis, transient urethral obstruction, bladder contracture, renal abscess; ocular symptoms reported

Dose

· Consult product literature

ImmuCyst® (Cambridge) \[\text{Bacillus Calmette-Guérin}\]

Bladder instillation, freeze-dried powder containing attenuated Mycobacterium bovis prepared from the Connaught strain of bacillus of Calmette and Guérin, net price 81-milligram vial = £79.23

OncoTICE® (Organon) \[\text{Bacillus Calmette-Guérin}\]

Bladder instillation, freeze-dried powder containing attenuated Mycobacterium bovis prepared from the TICE strain of bacillus of Calmette and Guérin, net price 12.5-milligram vial = £80.00

Glatiramer acetate

Glatiramer is an immunomodulating drug comprising synthetic polypeptides. It is licensed for reducing the frequency of relapses in ambulatory patients with relapsing-remitting multiple sclerosis who have had at least 2 clinical relapses in the past 2 years. Initiation of treatment with glatiramer should be supervised by a specialist.

NICE guidance (interferon beta and glatiramer for multiple sclerosis)

See p. 493

Provision of disease-modifying therapies for multiple sclerosis

See p. 493

Glatiramer Acetate

Indications see notes above

Cautions cardiac disorders; renal impairment (Appendix 3); breast-feeding (Appendix 5)

Contra-indications pregnancy (Appendix 4)

Side-effects flushing, chest pain, palpitation, tachycardia, and dyspnoea may occur within minutes of injection; nausea, constipation, diarrhoea; syncope, anxiety, asthenia, depression, dizziness, headache, tremor, sweating; oedema, lymphadenopathy; hyper-tonia, back pain, arthralgia, influenza-like symptoms; injection-site reactions, rash; rarely convulsions, hypersensitivity reactions
Lenalidomide and thalidomide

Lenalidomide is an immunomodulating drug with anti-neoplastic, anti-angiogenic, and pro-erythropoietic properties. It is licensed, in combination with dexamethasone, for the treatment of multiple myeloma in patients who have received at least one previous therapy.

The most serious side-effects of lenalidomide are venous thromboembolism and severe neutropenia. Lenalidomide is structurally related to thalidomide and there is a risk of teratogenesis.

Thalidomide is used in combination with melphalan and prednisolone as first-line treatment for untreated multiple myeloma, in patients aged 65 years and over or those not eligible for high-dose chemotherapy. It has immunomodulatory and anti-inflammatory activity. Thalidomide can cause drowsiness, constipation, and on prolonged use peripheral neuropathy.

**Pregnancy**

For women of child-bearing potential, pregnancy must be excluded before starting treatment (perform pregnancy test on initiation or within 3 days prior to initiation). Women must practise effective contraception at least 1 month before, during, and for at least 1 month after treatment (oral combined hormonal contraceptives and copper-releasing intrauterine devices not recommended) and men should use condoms during treatment and for at least 1 week after stopping. Women must be registered with a pregnancy prevention programme.

**Indications**

- **Thalidomide**: Patents and carers should be advised to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat) or of thrombocytopenia (such as bleeding) develop
- **Lenalidomide**: Pregnancy (important teratogenic risk): see notes above and Appendix 4; breast-feeding (Appendix 5)

**Dose**

- **ADULT over 18 years**: 200 mg once daily at bedtime for 6-week cycle; max. 12 cycles
- **Thalidomide Pharamion®** (Celgene) ▼STM
  - **Capsules**, thalidomide 50 mg, net price 28-cap pack = £298.48. Label: 2, counselling, symptoms of peripheral neuropathy and thromboembolism (see above)
- **Note**: Patient, prescriber, and supplying pharmacy must be registered with Celgene Ltd and comply with a pregnancy prevention programme

Natalizumab

Natalizumab is a monoclonal antibody that inhibits the migration of leucocytes into the central nervous system, hence reducing inflammation and demyelination. It is licensed for use in patients with highly active relapsing-remitting multiple sclerosis despite treatment with inter-

---

**BNF 57**

**8.2.4 Other immunomodulating drugs**
femon beta or those with rapidly evolving severe relapsing-remitting multiple sclerosis. Treatment with natalizumab should be initiated and supervised by a specialist.

Natalizumab is associated with an increased risk of opportunistic infection and progressive multifocal leucoencephalopathy (PML). Patients should be monitored for new or worsening neurological symptoms or signs of PML—treatment should be suspended until PML has been excluded. If a patient develops an opportunistic infection or PML, natalizumab should be permanently discontinued.

Infusion-related side-effects include nausea, vomiting, flushing, headache, dizziness, fatigue, rashes, pyrexia, arthralgia, urticaria, and pruritus. Patients should be observed for hypersensitivity reactions, including anaphylaxis, during the infusion and for 1 hour after completion of the infusion. Natalizumab should be discontinued permanently if hypersensitivity reaction occurs.

The Scottish Medicines Consortium has advised (August 2007) that natalizumab is accepted for restricted use as single disease-modifying therapy in highly active relapsing-remitting multiple sclerosis only in patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by 2 or more disabling relapses in 1 year and with 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI.

### Dose
- By intravenous infusion, ADULT over 18 years, 300 mg once every 4 weeks; discontinue if no response after 6 months

### Tysabri® *(Biogen)* ▼ *(Intravenous)*

Concentrate for intravenous infusion, natalizumab 20 mg/mL, net price 15-mL vial = £1130.00. Counseling, liver toxicity, progressive multifocal leucoencephalopathy, and hypersensitivity, patient alert card

### NICE guidance

**Natalizumab for the treatment of adults with highly active relapsing-remitting multiple sclerosis (August 2007)**

Natalizumab is an option for the treatment only of rapidly evolving severe relapsing-remitting multiple sclerosis (RES). RES is defined by 2 or more disabling relapses in 1 year, and 1 or more gadolinium-enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load compared with a previous MRI. Patients currently receiving natalizumab who do not meet the above criteria, should have the option to continue therapy until they and their consultants consider it appropriate to stop.

### Natalizumab

**Indications**  see notes above

**Cautions**  see notes above and consult product literature; prior treatment with immunosuppressants; monitor liver function (see below)

**Liver toxicity**  Liver dysfunction reported; advise patients to seek immediate medical attention if symptoms such as jaundice or dark urine develop; discontinue treatment if significant liver injury occurs

**Progressive multifocal leucoencephalopathy (PML)**  Patients should be given an alert card which includes information about the symptoms of PML; see also notes above

**Hypersensitivity reactions**  Patients should be told the importance of uninterrupted dosing, particularly in the early months of treatment (intermittent therapy may increase risk of sensitisation)

**Contra-indications**  progressive multifocal leucoencephalopathy; active infection (see notes above); concurrent use of interferon beta or glatiramer acetate; immunosuppression; active malignancies; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**  see notes above; also urinary-tract infection, nasopharyngitis, and arthralgia; less commonly hypersensitivity reactions (see above); liver toxicity also reported

### 8.3 Sex hormones and hormone antagonists in malignant disease

#### 8.3.1 Oestrogens

Diethylstilbestrol *(stilboestrol)* is sometimes used to treat prostate cancer, but it is not usually used first-line because of its side-effects. It is occasionally used in postmenopausal women with breast cancer. Toxicity is common and dose-related side-effects include nausea, fluid retention, and venous and arterial thrombosis. Impotence and gynaecomastia always occur in men, and withdrawal bleeding may be a problem in women. Hypercalcaemia and bone pain may also occur in breast cancer.

Ethynylestradiol *(ethinyloestradiol)* is the most potent oestrogen available; unlike other oestrogens it is only slowly metabolised in the liver. Ethynylestradiol is licensed for the palliative treatment of prostate cancer.

#### 8.3.2 Progestogens

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

Hormonal manipulation has an important role in the treatment of breast, prostate, and endometrial cancer, and a more marginal role in the treatment of hyperprolactaemia. These treatments are not curative, but may provide excellent palliation of symptoms in selected patients, sometimes for a period of years. Tumour response, and treatment toxicity should be carefully monitored and treatment changed if progression occurs or side-effects exceed benefit.

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

#### 8.3.1 Oestrogens

Diethylstilbestrol *(stilboestrol)* is sometimes used to treat prostate cancer, but it is not usually used first-line because of its side-effects. It is occasionally used in postmenopausal women with breast cancer. Toxicity is common and dose-related side-effects include nausea, fluid retention, and venous and arterial thrombosis. Impotence and gynaecomastia always occur in men, and withdrawal bleeding may be a problem in women. Hypercalcaemia and bone pain may also occur in breast cancer.

Ethynylestradiol *(ethinyloestradiol)* is the most potent oestrogen available; unlike other oestrogens it is only slowly metabolised in the liver. Ethynylestradiol is licensed for the palliative treatment of prostate cancer.

#### 8.3.2 Progestogens

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

#### 8.3.1 Oestrogens

#### 8.3.2 Progestogens

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

Hormonal manipulation has an important role in the treatment of breast, prostate, and endometrial cancer, and a more marginal role in the treatment of hyperprolactaemia. These treatments are not curative, but may provide excellent palliation of symptoms in selected patients, sometimes for a period of years. Tumour response, and treatment toxicity should be carefully monitored and treatment changed if progression occurs or side-effects exceed benefit.

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

#### 8.3.1 Oestrogens

#### 8.3.2 Progestogens

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

Hormonal manipulation has an important role in the treatment of breast, prostate, and endometrial cancer, and a more marginal role in the treatment of hyperprolactaemia. These treatments are not curative, but may provide excellent palliation of symptoms in selected patients, sometimes for a period of years. Tumour response, and treatment toxicity should be carefully monitored and treatment changed if progression occurs or side-effects exceed benefit.

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists

Hormonal manipulation has an important role in the treatment of breast, prostate, and endometrial cancer, and a more marginal role in the treatment of hyperprolactaemia. These treatments are not curative, but may provide excellent palliation of symptoms in selected patients, sometimes for a period of years. Tumour response, and treatment toxicity should be carefully monitored and treatment changed if progression occurs or side-effects exceed benefit.

#### 8.3.3 Androgens

#### 8.3.4 Hormone antagonists
**ETHINYLESTRADIOL (Ethinyloestradiol)**

**Indications** see notes above; other indications (section 6.4.1.1)

**Cautions** see section 6.4.1.1; interactions: Appendix 1 (oestrogens)

**Contra-indications** see section 6.4.1.1

**Side-effects** see section 6.4.1.1

**Dose**
- Breast cancer, 10–20 mg daily
- Prostate cancer, 1–3 mg daily

**Preparations**
- Tablets, diethylstilbestrol 1 mg, net price 28 = £39.68; 5 mg, 28 = £230.92

**NORETHISTERONE**

**Indications** see notes above; other indications (section 6.4.1.2)

**Cautions** see section 6.4.1.2 and notes above; interactions: Appendix 1 (progestogens)

**Contra-indications** see section 6.4.1.2 and notes above

**Side-effects** see section 6.4.1.2 and notes above

**Dose**
- Breast cancer, 40 mg daily, increased to 60 mg daily if required

**Preparations**
- Section 6.4.1.2

**8.3.2 Progestogens**

Progestogens have a role in the treatment of endometrial cancer; their use in breast cancer and renal cell cancer has declined. Progestogens are now rarely used to treat prostate cancer. **Medroxyprogesterone** or **megestrol** are usually chosen and can be given orally; high-dose or parenteral treatment cannot be recommended. Side-effects are mild but may include nausea, fluid retention, and weight gain.

**MEDROXYPROGESTERONE ACETATE**

**Indications** see notes above; contraception (section 7.3.2.2); other indications (section 6.4.1.2)

**Cautions** see section 6.4.1.2 and notes above; interactions: Appendix 1 (progestogens)

**Contra-indications** see section 6.4.1.2 and notes above

**Side-effects** see section 6.4.1.2 and notes above; glucocorticoid effects at high dose may lead to a cushingoid syndrome

**Dose**
- See preparations below

**Provera® (Pharmacia)**
- Tablets, medroxyprogesterone acetate 100 mg (scored), net price 60-tab pack = £29.98, 100-tab pack = £49.94; 200 mg (scored), 30-tab pack = £29.65, 400 mg, 30-tab pack = £58.67

**MEGESTROL ACETATE**

**Indications** see notes above

**Cautions** see under Medroxyprogesterone acetate (section 6.4.1.2) and notes above; interactions: Appendix 1 (progestogens)

**Contra-indications** see under Medroxyprogesterone acetate (section 6.4.1.2) and notes above

**Side-effects** see under Medroxyprogesterone acetate (section 6.4.1.2) and notes above

**Dose**
- Breast cancer, 160 mg daily in single or divided doses
- Endometrial cancer, 40–320 mg daily in divided doses

**Megace® (Bristol-Myers Squibb)**
- Tablets, scored, megestrol acetate 160 mg (off-white), 30-tab pack = £20.72

**8.3.3 Androgens**

Testosterone esters (section 6.4.2) have largely been superseded by other drugs for breast cancer.

**8.3.4 Hormone antagonists**

**8.3.4.1 Breast cancer**

The management of patients with breast cancer involves surgery, radiotherapy, drug therapy, or a combination of these.

For operable breast cancer, treatment before surgery (neoadjuvant therapy) reduces the size of the tumour and facilitates breast-conserving surgery; hormone antagonist therapy (e.g. letrozole) is chosen for steroid hormone-receptor-positive breast cancer and chemotherapy for steroid hormone-receptor-negative tumours or for younger women.

**Early breast cancer** All women should be considered for adjuvant therapy following surgical removal of the tumour. Adjuvant therapy is used to eradicate the micrometastases that cause relapses. Choice of adjuvant treatment is determined by the risk of recurrence, steroid hormone-receptor status of the primary tumour, and menopausal status.

Adjuvant therapy comprises either cytotoxic chemotherapy or hormone-antagonist therapy. Women with steroid hormone-receptor-positive breast cancer are considered for hormone-antagonist therapy (preceded by cytotoxic chemotherapy if necessary) whilst women with steroid hormone-receptor-negative breast cancer should be considered for cytotoxic chemotherapy.

The oestrogen-receptor antagonist tamoxifen is effective in premenopausal, perimenopausal, and postmenopausal women. The aromatase inhibitors anastrozole, exemestane, and letrozole are effective in postmenopausal women only. Adjuvant hormone antagonist therapy reduces the risk of cancer in the other breast and should generally be continued for 5 years following...
removal of the tumour. In those considered for extended adjuvant therapy, 5 years of tamoxifen is followed by an aromatase inhibitor such as letrozole for a further 3 years.

Trastuzumab is licensed for use in early breast cancer which overexpresses human epidermal growth factor-2 (HER2) in women who have received surgery, chemotherapy and radiotherapy (as appropriate). Premenopausal women may also benefit from treatment with a gonadorelin analogue or ovarian ablation.

**Advanced breast cancer** Tamoxifen is used in post-menopausal women with oestrogen-receptor-positive tumours, long disease-free interval following treatment for early breast cancer, and disease limited to bone or soft tissues. However, aromatase inhibitors, such as anastrozole or letrozole, may be more effective and are regarded as preferred treatment in postmenopausal women. Ovarian ablation or the gonadorelin analogue goserelin (Zoladex®) (section 8.3.4.2) should be considered in premenopausal women. Progestogens such as medroxyprogesterone acetate continue to have a role in postmenopausal women with advanced breast cancer. They are as effective as tamoxifen, but they are not as well tolerated; they are less effective than the aromatase inhibitors.

Cytotoxic chemotherapy is preferred for advanced steroid hormone-receptor-negative tumours and for aggressive disease, particularly where metastases involve visceral sites (e.g. the liver) or where the disease-free interval following treatment for early breast cancer is short.

**Chemoprevention** Recent evidence suggests that tamoxifen prophylaxis can reduce breast cancer in women at high risk of the disease. However, the adverse effects of tamoxifen preclude its routine use in most women.

**Cytotoxic drugs used in breast cancer** An anthracycline combined with fluorouracil (section 8.1.3) and cyclophosphamide (section 8.1.1), and sometimes also with methotrexate (section 8.1.3) is effective. Cyclophosphamide, methotrexate, and fluorouracil can be useful if an anthracycline is inappropriate (e.g. in cardiac disease).

**Metastatic disease** The choice of chemotherapy regimen will be influenced by whether the patient has previously received adjuvant treatment and the presence of any co-morbidity.

For women who have not previously received chemotherapy, an anthracycline such as doxorubicin or epirubicin combined with cyclophosphamide is the standard initial therapy for metastatic breast disease. Patients with anthracycline-refractory or resistant disease should be considered for treatment with a taxane (section 8.1.5) either alone or in combination with trastuzumab if they have tumours that overexpress HER2. Other cytotoxic drugs with activity against breast cancer include capecitabine (section 8.1.3), mitoxantrone, mitomycin (both section 8.1.2), and vinorelbine (section 8.1.4). Trastuzumab alone (section 8.1.5) is an option for chemotherapy-resistant cancers that overexpress HER2.

**Oestrogen-receptor antagonists**

**Tamoxifen** is an oestrogen-receptor antagonist that is licensed for breast cancer and anovulatory infertility (section 6.5.1).

**Fulvestrant** is licensed for the treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy.

**Toremifene** is licensed for steroid hormone-receptor-positive metastatic breast cancer in postmenopausal women, but it is not often used.

**Aromatase inhibitors** Aromatase inhibitors act predominantly by blocking the conversion of androgens to oestrogens in the peripheral tissues. They do not inhibit ovari an oestrogen synthesis and should not be used in premenopausal women.

**Anastrozole** and letrozole are non-steroidal aromatase inhibitors; exemestane is a steroidal aromatase inhibitor. Anastrozole and letrozole are at least as effective as tamoxifen for first-line treatment of metastatic breast cancer in postmenopausal women. However, it is not yet known whether the benefits of aromatase inhibitors persist over the long term.

The Scottish Medicines Consortium (p. 3) has advised (August 2005 and October 2006) that anastrozole (Arimidex®) is accepted for restricted use within NHS Scotland, within the licensed indications, for early breast cancer and early invasive breast cancer.

The Scottish Medicines Consortium (p. 3) has advised (October 2005) that exemestane (Aromasin®) is accepted for restricted use within NHS Scotland as an adjuvant treatment in postmenopausal women with oestrogen-receptor-positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy.

**Gonadorelin analogues** Goserelin (section 8.3.4.2), a gonadorelin analogue is licensed for the management of advanced breast cancer in premenopausal women.

**Other drugs used in breast cancer** Trilostane (section 6.7.3) is licensed for postmenopausal breast cancer. It is quite well tolerated but diarrhoea and abdominal discomfort may be a problem. Trilostane causes adrenal hypofunction and corticosteroid replacement therapy is needed.

The use of bisphosphonates (section 6.6.2) in patients with metastatic breast cancer may prevent skeletal complications of bone metastases.
pausal women following 2–3 years of tamoxifen therapy; advanced breast cancer in postmenopausal women which is oestrogen-receptor-positive or responsive to tamoxifen

Cautions laboratory test for menopause if doubt; susceptibility to osteoporosis (assess bone mineral density before treatment and at regular intervals)

Contra-indications pregnancy and breast-feeding; moderate or severe hepatic disease; moderate or severe renal impairment; not for premenopausal women

Side-effects hot flushes, vaginal dryness, vaginal bleeding, hair thinning, anorexia, nausea, vomiting, diarrhoea, headache, arthralgia, bone fractures, rash (including Stevens-Johnson syndrome); asthenia and drowsiness—may initially affect ability to drive or operate machinery; slight increases in total cholesterol levels reported; very rarely allergic reactions including angioedema and anaphylaxis

Dose

- 1 mg daily

Arimidex® (AstraZeneca) Tablets, f/c, anastrozole 1 mg. Net price 28-tab pack = £68.56

EXEMESTANE

Indications adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women following 2–3 years of tamoxifen therapy; advanced breast cancer in postmenopausal women in whom anti-oestrogen therapy has failed

Cautions hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (exemestane)

Contra-indications pregnancy and breast-feeding; not indicated for premenopausal women

Side-effects nausea, vomiting, abdominal pain, dyspepsia, constipation, anorexia; dizziness, fatigue, headache, depression, insomnia; hot flushes, sweating; fatigue, rash, less commonly drowsiness, asthenia, and peripheral oedema; rarely thrombocytopenia, leucopenia

Dose

- 25 mg daily

Aromasin® (Pharmacia) Tablets, s/c, exemestane 25 mg. Net price 30-tab pack = £88.80, 90-tab pack = £266.40. Label: 21

FULVестRANT

Indications treatment of oestrogen-receptor-positive metastatic or locally advanced breast cancer in postmenopausal women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy

Cautions hepatic impairment (avoid if severe; Appendix 2)

Contra-indications pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects hot flushes, nausea, vomiting, diarrhoea, anorexia, headache, back pain, rash, asthenia, venous thromboembolism, injection-site reactions, urinary-tract infections; less commonly vaginal haemorrhage, vaginal candidiasis, leucorrhoea, hypersensitivity reactions including angioedema, urticaria

Dose

- By deep intramuscular injection, 250 mg into gluteal muscle every 4 weeks

Faslodex® (AstraZeneca) Injection (oily), fulvestrant 50 mg/mL, net price 5-mL (250-mg) prefilled syringe = £348.27

LETROZOLE

Indications adjuvant treatment of oestrogen-receptor-positive early breast cancer in postmenopausal women; advanced breast cancer in postmenopausal women (including those in whom other anti-oestrogen therapy has failed); early invasive breast cancer in postmenopausal women after standard adjuvant tamoxifen therapy; pre-operative treatment in postmenopausal women with localised hormone-receptor-positive breast cancer to allow subsequent breast conserving surgery

Cautions renal impairment (Appendix 3); susceptibility to osteoporosis (assess bone mineral density before treatment and at regular intervals)

Contra-indications severe hepatic impairment; not indicated for premenopausal women; pregnancy (Appendix 4) and breast-feeding

Side-effects hot flushes, nausea, vomiting, fatigue, dizziness, headache, dyspepsia, constipation, diarrhoea, depression, anorexia, appetite increase, hypercholesterolaemia, alopecia, increased sweating, rash, peripheral oedema, musculoskeletal pain, osteoporosis, bone fracture; less commonly hypertension, palpitation, tachycardia, dyspnoea, cough, drowsiness, insomnia, anxiety, memory impairment, dysaesthesia, taste disturbance, pruritus, dry skin, urticaria, thrombophlebitis, abdominal pain, urinary frequency, urinary-tract infection, vaginal bleeding, vaginal discharge, breast pain, pyrexia, mucosal dryness, stomatitis, cataract, eye irritation, blurred vision, tumour pain, arthritis, leucopenia, general oedema; rarely pulmonary embolism, arterial thrombosis, cerebrovascular infarction

Dose

- 2.5 mg daily

Femara® (Novartis) Tablets, f/c, letrozole 2.5 mg. Net price 14-tab pack = £41.58, 28-tab pack = £83.16

TAMOXIFEN

Indications see under Dose and notes above; mastalgia [unlicensed indication] (section 6.7.2)

Cautions occasional cystic ovarian swellings in premenopausal women; increased risk of thromboembolic events when used with cytotoxics (see also below); breast-feeding (Appendix 5); endometrial changes (important: see below); porphyria (section 9.8.2); interactions: Appendix 1 (tamoxifen)

Endometrial changes Increased endometrial changes, including hyperplasia, polyps, cancer, and uterine sarcoma reported; prompt investigation required if abnormal vaginal bleeding including menstrual irregularities, vaginal discharge, and pelvic pain or pressure in those receiving (or who have received) tamoxifen.

Contra-indications pregnancy (exclude before commencing and advise non-hormonal contraception if appropriate—Appendix 4)

Side-effects hot flushes, vaginal bleeding and vaginal discharge (important: see also Endometrial Changes
under Cautions), suppression of menstruation in some premenopausal women, pruritus vulvae, gastro-intestinal disturbances, headache, light-headedness, tumour flare, decreased platelet counts; occasionally oedema, hypercalcaemia if bony metastases, alopecia, rashes, uterine fibroids; also visual disturbances (including corneal changes, cataracts, retinopathy); leucopenia (sometimes with anaemia and thrombocytoppenia), rarely neutropenia; hypertriglyceridaemia reported (sometimes with pancreatitis); thromboembolic events reported (see below); liver enzyme changes (rarely fatty liver, cholestasis, hepatitis); rarely interstitial pneumonitis, hypersensitivity reactions including angioedema, Stevens-Johnson syndrome, bullous pemphigoid; see also notes above.

**Risk of thromboembolism** Tamoxifen can increase the risk of thromboembolism particularly during and immediately after major surgery or periods of immobility. Patients should be made aware of the symptoms of thromboembolism and advised to report sudden breathlessness and any pain in the calf of one leg.

**Dose**
- Breast cancer, 20 mg daily
- CSA advice: The CSM has advised that tamoxifen in a dose of 20 mg daily substantially increases survival in early breast cancer, and that no further benefit has been demonstrated with higher doses. Patients should be told of the small risk of endometrial cancer (see under Cautions above) and encouraged to report relevant symptoms early. They can, however, be reassured that the benefits of treatment far outweigh the risks.
- Anovulatory infertility, 20 mg daily on days 2, 3, 4 and 5 of cycle; if necessary the daily dose may be increased to 40 mg then 80 mg for subsequent courses; if cycles irregular, start initial course on any day, with subsequent course starting 45 days later or on day 2 of cycle if menstruation occurs.

**Tamoxifen** (Non-proprietary) Tablets, tamoxifen (as citrate) 10 mg, net price 30-tab pack = £1.83; 20 mg, 30-tab pack = £1.90; 40 mg, 30-tab pack = £6.24.

Oral solution, tamoxifen (as citrate) 10 mg/5 mL, net price 150 mL = £29.61.

Brands include Soltamox.

**Nolvadex-D** (AstraZeneca) Tablets, tamoxifen (as citrate) 20 mg, net-price 30-tab pack = £8.71.

**TOREMIFENE**

**Indications** hormone-dependent metastatic breast cancer in postmenopausal women

**Cautions** hypercalcaemia may occur (especially if bone metastases and usually at beginning of treatment); interactions: Appendix 1 (toremifene)

**Endometrial changes** There is a risk of increased endometrial changes including hyperplasia, polyps and cancer. Abnormal vaginal bleeding including menstrual irregularities, vaginal discharge and symptoms such as pelvic pain or pressure should be promptly investigated.

**Contra-indications** endometrial hyperplasia, severe hepatic impairment (Appendix 2), history of severe thromboembolic disease; pregnancy and breast-feeding.

**Side-effects** hot flushes, vaginal bleeding or discharge (important: see also Cautions), dizziness, oedema, sweating, nausea, vomiting, chest or back pain, fatigue, headache, skin discoloration, weight increase, insomnia, constipation, dyspnoea, paresis, tremor, vertigo, pruritus, anorexia, corneal opacity (reversibility), asthenia; thromboembolic events reported; rarely dermatitis, alopecia, emotional lability, depression, jaundice, stiffness.

**Dose**
- 60 mg daily

**Fareston** (Orion) Tablets, toremifene (as citrate) 60 mg. Net price 30-tab pack = £30.37.

**8.3.4.2 Prostate cancer and gonadorelin analogues**

Metastatic cancer of the prostate usually responds to hormonal treatment aimed at androgen depletion. Standard treatments include bilateral subcapsular orchidectomy or use of a gonadorelin analogue (buserelin, goserelin, leuprolerein, or triptorelin). Response in most patients lasts for 12 to 18 months. No entirely satisfactory therapy exists for disease progression despite this treatment (hormone-refractory prostate cancer), but occasional patients respond to other hormone manipulation e.g. with an anti-androgen. Bone disease can often be palliated with irradiation or, if widespread, with strontium or prednisolone (section 6.3.2).

**Gonadorelin analogues**

Gonadorelin analogues are as effective as orchidectomy or diethylstilbestrol (section 8.3.1) but are expensive and require parenteral administration, at least initially. They cause initial stimulation then depression of luteinising hormone release by the pituitary. During the initial stage (1–2 weeks) increased production of testosterone may be associated with progression of prostate cancer. In susceptible patients this tumour ‘flare’ may cause spinal cord compression, ureteric obstruction or increased bone pain. When such problems are anticipated, alternative treatments (e.g. orchidectomy) or concomitant use of an anti-androgen such as cyproterone acetate or flutamide (see below) are recommended; anti-androgen treatment should be started 3 days before the gonadorelin analogue and continued for 3 weeks. Gonadorelin analogues are also used in women for breast cancer (section 8.3.4.1) and other indications (section 6.7.2).

**Cautions** Men at risk of tumour ‘flare’ (see above) should be monitored closely during the first month of therapy. Caution is required in patients with metabolic bone disease because reduced bone mineral density can occur. The injection site should be rotated.

**Side-effects** The gonadorelin analogues cause side-effects similar to the menopause in women and orchidectomy in men and include hot flushes and sweating, sexual dysfunction, vaginal dryness or bleeding, and gynaecomastia or changes in breast size. Signs and symptoms of prostate or breast cancer may worsen initially (managed in prostate cancer with anti-androgens, see above). Other side-effects include hypersensitivity reactions (rashes, pruritus, asthma, and rarely anaphylaxis), injection site reactions (see Cautions), headache (rarely migraine), visual disturbances, dizziness, arthralgia and possibly myalgia, hair loss, peripheral oedema, gastro-intestinal disturbances, weight changes, sleep disorders, and mood changes.
Anti-androgens

Cyproterone acetate, flutamide and bicalutamide are anti-androgens that inhibit the tumour ‘flare’ which may occur after commencing gonadorelin analogue administration. Cyproterone acetate and flutamide are also licensed for use alone in patients with metastatic prostate cancer refractory to gonadorelin analogue therapy. Bicalutamide is used for prostate cancer either alone or as an adjunct to other therapy, according to the clinical circumstances.

**BICALUTAMIDE**

**Indications** locally advanced prostate cancer at high risk of disease progression, either alone or as adjuvant treatment to prostatectomy or radiotherapy; locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention inappropriate; advanced prostate cancer in combination with gonadorelin analogue or surgical castration

**Cautions** hepatic impairment (Appendix 2), also consider periodic liver function tests; **interactions:** Appendix 1 (bicalutamide)

**Side-effects** nausea, diarrhoea, cholestasis, jaundice; asthenia, weight gain, gynaecomastia, breast tenderness, hot flushes, impotence, decreased libido; anaemia; alopecia, dry skin, hirsutism, pruritus; less commonly vomiting, abdominal pain, dyspepsia, interstitial lung disease, pulmonary fibrosis, depression, haematuria, thrombocytopenia, hypersensitivity reactions including angioneurotic oedema and urticaria; rarely cardiovascular disorders (including angina, heart failure, and arrhythmias), and hepatic failure

**Dose**

- Locally advanced prostate cancer at high risk of disease progression, 150 mg once daily
- Locally advanced, non-metastatic prostate cancer when surgical castration or other medical intervention inappropriate, 150 mg once daily
- Advanced prostate cancer, in combination with gonadorelin analogue or surgical castration, 50 mg once daily (started at the same time as surgical castration or at least 3 days before gonadorelin therapy, see also notes above)

**Note** The CSM has advised (October 2003) that bicalutamide should no longer be used for the treatment of localised prostate cancer

**Bicalutamide** (Non-proprietary) (AstraZeneca)

**Tablets**

- bicalutamide 50 mg, net price 28-tab pack = £114.92; 150 mg, 28-tab pack = £214.92
- Casodex® (AstraZeneca) (AstraZeneca)

**Tablets**

- f/c, bicalutamide 50 mg, net price 28-tab pack = £128.00; 150 mg, 28-tab pack = £240.00

**BUUSERELIN**

**Indications** advanced prostate cancer; other indications (section 6.7.2)

**Cautions** depression, see also notes above

**Side-effects** see notes above; worsening hypertension, palpitation, glucose intolerance, altered blood lipids, thrombocytopenia, leucopenia, nervousness, fatigue, memory and concentration disturbances, anxiety, increased thirst, hearing disorders, muscular-skeletal pain; nasal irritation, nose bleeds and altered sense of taste and smell (spray formulation only)

**CYPROTERONE ACETATE**

**Indications** prostate cancer, see under Dose and also notes above; other indications, see section 6.4.2

**Cautions** in prostate cancer, blood counts initially and throughout treatment; hepatic impairment (Appendix 2; see also under side-effects below); monitor hepatic function (liver function tests should be performed before treatment, see also under Side-effects below); monitor adrenocortical function regularly; risk of recurrence of thromboembolic disease; diabetes mellitus, sickle-cell anaemia, severe depression (in other indications some of these are contra-indicated, see section 6.4.2)

**Driving** Fatigue and lassitude may impair performance of skilled tasks (e.g. driving)

**Contra-indications** none in prostate cancer; for contra-indications relating to other indications see section 6.4.2

**Side-effects** see section 6.4.2

**Hepatotoxicity** Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (usually after several months) in patients treated with cyproterone acetate 200–300 mg daily. Liver function tests should be performed before and regularly during treatment and whenever symptoms suggestive of hepatotoxicity occur—if confirmed cyproterone should normally be withdrawn unless the hepatotoxicity can be explained by another cause such as metastatic disease (in which case cyproterone should be continued only if the perceived benefit exceeds the risk)

**Dose**

- Flare with initial gonadorelin therapy, 300 mg daily in 2–3 divided doses, reduced to 200 mg daily in 2–3 divided doses if necessary
- Long-term palliative therapy where gonadorelin analogue is contra-indicated, or where oral therapy preferred, 200–300 mg daily in 2–3 divided doses
- Hot flushes with gonadorelin therapy or after orchiectomy, initially 50 mg daily, adjusted according to response to 50–150 mg daily in 1–3 divided doses

**Cyproterone Acetate** (Non-proprietary) (Aventis Pharma) (Bayer)

**Tablets**

- cyproterone acetate 50 mg, net price 56-tab pack = £31.54; 100 mg, 84-tab pack = £77.50.
- Label: 21, counselling, driving

**Cypростat** (Bayer) (Bayer)

**Tablets**

- scored, cyproterone acetate 50 mg, net price 168-tab pack = £77.68; 100 mg, 84-tab pack = £77.68.
- Label: 21, counselling, driving

**FLUTAMIDE**

**Indications** advanced prostate cancer, see also notes above

**Dose**

- By subcutaneous injection, 500 micrograms every 8 hours for 7 days, then intranasally, 1 spray into each nostril 6 times daily (see also notes above)

**Counselling** Avoid use of nasal decongestants before and for at least 30 minutes after treatment.

**Suprefact®** (Aventis Pharma) (Aventis Pharma)

**Injection** buserelin (as acetate) 1 mg/mL. Net price 2 × 5.5-mL vial = £23.69

**Nasal spray** buserelin (as acetate) 100 micrograms/ metered spray. Net price treatment pack of 4 × 10-g bottle with spray pump = £87.68. Counselling, see above
Malignant disease and immunosuppression

**Cautions**
cardiac disease (oedema reported); hepatic impairment, also liver function tests, monthly for first 4 months, periodically thereafter and at the first sign or symptom of liver disorder (e.g. pruritus, dark urine, persistent anorexia, jaundice, abdominal pain, unexplained influenza-like symptoms); avoid excessive alcohol consumption; **interactions**: Appendix 1

**Side-effects**
gynaecostasia (sometimes with galactorrhea); nausea, vomiting, diarrhoea, increased appetite, insomnia, tiredness; other side-effects reported include decreased libido, reduced sperm count, gastric and chest pain, hypertension, headache, dizziness, oedema, blurred vision, thirst, rash, pruritus, haemolytic anaemia, systemic lupus erythematosus-like syndrome, and lymphoedema; hepatic injury (with transaminase abnormalities, cholestatic jaundice, hepatic necrosis, hepatic encephalopathy and occasional fatality) reported

**Dose**
- 250 mg 3 times daily (see also notes above)

**Flutamide**

(Flutamide)

**Indications**
locally advanced prostate cancer as an alternative to surgical castration; adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer; neoadjuvant treatment prior to radiotherapy in patients with high-risk localised or locally advanced prostate cancer; metastatic prostate cancer; advanced breast cancer; oestrogen-receptor-positive early breast cancer (section 8.3.4.1); endometriosis, endometrial thinning, uterine fibroids, assisted reproduction (section 6.7.2)

**Cautions**
see notes above; diabetes; risk of ureteric obstruction and spinal cord compression in men

**Contra-indications**
pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**
see notes above; also dry mouth, transient hyperglycaemia (in patients with metastatic breast cancer)

**Dose**
- See under preparations below

**Prostap® SR**

(Wyeth)

**Injection**
(microsphere powder for reconstitution), leuprolrelin acetate, net price 3.75-mg vial with 1-mL vehicle-filled syringe = £125.40

**Dose**
prostate cancer (see indications), by subcutaneous or by intramuscular injection, 3.75 mg every 4 weeks

**Prostap® 3**

(Wyeth)

**Injection**
(microsphere powder for reconstitution), leuprolrelin acetate, net price 11.25-mg vial with 2-mL vehicle-filled syringe = £376.20

**Dose**
prostate cancer (see indications), by subcutaneous injection, 11.25 mg every three months

**GOSERELIN**

**Indications**
locally advanced prostate cancer as an alternative to surgical castration; adjuvant treatment to radiotherapy or radical prostatectomy in patients with high-risk localised or locally advanced prostate cancer; metastatic prostate cancer; endometriosis, endometrial thinning, uterine fibroids (section 6.7.2)

**Cautions**
see notes above and section 6.7.2; risk of ureteric obstruction and spinal cord compression in men

**Contra-indications**
pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**
see notes above and section 6.7.2; also fatigue, muscle weakness, paraesthesia, hypertension, palpitation, alteration of glucose tolerance and of blood lipids; hypotension, jaundice, thrombocytopenia and leucopenia reported

**Dose**
- See under preparations below

**TRIPTORELIN**

**Indications**
prostate cancer; endometriosis, precocious puberty, reduction in size of uterine fibroids (section 6.7.2)

**Cautions**
see notes above; risk of ureteric obstruction and spinal cord compression in men

**Contra-indications**
pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects**
see notes above; also dry mouth, transient hypertension, paraesthesia, and increased dysuria

**Dose**
- See under preparations below

**Decapeptyl® SR**

(Ipsen)

**Injection**
(powder for suspension), m/r, triptorelin (as acetate), net price 3-mg vial with 1-mL vehicle-filled syringe = £169.00

**Dose**
locally advanced non-metastatic prostate cancer as an alternative to surgical castration, metastatic prostate cancer, by intramuscular injection, 3 mg every 4 weeks

**Note**
each vial includes an overage to allow accurate administration of a 3-mg dose

**Injection**
(powder for suspension), m/r, triptorelin (as acetate), net price 11.25-mg vial with 2-mL vehicle-filled syringe = £207.00

**Dose**
locally advanced non-metastatic prostate cancer as an alternative to surgical castration, metastatic prostate cancer, by intramuscular injection, 11.25 mg every 3 months (see also notes above)

**Note**
each vial includes an overage to allow accurate administration of an 11.25-mg dose

**Gonapente Depot®**

(Ferring)

**Injection**
(powder for suspension), triptorelin (as acetate), net price 3.75-mg prefilled syringe (with prefilled syringe of vehicle) = £85.00

**Dose**
advanced prostate cancer, by subcutaneous or deep intramuscular injection, 3.75 mg every 4 weeks (see also notes above)
8.3.4 Somatostatin analogues

**LANREOTIDE**

**Indications** see notes above

**Cautions** see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (lanreotide)

**Side-effects** see notes above; also reported asthenia, fatigue, raised bilirubin; less commonly skin nodule, hot flushes, leg pain, malaise, headache, tenesmus, decreased libido, drowsiness, pruritus, increased sweating; rarely hypothyroidism (monitor as necessary)

**Dose** 

- See under preparations

**Somatuline® LA** (Ipsen) (mixture)

**Injection** (copolymer microparticles for aqueous suspension), lanreotide (as acetate) 30-mg vial (with vehicle) = £340.00

**Dose** by intramuscular injection, acromegaly and neuroendocrine (particularly carcinoid) tumours, initially 30 mg every 14 days, frequency increased to every 7–10 days according to response

Thyroid tumours, 30 mg every 14 days, frequency increased to every 10 days according to response

**SANDOSTATIN®** (Novartis) (mixture)

**Injection** (microsphere powder for aqueous suspension), octreotide (as acetate) 10-mg vial = £637.50; 20-mg vial = £850.00; 30-mg vial = £1062.50 (all supplied with 2.5-mL diluent-filled syringe)

**Dose** acromegaly (test dose by subcutaneous injection) 50–100 micrograms if subcutaneous octreotide not previously given), neuroendocrine (particularly carcinoid) tumour adequately controlled by subcutaneous octreotide, by deep intramuscular injection into gluteal muscle, initially 20 mg every 4 weeks for 3 months then adjusted according to response, max. 30 mg every 4 weeks

For acromegaly, start depot octreotide 1 day after the last dose of subcutaneous octreotide (for pituitary surgery give last dose of depot octreotide at least 3 weeks before surgery); for neuroendocrine tumours, continue subcutaneous octreotide for 2 weeks after first dose of depot octreotide

---

**OCTREOTIDE**

**Indications** see under Dose

**Cautions** see notes above; hepatic impairment; pregnancy (Appendix 4); breast-feeding (Appendix 5); monitor thyroid function on long-term therapy; interactions: Appendix 1 (octreotide)

**Side-effects** see notes above; rarely altered liver function tests, hepatitis and transient alopecia

**Dose**

- Symptoms associated with carcinoid tumours with features of carcinoid syndrome, VIPomas, glucagonomas, by subcutaneous injection, initially 50 micrograms once or twice daily, gradually increased according to response to 200 micrograms 3 times daily (higher doses required exceptionally); maintenance doses variable; in carcinoid tumours discontinue after 1 week if no effect; if rapid response required, initial dose by intravenous injection (with ECG monitoring and after dilution to a concentration of 10–50% with sodium chloride 0.9% injection)

- Acromegaly, short-term treatment before pituitary surgery or long-term treatment in those inadequately controlled by other treatment or until radiotherapy becomes fully effective by subcutaneous injection, 100–200 micrograms 3 times daily; discontinue if no improvement within 3 months

- Prevention of complications following pancreatic surgery, consult product literature

---

**Somatuline AutoGel®** (Ipsen) **Injection**, prefilled syringe, lanreotide (as acetate) 60 mg = £573.00; 90 mg = £665.00; 120 mg = £989.00

**Dose** by deep subcutaneous injection into the gluteal region, acromegaly (if somatostatin analogue not given previously), initially 60 mg every 28 days, adjusted according to response; for patients treated previously with somatostatin analogue, consult product literature for initial dose

Neuroendocrine (particularly carcinoid) tumours, initially 60–120 mg every 28 days, adjusted according to response

---

**Somatuline®** (Ipsen) **Injection**, lanreotide (as acetate) 60 mg = £573.00; 90 mg = £665.00; 120 mg = £989.00

**Dose** by deep subcutaneous injection into the gluteal region, acromegaly (if somatostatin analogue not given previously), initially 60 mg every 28 days, adjusted according to response; for patients treated previously with somatostatin analogue, consult product literature for initial dose

Neuroendocrine (particularly carcinoid) tumours, initially 60–120 mg every 28 days, adjusted according to response

---

**Gallstones** have been reported after long-term treatment; hypoglycaemia has also been reported. Rarely, persistent hyperglycaemia occurs with chronic administration. Hypoglycaemia has also been reported. Gallstones have been reported after long-term treatment (abrupt withdrawal of short-acting octreotide—see Side-effects below). In insulinoma an increase in the depth and duration of hypoglycaemia may occur (observe patients when initiating treatment and changing doses). In diabetes mellitus, insulin or oral antidiabetic requirements may be reduced.

---

**SANDOSTATIN®** (Novartis) (mixture)

**Injection** (microsphere powder for aqueous suspension), octreotide (as acetate) 50 micrograms/mL, net price 1-mL amp = £3.72; 100 micrograms/mL, 1-mL amp = £6.53; 200 micrograms/mL 5-mL vial = £69.66; 500 micrograms/mL, 1-mL amp = £33.87

---

**Depot preparation**

**Sandostatin LAR®** (Novartis) (mixture)

**Injection** (microsphere powder for aqueous suspension), octreotide (as acetate) 10-mg vial = £637.50; 20-mg vial = £850.00; 30-mg vial = £1062.50 (all supplied with 2.5-mL diluent-filled syringe)

**Dose** acromegaly (test dose by subcutaneous injection) 50–100 micrograms if subcutaneous octreotide not previously given), neuroendocrine (particularly carcinoid) tumour adequately controlled by subcutaneous octreotide, by deep intramuscular injection into gluteal muscle, initially 20 mg every 4 weeks for 3 months then adjusted according to response, max. 30 mg every 4 weeks

For acromegaly, start depot octreotide 1 day after the last dose of subcutaneous octreotide (for pituitary surgery give last dose of depot octreotide at least 3 weeks before surgery); for neuroendocrine tumours, continue subcutaneous octreotide for 2 weeks after first dose of depot octreotide
Before initiating treatment for anaemia it is essential to determine which type is present. Iron salts may be harmful and result in iron overload if given alone to patients with anaemias other than those due to iron deficiency.

### 9.1.1 Iron-deficiency anaemias

#### 9.1.1.1 Oral iron

Iron salts should be given by mouth unless there are good reasons for using another route. Ferrous salts show only marginal differences between one another in efficiency of absorption of iron. Haemoglobin regeneration rate is little affected by the type of salt used provided sufficient iron is given, and in most patients the speed of response is not critical. Choice of preparation is thus usually decided by the incidence of side-effects and cost.
The oral dose of elemental iron for iron-deficiency anaemia should be 100 to 200 mg daily. It is customary to give this as dried ferrous sulphate, 200 mg (= 65 mg elemental iron) three times daily; for prophylaxis of iron-deficiency anaemia, a dose of ferrous sulphate 200 mg once or twice daily may be effective. For treatment of iron-deficiency anaemia in children and for prophylaxis of iron-deficiency anaemia in babies of low birth weight, see BNF for Children.

### Iron content of different iron salts

<table>
<thead>
<tr>
<th>Iron salt</th>
<th>Amount</th>
<th>Content of ferrous iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Ferrous sulphate</td>
<td>300 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Ferrous sulphate, dried</td>
<td>200 mg</td>
<td>65 mg</td>
</tr>
</tbody>
</table>

**Therapeutic response** The haemoglobin concentration should rise by about 100–200 mg/100 mL (1–2 g/litre) per day or 2 g/100 mL (20 g/litre) over 3–4 weeks. When the haemoglobin is in the reference range, treatment should be continued for a further 3 months to replenish the iron stores. Epithelial tissue changes such as atrophic glossitis and koilonychia are usually improved, but the response is often slow.

**Side-effects** Gastro-intestinal irritation can occur with iron salts. Nausea and epigastric pain are dose-related but the relationship between dose and altered bowel habit (constipation or diarrhoea) is less clear. Oral iron, particularly modified-release preparations, can exacerbate diarrhoea in patients with inflammatory bowel disease; care is also needed in patients with intestinal strictures and diverticular disease.

Iron preparations taken orally can be constipating, particularly in older patients and occasionally lead to faecal impaction.

If side-effects occur, the dose may be reduced; alternatively, another iron salt may be used but an improvement in tolerance may simply be a result of a lower iron content of different iron salts.

**Counselling** Although iron preparations are best absorbed on an empty stomach they may be taken after food to reduce gastro-intestinal side-effects; they may discolour stools.

**Compartment preparations** Preparations containing iron and folic acid are used during pregnancy in women who are at high risk of developing iron and folic acid deficiency; they should be distinguished from those used for the prevention of neural tube defects in women planning a pregnancy (see p. 508).

It is important to note that the small doses of folic acid contained in these preparations are inadequate for the treatment of megaloblastic anaemias. Some oral preparations contain ascorbic acid to aid absorption of the iron but the therapeutic advantage of such preparations is minimal and cost may be increased.

There is no justification for the inclusion of other ingredients, such as the B group of vitamins (except folic acid for pregnant women, see notes above and on p. 508).

### Modified-release preparations

Modified-release preparations of iron are licensed for once-daily dosage, but have no therapeutic advantage and should not be used. These preparations are formulated to release iron gradually; the low incidence of side-effects may reflect the small amounts of iron available for absorption as the iron is carried past the first part of the duodenum into an area of the gut where absorption may be poor.

#### FERROUS SULPHATE

**Indications** iron-deficiency anaemia

**Cautions** interactions: Appendix 1 (iron)

**Side-effects** see notes above

**Dose**
- See under preparations below and notes above

**Ferrograd Sulphate** (Non-proprietary)

| Tablets, coated, dried ferrous sulphate 200 mg (65 mg iron), net price 28-tab pack = £1.44 |

| Dose | ADULT and CHILD over 6 years, prophylactic, 0.6 mL daily; CHILD under 6 years, see BNF for Children |

**Ironorm** Drops (Wallace Mfg)

| Oral drops, ferrous sulphate 125 mg (25 mg iron)/mL, Net price 15-mL = £3.35 |

| Dose | ADULT and-child over 6 years, prophylactic, 0.6 mL daily; CHILD under 6 years, see BNF for Children |

**Ferrous Sulphate**

| Tablets, coated, dried ferrous sulphate 200 mg (65 mg iron), net price 28-tab pack = £1.44 |

| Dose | ADULT and CHILD over 6 years, prophylactic, 0.6 mL daily; CHILD under 6 years, see BNF for Children |

**With folic acid**

| Fefol® (Intrapharm) |

| Spansule® (= capsules m/r), clear/red, enclosing green and brown pellets, dried ferrous sulphate 150 mg (47 mg iron), Net price 30-cap pack = £1.65. |

| Dose | 1–2 capsule daily; CHILD over 1 year, 1 capsule daily; can be opened and sprinkled on food |

**With ascorbic acid**

| Ferrograd Folic® (Teofarma) |

| Tablets, f/c, m/r, red, dried ferrous sulphate 325 mg (105 mg iron) NET price 30-tab pack = £1.18. |

| Dose | ADULT and CHILD over 12 years, prophylactic and therapeutic, 1 tablet daily before food |

**With folic acid**

| Fefol® (Intrapharm) |

| Spansule® (= capsules m/r), clear/green, enclosing brown, yellow, and white pellets, dried ferrous sulphate 150 mg (47 mg iron), folic acid 500 micrograms. Net price 30-cap pack = £1.69. |

| Dose | 1 capsule daily |

**With ascorbic acid**

| Ferrograd Folic® (Teofarma) |

| Tablets, f/c, red/yellow, dried ferrous sulphate 325 mg (105 mg iron) for sustained release, folic acid 350 micrograms. Net price 30-tab pack = £1.32. |

| Dose | ADULT and CHILD over 12 years, 1 tablet daily before food |

**With folic acid**

| Fefol® (Intrapharm) |

| Spansule® (= capsules m/r), clear/green, enclosing brown, yellow, and white pellets, dried ferrous sulphate 150 mg (47 mg iron), folic acid 500 micrograms. Net price 30-cap pack = £1.69. |

| Dose | 1 capsule daily |

**With ascorbic acid**

| Ferrograd Folic® (Teofarma) |

| Tablets, f/c, red, dried ferrous sulphate 325 mg (105 mg iron) for sustained release, ascorbic acid 500 mg (as sodium salt). Net price 30-tab pack = £1.71. |

| Dose | ADULT and CHILD over 12 years, 1 tablet daily before food |
FERROUS FUMARATE

Indications  iron-deficiency anaemia

Cautions  interactions: Appendix 1 (iron)

Side-effects  see notes above

Dose
- See under preparations below and notes above

Fersaday® (Goldshield)

Tablets, brown, f/c, ferrous fumarate 322 mg (100 mg iron). Net price 28-tab pack = 79p
Dose  prophylactic, 1 tablet daily; therapeutic, 1 tablet twice daily

Fersamal® (Goldshield)

Tablets, brown, ferrous fumarate 210 mg (68 mg iron), net price 20 = 29p
Dose  prophylactic and therapeutic, 1–2 tablets 3 times daily, but see notes above

Syrup, brown, ferrous fumarate approx. 140 mg (45 mg iron)/5 mL, net price 200 mL = £3.11
Dose  prophylactic and therapeutic, 10–20 mL twice daily, but see notes above; CHILD see BNF for Children

Galfer® (Thornton & Ross)

Capsules, red/green, ferrous fumarate 305 mg (100 mg iron), net price 20 = 36p
Dose  ADULT and CHILD over 12 years, prophylactic, 1 capsule daily; therapeutic, 1 capsule twice daily

Syrup, brown, sugar-free ferrous fumarate 140 mg (45 mg iron)/5 mL, net price 300 mL = £4.86
Dose  ADULT and CHILD over 12 years, prophylactic, 10 mL once daily; therapeutic, 10 mL 1–2 times daily; PRETERM NEONATE and NEONATE, see BNF for Children, CHILD 1 month–12 years, prophylactic and therapeutic, 0.5 mL/kg/day in 2–3 divided doses; max. 20 mL/day

With folic acid

Galfer FA® (Thornton & Ross)

Capsules, red/yellow, ferrous fumarate 305 mg (100 mg iron), folic acid 350 micrograms. Net price 30-cap pack = £1.10
Dose  1 capsule daily before food

pregaday® (UCB Pharma)

Tablets, brown, f/c, ferrous fumarate equivalent to 100 mg iron, folic acid 350 micrograms. Net price 28-tab pack =£1.25
Dose  1 tablet daily

With vitamins B and C

Givitol® (Galen)

Capsules, red/maroon, ferrous fumarate 305 mg (100 mg iron) with vitamins B group and C. Net price 20 = 88p
Dose  1 capsule daily before food

FERROUS GLUCONATE

Indications  iron-deficiency anaemia

Cautions  interactions: Appendix 1 (iron)

Side-effects  see notes above

Dose
- See under preparations below and notes above

Ferrous Gluconate (Non-proprietary)

Tablets, red, coated, ferrous gluconate 300 mg (35 mg iron). Net price 20 = 73p
Dose  prophylactic, 2 tablets daily before food; therapeutic, 4–6 tablets daily in divided doses before food; CHILD 6–12 years, prophylactic and therapeutic, 1–3 tablets daily

POLYSACCHARIDE–IRON COMPLEX

Indications  iron-deficiency anaemia

Cautions  interactions: Appendix 1 (iron)

Side-effects  see notes above

Dose
- See under preparation below and notes above

Niferex® (TJomed)

Elixir, brown, sugar-free, polysaccharide–iron complex equivalent to 100 mg of iron/5 mL. Net price 240-mL pack = £8.06; 30-mL dropper bottle for paediatric use = £2.16. Counselling, use of dropper
Dose  prophylactic 2.5 mL daily; therapeutic, 5 mL 1–2 times daily (once daily if required during second and third trimester of pregnancy); PRETERM NEONATE, NEONATE, and INFANT (from dropper bottle) 1 drop (approx. 500 micrograms iron) per 450 g body-weight 3 times daily; CHILD 2–6 years 2.5 mL daily; 6–12 years 5 mL daily
1. except 30 mL paediatric dropper bottle for prophylaxis and treatment of iron deficiency in infants born prematurely; endorse prescription ‘SLS’

SODIUM FEREDETATE

(Sodium ironedetate)

Indications  iron-deficiency anaemia

Cautions  interactions: Appendix 1 (iron)

Side-effects  see notes above

Dose
- See under preparation below and notes above

Sytron® (Link)

Elixir, sugar free, sodium feredetate 190 mg equivalent to 27.5 mg of iron/5 mL, net price 100 mL = 89p
Dose  therapeutic, 5 mL increasing gradually to 10 mL 3 times daily; CHILD under 1 year, see BNF for Children; CHILD 1–5 years, therapeutic, 2.5 mL 3 times daily; 6–12 years, therapeutic; 5 mL 3 times daily

9.1.1.2 Parenteral iron

Iron can be administered parenterally as iron dextran, iron sucrose, or as ferric carboxymaltose. Parenteral iron is generally reserved for use when oral therapy is unsuccessful because the patient cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss, or in malabsorption. Parenteral iron may also have a role in the management of chemotherapy-induced anaemia, when given with erythropoietins, in specific patient groups (see NICE guidance, p. 510).

Many patients with chronic renal failure who are receiving haemodialysis (and some who are receiving peritoneal dialysis) also require iron by the intravenous route on a regular basis (see also Erythropoietins, section 9.1.3).

With the exception of patients with severe renal failure receiving haemodialysis, parenteral iron does not produce a faster haemoglobin response than oral iron provided that the oral iron preparation is taken reliably and is absorbed adequately.

Anaphylactoid reactions can occur with parenteral administration of iron complexes. Depending on the preparation, patients may be required to have a small test dose initially, see preparations for details; facilities for cardiopulmonary resuscitation must be available.
**FERRIC CARBOXYMALTOSE**
A ferric carboxymaltose complex containing 5% (50 mg/mL) of iron

**Indications** iron-deficiency anaemia, see notes above

**Cautions** hypersensitivity can occur with parenteral iron and facilities for cardiopulmonary resuscitation must be available; oral iron should not be given concomitantly; allergic disorders including asthma and eczema; injection (discontinue if ongoing bacteraemia); hepatic impairment (Appendix 2); pregnancy (Appendix 4)

**Side-effects** gastro-intestinal disturbances; headache, dizziness; rash, injection-site reactions; less commonly hypotension, flushing, chest pain, peripheral oedema, fatigue, paraesthesia, malaise, pyrexia, rigors, myalgia, arthralgia, back pain, pruritus, and urticaria

**Dose**  
- By slow intravenous injection or by intravenous infusion, ADULT and CHILD over 14 years, calculated according to body-weight and iron deficit, consult product literature

**Ferinject** (Syner-Med) ▼ (wh)

Injection, iron (as ferric carboxymaltose) 50 mg/mL, net price 2-mL vial = £21.75, 10-mL vial = £108.75

*Electrolytes Na 0.24 mmol/mL.*

**IRON DEXTRAN**
A complex of ferric hydroxide with dextran containing 5% (50 mg/mL) of iron

**Indications** iron-deficiency anaemia, see notes above

**Cautions** oral iron not to be given until 5 days after last injection; pregnancy (Appendix 4)  
**Anaphylaxis** Anaphylactic reactions can occur with parenteral iron and a test dose is recommended before each dose; the patient should be carefully observed for 60 minutes after the first test dose and for 15 minutes after subsequent test doses (subsequent test doses not necessary for intra-muscular administration). Facilities for cardiopulmonary resuscitation must be available; risk of allergic reactions increased in immune or inflammatory conditions

**Contra-indications** history of allergic disorders including asthma, eczema and anaphylaxis

**Side-effects** less commonly nausea, vomiting, abdominal pain, flushing, dyspnoea, anaphylactic reactions (see Anaphylaxis above), fatigue, asthenia, and paraesthesia; confusion, arthralgia, and increased sweating also reported

**Dose**  
- By slow intravenous injection or by intravenous infusion, calculated according to body-weight and iron deficit, consult product literature; CHILD not recommended

**Venofe®** (Syner-Med) ▼ (wh)

Injection, iron (as iron sucrose) 20 mg/mL, net price 5-mL amp = £7.08

**IRON SUCROSE**
A complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron

**Indications** iron-deficiency anaemia, see notes above

**Cautions** oral iron therapy should not be given until 5 days after last injection; infection (discontinue if ongoing bacteraemia); hepatic impairment (Appendix 2); pregnancy (Appendix 4)  
**Anaphylaxis** Anaphylactic reactions can occur with parenteral iron and a test dose is recommended before the first dose; the patient should be carefully observed for 15 minutes. Facilities for cardiopulmonary resuscitation must be available

**Contra-indications** history of allergic disorders including asthma, eczema and anaphylaxis

**Side-effects** taste disturbances; less commonly nausea, vomiting, abdominal pain, diarrhoea, hypotension, tachycardia, flushing, palpitation, chest pain, bronchospasm, dyspnoea, headache, dizziness, fever, myalgia, pruritus, rash, and injection-site reactions; rarely peripheral oedema, anaphylactic reactions (see Anaphylaxis above), fatigue, asthma, and paraesthesia; confusion, arthralgia, and increased sweating also reported

**Dose**  
- By slow intravenous injection or by intravenous infusion, calculated according to body-weight and iron deficit, consult product literature; CHILD not recommended

**9.1.2 Drugs used in megaloblastic anaemias**

Most megaloblastic anaemias result from a lack of either vitamin B12 or folate, and it is essential to establish in every case which deficiency is present and the underlying cause. In emergencies, when delay might be dangerous, it is sometimes necessary to administer both substances after the bone marrow test while plasma assay results are awaited. Normally, however, appropriate treatment should be instituted only when the results of tests are available.

One cause of megaloblastic anaemia in the UK is pernicious anaemia in which lack of gastric intrinsic factor resulting from an autoimmune gastritis causes malabsorption of vitamin B12. Vitamin B12 is also needed in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia, which inactivates the vitamin, and in the rare syndrome of congenital transcobalamin II deficiency.

Vitamin B12 should be given prophylactically after total gastrectomy or total ileal resection (or after partial gastrectomy if a vitamin B12 absorption test shows vitamin B12 malabsorption).

Apart from dietary deficiency, all other causes of vitamin B12 deficiency are attributable to malabsorption. There is little place for the use of low-dose vitamin B12 orally and none for vitamin B12 intrinsic factor complexes given by mouth. Vitamin B12 in larger oral doses of 1–2 mg daily [unlicensed] may be effective.
Hydroxocobalamin has completely replaced cyanocobalamin as the form of vitamin B of choice for therapy; it is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months. Treatment is generally initiated with frequent administration of intramuscular injections to replenish the depleted body stores. Thereafter, maintenance treatment, which is usually for life, can be instituted. There is no evidence that doses larger than those recommended provide any additional benefit in vitamin B neuropathy.

Folic acid has few indications for long-term therapy since most causes of folate deficiency are self-limiting or will yield to a short course of treatment. It should not be used in undiagnosed megaloblastic anaemia unless vitamin B is administered concurrently otherwise neuropathy may be precipitated (see above).

In folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy, or antiepileptic drugs), daily folic acid supplementation for 4 months brings about haematological remission and replenishes body stores. For prophylaxis in chronic haemolytic states, folate acid is given daily or sometimes weekly, depending on the diet and the rate of haemolysis.

For prophylaxis in pregnancy, see Prevention of Neural Tube Defects below.

Folinic acid is also effective in the treatment of folate-deficient megaloblastic anaemia but it is generally used in association with cytotoxic drugs (see section 8.1); it is given as calcium folinate.

Prevention of neural tube defects Folic acid supplements taken before and during pregnancy can reduce the occurrence of neural tube defects. The risk of a neural tube defect occurring in a child should be assessed and folic acid given as follows:

- Women at a low risk of conceiving a child with a neural tube defect should be advised to take folic acid as a medicinal or food supplement at a dose of 400 micrograms daily before conception and until week 12 of pregnancy. Women who have not been taking folic acid and who suspect they are pregnant should start at once and continue until week 12 of pregnancy.
- Couples are at a high risk of conceiving a child with a neural tube defect if either partner has a neural tube defect (or either partner has a family history of neural tube defects), if they have had a previous pregnancy affected by a neural tube defect, or if the woman has coeliac disease (or other malabsorption state), diabetes mellitus, sickle-cell anaemia, or is taking antiepileptic medicines (see also section 4.6.1).
- Women in the high risk group who wish to become pregnant (or who are at risk of becoming pregnant) should be advised to take folic acid 5 mg daily and continue until week 12 of pregnancy (women with sickle-cell disease should continue taking their normal dose of folic acid 5 mg daily throughout pregnancy).

There is no justification for prescribing multiple-ingredient vitamin preparations containing vitamin B or folic acid.

### HYDROXOCOBALAMIN

**Indications** see under dose below

**Cautions** should not be given before diagnosis fully established but see also notes above; **Interactions:** Appendix 1 (hydroxocobalamin)

**Side-effects** nausea, headache, dizziness; fever, hypersensitivity reactions including rash and pruritus; injection-site pain; hypokalaemia during initial treatment

**Dose**
- By intramuscular injection, pernicious anaemia and other macrocytic anaemias without neurological involvement, initially 1 mg 3 times a week for 2 weeks then 1 mg every 3 months
- Pernicious anaemia and other macrocytic anaemias with neurological involvement, initially 1 mg on alternate days until no further improvement, then 1 mg every 2 months
- Prophylaxis of macrocytic anaemias associated with vitamin B12 deficiency, 1 mg every 2–3 months
- Tobacco amylplia and Leber’s optic atrophy, initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, thereafter 1 mg every 1–3 months

**CHILD** see BNF for Children
- Cyanide poisoning [not licensed], see p. 34

### CYANOCOBALAMIN

**Indications** see notes above

**Dose**
- By mouth, vitamin B12 deficiency of dietary origin, 50–150 micrograms or more daily taken between meals; **CHILD** 50–105 micrograms daily in 1–3 divided doses
- By intramuscular injection, initially 1 mg repeated 10 times at intervals of 2–3 days, maintenance 1 mg every month, but see notes above

### CYANOCOBALAMIN

**Indications** see notes above

**Dose**
- By mouth, vitamin B12 deficiency of dietary origin, 50–150 micrograms or more daily taken between meals; **CHILD** 50–105 micrograms daily in 1–3 divided doses
- By intramuscular injection, initially 1 mg repeated 10 times at intervals of 2–3 days, maintenance 1 mg every month, but see notes above

**Cyanocobalamin** (Non-proprietary) 

**Injection**, hydroxocobalamin 1 mg/mL. Net price 1 mL amp = £2.46

**Note** The BP directs that when vitamin B12 injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied

**Brands** include Cobalin-H, Neo-Cytamen

**Cyanocobalamin** (Non-proprietary) 

**Tablets**, cyanocobalamin 50 micrograms. Net price 50-tab pack = £5.67

**Brands** include Cytamen

**Liquid**, cyanocobalamin 35 micrograms/5 mL. Net price 200 mL = £2.77

**Brands** include Cytamen

**Injection**, cyanocobalamin 1 mg/mL. Net price 1 mL amp = £1.67

**Brands** include Cytamen

**Note** The BP directs that when vitamin B12 injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied

1. **except to treat or prevent vitamin B12 deficiency in a patient who is a vegan or who has a proven vitamin B12 deficiency of dietary origin; endorse prescription ‘SLS’; currently available brands may not be suitable for vegans—cyanocobalamin injection may be a suitable alternative
FOLIC ACID

Indications see notes above and under dose

Cautions should never be given alone for pernicious anaemia and other vitamin-B deficiency states (may precipitate subacute combined degeneration of the spinal cord); interactions: Appendix 1 (folates)

Side-effects rarely gastro-intestinal disturbances

Dose

- Folate-deficient megaloblastic anaemia, by mouth, ADULT and CHILD over 1 year, 5 mg daily for 4 months (until term in pregnant women); up to 15 mg daily may be required in malabsorption states; maintenance, 5 mg every 1–7 days; CHILD under 1 year, 500 micrograms/kg daily for up to 4 months; maintenance 500 micrograms/kg every 1–7 days

- Prevention of neural tube defects, by mouth, see notes above

- Prevention of methotrexate-induced side-effects in rheumatic disease [unlicensed], by mouth, ADULT over 18 years 5 mg once weekly; CHILD 2–18 years see BNF for Children

- Prophylaxis in chronic haemolytic states, by mouth, ADULT 5 mg every 1–7 days depending on underlying disease

- Prophylaxis of folate deficiency in dialysis, by mouth, ADULT 5 mg every 1–7 days; CHILD 1–12 years 250 micrograms/kg (max. 10 mg) once daily, CHILD 12–18 years 5–10 mg once daily

Folic Acid (Non-proprietary) \( ^{\text{1}} \)

Tablets, folic acid 400 micrograms, net price 90-tab pack = £2.32; 5 mg, 28-tab pack = 88p

Syrup, folic acid 2.5 mg/5 mL, net price 150 mL = £9.16; 400 micrograms/5 mL, 150 mL = £1.40

Brands include Folicare, Lexpec (sugar-free)

Injection, folic acid 15 mg, net price 1-mL amp = £1.34

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 939

1. Can be sold to the public provided daily doses do not exceed 500 micrograms

Erythropoietins

Epoetins (recombinant human erythropoietins) are used to treat symptomatic anaemia associated with erythropoietin deficiency in chronic renal failure, to increase the yield of autologous blood in normal individuals and to shorten the period of symptomatic anaemia in patients receiving cytotoxic chemotherapy. Epoetin beta is also used for the prevention of anaemia in preterm neonates of low birth-weight; only unscreened formulations should be used in neonates because other preparations may contain benzyl alcohol (see Excipients, p. 2).

Darbepoetin, is a hyperglycosylated derivative of epoetin; it has a longer half-life and can be administered less frequently than epoetin.

Methodox polyethylene glycol-epoetin beta (pegzerepoetin alfa) is a continuous erythropoietin receptor activator that is licensed for the treatment of symptomatic anaemia associated with chronic kidney disease. It has a longer duration of action than epoetin.

Other factors, such as iron or folate deficiency, that contribute to the anaemia of chronic renal failure should be corrected before treatment and monitored during therapy. Supplemental iron may improve the response in resistant patients. Aluminium toxicity, concurrent infection, or other inflammatory disease can impair the response to erythropoietin.
9 Nutrition and blood

### 9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias

BNF 57

See also MHRA/CHM advice above.

See also MHRA/CHM advice below.

#### DARBEPOETIN ALFA

**Indications** see under Dose below

**Cautions** see Epoetin; hepatic disease; pregnancy (Appendix 4)

**Contra-indications** see Epoetin; breast-feeding (Appendix 5)

**Side-effects** see Epoetin; also, oedema, injection-site pain; isolated reports of pure red cell aplasia, particularly following subcutaneous administration in patients with chronic renal failure (discontinue therapy)—see also CSM advice above

**Dose**

- Symptomatic anaemia associated with chronic renal failure in patients on dialysis (see also MHRA/CHM advice, above), ADULT and CHILD over 11 years, by subcutaneous or intravenous injection, initially 450 nanograms/kg once weekly, adjusted according to response by approx. 25% at intervals of at least 4 weeks; maintenance dose, given once weekly or once every 2 weeks

- Symptomatic anaemia associated with chronic renal failure in patients not on dialysis (see also MHRA/CHM advice, above), ADULT and CHILD over 11 years, by subcutaneous or intravenous injection, initially 450 nanograms/kg once weekly or by subcutaneous injection, initially 750 nanograms/kg once every 2 weeks; adjusted according to response by approx. 25% at intervals of at least 4 weeks; maintenance dose, given subcutaneously or intravenously once weekly or subcutaneously once every 2 weeks or subcutaneously once every month

**Note** Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL; if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. When changing route give same dose then reduce by approx. 25% and then restart at a dose approximately 25% lower than the previous dose. When changing route give same dose then reduce by approx. 25% and then restart at a dose approximately 25% lower than the previous dose.

---

**MHRA/CHM advice (December 2007) Erythropoietins—haemoglobin concentration**

Overcorrection of haemoglobin concentration in patients with chronic kidney disease may increase the risk of thrombosis and related complications:

- patients should not be treated with erythropoietins for the licensed indications in chronic kidney disease or cancer in patients receiving chemotherapy unless symptoms of anaemia are present;
- the haemoglobin concentration should be maintained within the range 10–12 g/100 mL;
- haemoglobin concentrations higher than 12 g/100 mL should be avoided;
- the aim of treatment is to relieve symptoms of anaemia, and in patients with chronic kidney disease to avoid the need for blood transfusion; the haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia (in some patients, this may be achieved at concentrations lower than the recommended range).

See also MHRA/CHM advice above.

**MHRA/CHM advice (December 2007 and July 2008) Erythropoietins—tumour progression and survival in patients with cancer**

Clinical trial data show an unexplained excess mortality and increased risk of tumour progression in patients with anaemia associated with cancer who have been treated with erythropoietins. Many of these trials used erythropoietins outside of the licensed indications (i.e. overcorrected haemoglobin concentration or given to patients who have not received chemotherapy):

- erythropoietins licensed for the treatment of symptomatic anaemia associated with cancer, are licensed only for patients who are receiving chemotherapy;
- the decision to use erythropoietins should be based on an assessment of the benefits and risks for individual patients; blood transfusion may be the preferred treatment for anaemia associated with cancer chemotherapy, particularly in those with a good cancer prognosis.

See also MHRA/CHM advice above.

**CSM advice (pure red cell aplasia)**

There have been very rare reports of pure red cell aplasia in patients treated with epoetin alfa. The CSM has advised that in patients developing lack of efficacy with epoetin alfa, with a diagnosis of pure red cell aplasia, treatment with epoetin alfa must be discontinued and testing for erythropoietin antibodies considered. Patients who develop pure red cell aplasia should not be switched to another form of erythropoietin.

**NICE guidance**

Epoetin alfa, beta and darbepoetin alfa for cancer treatment-induced anaemia (May 2008)

Erythropoietin analogues are not recommended for routine use in the management of cancer treatment-induced anaemia, but may be considered, in combination with intravenous iron, for:

- women receiving platinum-based chemotherapy for ovarian cancer who have symptomatic anaemia with a haemoglobin concentration of 8 g/100 mL or lower (the use of erythropoietin analogues does not preclude the use of existing approaches to the management of anaemia, including blood transfusion when necessary);
- patients who cannot be given blood transfusions and who have profound cancer treatment-related anaemia that is likely to have an impact on survival.

Patients currently treated with erythropoietin analogues for the management of cancer treatment-related anaemia who do not fulfil the criteria outlined above can continue therapy until they and their specialists consider it appropriate to stop.
● Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy (see also MHRA/CHM advice, p. 510), by subcutaneous injection, initially 6.75 micrograms/kg once every 3 weeks or 2.25 micrograms/kg once weekly (if response inadequate after 9 weeks further treatment may not be effective); if adequate response obtained, reduce dose by 25–50%.

**Note** Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25–50% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

**Aranesp** (Amgen) ▼ \[514x492] Injection, prefilled syringe, darbepoetin alfa, 25 micrograms/mL, net price 0.4 mL (10 micrograms) = £15.59; 40 micrograms/mL, 0.375 mL (15 micrograms) = £23.38; 0.5 mL (20 micrograms) = £31.17; 100 micrograms/mL, 0.3 mL (30 micrograms) = £46.76; 0.4 mL (40 micrograms) = £62.34; 0.5 mL (50 micrograms) = £77.93; 200 micrograms/mL, 0.3 mL (60 micrograms) = £93.51; 0.4 mL (80 micrograms) = £124.68; 0.5 mL (100 micrograms) = £155.85; 0.65 mL (130 micrograms) = £202.61; 500 micrograms/mL, 0.3 mL (150 micrograms) = £233.78; 0.6 mL (300 micrograms) = £467.55, 1 mL (500 micrograms) = £779.25

**Injection** (Aranesp®SureClick), prefilled disposable injection device, darbepoetin alfa, 40 micrograms/mL, net price 0.5 mL (20 micrograms) = £31.17; 100 micrograms/mL, 0.4 mL (40 micrograms) = £62.34; 200 micrograms/mL, 0.3 mL (60 micrograms) = £93.51; 0.4 mL (80 micrograms) = £124.68; 0.5 mL (100 micrograms) = £155.85; 0.65 mL (130 micrograms) = £202.61; 500 micrograms/mL, 0.3 mL (150 micrograms) = £233.78; 0.6 mL (300 micrograms) = £467.55, 1 mL (500 micrograms) = £779.25

**EPOETIN ALFA, BETA, and ZETA** (Recombinant human erythropoietins)

**Note** The prescriber must specify which epoetin is required, see also Biosimilar medicines, p. 1

**Indications** see under preparations, below

**Cautions** see notes above; also inadequately treated or poorly controlled blood pressure (monitor closely blood pressure, reticuloocyte counts, haemoglobin, and electrolytes), interrupt treatment if blood pressure uncontrolled; sudden stabling mige-like pain is warning of hypertensive crisis; sickle-cell disease (lower target haemoglobin concentration may be appropriate), exclude other causes of anaemia (e.g. folic acid or vitamin B12 deficiency) and give iron supplements if necessary (see also notes above); ischaemic vascular disease; thrombocytosis (monitor platelet count for first 8 weeks); epilepsy; malignant disease; chronic liver failure (Appendix 2); increase in hepatic dose may be needed; risk of thrombosis may be increased when used for anaemia in adults receiving cancer chemotherapy; risk of thrombosis may be increased when used for anaemia before orthopaedic surgery—avoid in cardiovascular disease including recent myocardial infarction or cerebrovascular accident; pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Contra-indications** pure red cell aplasia following erythropoietin therapy (see also CSM advice above); uncontrollable hypertension; patients unable to receive thrombopoephilaxis; avoid injections containing benzyl alcohol in neonates (see under preparations, below)

**Side-effects** diarrhoea, nausea, vomiting; dose-dependent increase in blood pressure or aggravation of hypertension; in isolated patients with normal or low blood pressure, hypertensive crisis with encephalopathy-like symptoms and generalised tonic-clonic seizures requiring immediate medical attention; headache; dose-dependent increase in platelet count (but thrombocytosis rare) regressing during treatment; influenza-like symptoms (may be reduced if intravenous injection given over 5 minutes); cardiovascular events; shunt thrombosis especially if tendency to hypotension or arteriovenous shunt complications; very rarely sudden loss of efficacy because of pure red cell aplasia, particularly following subcaneous administration in patients with chronic renal failure (discontinue erythropoietin therapy)—see also CSM advice above; hyperkalaemia, hypersensitivity reactions (including anaphylaxis and angioedema), skin reactions, and peripheral oedema also reported

**Dose**

● See under preparations, below

**Epoetin alfa**

**Binocrit** (Sandoz) ▼ \[514x479\]

**Injection**, prefilled syringe, epoetin alfa, net price 1000 units = £5.09; 2000 units = £10.18; 3000 units = £15.27; 4000 units = £20.36; 5000 units = £25.46; 6000 units = £30.55; 8000 units = £40.73; 10 000 units = £50.91

**Note** Biosimilar medicine, p. 1

**Dose** symptomatic anaemia associated with chronic renal failure in patients on haemodialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes; for adults on haemodialysis, 50 units/kg 3 times weekly adjusted according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose, usually 25–100 units/kg 3 times weekly; **Child** by intravenous injection initially as for adults; maintenance dose, body-weight < 10 kg usually 75–150 units/kg 3 times weekly, body-weight 10–30 kg usually 60–150 units/kg 3 times weekly, body-weight > 30 kg usually 30–100 units/kg 3 times weekly Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes, initially; 450 units/kg once weekly, increased if appropriate rise in haemoglobin concentration (reticuloocyte count) not achieved after 4 weeks at higher dose

**Note** Avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks

Symptomatic anaemia in adults receiving cancer chemotherapy (see also MHRA/CHM advice, p. 510), by subcutaneous injection (max. 1 mL per injection site), initially 150 units/kg 3 times weekly (or 450 units/kg once weekly), increased if appropriate rise in haemoglobin concentration not achieved after 4 weeks to 300 units/kg 3 times weekly; discontinue if inadequate response after 4 weeks at higher dose

**Note** Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration exceeds 12 g/100 mL, if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then

**BNF 57**

9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias 511

**Nutrition and blood**
Intravenous route preferred; reduce dose by approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

Moderate anaemia (haemoglobin concentration decreases 100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable, by subcutaneous injection (max. 1 mL per injection site). Initially 50 units/kg 3 times weekly adjusted according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose, usually a total of 75–300 units/kg weekly (as a single dose or in divided doses); CHILD by intravenous injection initially 40 units/kg 3 times weekly; maintenance dose, body-weight over 10 kg usually 75–150 units/kg 3 times weekly, body-weight 10–30 kg usually 60–150 units/kg 3 times weekly, body-weight over 30 kg usually 30–100 units/kg 3 times weekly

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes or by subcutaneous injection (max. 1 mL per injection site), initially 50 units/kg twice weekly; maintenance dose 25–50 units/kg twice weekly

Severe symptomatic anaemia of renal origin in adults with renal insufficiency who cannot yet start on dialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes or by subcutaneous injection (max. 1 mL per injection site), initially 50 units/kg 3 times weekly increased according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose 17–33 units/kg 3 times weekly; max. 200 units/kg 3 times weekly

Note Intravenous route preferred; reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia in adults receiving cancer chemotherapy (see also MHRA/CHM advice, p. 510), by subcutaneous injection (max. 1 mL per injection site), initially 150 units/kg 3 times weekly (or 450 units/kg once weekly), increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks to 300 units/kg 3 times weekly; discontinue if inadequate response after 4 weeks at higher dose

Note Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery, by intravenous injection over 1–5 minutes, 600 units/kg twice weekly for 3 weeks before surgery; consult product literature for details and advice on ensuring high iron stores

Moderate anaemia (haemoglobin concentration decreases 10–13 g/100 mL) before elective orthopaedic surgery in adults with expected moderate blood loss to reduce exposure to allogeneic blood transfusion or if autologous transfusion unavailable, by subcutaneous injection (max. 1 mL per injection site). 600 units/kg every week for 3 weeks before surgery and on day of surgery or 300 units/kg daily for 15 days starting 10 days before surgery; consult product literature for details

Epoetin beta

Neorecormon® (Roche) (tm)

Injection, prefilled syringe, epoetin beta, net price 500 units = £3.90; 1000 units = £7.79; 2000 units = £15.59; 3000 units = £23.38; 4000 units = £31.17; 5000 units = £38.97; 6000 units = £46.76; 10 000 units = £77.93; 20 000 units = £155.87; 30 000 units = £233.81

Excipients include phenylalanine up to 300 micrograms/syringe (section 9.4)

Multidose injection, powder for reconstitution, epoetin beta, net price 50 000-unit vial = £419.01; 100 000-unit vial = £838.01 (both with solvent)

Excipients include phenylalanine up to 5 mg/vial (section 9.4.1), benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Note Avoid contact of reconstituted injection with glass; use only plastic materials

Reco-Pen, (for subcutaneous use), double-chamber cartridges (containing epoetin beta and solvent), net price 10 000-unit cartridge = £77.93; 20 000-unit cartridge = £155.87; for use with Reco-Pen injection device and needles (both available free from Roche)

Epoetin alpha, net price 50 000-unit vial = £383.01 (both with solvent)

Excipients include phenylalanine up to 5 mg/vial (section 9.4.1), benzyl alcohol (avoid in neonates, see Excipients, p. 2)

Dose symptomatic anaemia associated with chronic renal failure (see also MHRA/CHM advice, p. 510), by subcutaneous injection, ADULT and CHILD, initially 20 units/kg 3 times weekly for 4 weeks, increased according to response at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; total weekly dose may be divided into daily doses; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; weekly maintenance dose may be given as a single dose or in 3 or 7 divided doses, max. 720 units/kg weekly

By intravenous injection over 2 minutes, ADULT and CHILD, initially 40 units/kg 3 times weekly for 4 weeks, increased according to response to 80 units/kg 3 times weekly after 4 weeks, with further increases if needed at intervals of 4 weeks in steps of 20 units/kg 3 times weekly; maintenance dose, initially reduce dose by half then adjust according to response at intervals of 1–2 weeks; max. 720 units/kg weekly

Note Reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration approaches or exceeds 12 g/100 mL, if haemoglobin concentration continues to rise despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Subcutaneous route preferred in patients not on haemodialysis

Prevention of anaemia of prematurity in neonates with birth-weight of 0.75–1.5 kg and gestational age of less than 34 weeks, by subcutaneous injection (of single-dose, unpreserved injection), 250 units/kg 3 times weekly preferably starting within 3 days of birth and continued for 6 weeks

Symptomatic anaemia in adults with non-myeloid malignancies receiving chemotherapy (see also MHRA/CHM advice, p. 510), by subcutaneous injection (max. 1 mL per injection site), initially 150 units/kg 3 times weekly (or 450 units/kg once weekly), increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks to 300 units/kg 3 times weekly; discontinue if inadequate response after 4 weeks at higher dose

Note Discontinue treatment if haemoglobin concentration does not increase by at least 1 g/100 mL after 8 weeks of therapy (response unlikely). Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia when blood-conserving procedures are insufficient or unavailable, consult product literature

Epoetin zeta

Retacrit® ( Hospira ) ▼ (R)

Injection, prefilled syringe, epoetin zeta, net price 1000 units = £5.66; 2000 units = £11.31; 3000 units = £23.38; 4000 units = £31.17; 5000 units = £38.97; 6000 units = £46.76; 10 000 units = £77.93; 20 000 units = £155.87; 30 000 units = £233.81

Note Intravenous route preferred; reduce dose by approximately 25% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration continues to rise despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose.

Symptomatic anaemia in adults receiving cancer chemotherapy (see also MHRA/CHM advice, p. 510), by subcutaneous injection (max. 1 mL per injection site), initially 150 units/kg 3 times weekly (or 450 units/kg once weekly), increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks to 300 units/kg 3 times weekly; discontinue if inadequate response after 4 weeks at higher dose
Symptomatic anaemia associated with chronic kidney failure in patients on haemodialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes, initially 50 units/kg 3 times weekly adjusted according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose, usually 25–100 units/kg 3 times weekly.

CHILD

by intravenous injection initially as for adults; maintenance dose, body-weight under 10 kg usually 75–150 units/kg 3 times weekly, body-weight 10–30 kg usually 60–150 units/kg 3 times weekly, body-weight over 30 kg usually 30–100 units/kg 3 times weekly.

Symptomatic anaemia associated with chronic renal failure in adults on peritoneal dialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes, initially 50 units/kg 3 times weekly; maintenance dose 25–50 units/kg 3 times weekly.

Severe symptomatic anaemia of renal origin in adults with renal insufficiency not yet on dialysis (see also MHRA/CHM advice, p. 510), by intravenous injection over 1–5 minutes, initially 50 units/kg 3 times weekly increased according to response in steps of 25 units/kg 3 times weekly at intervals of at least 4 weeks; maintenance dose 17–33 units/kg 3 times weekly; max. 200 units/kg 3 times weekly.

Note

Avoid increasing haemoglobin concentration at a rate exceeding 2 g/100 mL over 4 weeks.

Symptomatic anaemia in adults receiving cancer chemotherapy (see also MHRA/CHM advice, p. 510), by subcutaneous injection (max. 1 mL per injection site), initially 150 units/kg 3 times weekly (or 450 units/kg once weekly), increased if appropriate rise in haemoglobin (or reticulocyte count) not achieved after 4 weeks to 300 units/kg 3 times weekly; discontinue if inadequate response after 4 weeks at higher dose.

Note

Reduce dose by approximately 25–50% if rise in haemoglobin concentration exceeds 2 g/100 mL over 4 weeks or if haemoglobin concentration increases 12 g/100 mL if haemoglobin concentration continues to rise, despite dose reduction, suspend treatment until haemoglobin concentration decreases and then restart at a dose approximately 25% lower than the previous dose. Discontinue approximately 4 weeks after ending chemotherapy.

To increase yield of autologous blood (to avoid homologous blood) in predonation programme in moderate anaemia either when large volume of blood required or when sufficient blood cannot be saved for elective major surgery, by intravenous injection over 1–5 minutes, 600 units/kg 3 times weekly for 3 weeks before surgery; consult product literature for details and advice on ensuring high iron stores.

Iron overload

Severe tissue iron overload can occur in aplastic and other refractory anaemias, mainly as the result of repeated blood transfusions. It is a particular problem in refractory anaemias with hyperplastic bone marrow, especially thalassaemia major, where excessive iron absorption from the gut and inappropriate iron therapy can add to the tissue siderosis.

Iron overload associated with haemochromatosis can be treated with repeated venesection. Venesection may also be used for patients who have received multiple transfusions and whose bone marrow has recovered. Where venesection is contra-indicated, the long-term administration of the iron chelating compound desferrioxamine mesilate is useful. Subcutaneous infusions of desferrioxamine are given over 8–12 hours, 3–7 times a week. The dose should reflect the degree of iron overload. For children starting therapy (and who have low iron overload) the dose should not exceed 30 mg/kg. For established overload the dose is usually between 20 and 50 mg/kg daily. Desferrioxamine (up to 2 g per unit of blood) may also be given at the time of blood transfusion, provided that the desferrioxamine is not added to the blood and is not given through the same line as the blood (but the two may be given through the same cannula).

Iron excretion induced by desferrioxamine is enhanced by administration of ascorbic acid (vitamin C, section 9.6.3) 200 mg daily by mouth (100 mg in infants); it should be given separately from food since it also enhances iron absorption. Ascorbic acid should not be given to patients with cardiac dysfunction; in patients with normal cardiac function ascorbic acid should be introduced 1 month after starting desferrioxamine.

Desferrioxamine infusion can be used to treat aluminium overload in dialysis patients; theoretically 100 mg of desferrioxamine binds with 4.1 mg of aluminium.

Deferasirox, an oral iron chelator, is licensed for the treatment of chronic iron overload in adults and children over 6 years with thalassaemia major who receive frequent blood transfusions (more than 7 mL/kg/month of packed red blood cells). It is also licensed for chronic iron overload when desferrioxamine is contra-indicated or inadequate in patients with thalassaemia major who...
9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias

**DEFERASIROX**

**Indications** see notes above

**Cautions** eye and ear examinations required before treatment and annually during treatment; monitor body-weight, height, and sexual development in children; test liver function before treatment, then every 2 weeks during the first month of treatment and monthly thereafter; test for proteinuria monthly; see also renal impairment (Appendix 3); measure baseline serum creatinine and monitor renal function weekly during the first month of treatment and monthly thereafter; test for proteinuria monthly; see also renal impairment (Appendix 3); pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (deferasirox)

**Side-effects** gastro-intestinal disturbances (including ulceration and haemorrhage); headache; proteinuria; pruritus, rash; less commonly, hepatitis, cholelithiasis, oedema, fatigue, anxiety, sleep disorder, dizziness, pyrexia, pharyngitis, glucosuria, renal tubulopathy, disturbances of hearing and vision (including lens opacity and maculopathy), and skin pigmentation; hepatic failure, acute renal failure, blood disorders (including agranulocytosis, neutropenia, and thrombocytopenia), hypersensitivity reactions (including anaphylaxis and angioedema) also reported

**Dose**
- **ADULT** and **CHILD** over 2 years initially 10–30 mg/kg once daily according to serum-ferritin concentration and amount of transfused blood (consult product literature); maintenance, adjust dose every 3–6 months in steps of 5–10 mg/kg according to serum-ferritin concentration; max. 30 mg/kg daily

**Exjade** (Novartis) ▼ (Swedish Orphan)

- **Dispersible tablets**, deferasirox 125 mg, net price 28-tab pack = £117.60; 250 mg, 28-tab pack = £235.20; 500 mg, 28-tab pack = £470.40. Label: 13, 22, counselling, administration
- **Counselling** Tablets may be dispersed in water, orange juice, or apple juice; if necessary resuspend residue

**DEFERIPRONE**

**Indications** see notes above

**Cautions** monitor neutrophil count weekly and discontinue treatment if neutropenia develops; monitor plasma-zinc concentration; hepatic impairment (Appendix 2); renal impairment (Appendix 3)

**Blood disorders** Patients or their carers should be told how to recognise signs of neutropenia and advised to seek immediate medical attention if symptoms such as fever or sore throat develop

**Contra-indications** history of agranulocytosis or recurrent neutropenia; pregnancy (contraception advised in women of child-bearing potential; important teratogenic risk: see Appendix 4); breast-feeding (Appendix 5)

**Side-effects** gastro-intestinal disturbances (reducing dose and increasing gradually may improve tolerance), increased appetite; headache; red-brown urine discoloration; neutropenia, agranulocytosis; zinc deficiency; arthropathy

**Dose**
- **ADULT** and **CHILD** over 6 years 25 mg/kg 3 times daily (max. 100 mg/kg daily)

**Ferriprox** (Swedish Orphan) ▼

- **Tablets**, f/c, scored, deferiprone 500 mg, net price 100-tab pack = £152.39. Label: 14, counselling, blood disorders
- **Oral solution**, red, deferiprone 100 mg/mL, net price 500 mL = £152.39. Label: 14, counselling, blood disorders

**DESFERRIOXAMINE MESILATE** (Deferoxamine Mesilate)

**Indications** see notes above; iron poisoning. see Emergency Treatment of Poisoning, p. 32

**Cautions** renal impairment; eye and ear examinations required before treatment and at 3-month intervals during treatment; monitor body-weight and height in children at 3-month intervals—risk of growth retardation with excessive doses; aluminium-related encephalopathy (may exacerbate neurological dysfunction); pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (deferoxamine)

**Side-effects** hypotension (especially when given too rapidly by intravenous injection), disturbances of hearing and vision (including lens opacity and retinopathy); injection-site reactions, gastro-intestinal disturbances, asthma, fever, headache, arthralgia and myalgia; very rarely, anaphylaxis, acute respiratory distress syndrome, neurological disturbances (including dizziness, neuropathy and paraesthesia), Yersinia and mucormycosis infections, rash, renal impairment, and blood dyscrasias

**Dose**
- **See notes above; iron poisoning. see Emergency Treatment of Poisoning, p. 32**

**Note** For full details and warnings relating to administration, consult product literature

**Desferrioxamine mesilate** (Non-proprietary) ▼

- **Injection**, powder for reconstitution, desferrioxamine mesilate, net price 500-mg vial = £4.26; 2-g vial = £17.05

**Desferal** (Novartis) ▼

- **Injection**, powder for reconstitution, desferrioxamine mesilate, net price 500-mg vial = £4.44; 2-g vial = £17.77

**Paroxysmal nocturnal haemoglobinuria**

Eculizumab, a recombinant monoclonal antibody, inhibits terminal complement activation at the C5 protein and thereby reduces haemolysis. It is licensed for the
treatment of paroxysmal nocturnal haemoglobinuria, a severe and disabling form of haemolytic anaemia.

ECULIZUMAB

Indications paroxysmal nocturnal haemoglobinuria (specialist use only)

Cautions active systemic infection; intravascular haemolysis—monitor serum lactate dehydrogenase during treatment and for at least 8 weeks after discontinuation

Meningococcal infection Vaccinate against Neisseria meningitidis at least 2 weeks before treatment (tetravalent vaccine against serotypes A, C, W135 and Y recommended); revaccinate according to current medical guidelines. Advise patient to report promptly any signs of meningococcal infection. Other immunisations should also be up to date (section 14.1)

Contra-indications unresolved Neisseria meningitidis infection; patients unvaccinated against Neisseria meningitidis (see Cautions above); known or suspected hereditary complement deficiencies; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects gastro-intestinal disturbances; nasopharyngitis, sinusitis, cough, pharyngolaryngeal pain, epistaxis; headache, fatigue, dizziness, insomnia; infection (including meningococcal infection), pyrexia, influenza-like symptoms; muscle cramp, pain in extremities; rash, pruritus

Dose

• By intravenous infusion, ADULT over 18 years, initially 600 mg once a week for 4 weeks, then 900 mg on week 5; maintenance, 900 mg once every 12–16 days

Soliris® (Alexion) ▼ Price

Concentrate for intravenous infusion, eculizumab 10 mg/mL, net price 30-mL vial = £3150.00. Counselling, meningococcal infection, patient information card

Electrolytes Na 5 mmol/vial

9.1.4 Drugs used in platelet disorders

Acute idiopathic thrombocytopenic purpura is usually self-limiting in children. In adults, idiopathic thrombocytopenic purpura can be treated with a corticosteroid, e.g. prednisolone 1 mg/kg daily, gradually reducing the dose over several weeks. Splenectomy is considered if a satisfactory platelet count is not achieved or if there is a relapse on reducing the dose of corticosteroid or withdrawing it.

Immunoglobulin preparations (section 14.5), are also used in idiopathic thrombocytopenic purpura or where a temporary rapid rise in platelets is needed, as in pregnancy or pre-operatively; they are also used for children often in preference to a corticosteroid. Anti-D (Rh) immunoglobulin (section 14.5) is effective in raising the platelet count in about 80% of unspalenectomised rhesus-positive individuals; its effects may last longer than normal immunoglobulin for intravenous use, but further doses are usually required.

Other therapy that has been tried in refractory idiopathic thrombocytopenic purpura includes azathioprine (section 8.2.1), cyclophosphamide (section 8.1.1), vincristine (section 8.1.4), cyclosporin (section 8.2.2), and danazol (section 6.7.2). Rituximab (section 8.2.3) may also be effective and in some cases induces prolonged remission. For patients with chronic severe thrombocytopenia refractory to other therapy, tranexamic acid (section 2.11) may be given to reduce the severity of haemorrhage.

Anagrelide inhibits platelet formation. It is licensed for essential thrombocytopenia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs.

ANAGRELIDE

Indications essential thrombocythaemia in at-risk patients who have not responded adequately to other therapy or who are intolerant of it (initiated under specialist supervision)

Cautions cardiac disease; assess cardiac function before and during treatment; concomitant aspirin in patients with a history of haemorrhage or severely raised platelet count; monitor full blood count (monitor platelet count every 2 days for 1 week, then weekly until maintenance dose established), liver function, serum creatinine and urea; hepatic impairment (Appendix 2); renal impairment (Appendix 3); interactions: Appendix 1 (anagrelide)

Driving Dizziness may affect performance of skilled tasks (e.g. driving)

Contra-indications pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects gastro-intestinal disturbances; palpitation, tachycardia, fluid retention; headache, dizziness, fatigue; anaemia; rash; less commonly pancreatitis, gastro-intestinal haemorrhage, congestive heart failure, hypertension, arrhythmias, syncope, chest pain, dyspnoea, sleep disturbances, paraesthesia, hypoaesthesia, depression, nervousness, confusion, amnesia, fever, weight changes, impotence, blood disorders, myalgia, arthritis, epistaxis, dry mouth, alopecia, skin discoloration, and pruritus; rarely gastrointestinal, colitis, postural hypotension, angina, myocardial infarction, vasodilatation, pulmonary hypertension, pulmonary infiltrates, migraine, drowsiness, impaired co-ordination, dysarthria, ashenha, tinnitus, renal failure, nocturia, visual disturbances, and gingival bleeding; allergic alveolitis also reported

Dose

• Initially 500 micrograms twice daily adjusted according to response in steps of 500 micrograms daily at weekly intervals to max. 10 mg daily (max. single dose 2.5 mg); usual dose range 1–3 mg daily in divided doses

Xagrid® (Shire) ▼ Price

Capsules, anagrelide (as hydrochloride), 500 micrograms, net price 100-cap pack = £337.14. Counselling, driving, see above

9.1.5 G6PD deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is highly prevalent in individuals originating from most parts of Africa, from most parts of Asia, from Oceania, and from Southern Europe; it can also occur, rarely, in any other individuals. G6PD deficiency is more common in males than it is in females.
Individuals with G6PD deficiency are susceptible to developing acute haemolytic anaemia on taking a number of common drugs. They are also susceptible to developing acute haemolytic anaemia upon ingestion of fava beans (broad beans, *Vicia faba*); this is termed favism and can be more severe in children or when the fresh fava beans are eaten raw.

When prescribing drugs for patients with G6PD deficiency, the following three points should be kept in mind:

- G6PD deficiency is genetically heterogeneous; susceptibility to the haemolytic risk from drugs varies; thus, a drug found to be safe in some G6PD-deficient individuals may not be equally safe in others;
- manufacturers do not routinely test drugs for their effects in G6PD-deficient individuals;
- the risk and severity of haemolysis is almost always dose-related.

The lists below should be read with these points in mind. Ideally, information about G6PD deficiency should be available before prescribing a drug listed below. However, in the absence of this information, the possibility of haemolysis should be considered, especially if the patient belongs to a group in which G6PD deficiency is common.

A very few G6PD-deficient individuals with chronic non-spherocytic haemolytic anaemia have haemolysis even in the absence of an exogenous trigger. These patients must be regarded as being at high risk of severe exacerbation of haemolysis following administration of any of the drugs listed below.

### Drugs with definite risk of haemolysis in most G6PD-deficient individuals

Dapsone and other sulphones (higher doses for dermatitis herpetiformis more likely to cause problems)

Methylthioninium chloride (methylene blue)

Niridazole (not on UK market)

Nitrofurantoin

Pamaquin [not on UK market]

Primaqune (30 mg weekly for 8 weeks has been found to be without undue harmful effects in African and Asian people, see section 5.4.1)

Quinolones (including ciprofloxacin, moxifloxacin, nalidixic acid, norfloxacin, and ofloxacin)

Sulphonamides (including co-trimoxazole; some sulphonamides, e.g. sulfadiazine, have been tested and found not to be haemolytic in many G6PD-deficient individuals)

### Drugs with possible risk of haemolysis in some G6PD-deficient individuals

Aspirin (acceptable up to a dose of at least 1 g daily in most G6PD-deficient individuals)

Chloroquine (acceptable in acute malaria and malaria chemoprophylaxis)

Menadione, water-soluble derivatives (e.g. menadiol sodium phosphate)

Probenecid [not on UK market]

Quinidine (acceptable in acute malaria) [not on UK market]

Quinine (acceptable in acute malaria)

Rasburicase

**Note** Naphthalene in mothballs also causes haemolysis in individuals with G6PD deficiency

### Recombinant human granulocyte-colony stimulating factor (rG-CSF)

Recombinant human granulocyte-colony stimulating factor (rhG-CSF) stimulates the production of neutrophils and may reduce the duration of chemotherapy-induced neutropenia and thereby reduce the incidence of associated sepsis; there is as yet no evidence that it improves overall survival. **Filgrastim** (unglycosylated rhG-CSF) and lenograstim (glycosylated rhG-CSF) have similar effects; both have been used in a variety of clinical settings but they do not have any clear-cut routine indications. In congenital neutropenia filgrastim usually elevates the neutrophil count with appropriate clinical response. Prolonged use may be associated with an increased risk of myeloid malignancy. **Pegfilgrastim** is a polyethylene glycol-conjugated (‘pegylated’) derivative of filgrastim; pegylation increases the duration of filgrastim activity.

Treatment with recombinant human growth factors should only be prescribed by those experienced in their use.

### Cautions

Recombinant human growth factors should be used with caution in patients with pre-malignant or malignant myeloid conditions. Full blood counts including differential white cell and platelet counts should be monitored. Treatment should be withdrawn in patients who develop signs of pulmonary infiltration. There have been reports of pulmonary infiltrates leading to acute respiratory distress syndrome—patients with a history of pulmonary infiltrates or pneumonia may be at higher risk. Splenic rupture following administration of granulocyte-colony stimulating factors has been reported—monitor spleen size. Recombinant human growth factors should be used with caution in patients with sickle-cell disease. Recombinant human growth factors are not recommended in pregnancy (Appendix 4) or breast-feeding (Appendix 5).

### Side-effects

Side-effects of granulocyte-colony stimulating factors include gastro-intestinal disturbances (including nausea, vomiting, and diarrhoea), anorexia, headache, asthenia, fever, musculoskeletal pain, bone pain, rash, alopecia, injection-site reactions, thrombocytopenia, and leucocytosis. *Less commonly* chest pain, hypersensitivity reactions (including anaphylaxis and bronchospasm) and arthralgia. *Rarely* pulmonary side-effects, particularly interstitial pneumonia, can occur (see Cautions above).

### Filgrastim

(Recombinant human granulocyte-colony stimulating factor, G-CSF)

**Indications** (specialist use only) reduction in duration of neutropenia and incidence of febrile neutropenia in cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes); reduction in duration of neutropenia (and associated sequelae) in myeloablative therapy followed by bone-marrow transplantation; mobilisation of peripheral blood progenitor cells for harvesting and subsequent autologous or allogeneic infusion; severe congenital neutropenia, cyclic neutropenia, or idio-
pathic neutropenia and history of severe or recurrent infections (distinguish carefully from other haematological disorders, consult product literature); persistent neutropenia in advanced HIV infection

**Cautions** see notes above; also reduced myeloid precursors; regular morphological and cytogenetic bone-marrow examinations recommended in severe congenital neutropenia (possible risk of myelodysplastic syndromes or leukaemia); secondary acute myeloid leukaemia, sickle-cell disease; monitor spleen size (risk of rupture); osteoporotic bone disease (monitor bone density if given for more than 6 months);

**interactions:** Appendix 1 (filgrastim)

**Contra-indications** severe congenital neutropenia (Kostmann’s syndrome) with abnormal cytogenetics

**Side-effects** see notes above; also splenic enlargement, hepatomegaly, transient hypotension, epistaxis, urinary abnormalities (including dysuria, proteinuria, and haematuria), osteoporosis, exacerbation of rheumatoid arthritis, acute febrile neutrophilic dermatosis, cutaneous vasculitis, anaemia, transient decrease in blood glucose, raised uric acid

**Dose**

- Cytotoxic-induced neutropenia, preferably by *subcutaneous injection* or *by intravenous infusion* (over 30 minutes), **ADULT** and **CHILD**, 500 000 units/kg daily started at least 24 hours after cytotoxic chemotherapy, continued until neutrophil count in normal range, usually for up to 14 days (up to 38 days in acute myeloid leukaemia)

- Myeloablative therapy followed by bone-marrow transplantation, by *intravenous infusion* over 30 minutes or over 24 hours or *by subcutaneous infusion* over 24 hours, 1 million units/kg daily, started at least 24 hours following cytotoxic chemotherapy (and within 24 hours of bone-marrow infusion), then adjusted according to neutrophil count (consult product literature)

- Mobilisation of peripheral blood progenitor cells for autologous infusion, used alone, by *subcutaneous injection* or *by subcutaneous infusion* over 24 hours, 1 million units/kg daily for 5–7 days; used following adjunctive myelosuppressive chemotherapy (to improve yield), *by subcutaneous injection*, 500 000 units/kg daily, started the day after completing chemotherapy and continued until neutrophil count in normal range; for timing of leucopheresis consult product literature

- Mobilisation of peripheral blood progenitor cells in normal donors for allogeneic infusion, by *subcutaneous injection*, **ADULT** under 60 years and **ADOLESCENT** over 16 years, 1 million units/kg daily for 4–5 days; for timing of leucopheresis consult product literature

- Severe chronic neutropenia, by *subcutaneous injection*, **ADULT** and **CHILD**, in severe congenital neutropenia, initially 1.2 million units/kg daily in single or divided doses (initially 500 000 units/kg daily in idiopathic or cyclic neutropenia), adjusted according to response (consult product literature)

- Persistent neutropenia in HIV infection, by *subcutaneous injection*, initially 100 000 units/kg daily, increased as necessary until neutrophil count in normal range (usual max. 400 000 units/kg daily), then adjusted to maintain neutrophil count in normal range (consult product literature)

---

**Neupogen®** (Amgen) (NH)

**Injection**, filgrastim 30 million-units (300 micro-grams)/mL, net price 1-mL vial = £68.41

**Injection** (*Singleject*®), filgrastim 60 million-units (600 micro-grams)/mL, net price 0.5-mL prefilled syringe = £68.41; 96 million-units (960 micro-grams)/mL, 0.5-mL prefilled syringe = £109.11

**Ratiogranstim®** (Ratiopharm UK) ▼ (NH)

**Injection**, prefilled syringe, filgrastim, net price 30 million-units (300 micrograms)/0.5 mL = £62.25; 48 million-units (480 micrograms)/0.8 mL = £99.29

**Note** Biosimilar medicine, p. 1

---

**LENOGRASTIM** (Recombinant human granulocyte-colony stimulating factor, rHuG-CSF)

**Indications** (specialist use only) reduction in the duration of neutropenia and associated complications following peripheral stem cells or bone-marrow transplantation for non-myeloid malignancy, or following treatment with cytotoxic chemotherapy associated with a significant incidence of febrile neutropenia; mobilisation of peripheral blood progenitor cells for harvesting and subsequent infusion

**Cautions** see notes above; also pre-malignant myeloid conditions; reduced myeloid precursors; sickle cell disease; monitor spleen size (risk of rupture)

**Side-effects** see notes above; also splenic rupture, cutaneous vasculitis, acute febrile neutrophilic dermatosis, toxic epidermal necrolysis

**Dose**

- Following peripheral stem cells or bone-marrow transplantation, by *intravenous infusion* or *by subcutaneous injection*, **ADULT** and **CHILD** over 2 years 19.2 million units/m daily started the day after transplantation, continued until neutrophil count stable in acceptable range (max. 28 days)

- Cytotoxic-induced neutropenia, *by subcutaneous injection*, **ADULT** 19.2 million units/m daily started the day after completion of chemotherapy, continued until neutrophil count stable in acceptable range (max. 28 days)

- Mobilisation of peripheral blood progenitor cells, used alone, *by subcutaneous injection*, **ADULT** 1.28 million units/kg daily for 4–6 days (5–6 days in healthy donors); used following adjunctive myelosuppressive chemotherapy (to improve yield), *by subcutaneous injection*, 19.2 million units/m daily, started 1–5 days after completion of chemotherapy and continued until neutrophil count in acceptable range; for timing of leucopheresis consult product literature

**Granocyte®** (Chugai) (NH)

**Injection**, powder for reconstitution, lenograstim, net price 13.4 million-unit (105-microgram) vial = £42.00; 33.6 million-unit (263-microgram) vial = £67.09 (both with 1-mL prefilled syringe water for injections)

**Excipients** include phenylalanine (section 9.4.1)

**PEGFILGRASTIM** (Pegylated recombinant methionyl human granulocyte-colony stimulating factor)

**Indications** (specialist use only) reduction in duration of neutropenia and incidence of febrile neutropenia in
corticosteroids, hormone therapy, cytotoxic chemotherapy for malignancy (except chronic myeloid leukaemia and myelodysplastic syndromes)

**Cautions** see notes above; also acute leukaemia and myelosuppressive chemotherapy; sickle-cell disease; monitor spleen size (risk of rupture); **interactions**: Appendix 1 (filgrastim)

**Side-effects** see notes above; also very rarely acute febrile neutrophilic dermatosis, cutaneous vasculitis, and splenic rupture

**Dose**

**Note** Dose expressed as filgrastim.

- By subcutaneous injection, **ADULT** over 18 years, 6 mg (0.6 mL) for each chemotherapy cycle, starting 24 hours after chemotherapy

Neulasta® (Amgen) Injection, pegfilgrastim (expressed as filgrastim) 10 mg/mL, net price 0.6-mL (6-mg) prefilled syringe = £714.24; SureClick® prefilled disposable injection device 0.6 mL (6 mg) = £714.24

### 9.2 Fluids and electrolytes

**9.2.1 Oral preparations for fluid and electrolyte imbalance**

Sodium and potassium salts, which may be given by mouth to prevent deficiencies or to treat established deficiencies of mild or moderate degree, are discussed in this section. Oral preparations for removing excess potassium and preparations for oral rehydration therapy are also included here. Oral bicarbonate, for metabolic acidosis, is also described in this section.

For reference to calcium, magnesium, and phosphate, see section 9.5.

**9.2.1.1 Oral potassium**

Compensation for potassium loss is especially necessary:

- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmias;
- in patients in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, cirrhosis of the liver, the nephrotic syndrome, and severe heart failure;
- in patients with excessive losses of potassium in the faeces, e.g. chronic diarrhoea associated with intestinal malabsorption or laxative abuse.

Measures to compensate for potassium loss may also be required in the elderly since they frequently take inadequate amounts of potassium in the diet (but see below for warning on renal insufficiency). Measures may also be required during long-term administration of drugs known to induce potassium loss (e.g. corticosteroids). Potassium supplements are **seldom required** with the small doses of diuretics given to treat hypertension; **potassium-sparing diuretics** (rather than potassium supplements) are recommended for prevention of hypokalaemia due to diuretics such as furosemide (fruse-
Dose
If potassium salts are used for the prevention of hypokalaemia, then doses of potassium chloride 2 to 4 g (approx. 25 to 50 mmol) daily (in divided doses) by mouth are suitable in patients taking a normal diet. Smaller doses must be used if there is renal insufficiency (common in the elderly) otherwise there is danger of hyperkalaemia. Potassium salts cause nausea and vomiting therefore poor compliance is a major limitation to their effectiveness; where appropriate, potassium-sparing diuretics are preferable (see also above).

Regular monitoring of plasma-potassium concentration is essential in those receiving potassium supplements. When there is established potassium depletion larger doses may be necessary, the quantity depending on the severity of any continuing potassium loss (monitoring of plasma-potassium concentration and specialist advice would be required). Potassium depletion is frequently associated with chloride depletion and with metabolic alkalosis, and these disorders require correction.

Administration
Potassium salts are preferably given as a liquid (or effervescent) preparation, rather than modified-release tablets; they should be given as the chloride (the use of effervescent potassium tablets BPC 1968 should be restricted to hyperchloraemic states, section 9.2.1.3).

Salt substitutes
A number of salt substitutes which contain significant amounts of potassium chloride are readily available as health food products (e.g. LoSalt and Ruthmol). These should not be used by patients with renal failure as potassium intoxication may result.

POLYSTYRENE SULPHONATE RESINS
Indications
hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients

Cautions
children (impaction of resin with excessive dosage or inadequate dilution); monitor for electrolyte disturbances (stop if plasma-potassium concentration below 5 mmol/litre); pregnancy and breast-feeding; sodium-containing resin in congestive heart failure, hypertension, renal impairment, and oedema; interactions: Appendix 1 (polystyrene sulphonate resins)

Contra-indications
obstructive bowel disease; oral administration or reduced gut motility in neonates; avoid calcium-containing resin in hyperparathyroidism, multiple myeloma, sarcoidosis, or metastatic carcinoma

Side-effects
rectal ulceration following rectal administration; colonic necrosis reported following enemas containing sorbitol; sodium retention, hypercalcaemia, gastric irritation, anorexia, nausea and vomiting, constipation (discontinue treatment—avoid magnesium-containing laxatives), diarrhoea; calcium-containing resin can cause hypercalcaemia (in dialysed patients and occasionally in those with renal impairment), hypomagnesaemia

Dose
• By mouth, 15 g 3–4 times daily in water (not fruit squash which has a high potassium content) or as a paste; CHILD 0.5–1 g/kg daily in divided doses
• By rectum, as an enema, 30 g in methylcellulose solution, retained for 9 hours followed by irrigation to remove resin from colon; NEONATE and CHILD, 0.5–1 g/kg daily

Management of hyperkalaemia
Acute severe hyperkalaemia (plasma-potassium concentration above 6.5 mmol/L or in the presence of ECG changes) calls for urgent treatment with 10–20 mL of calcium gluconate 10% by slow intravenous injection, titrated and adjusted to ECG improvement, to temporarily protect against myocardial excitability. An intravenous injection of soluble insulin (5–10 units) with 50 mL glucose 50% given over 5–15 minutes, reduces serum-potassium concentration; this is repeated if necessary or a continuous infusion instituted. The correction of causal or complicating acidosis with sodium bicarbonate infusion (section 9.2.2) should be considered (important: preparations of sodium bicarbonate and calcium salts should not be administered in the same line—risk of precipitation). Drugs exacerbating hyperkalaemia should be reviewed and stopped as appropriate; occasionally haemodialysis is needed.

Ion-exchange resins may be used to remove excess potassium in mild hyperkalaemia or in moderate hyperkalaemia when there are no ECG changes.

Modifying-release preparations
Avoid unless effervescent tablets or liquid preparations inappropriate

Slow-K® (Alliance) Tablets, m/r, orange, s/c, potassium chloride 600 mg (8 mmol each of K⁺ and Cl⁻). Net price 20 = 54p.
Label: 25, 27, counselling, swallow whole with fluid during meals while sitting or standing.
9.2.1 Oral preparations for fluid and electrolyte imbalance  

**Calcium Resonium®** (Sanofi-Synthelabo)  
**Powder**, buff, calcium polystyrene sulphonate. Net price 300 g = £47.55. Label: 13  
**Resonium A®** (Sanofi-Synthelabo)  
**Powder**, buff, sodium polystyrene sulphonate. Net price 454 g = £70.24. Label: 13

### 9.2.1.2 Oral sodium and water

Sodium chloride is indicated in states of sodium depletion and usually needs to be given intravenously (section 9.2.2). In chronic conditions associated with mild or moderate degrees of sodium depletion, e.g. in salt-losing bowel or renal disease, oral supplements of sodium chloride or sodium bicarbonate (section 9.2.1.3), according to the acid-base status of the patient, may be sufficient.

**SODIUM CHLORIDE**

**Indications** sodium depletion—see also 9.2.2.1; nebuliser diluent (section 3.1.5); eye (section 11.8.1); oral hygiene (section 12.3.4); wound irrigation (section 13.11.1)

**Slow Sodium®** (HK Pharma)  
**Tablets**, m/r, sodium chloride 600 mg (approx. 10 mmol each of Na⁺ and Cl⁻). Net price 100-tab pack = £6.05. Label: 25

**Dose** prophylaxis of sodium chloride deficiency 4–8 tablets daily with water (in severe depletion up to max. 20 tablets daily). Chronic renal salt wasting, up to 20 tablets daily with appropriate fluid intake

**CHILD** see BNF for Children

### Oral rehydration therapy (ORT)

As a worldwide problem *diarrhoea* is by far the most important indication for fluid and electrolyte replacement. Intestinal absorption of sodium and water is enhanced by glucose (and other carbohydrates). Replacement of fluid and electrolytes lost through diarrhoea can therefore be achieved by giving solutions containing sodium, potassium, and glucose or another carbohydrate such as rice starch.

**Oral rehydration solutions should:**

- enhance the absorption of water and electrolytes;
- replace the electrolyte deficit adequately and safely;
- contain an alkalinising agent to counter acidosis;
- be slightly hypo-osmolar (about 250 mmol/litre) to enhance the absorption of water and electrolytes;
- prevent the possible induction of osmotic diarrhea;
- be simple to use in hospital and at home;
- be palatable and acceptable, especially to children;
- be readily available.

It is the policy of the World Health Organization (WHO) to promote a single oral rehydration solution but to use it flexibly (e.g. by giving extra water between drinks of oral rehydration solution to moderately dehydrated infants).

**Oral rehydration solutions used in the UK are lower in sodium (50–60 mmol/litre) than the WHO formulation since, in general, patients suffer less severe sodium loss.**

Rehydration should be rapid over 3 to 4 hours (except in hypernatraemic dehydration in which case rehydration should occur more slowly over 12 hours). The patient should be reassessed after initial rehydration and if still dehydrated rapid fluid replacement should continue.

Once rehydration is complete further dehydration is prevented by encouraging the patient to drink normal volumes of an appropriate fluid and by replacing continuing losses with an oral rehydration solution; in infants, breast-feeding or formula feeds should be offered between oral rehydration drinks.

For intravenous rehydration see section 9.2.2.

### ORAL REHYDRATION SALTS (ORS)

**Indications** fluid and electrolyte loss in diarrhoea, see notes above

**Dose**  
- According to fluid loss, usually 200–400 mL solution after every loose motion; **INFANT** 1–1½ times usual feed volume; **CHILD** 200 mL after every loose motion

**UK formulations**  
**Note** After reconstitution any unused solution should be discarded no later than 1 hour after preparation unless stored in a refrigerator when it may be kept for up to 24 hours

**Dioralyte®** (Sanofi-Aventis)  
**Oral powder**, sodium chloride 470 mg, potassium chloride 300 mg, disodium hydrogen citrate 530 mg, glucose 3.56 g/sachet, net price 6-sachet pack = £2.11. 20-sachet pack (black currant- or citrus-flavoured or natural) = £6.99

**Note** Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets reconstituted with 1 litre of water provide Na 60 mmol, K 20 mmol, Cl 60 mmol, citrate 10 mmol, and glucose 90 mmol

**Dioralyte® Relief** (Sanofi-Aventis)  
**Oral powder**, sodium chloride 350 mg, potassium chloride 300 mg, sodium citrate 580 mg, cooked rice powder 6 g/sachet, net price 6-sachet pack (apricot-, black currant- or raspberry-flavoured) = £2.35. 20-sachet pack (apricot-flavoured) = £7.42

**Note** Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na 60 mmol, K 20 mmol, Cl 60 mmol, citrate 10 mmol, and glucose 91 mmol

**Electrolade®** (Actavis)  
**Oral powder**, sodium chloride 236 mg, potassium chloride 300 mg, sodium bicarbonate 500 mg, anhydrous glucose 4 g/sachet (banana-, black currant-, lemon and lime-, or orange-flavoured). Net price 6-sachet pack (plain or multiflavoured) pack = £1.33. 20-sachet pack (single- or multiflavoured) pack = £4.99

**Note** Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na 50 mmol, K 20 mmol, Cl 40 mmol, HCO₂ 30 mmol, and glucose 111 mmol

**Rapolyte®** (KoGEN)  
**Oral powder**, sodium chloride 350 mg, potassium chloride 300 mg, sodium citrate 600 mg, anhydrous glucose 4 g, net price 20-sachet pack (black currant- or raspberry-flavoured) = £4.28

**Note** Reconstitute 1 sachet with 200 mL of water (freshly boiled and cooled for infants); 5 sachets when reconstituted with 1 litre of water provide Na 60 mmol, K 20 mmol, Cl 50 mmol, citrate 10 mmol, and glucose 110 mmol
9.2.2 Parenteral preparations for fluid and electrolyte imbalance

9.2.2.1 Electrolytes and water

Solutions of electrolytes are given intravenously, to meet normal fluid and electrolyte requirements or to replenish substantial deficits or continuing losses, when the patient is nauseated or vomiting and is unable to take adequate amounts by mouth. When intravenous administration is not possible, fluid (as sodium chloride 0.9% or glucose 5%) can also be given by subcutaneous infusion (hypodermoclysis).

The nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical investigations. Sodium, potassium, chloride, magnesium, phosphate, and water depletion can occur singly and in combination with or without disturbances of acid-base balance; for reference to the use of magnesium and phosphates, see section 9.5.

Isotonic solutions may be infused safely into a peripheral vein. Solutions more concentrated than plasma, e.g. 20% glucose, are best given through an indwelling catheter positioned in a large vein.

9.2.2.2 Plasma and plasma substitutes

Intravenous sodium

Sodium chloride in isotonic solution provides the most important extracellular ions in near physiological concentration and is indicated in sodium depletion which may arise from such conditions as gastro-enteritis, diabetic ketoacidosis, ileus, and ascites. In a severe deficit of from 4 to 8 litres, 2 to 3 litres of isotonic sodium chloride may be given over 2 to 3 hours; thereafter the infusion can usually be at a slower rate. Excessive administration should be avoided; the jugular venous pressure should be assessed, the bases of the lungs should be examined for crepitations, and in elderly or seriously ill patients it is often helpful to monitor the right atrial (central) venous pressure.

Chronic hyponatraemia arising from inappropriate secretion of antidiuretic hormone should ideally be corrected by fluid restriction. However, if sodium chloride is required for acute or chronic hyponatraemia, regardless of the cause, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome and the rise in plasma-sodium concentration should not exceed 10 mmol/litre in 24 hours. In severe...
Nutrition and Blood

Intravenous infusion, sodium chloride 0.45% (Na⁺ and Cl⁻ each 75 mmol/litre), glucose 2.5%
In hospitals, usually 500-mL packs and sometimes other sizes are available

Intravenous infusion, sodium chloride 0.45% (Na⁺ and Cl⁻ each 75 mmol/litre), glucose 5%
In hospitals, usually 500-mL packs and sometimes other sizes are available

Intravenous infusion, sodium chloride 0.9% (Na⁺ and Cl⁻ each 150 mmol/litre), glucose 5%
In hospitals, usually 500-mL packs and sometimes other sizes are available

Note
See above for warning on hyponatraemia especially in children and elderly

Ringer’s Solution for Injection
Calcium chloride (dihydrate) 322 micrograms, potassium chloride 300 micrograms, sodium chloride 8.6 mg/mL, providing the following ions (in mmol/litre), Ca²⁺ 2.2, K⁺ 4, Na⁺ 147, Cl⁻ 156
In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Sodium Lactate Intravenous Infusion, Compound
(Hartmann’s Solution for Injection; Ringer-Lactate Solution for Injection)
Intravenous infusion, sodium chloride 0.6%, sodium lactate 0.25%, potassium chloride 0.04%, calcium chloride 0.027% (containing Na⁺ 131 mmol, K⁺ 5 mmol, Ca²⁺ 2 mmol, HCO₃⁻ (as lactate) 29 mmol, Cl⁻ 111 mmol/litre)
In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

Intravenous glucose
Glucose solutions (5%) are used mainly to replace water deficit and should be given alone only when there is no significant loss of electrolytes; prolonged administration of glucose solutions without electrolytes can lead to hyponatraemia and other electrolyte disturbances. Average water requirements in a healthy adult are 1.5 to 2.5 litres daily and this is needed to balance unavoidable losses of water through the skin and lungs and to provide sufficient for urinary excretion. Water depletion (dehydration) tends to occur when these losses are not matched by a comparable intake, as may occur in coma or dysphagia or in the elderly or apathetic who may not drink enough water on their own initiative.

Excessive loss of water without loss of electrolytes is uncommon, occurring in fevers, hyperthyroidism, and in uncommon water-losing renal states such as diabetes insipidus or hypercalcaemia. The volume of glucose solution needed to replace deficits varies with the severity of the disorder, but usually lies within the range of 2 to 6 litres.

Glucose solutions are also used to correct and prevent hypoglycaemia and to provide a source of energy in those too ill to be fed adequately by mouth; glucose solutions are a key component of parenteral nutrition (section 9.3).

Glucose solutions are given in regimens with calcium and insulin for the emergency management of hyperkalaemia (see p. 519). They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuing insulin infusion.
**GLUCOSE**
(Dextrose Monohydrate)

Note Glucose BP is the monohydrate but Glucose Intravenous Infusion BP is a sterile solution of anhydrous glucose or glucose monohydrate, potency being expressed in terms of anhydrous glucose

**Indications** fluid replacement (see notes above), provision of energy (section 9.3); hypoglycaemia (section 6.1.4)

**Side-effects** glucose injections especially if hypertonic may have a low pH and may cause venous irritation and thrombophlebitis

**Dose**
- Water replacement, see notes above; energy source, 1–3 litres daily of 20–50% solution

**Glucose Intravenous Infusion** (Non-proprietary) (Non-proprietary)
Intravenous infusion, glucose or anhydrous glucose (potency expressed in terms of anhydrous glucose), usual strength 5% (50 mg/mL) and 10% (100 mg/mL); 25% solution, net price 25-mL amp = £2.21; 50% solution, 25-mL amp = £3.80, 50-mL amp = £1.63
In hospitals, 500- and 1000-mL packs, and sometimes other sizes and strengths, are available, also available as Min-I-Jet Glucose, 50% in 50-mL disposable syringe

1. (NF) restriction does not apply where administration is for saving life in emergency

**Intravenous potassium**
Potassium chloride and sodium chloride intravenous infusion is the initial treatment for the correction of severe hypokalaemia and when sufficient potassium cannot be taken by mouth. Ready-mixed infusion solutions should be used when possible; alternatively, potassium chloride concentrate, as ampoules containing 1.5 g (K+ 20 mmol) in 10 mL, is thoroughly mixed with 500 mL of sodium chloride 0.9% intravenous infusion and given slowly over 2 to 3 hours, with specialist advice and ECG monitoring in difficult cases. Higher concentrations of potassium chloride may be given in very severe depletion, but require specialist advice.

Repeated measurement of plasma-potassium concentration is necessary to determine whether further infusions are required and to avoid the development of hyperkalaemia, which is especially likely in renal impairment.

Initial potassium replacement therapy should not involve glucose infusions, because glucose may cause a further decrease in the plasma-potassium concentration.

**POTASSIUM CHLORIDE**

**Indications** electrolyte imbalance; see also oral potassium supplements, section 9.2.1.1

**Caution** for intravenous infusion the concentration of solution should not usually exceed 3 g (40 mmol)/litre; specialist advice and ECG monitoring (see notes above); renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); interactions: Appendix 1 (potassium salts)

**Contra-indications** plasma-potassium concentration above 5 mmol/litre

**Side-effects** rapid infusion toxic to heart

**Dose**
- By slow intravenous infusion, depending on the deficit or the daily maintenance requirements, see also notes above

**Potassium Chloride and Glucose Intravenous Infusion** (Non-proprietary) (Non-proprietary)

Intravenous infusion, usual strength potassium chloride 0.3% (3 g, 40 mmol each of K+ and Cl− /litre) or 0.15% (1.5 g, 20 mmol each of K+ and Cl− /litre) with 5% of anhydrous glucose

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Potassium Chloride and Sodium Chloride Intravenous Infusion** (Non-proprietary) (Non-proprietary)

Intravenous infusion, usual strength potassium chloride 0.15% (1.5 g/litre) with sodium chloride 0.9% (9 g/litre), containing K+ 20 mmol, Na+ 150 mmol, and Cl− 170 mmol/litre or potassium chloride 0.3% (3 g/litre) with sodium chloride 0.9% (9 g/litre), containing K+ 40 mmol, Na+ 150 mmol, and Cl− 190 mmol/litre

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Potassium Chloride, Sodium Chloride, and Glucose Intravenous Infusion** (Non-proprietary) (Non-proprietary)

Intravenous infusion, sodium chloride 0.45% (4.5 g, Na+ 75 mmol/litre) with 5% of anhydrous glucose and usually sufficient potassium chloride to provide K+ 10–40 mmol/litre (to be specified by the prescriber)

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Potassium Chloride Concentrate, Sterile** (Non-proprietary) (Non-proprietary)

Sterile concentrate, potassium chloride 15% (150 mg, approximately 2 mmol each of K+ and Cl− /mL). Net price 10-mL amp = 48p

Important Must be diluted with not less than 50 times its volume of sodium chloride intravenous infusion 0.9% or other suitable diluent and mixed well

Solutions containing 10 and 20% of potassium chloride are also available in both 5- and 10-mL ampoules

**Bicarbonate and lactate**
Sodium bicarbonate is used to control severe metabolic acidosis (pH < 7.1) particularly that caused by loss of bicarbonate (as in renal tubular acidosis or from excessive gastro-intestinal losses). Mild metabolic acidosis associated with volume depletion should first be managed by appropriate fluid replacement because acidosis usually resolves as tissue and renal perfusion are restored. In more severe metabolic acidosis or when the acidosis remains unresponsive to correction of anoxia or hypovolaemia, sodium bicarbonate (1.26%) can be infused over 3–4 hours with plasma-pH and electrolyte monitoring. In severe shock (section 2.7.1), for example in cardiac arrest, metabolic acidosis can develop without sodium or volume depletion; in these circumstances sodium bicarbonate is best given as a
small volume of hypertonic solution, such as 50 mL of 8.4% solution intravenously; plasma-pH and electrolytes should be monitored.

**Sodium lactate** intravenous infusion is no longer used in metabolic acidosis because of the risk of producing lactic acidosis, particularly in seriously ill patients with poor tissue perfusion or impaired hepatic function.

For **chronic acidotic states**, sodium bicarbonate can be given by mouth (section 9.2.1.3).

### SODIUM BICARBONATE

**Indications** metabolic acidosis, see also notes above

- By slow intravenous injection, a strong solution (up to 8.4%), or by **continuous intravenous infusion**, a weaker solution (usually 1.26%), an amount appropriate to the body base deficit (see notes above)

**Sodium Bicarbonate Intravenous Infusion**

Usual strength sodium bicarbonate 1.26% (12.6 g, 150 mmol each of Na⁺ and HCO⁻ /litre); various other strengths available

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Min-I-Jet® Sodium Bicarbonate** (UCB Pharma) Intravenous injection, sodium bicarbonate in disposable syringe, net price 4.2%, 10 mL = £5.82; 8.4%, 10 mL = £6.00, 50 mL = £8.14

### SODIUM LACTATE

**Indications** see notes above

**Sodium Lactate** (Non-proprietary) Intravenous infusion, sodium lactate m/6, contains the following ions (in mmol/litre), Na⁺ 167, HCO⁻ (as lactate) 167

### Water

**Water for Injections**

Net price 1-mL amp = 18p; 2-mL amp = 18p; 5-mL amp = 33p; 10-mL amp = 33p; 20-mL amp = 92p; 50-mL amp = £1.91; 100-mL vial = 23p

### 9.2.2.2 Plasma and plasma substitutes

Plasma and plasma substitutes (‘colloids’) contain large molecules that do not readily leave the intravascular space where they exert osmotic pressure to maintain circulatory volume. Compared to fluids containing electrolytes such as sodium chloride and glucose (‘crystalloids’), a smaller volume of colloid is required to produce the same expansion of blood volume, thereby shifting salt and water from the extravascular space. If resuscitation requires a volume of fluid that exceeds the maximum dose of the colloid then crystalloids can be given; packed red cells may also be required.

**Albumin solutions**, prepared from whole blood, contain soluble proteins and electrolytes but no clotting factors, blood group antibodies, or plasma cholinesterases; they may be given without regard to the recipient’s blood group.

Albumin should usually be used after the acute phase of illness, to correct a plasma-volume deficit in patients with salt and water retention and oedema; hypoalbuminaemia itself is not an appropriate indication. The use of albumin solutions in acute plasma or blood loss may be wasteful; plasma substitutes are more appropriate. Concentrated albumin solutions may also be used to obtain a diuresis in hypoalbuminaemic patients (e.g. in hepatic cirrhosis).

Recent evidence does not support the previous view that the use of albumin increases mortality.

### Plasma and plasma substitutes are often used in very ill patients whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the patient’s condition at all times.

**ALBUMIN SOLUTION** (Human Albumin Solution)

A solution containing protein derived from plasma, serum, or normal placentas; at least 95% of the protein is albumin. The solution may be isotonic (containing 4–5% protein) or concentrated (containing 15–25% protein).

**Indications** see under preparations, and also notes above

**Cautions** history of cardiac or circulatory disease (administer slowly to avoid rapid rise in blood pressure and cardiac failure, and monitor cardiovascular and respiratory function); increased capillary permeability; correct dehydration when administering concentrated solution

**Contra-indications** cardiac failure; severe anaemia

**Side-effects** hypersensitivity reactions (including anaphylaxis) with nausea, vomiting, increased salivation, fever, tachycardia, hypotension and chills reported

#### Isotonic solutions

**Indications**: acute or sub-acute loss of plasma volume e.g. in burns, pancreatitis, trauma, and complications of surgery; plasma exchange

Available as: Human Albumin Solution 4.5% (50-, 100-, 250- and 400-mL bottles—Baxter); Human Albumin Solution 5% (250- and 500-mL bottles—Baxter); Octalbin® 5% (100- and 250-mL bottles—Octapharm); Zenalb® 4.5% (50-, 100-, 250-, and 500-mL bottles—BPL)

#### Concentrated solutions (20–25%)

**Indications**: severe hypoalbuminaemia associated with low plasma volume and generalised oedema where salt and water restriction with plasma volume expansion are required; adjunct in the treatment of hyperbilirubinaemia by exchange transfusion in the newborn; paracentesis of large volume ascites associated with portal hypertension

Available as: Human Albumin Solution 20% (50- and 100-mL vials—Baxter); Flexbumin® 20% (50- and 100-mL bags—Baxter); Octalbin® 20% (50- and 100-mL bottles—Octapharm); Zenalb® 20% (50- and 100-mL bottles—BPL)
Plasma substitutes

Dextran, gelatin, and the etherified starches (heta-starch, pentastarch, and tetrastarch) are macromolecular substances which are metabolised slowly; they may be used at the outset to expand and maintain blood volume in shock arising from conditions such as burns or septicemia. Plasma substitutes may be used as an immediate short-term measure to treat haemorrhage until blood is available. They are rarely needed when shock is due to sodium and water depletion because, in these circumstances, the shock responds to water and electrolyte repletion; see also section 2.7.1 for the management of shock.

Plasma substitutes should not be used to maintain plasma volume in conditions such as burns or peritonitis where there is loss of plasma protein, water, and electrolytes over periods of several days or weeks. In these situations, plasma or plasma protein fractions containing large amounts of albumin should be given.

Large volumes of some plasma substitutes can increase the risk of bleeding through depletion of coagulation factors.

Dextran 70 by intravenous infusion is used for volume expansion. Dextran may interfere with blood group cross-matching or biochemical measurements, and these should be carried out before infusion is begun.

Cautions Plasma substitutes should be used with caution in patients with cardiac disease, liver disease, or renal impairment; urine output should be monitored. Care should be taken to avoid haematocrit concentration from falling below 25–30% and the patient should be monitored for hypersensitivity reactions.

Side-effects Hypersensitivity reactions may occur including, rarely, severe anaphylactoid reactions. Transient increase in bleeding time may occur.

**DEXTRAN 70**

Dextrans of weight average molecular weight about ‘70,000’

**Indications** short-term blood volume expansion

**Cautions** see notes above; can interfere with some laboratory tests (see also above); where possible, monitor central venous pressure; pregnancy (Appendix 4)

**Side-effects** see notes above

**Dose**

- See under preparation below

**Hypertonic solution**

RescueFlow® (Vitaline) [FM]

Intravenous infusion, dextran 70 intravenous infusion 6% in sodium chloride intravenous infusion 7.5%. Net price 250–mL bag = £28.50

**Cautions** see notes above; severe hyperglycaemia and hyperosmolality

**Dose** initial treatment of hypovolaemia with hypotension induced by traumatic injury. by intravenous infusion over 2–5 minutes, 250 mL, followed immediately by administration of isotonic fluids

**GELATIN**

Note The gelatin is partially degraded

**Indications** low blood volume (but see notes above)

**Cautions** see notes above; pregnancy (Appendix 4)

**Side-effects** see notes above

**Dose**

- By intravenous infusion, initially 500–1000 mL of a 3.5–4% solution (see notes above)

**Gelofusine® (Braun) [FM]**

Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30,000) 40 g (4%). Na+ 154 mmol, Cl 120 mmol/litre, net price 500–mL Ecobag® = £4.70, 1-litre Ecobag® = £9.45

**Geloplasm® (Fresenius Kabi) [FM]**

Intravenous infusion, partially hydrolysed and succinylated gelatin (modified liquid gelatin) (as anhydrous gelatin) 30 g (3%). Na+ 150 mmol, K+ 5 mmol, Mg 1.5 mmol, Cl 100 mmol, lactate 30 mmol/litre, net price 500–mL bag = £5.05

**Haemaccel® (KoRa) [FM]**

Intravenous infusion, polygeline (gelatin derivative, average molecular weight 30,000) 35 g (3.5%). Na+ 145 mmol, K+ 5.1 mmol, Ca 6.25 mmol, Cl 145 mmol/litre, net price 500–mL bottle = £5.00

**Isoplex® (IS Pharmaceuticals) [FM]**

Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30,000) 40 g (4%). Na+ 145 mmol, K+ 4 mmol, Mg 0.9 mmol, Cl 105 mmol, lactate 25 mmol/litre, net price 500–mL bag = £7.53, 1-litre bag = £14.54

**Volplex® (IS Pharmaceuticals) [FM]**

Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30,000) 40 g (4%). Na+ 154 mmol, Cl 125 mmol/litre, net price 500–mL bag = £4.70, 1-litre bag = £9.09

**ETHERIFIED STARCH**

A starch composed of more than 90% of amylpectin that has been etherified with hydroxyethyl groups; the terms tetrastarch, pentastarch, and hetastarch reflect the degree of etherification

**Indications** low blood volume

**Cautions** see notes above; children

**Side-effects** see notes above; also pruritus, raised serum amylase

**Dose**

- See under preparations below

**Hetastarch**

Hetastarch (Non-proprietary) [FM]

Intravenous infusion, hetastarch (weight average molecular weight 450,000) 6% in sodium chloride intravenous infusion 0.9%, net price 500–mL bag = £8.00

**Dose** by intravenous infusion, 500–1000 mL, usual daily max. 1500 mL (see notes above)

**Pentastarch**

Pentastarch (Non-proprietary) [FM]

Intravenous infusion, pentastarch (weight average molecular weight 200,000), net price (in sodium chloride intravenous infusion 0.9%) 10%, 500–mL bag = £9.24

**Dose** by intravenous infusion, pentastarch 10%, 500–1000 mL; max. 1500 mL daily (see notes above)
Nutrition and blood

Volven® (Fresenius Kabi) Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 0% in sodium chloride intravenous infusion 0.9%, net price 500 mL = £16.50
Dose by intravenous infusion, up to 1500 mL daily (see notes above)

Hemohes® (Braun) Intravenous infusion, pentastarch (weight average molecular weight 200 000), net price (both in sodium chloride intravenous infusion 0.9%) 6%, 500 mL = £12.50; 10%, 500 mL = £16.50
Cautions see notes above
Dose by intravenous infusion, pentastarch 6%, up to 2500 mL daily; pentastarch 10%, up to 1500 mL daily (see notes above)

Tetraspan® (Braun) Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 6% in sodium chloride 0.625%, containing Na⁺ 140 mmol, K⁺ 4 mmol, Mg 1 mmol, Cl 110 mmol, Ca 2.5 mmol, acetate 24 mmol, malate 5 mmol/litre, net price 500-mL bag = £13.50
Dose by intravenous infusion, up to 50 mL/kg daily (see notes above)

Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 10% in sodium chloride 0.625%, containing Na⁺ 140 mmol, K⁺ 4 mmol, Mg 1 mmol, Cl 110 mmol, Ca 2.5 mmol, acetate 24 mmol, malate 5 mmol/litre, net price 500-mL bag = £18.15
Dose by intravenous infusion, up to 30 mL/kg daily (see notes above)

Venofundin® (Braun) Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 6% in sodium chloride intravenous infusion 0.9%, net price 500-mL bag = £12.90
Dose by intravenous infusion, up to 50 mL/kg daily (see notes above)

Volulyte® (Fresenius Kabi) Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 6% in sodium chloride intravenous infusion 0.9%, net price 500-mL bag = £13.50
Dose by intravenous infusion, up to 50 mL/kg daily (see notes above)

Volven® (Fresenius Kabi) Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 6% in sodium chloride intravenous infusion 0.9%, net price 500-mL bag = £12.50
Dose by intravenous infusion, up to 50 mL/kg daily (see notes above)

HyperHAES® (Fresenius Kabi) Intravenous infusion, hydroxyethyl starch (weight average molecular weight 200 000) 6% in sodium chloride intravenous infusion 7.2%, net price 250-mL bag = £28.00
Cautions see notes above; also diabetes
Dose by intravenous injection over 2–5 minutes, 4 mL/kg as a single dose, followed immediately by administration of appropriate replacement fluids

When adequate feeding through the alimentary tract is not possible, nutrients may be given by intravenous infusion. This may be in addition to ordinary oral or tube feeding—supplemental parenteral nutrition, or may be the sole source of nutrition—total parenteral nutrition (TPN). Indications for this method include preparation of undernourished patients for surgery, chemotherapy, or radiation therapy; severe or prolonged disorders of the gastro-intestinal tract; major surgery, trauma, or burns; prolonged coma or refusal to eat; and some patients with renal or hepatic failure. The composition of proprietary preparations available is given in the table Proprietary Infusion Fluids for Parenteral Feeding, p. 527.

Parenteral nutrition requires the use of a solution containing amino acids, glucose, fat, electrolytes, trace elements, and vitamins. This is now commonly provided by the pharmacy in the form of a 3-litre bag. A single dose of vitamin B₁, as hydroxocobalamin, is given by intramuscular injection; regular vitamin B₁ injections are not usually required unless total parenteral nutrition continues for many months. Folic acid is given in a dose of 15 mg once or twice each week, usually in the nutrition solution. Other vitamins are usually given daily; they are generally introduced in the parenteral nutrition solution. Alternatively, if the patient may be able to take small amounts by mouth, vitamins may be given orally.

The nutrition solution is infused through a central venous catheter inserted under full surgical precautions. Alternatively infusion through a peripheral vein may be used for supplementary as well as total parenteral nutrition for periods of up to a month, depending on the availability of peripheral veins; factors prolonging cannula life and preventing thrombophlebitis include the use of soft polyurethane paediatric cannulas and use of feeds of low osmolality and neutral pH. Only nutritional fluids should be given by the dedicated intravenous line.

Before starting, the patient should be well oxygenated with a near normal circulating blood volume and attention should be given to renal function and acid-base status. Appropriate biochemical tests should have been carried out beforehand and serious deficits corrected. Nutritional and electrolyte status must be monitored throughout treatment. Complications of long-term parenteral nutrition include gall bladder sludging, gall stones, cholestasis and abnormal liver function tests. For details of the prevention and management of parenteral nutrition complications, specialist literature should be consulted.

Protein is given as mixtures of essential and non-essential synthetic L-amino acids. Ideally, all essential amino acids should be included with a wide variety of non-essential ones to provide sufficient nitrogen together with electrolytes (see also section 9.2.2). Solutions vary in their composition of amino acids; they often contain an energy source (usually glucose) and electrolytes.

Energy is provided in a ratio of 0.6 to 1.1 megajoules (150–250 kcal) per gram of protein nitrogen. Energy requirements must be met if amino acids are to be utilised for tissue maintenance. A mixture of carbohydrate and fat energy sources (usually 30–50% as fat) gives better utilisation of amino acids than glucose alone.
## Proprietary Infusion Fluids for Parenteral Feeding

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoplasmal 5% E (Braun)</td>
<td>8</td>
<td>25</td>
<td>2.6</td>
<td>43</td>
</tr>
<tr>
<td>Aminoplasmal 10% (Braun)</td>
<td>16</td>
<td>57</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aminoven 25 (Fresenius Kabi)</td>
<td>25.7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinimix N9G20E (Baxter)</td>
<td>4.55</td>
<td>1680</td>
<td>30</td>
<td>2.5</td>
</tr>
<tr>
<td>Clinimix N14G30E (Baxter)</td>
<td>7</td>
<td>2520</td>
<td>30</td>
<td>2.5</td>
</tr>
<tr>
<td>ClinOleic 20% (Baxter)</td>
<td>8360</td>
<td>purified olive and soya oil 200 g, glycerol 22.5 g, egg phosphatides 12 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gamin (Fresenius Kabi)</td>
<td>22.4</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperamine 30 (Braun)</td>
<td>30</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intralipid 10% (Fresenius Kabi)</td>
<td>4600</td>
<td>soya oil 100 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intralipid 20% (Fresenius Kabi)</td>
<td>8400</td>
<td>soya oil 200 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intralipid 30% (Fresenius Kabi)</td>
<td>12600</td>
<td>soya oil 300 g, glycerol 16.7 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kabiven (Fresenius Kabi)</td>
<td>5.3</td>
<td>3275</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Kabiven Peripheral (Fresenius Kabi)</td>
<td>3.75</td>
<td>2625</td>
<td>17</td>
<td>2.8</td>
</tr>
<tr>
<td>Lipidem (Braun)</td>
<td>7900</td>
<td>omega-3-acid triglycerides 20 g, soya oil 80 g, medium-chain triglycerides 100 g</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipofundin MCT/LCT 10% (Braun)</td>
<td>4430</td>
<td>soya oil 50 g, medium-chain triglycerides 50 g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Note: 1000 kcal = 4200 kJ; 1000 kJ = 238.8 kcal. All entries are BNF 57 9.3 Intravenous nutrition 527
2. Excludes protein- or amino acid-derived energy
<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1 Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipofundin MCT/LCT 20% (Braun)</td>
<td>8000</td>
<td>K⁺ 1</td>
<td>Mg 2</td>
<td>Na⁺ 5</td>
</tr>
<tr>
<td>Nutriflex basal (Braun)</td>
<td>4.6</td>
<td>2095 30</td>
<td>5.7 49.9 35 50</td>
<td>Ca 3.6 mmol, acid phosphate 12.8 mmol, anhydrous glucose 125 g</td>
</tr>
<tr>
<td>Nutriflex peri (Braun)</td>
<td>5.7</td>
<td>1340 15 4</td>
<td>27 19.5 31.6</td>
<td>Ca 2.5 mmol, acid phosphate 5.7 mmol, anhydrous glucose 80 g</td>
</tr>
<tr>
<td>Nutriflex plus (Braun)</td>
<td>6.8</td>
<td>2510 25 5.7</td>
<td>37.2 22.9 35.5</td>
<td>Ca 3.6 mmol, acid phosphate 20 mmol, anhydrous glucose 150 g</td>
</tr>
<tr>
<td>Nutriflex special (Braun)</td>
<td>10</td>
<td>4020 25.7 5</td>
<td>40.5 22 49.5</td>
<td>Ca 4.1 mmol, acid phosphate 14.7 mmol, anhydrous glucose 240 g</td>
</tr>
<tr>
<td>Nutriflex Lipid peri (Braun)</td>
<td>4.56</td>
<td>2664 24 2.4</td>
<td>40 32 38.4</td>
<td>Ca 2.4 mmol, Zn 24 micromol, phosphate 6 mmol, anhydrous glucose 64 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>Nutriflex Lipid plus (Braun)</td>
<td>5.44</td>
<td>3600 28 3.2</td>
<td>40 36 36</td>
<td>Ca 3.2 mmol, Zn 24 micromol, phosphate 12 mmol, anhydrous glucose 120 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>Nutriflex Lipid plus without Electrolytes (Braun)</td>
<td>5.44</td>
<td>3600</td>
<td></td>
<td>anhydrous glucose 120 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>Nutriflex Lipid special (Braun)</td>
<td>8</td>
<td>4004 37.6 4.24</td>
<td>53.6 48 48</td>
<td>Ca 4.24 mmol, Zn 32 micromol, phosphate 16 mmol, anhydrous glucose 144 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
<tr>
<td>Nutriflex Lipid special without Electrolytes (Braun)</td>
<td>8</td>
<td>4004</td>
<td></td>
<td>anhydrous glucose 144 g, soya oil 20 g, medium-chain triglycerides 20 g</td>
</tr>
</tbody>
</table>

1. Note. 1000 kcal = 4200 kJ; 1000 kJ = 238.8 kcal. All entries are [mmol/litre].
2. Excludes protein- or amino acid-derived energy.
<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1. Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td>OliClinomel N4-550E (Baxter)</td>
<td>3.6</td>
<td>2184</td>
<td>16 2 21 30 33</td>
<td>Ca 2 mmol, phosphate 8.5 mmol, refined olive and soya oil 20 g, anhydrous glucose 80 g</td>
</tr>
<tr>
<td>OliClinomel N4-720E (Baxter)</td>
<td>3.64</td>
<td>3024</td>
<td>24 2 28 40 40</td>
<td>Ca 1.8 mmol, phosphate 8 mmol, refined olive and soya oil 40 g, anhydrous glucose 80 g</td>
</tr>
<tr>
<td>OliClinomel N5-800E (Baxter)</td>
<td>4.6</td>
<td>3360</td>
<td>24 2.2 32 49 44</td>
<td>Ca 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 100 g</td>
</tr>
<tr>
<td>OliClinomel N6-900E (Baxter)</td>
<td>5.6</td>
<td>3696</td>
<td>24 2.2 32 53 46</td>
<td>Ca 2 mmol, phosphate 10 mmol, refined olive and soya oil 40 g, anhydrous glucose 120 g</td>
</tr>
<tr>
<td>OliClinomel N7-1000 (Baxter)</td>
<td>6.6</td>
<td>4368</td>
<td>37 16</td>
<td>phosphate 3 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g</td>
</tr>
<tr>
<td>OliClinomel N7-1000E (Baxter)</td>
<td>6.6</td>
<td>4368</td>
<td>24 2.2 32 57 48</td>
<td>Ca 2 mmol, phosphate 2.25 mmol, refined olive and soya oil 30 g, anhydrous glucose 125 g</td>
</tr>
<tr>
<td>OliClinomel N8-800 (Baxter)</td>
<td>8.25</td>
<td>3360</td>
<td>42.5 20</td>
<td>phosphate 2.25 mmol, refined olive and soya oil 40 g, anhydrous glucose 160 g</td>
</tr>
<tr>
<td>Omegaven (Fresenius Kabi)</td>
<td></td>
<td></td>
<td></td>
<td>highly refined fish oil 100 g, glycerol 25 g, egg phosphatide 12 g</td>
</tr>
<tr>
<td>Plasma-Lyte 148 (water) (Baxter)</td>
<td></td>
<td></td>
<td></td>
<td>gluconate 23 mmol</td>
</tr>
<tr>
<td>Plasma-Lyte 148 (dextrose 5%) (Baxter)</td>
<td></td>
<td></td>
<td></td>
<td>gluconate 23 mmol, anhydrous glucose 50 g</td>
</tr>
<tr>
<td>Plasma-Lyte M (dextrose 5%) (Baxter)</td>
<td></td>
<td></td>
<td></td>
<td>Ca 2.5 mmol, lactate 12 mmol, anhydrous glucose 50 g</td>
</tr>
<tr>
<td>Primene 10% (Baxter)</td>
<td>15</td>
<td></td>
<td></td>
<td>fish oil 30 g, olive oil 50 g, soya oil 60 g, medium-chain triglycerides 60 g</td>
</tr>
<tr>
<td>SMOFlipid (Fresenius Kabi)</td>
<td>8400</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Note. 1000 kcal = 4200 kJ; 1000 kJ = 238.8 kcal. All entries are [HRE]
2. Excludes protein- or amino acid-derived energy
3. For use in neonates and children only

9.3 Intravenous nutrition

Nutrition and blood
### Preparation

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Nitrogen g/litre</th>
<th>1</th>
<th>Energy kJ/litre</th>
<th>Electrolytes mmol/litre</th>
<th>Other components/litre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1:2</td>
<td>2</td>
<td>K+</td>
<td>Mg</td>
<td>Na+</td>
</tr>
<tr>
<td><strong>Structokabiven Electrolyte Free (Fresenius Kabi)</strong></td>
<td>8</td>
<td>3685</td>
<td>74.5</td>
<td>phosphate 2.8 mmol, anhydrous glucose 127 g, glycerol 4.23 g, egg phospholipids 4.56 g, purified structured triglyceride 38.5 g (contains coconut oil, palm kernel oil and soya oil triglycerides)</td>
<td></td>
</tr>
<tr>
<td><strong>Net price (triple compartment bag of amino acids 500 mL, 750 mL or 1000 mL; glucose 42% 298 mL, 446 mL or 595 mL; lipid emulsion 188 mL, 281 mL or 375 mL) 986 mL = £66.50, 1477 mL = £90.00, 1970 mL = £74.00</strong></td>
<td><strong>8</strong></td>
<td><strong>3685</strong></td>
<td><strong>74.5</strong></td>
<td><strong>phosphate 2.8 mmol, anhydrous glucose 127 g, glycerol 4.23 g, egg phospholipids 4.56 g, purified structured triglyceride 38.5 g (contains coconut oil, palm kernel oil and soya oil triglycerides)</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Structolipid 20% (Fresenius Kabi)</strong></td>
<td><strong>20%</strong></td>
<td><strong>8200</strong></td>
<td><strong>purified structured triglyceride 200 g (contains coconut oil, palm kernel oil, and soya oil triglycerides)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vamin 9 Glucose (Fresenius Kabi)</strong></td>
<td><strong>Net price 100 mL = £3.80; 500 mL = £7.70; 1000 mL = £13.40</strong></td>
<td><strong>9.4</strong></td>
<td><strong>1700</strong></td>
<td><strong>20</strong></td>
<td><strong>1.5</strong></td>
</tr>
<tr>
<td><strong>Vamin 14 (Fresenius Kabi)</strong></td>
<td><strong>Net price 500 mL = £10.80; 1000 mL = £18.30</strong></td>
<td><strong>13.5</strong></td>
<td><strong>50</strong></td>
<td><strong>8</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>
| **Vaminolact (Fresenius Kabi)** | **Net price 100 mL = £4.35; 500 mL = £10.00** | **9.3** | **Note.** | 1000 kcal = 4200 kJ; 1000 kJ = 238.8 kcal. All entries are (x)  
2. Excludes protein- or amino acid-derived energy |
**Glucose** is the preferred source of carbohydrate, but if more than 180 g is given per day frequent monitoring of blood glucose is required, and insulin may be necessary. Glucose in various strengths from 10 to 50% must be infused through a central venous catheter to avoid thrombosis.

In parenteral nutrition regimens, it is necessary to provide adequate phosphate in order to allow phosphorylation of glucose and to prevent hypophosphataemia; between 20 and 30 mmol of phosphate is required daily.

Fructose and sorbitol have been used in an attempt to avoid the problem of hyperosmolar hyperglycaemic non-ketotic acidosis but other metabolic problems may occur, as with xylitol and ethanol which are now rarely used.

**Fat** emulsions have the advantages of a high energy to fluid volume ratio, neutral pH, and iso-osmolarity with plasma, and provide essential fatty acids. Several days of adaptation may be required to attain maximal utilisation. Reactions include occasional febrile episodes (usually only with 20% emulsions) and rare anaphylactic responses. Interference with biochemical measurements such as those for blood gases and calcium may occur if samples are taken before fat has been cleared. Daily checks are necessary to ensure complete clearance from the plasma in conditions where fat metabolism may be disturbed. Additives may only be mixed with fat emulsions where compatibility is known.

### Supplementary preparations

**Compatibility with the infusion solution must be ascertained before adding supplementary preparations.**

**Addiphos** (Fresenius Kabi) [PDF]
- **Solution**, sterile, phosphate 40 mmol, K⁺ 30 mmol, Na⁺ 30 mmol/20 mL. For addition to Vamin® solutions and glucose intravenous infusions. Net price 20-mL vial = £1.53

**Additrace** (Fresenius Kabi) [PDF]
- **Solution**, trace elements for addition to Vamin® solutions and glucose intravenous infusions, traces of Fe, Zn, Cu, Mn, Cr, Se, Mo, F, I. For adults and children over 40 kg. Net price 40-mL vial = £2.00

**Cernevit** (Baxter) [PDF]
- **Solution**, dl-alpha tocopherol 11.2 units, ascorbic acid 125 mg, biotin 69 micrograms, colecalciferol 220 units, cyanocobalamin 6 micrograms, folic acid 414 micrograms, glycine 250 mg, nicotinamide 46 mg, pantothenic acid (as dextanphenol) 17.25 mg, pyridoxine hydrochloride 5.5 mg, vitamin A (as palmitate) 3500 units, riboflavin (as dihydrated sodium phosphate) 4.14 mg, thiamine (as cocarboxylase tetrahydride) 3.51 mg. Dissolve in 5 mL water for injections. Net price per vial = £3.32

**Decan** (Baxter) [PDF]
- **Solution**, trace elements for addition to infusion solutions, Fe, Zn, Cu, Mn, F, Co, I, Se, Mo, Cr. For adults and children over 40 kg. Net price 40-mL vial = £2.00

**Dipeptiven** (Fresenius Kabi) [PDF]
- **Solution**, (providing L-alanine 82 mg, l-glutamine 134.6 mg). For addition to infusion solutions containing amino acids. Net price 50 mL = £16.40, 100 mL = £30.50
- **Dose** amino acid supplement for hypercatabolic or hypermetabolic states, 300–400 mg/kg daily, max. 400 mg/kg daily, dose not to exceed 20% of total amino acid intake

**Glycophos Sterile Concentrate** (Fresenius Kabi) [PDF]
- **Solution**, sterile, phosphate 20 mmol, Na⁺ 40 mmol/20 mL. For addition to Vamin® and Vaminolact® solutions, and glucose intravenous infusions. Net price 20-mL vial = £4.60

**Peditrace** (Fresenius Kabi) [PDF]
- **Solution**, trace elements for addition to Vaminolact®, Vamin® 14 Electrolyte-Free solutions and glucose intravenous infusions, traces of Zn, Cu, Mn, Se, F, I. For use in neonates (when kidney function established, usually second day of life), infants, and children. Net price 10-mL vial = £4.18

**Solivito N** (Fresenius Kabi) [PDF]
- **Solution**, powder for reconstitution, biotin 60 micrograms, cyanocobalamin 5 micrograms, folic acid 400 micrograms, glycine 300 mg, nicotinamide 40 mg, pyridoxine hydrochloride 4.9 mg, riboflavin sodium phosphate 4.9 mg, sodium ascorbate 113 mg, sodium pantothenate 16.5 mg, thiamine mononitrate 3.1 mg. Dissolve in water for injections or glucose intravenous infusion for adding to glucose intravenous infusion or Intralipid®; dissolve in Vitlipid N® or Intralipid® for adding to Intralipid® only. Net price per vial = £2.32

**Vitlipid N** (Fresenius Kabi) [PDF]
- **Emulsion, adult**, vitamin A 330 units, ergocalciferol 20 units, dl-alpha tocopherol 1 unit, phytomenadione 15 micrograms/mL. For addition to Intralipid®. For adults and children over 11 years. Net price 10-mL amp = £2.32
- **Emulsion, infant**, vitamin A 230 units, ergocalciferol 40 units, dl-alpha tocopherol 0.7 unit, phytomenadione 20 micrograms/mL. For addition to Intralipid®. Net price 10-mL amp = £2.32
9.4 Oral nutrition

9.4.1 Foods for special diets

These are preparations that have been modified to eliminate a particular constituent from a food or are nutrient mixtures formulated as substitutes for the food. They are for patients who either cannot tolerate or cannot metabolise certain common constituents of food.

Phenylketonuria Phenylketonuria (phenylalaninaemia), which results from the inability to metabolise phenylalanine, is managed by restricting its dietary intake to a small amount sufficient for tissue building and repair. Aspartame (as a sweeter in some foods and medicines) contributes to the phenylalanine intake and may affect control of phenylketonuria. Where the presence of aspartame is specified in the product literature this is indicated in the BNF against the preparation.

Coeliac disease Coeliac disease, which results from an intolerance to gluten, is managed by completely eliminating gluten from the diet.

ACBS In certain clinical conditions some foods may have the characteristics of drugs and the Advisory Committee on Borderline Substances advises as to the circumstances in which such foods may be regarded as drugs and so can be prescribed in the NHS. Prescriptions for these foods issued in accordance with the advice of this committee and endorsed ‘ACBS’ will normally not be investigated. See Appendix 7 for details of these foods and a listing by clinical condition (consult Drug Tariff for late amendments).

Preparations For preparations on the ACBS list see Appendix 7.

9.4.2 Enteral nutrition

The body’s reserves of protein rapidly become exhausted in severely ill patients, especially during chronic illness or in those with severe burns, extensive trauma, pancreatitis, or intestinal fistula. Much can be achieved by frequent meals and by persuading the patient to take supplementary snacks of ordinary food between the meals.

However, extra calories, protein, other nutrients, and vitamins are often best given by supplementing ordinary meals with sip or tube feeds of one of the nutritionally complete foods.

When patients cannot feed normally at all, for example, patients with severe facial injury, oesophageal obstruction, or coma, a diet composed solely of nutritionally complete foods must be given. This is planned by a dietitian who will take into account the protein and total energy requirement of the patient and decide on the form and relative contribution of carbohydrate and fat to the energy requirements.

There are a number of nutritionally complete foods available and their use reduces an otherwise heavy workload in hospital or in the home. Most contain protein derived from milk or soya. Some contain protein hydrolysates or free amino acids and are only appropriate for patients who have diminished ability to break down protein, as may be the case in inflammatory bowel disease or pancreatic insufficiency.

Even when nutritionally complete foods are being given it may be important to monitor water and electrolyte balance. Extra minerals (e.g. magnesium and zinc) may be needed in patients where gastro-intestinal secretions are being lost. Additional vitamins may also be needed. Regular haematological and biochemical tests may be needed particularly in the unstable patient.

Some feeds are supplemented with vitamin K; for drug interactions of vitamin K see Appendix 1 (vitamins).

Children Infants and young children have special requirements and in most situations liquid feeds prepared for adults are totally unsuitable and should not be given. Expert advice should be sought.

Preparations See Appendix 7.

9.5 Minerals

9.5.1 Calcium and magnesium

9.5.1.1 Calcium supplements

9.5.1.2 Hypercalcaemia and hypercalciuria

9.5.1.3 Magnesium

Calcium supplements are usually only required where dietary calcium intake is deficient. This dietary requirement varies with age and is relatively greater in childhood, pregnancy, and lactation, due to an increased demand, and in old age, due to impaired absorption. In osteoporosis, a calcium intake which is double the recommended amount reduces the rate of bone loss. If the actual dietary intake is less than the recommended amount, a supplement of as much as 40 mmol is appropriate, see also Osteoporosis, p. 414 and Vitamin D, p. 541.

In severe acute hypocalcaemia or hypocalcaemic tetany, an initial slow intravenous injection of 10–20 mL of calcium gluconate injection 10% (providing
Calcium should be given, with plasma-calcium and ECG monitoring (risk of arrhythmias if given too rapidly), and either repeated as required or, if only temporary improvement, followed by a continuous intravenous infusion to prevent recurrence. For infusion, dilute 100 mL of calcium gluconate 10% in 1 litre of glucose 5% or sodium chloride 0.9% and give at an initial rate of 50 mL/hour adjusted according to response. Oral supplements of calcium and vitamin D may also be required in persistent hypocalcaemia (see also section 9.6.4). Concurrent hypomagnesaemia should be corrected with magnesium sulphate (section 9.5.1.3).

For the role of calcium gluconate in temporarily reducing the toxic effects of hyperkalaemia, see p. 519.

# CALCIAL SALTS

## Indications
See notes above; calcium deficiency

## Cautions
Renal impairment; sarcoidosis; history of nephrolithiasis; avoid calcium in respiratory acidosis or respiratory failure; interactions: Appendix 1 (antacids, calcium salts)

## Contra-indications
Conditions associated with hypercalcaemia and hypercalciuria (e.g. some forms of malignant disease)

## Side-effects
Gastro-intestinal disturbances; bradycardia, arrhythmias; with injection, peripheral vasodilatation, fall in blood pressure, injection-site reactions

### Dose
- By mouth, daily in divided doses, see notes above
- By slow intravenous injection, acute hypocalcaemia, calcium gluconate 1–2 g (Ca 2.25–4.5 mmol); CHILD see BNF for Children
- By continuous intravenous infusion, acute hypocalcaemia, see notes above

## Oral preparations

### Calcium Gluconate
- **(Non-proprietary)**
  - **Tablets**, calcium gluconate 600 mg (calcium 53.4 mg or Ca 1.35 mmol), net price 20-tab pack = £1.43. Label: 24
  - **Effervescent tablets**, calcium gluconate 1 g (calcium 89 mg or Ca 2.23 mmol), net price 28-tab pack = £8.83. Label: 13
  - **Note** Each tablet usually contains 4.46 mmol Na

### Calcium Lactate
- **(Non-proprietary)**
  - **Tablets**, calcium lactate 300 mg (calcium 39 mg or Ca 1 mmol), net price 84 = £3.01

### Adcal®
- **(ProStrakan)**
  - **Chewable tablets**, fruit flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca 15 mmol), net price 100-tab pack = £7.25. Label: 24

### Cacit®
- **(Procter & Gamble Pharm.)**
  - **Tablets**, effervescent, pink, calcium carbonate 1.25 g, providing calcium citrate when dispersed in water (calcium 500 mg or Ca 12.5 mmol), net price 76-tab pack = £6.87. Label: 13

### Calcichew®
- **(Shire)**
  - **Tablets** (chewable), orange flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca 12.5 mmol), net price 100-tab pack = £9.33. Label: 24
  - **Forte tablets** (chewable), orange flavour, scored, calcium carbonate 2.5 g (calcium 1 g or Ca 25 mmol), net price 60-tab pack = £13.16. Label: 24

### Excipients
Include aspartame (section 9.4.1)

## Parenteral preparations

### Calcium Gluconate
- **(Non-proprietary)**
  - **Injection**, calcium gluconate 10% (calcium 8.4 mg or Ca 226 micromol/mL), net price 10-mL amp = 60p

### Calcium Chloride
- **(Non-proprietary)**
  - **Injection**, calcium chloride dihydrate 10% (calcium 27.3 mg or Ca 680 micromol/mL), net price 10-mL disposable syringe = £4.64
  - **Brands** include Minject Calcium Chloride 10%

### With vitamin D
Section 9.6.4

### With disodium etidronate
Section 6.6.2

### With risedronate sodium and colecalciferol
Section 6.6.2

## Severe hypercalcaemia
Severe hypercalcaemia calls for urgent treatment before detailed investigation of the cause. Dehydration should be corrected first with intravenous infusion of sodium chloride 0.9%. Drugs (such as thiazides and vitamin D compounds) which promote hypercalcaemia, should be discontinued and dietary calcium should be restricted.

If severe hypercalcaemia persists drugs which inhibit mobilisation of calcium from the skeleton may be required. The bisphosphonates are useful and disodium pamidronate (section 6.6.2) is probably the most effective.

### Corticosteroids
Section 6.3 are widely given, but may only be useful where hypercalcaemia is due to sarcoidosis or vitamin D intoxication; they often take several days to achieve the desired effect.
Calcitonin (section 6.6.1) is relatively non-toxic but its effect can wear off after a few days despite continued use; it is rarely effective where bisphosphonates have failed to reduce serum calcium adequately.

After treatment of severe hypercalcaemia the underlying cause must be established. Further treatment is governed by the same principles as for initial therapy. Salt and water depletion and drugs promoting hypercalciuria should be avoided; oral administration of a bisphosphate may be useful.

Hyperparathyroidism Cinacalcet is licensed for the treatment of secondary hyperparathyroidism in dialysis patients with end-stage renal disease (but see NICE guidance below), for primary hyperparathyroidism in patients where parathyroidectomy is inappropriate, and for the treatment of hypercalcaemia in parathyroid carcinoma. Cinacalcet reduces parathyroid hormone which leads to a decrease in serum calcium concentrations.

Paricalcitol (section 9.6.4) is also licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure. Parathyroidectomy may be indicated for hyperparathyroidism.

NICE guidance
Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis (January 2007)
Cinacalcet is not recommended for the routine treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy.
Cinacalcet is recommended for the treatment of refractory secondary hyperparathyroidism in patients with end-stage renal disease (including those with calciphylaxis) only in those:

- who have ‘very uncontrolled’ plasma concentration of intact parathyroid hormone (defined as greater than 85 picomol/litre) refractory to standard therapy, and a normal or high adjusted serum calcium concentration, and
- in whom surgical parathyroidectomy is contra-indicated, in that the risks of surgery outweigh the benefits.

Response to treatment should be monitored regularly and treatment should be continued only if a reduction in the plasma concentration of intact parathyroid hormone of 30% or greater is seen within 4 months of treatment.

Hypercalciuria
Hypercalciuria should be investigated for an underlying cause, which should be treated. Where a cause is not identified (idiopathic hypercalciuria), the condition is managed by increasing fluid intake and giving bendroflumethiazide in a dose of 2.5 mg daily (a higher dose is not usually necessary). Reducing dietary calcium intake may be beneficial but severe restriction of calcium intake has not proved beneficial and may even be harmful.

9.5.1 Calcium and magnesium
BNF 57

**CINACALCET**

**Indications** see under Dose and notes above

**Cautions** measure serum-calcium concentration before initiation of treatment and within 1 week after starting treatment or adjusting dose, then monthly for secondary hyperparathyroidism and every 2–3 months for primary hyperparathyroidism and parathyroid carcinoma; treatment should not be initiated in patients with hypocalcaemia; in secondary hyperparathyroidism measure parathyroid hormone concentration 1–4 weeks after starting treatment or adjusting dose; then every 1–3 months; dose adjustment may be necessary if smoking started or stopped during treatment; hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (cinacalcet)

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** nausea, vomiting, anorexia; dizziness, paraesthesia, asthenia; reduced testosterone concentrations; myalgia; rash; less commonly dyspepsia, diarrhoea, and seizures; hypotension and heart failure also reported

**Dose**

- Secondary hyperparathyroidism in patients with end-stage renal disease on dialysis (but see notes above), ADULT over 18 years, initially 30 mg once daily, adjusted every 2–4 weeks to max. 180 mg daily
- Hypercalcaemia of primary hyperparathyroidism or parathyroid carcinoma, ADULT over 18 years, initially 30 mg twice daily, adjusted every 2–4 weeks according to response up to max. 90 mg 4 times daily

**Mimpara** (Amgen)

Tablets, green, f/c, cinacalcet (as hydrochloride) 30 mg, net price 28-tab pack = £126.28; 60 mg, 28-tab pack = £232.96; 90 mg, 28-tab pack = £349.44.
Label: 21

9.5.1.3 Magnesium

Magnesium is an essential constituent of many enzyme systems, particularly those involved in energy generation; the largest stores are in the skeleton.

Magnesium salts are not well absorbed from the gastrointestinal tract, which explains the use of magnesium sulphate (section 1.6.4) as an osmotic laxative.

Magnesium is excreted mainly by the kidneys and is therefore retained in renal failure, but significant hypomagnesaemia (causing muscle weakness and arrhythmias) is rare.

**Hypomagnesaemia** Since magnesium is secreted in large amounts in the gastro-intestinal fluid, excessive losses in diarrhoea, stoma or fistula are the most common causes of hypomagnesaemia; deficiency may also occur in alcoholism or as a result of treatment with certain drugs. Hypomagnesaemia often causes secondary hypercalcaemia, and also hypokalaemia and hypophatremia.

Symptomatic hypomagnesaemia is associated with a deficit of 0.5–1 mmol/kg; up to 160 mmol Mg over up to 5 days may be required to replace the deficit (allowing for urinary losses). Magnesium is given initially by intravenous infusion or by intramuscular injection of magnesium sulphate; the intramuscular injection is painful. Plasma magnesium concentration should
be measured to determine the rate and duration of infusion and the dose should be reduced in renal impairment. To prevent recurrence of the deficit, magnesium may be given by mouth in a dose of 24 mmol Mg daily in divided doses; suitable preparations are magnesium glycerophosphate tablets or liquid [unlicensed], available from ‘special-order’ manufacturers or specialist importing companies, see p. 939. For maintenance (e.g. in intravenous nutrition), parenteral doses of magnesium are of the order of 10–20 mmol Mg daily (often about 12 mmol Mg daily).

**Arrhythmias** Magnesium sulphate has also been recommended for the emergency treatment of serious arrhythmias, especially in the presence of hypokalaemia (when hypomagnesaemia may also be present) and when salvos of rapid ventricular tachycardia show the characteristic twisting wave front known as *torsade de points* (see also section 2.3.1). The usual dose of magnesium sulphate by intravenous injection is 2 g (8 mmol Mg) over 10–15 minutes (repeated once if necessary).

**Myocardial infarction** Limited evidence that magnesium sulphate prevents arrhythmias and reperfusion injury in patients with suspected myocardial infarction has not been confirmed by large studies. Routine use of magnesium sulphate for this purpose is not recommended. For the management of myocardial infarction, see section 2.10.1.

**Eclampsia and pre-eclampsia** Magnesium sulphate is the drug of choice for the prevention of recurrent seizures in *eclampsia*; see also Appendix 4. Regimens may vary between hospitals. Calcium gluconate injection is used for the management of magnesium toxicity. Magnesium sulphate is also of benefit in women with *pre-eclampsia* in whom there is concern about developing eclampsia. The patient should be monitored carefully (see under Magnesium Sulphate).

### MAGNESIUM SULPHATE

**Indications** see notes above; constipation (section 1.6.4); severe acute asthma (section 3.1); paste for boils (section 13.10.5)

**Cautions** see notes above; hepatic impairment (Appendix 2); renal impairment (Appendix 3); in severe hypomagnesaemia administer initially via controlled infusion device (preferably syringe pump); monitor blood pressure, respiratory rate, urinary output and for signs of overdosage (loss of patellar reflexes, weakness, nausea, sensation of warmth, flushing, drowsiness, double vision, and slurred speech); pregnancy (Appendix 4); **interactions:** Appendix 1 (magnesium, parenteral)

**Side-effects** generally associated with hypermagnesaemia, nausea, vomiting, thirst, flushing of skin, hypotension, arrhythmias, coma, respiratory depression, drowsiness, confusion, loss of tendon reflexes, muscle weakness; colic and diarrhoea following oral administration

**Dose**

- Hypomagnesaemia, see notes above
- Arrhythmias, see notes above
- Prevention of seizure recurrence in eclampsia, initially by intravenous injection over 5–15 minutes, 4 g, followed by intravenous infusion, 1 g/hour for at least 24 hours after last seizure; if seizure recurs, additional dose by intravenous injection, 2 g (4 g if body-weight over 70 kg)
- Prevention of seizures in pre-eclampsia [unlicensed indication], initially by intravenous injection over 5–15 minutes, 4 g followed by intravenous infusion, 1 g/hour for 24 hours; if seizure occurs, additional dose by intravenous injection, 2 g

**Intravenous administration** For intravenous injection concentration of magnesium sulphate should not exceed 20% (dilute 1 part of magnesium sulphate injection 50% with at least 1.5 parts of water for injections)

**Note** Magnesium sulphate 1 g equivalent to Mg approx. 4 mmol

**Magnesium Sulphate (Non-proprietary)**

**Injection**, magnesium sulphate 20% (Mg approx. 0.8 mmol/mL), net price 20-ML (4-g) amp = £2.75; 50% (Mg approx. 2 mmol/mL), 2-ML (1-g) amp = £3.80, 4-ML (2-g) prefilled syringe = £6.40, 5-ML (2.5-g) amp = £3.00, 10-ML (5-g) amp = £3.35; 10-ML (5-g) prefilled syringe = £4.95

**Brands include**

- Minijet Magnesium Sulphate 50%

### 9.5.2 Phosphorus

#### 9.5.2.1 Phosphate supplements

**Phosphate supplements**

Oral phosphate supplements may be required in addition to vitamin D in a small minority of patients with hypophosphataemic vitamin D-resistant rickets. Diarrhoea is a common side-effect and should prompt a reduction in dosage.

Phosphate infusion is occasionally needed in alcohol dependence or in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis. For established hypophosphataemia, monobasic potassium phosphate may be infused at a rate of 9 mmol every 12 hours. In critically ill patients, the dose of phosphate can be increased up to 500 micro- mol/kg (approx. 30 mmol in adults, max. 50 mmol), infused over 6–12 hours, according to severity. Excessive doses of phosphates may cause hypocalcaemia and metastatic calcification; it is essential to monitor closely plasma concentrations of calcium, phosphate, potassium, and other electrolytes.

For phosphate requirements in total parenteral nutrition regimens, see section 9.3.

**Phosphates** (Fresenius Kabi) Intravenous infusion, phosphates (providing PO 100 mmol, K+ 19 mmol, and Na+ 162 mmol/litre), net price 500 mL (Polyfu®) = £3.75.

For the treatment of moderate to severe hypophosphatemia

**Phosphate-Sandoz** (HK Pharma) Tablets, effervescent, anhydrous sodium acid phosphate 1.936 g, sodium bicarbonate 350 mg, potassium bicarbonate 315 mg, equivalent to phosphorus 500 mg (phosphate 16.1 mmol), sodium 468.8 mg (Na+ 0.8 mmol/mL), net price 20-ML (4-g) amp = £2.75; 50% (Mg approx. 2 mmol/mL), 2-ML (1-g) amp = £3.80, 4-ML (2-g) prefilled syringe = £6.40, 5-ML (2.5-g) amp = £3.00, 10-ML (5-g) amp = £3.35; 10-ML (5-g) prefilled syringe = £4.95

**Brands include**

- Polyfusor

**9.5.2.2 Phosphate-binding agents**

- 1.5 parts of water for injections)

**9.5.2.2 Phosphate-binding agents**

**Intravenous administration**

- Prevention of seizures in pre-eclampsia [unlicensed indication], initially by intravenous injection over 5–15 minutes, 4 g followed by intravenous infusion, 1 g/hour for 24 hours; if seizure occurs, additional dose by intravenous injection, 2 g

**Note** Magnesium sulphate 1 g equivalent to Mg approx. 4 mmol

**Magnesium Sulphate (Non-proprietary)**

**Injection**, magnesium sulphate 20% (Mg approx. 0.8 mmol/mL), net price 20-ML (4-g) amp = £2.75; 50% (Mg approx. 2 mmol/mL), 2-ML (1-g) amp = £3.80, 4-ML (2-g) prefilled syringe = £6.40, 5-ML (2.5-g) amp = £3.00, 10-ML (5-g) amp = £3.35; 10-ML (5-g) prefilled syringe = £4.95

**Brands include**

- Minijet Magnesium Sulphate 50%

### 9.5.2 Phosphorus

#### 9.5.2.1 Phosphate supplements

**Phosphate supplements**

Oral phosphate supplements may be required in addition to vitamin D in a small minority of patients with hypophosphataemic vitamin D-resistant rickets. Diarrhoea is a common side-effect and should prompt a reduction in dosage.

Phosphate infusion is occasionally needed in alcohol dependence or in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis. For established hypophosphataemia, monobasic potassium phosphate may be infused at a rate of 9 mmol every 12 hours. In critically ill patients, the dose of phosphate can be increased up to 500 micro-mol/kg (approx. 30 mmol in adults, max. 50 mmol), infused over 6–12 hours, according to severity. Excessive doses of phosphates may cause hypocalcaemia and metastatic calcification; it is essential to monitor closely plasma concentrations of calcium, phosphate, potassium, and other electrolytes.

For phosphate requirements in total parenteral nutrition regimens, see section 9.3.

**Phosphates** (Fresenius Kabi) Intravenous infusion, phosphates (providing PO 100 mmol, K+ 19 mmol, and Na+ 162 mmol/litre), net price 500 mL (Polyfu®) = £3.75.

For the treatment of moderate to severe hypophosphatemia

**Phosphate-Sandoz** (HK Pharma) Tablets, effervescent, anhydrous sodium acid phosphate 1.936 g, sodium bicarbonate 350 mg, potassium bicarbonate 315 mg, equivalent to phosphorus 500 mg (phosphate 16.1 mmol), sodium 468.8 mg (Na+ 0.8 mmol/mL), net price 20-ML (4-g) amp = £2.75; 50% (Mg approx. 2 mmol/mL), 2-ML (1-g) amp = £3.80, 4-ML (2-g) prefilled syringe = £6.40, 5-ML (2.5-g) amp = £3.00, 10-ML (5-g) amp = £3.35; 10-ML (5-g) prefilled syringe = £4.95

**Brands include**

- Polyfusor

**9.5.2.2 Phosphate-binding agents**

- 1.5 parts of water for injections)

**9.5.2.2 Phosphate-binding agents**

**Intravenous administration**
**9.5.3 Fluoride**

Availability of adequate fluoride confers significant resistance to dental caries. It is now considered that the topical action of fluoride on enamel and plaque is more important than the systemic effect.

Where the fluoride content of the drinking water is less than 700 micrograms per litre (0.7 parts per million), daily administration of fluoride tablets or drops is a suitable means of supplementation. Systemic fluoride supplements should not be prescribed without reference to the fluoride content of the local water supply. Infants need not receive fluoride supplements until the age of 6 months.

Dentifrices which incorporate sodium fluoride or monofluorophosphate are also a convenient source of fluoride.

Individuals who are either particularly caries prone or medically compromised may be given additional prophylaxis by use of fluoride rinses or by application of

---

**Indications** hyperphosphataemia in patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD). **Contra-indications** pregnancy (Appendix 4)** Side-effects** gastro-intestinal disturbances; hypocalcaemia; less commonly anorexia, increased appetite, taste disturbances, dry mouth, thirst, stomatitis, chest pain, peripheral oedema, headache, dizziness, vertigo, asthenia, fatigue, malaise, hyperglycaemia, hyperparathyroidism, hypercalcaemia, hypophosphataemia, eosinophilia, arthralgia, myalgia, osteoporosis, sweating, alopecia, pruritus, and erythematous rash; accumulation of lanthanum in bone, and transient changes in QT interval also reported

**Dose**
- **ADULT** over 18 years, initially 750 mg daily in divided doses chewed with or immediately after meals, adjusted according to plasma-phosphate concentration every 2–3 weeks (usual dose range 1.5–3 g daily in divided doses)

**Fosrenol** (Shire) Tablets (chewable), lanthanum (as carbonate hydrate) 500 mg, net price 90-tab pack = £114.13; 750 mg, 90-tab pack = £152.17; 1 g, 90-tab pack = £161.33. Label: 21, counselling, to be chewed

**SEVELAMER**

**Indications** hyperphosphataemia in patients on haemodialysis or peritoneal dialysis **Cautions** gastro-intestinal disorders; pregnancy (Appendix 4); breast-feeding (Appendix 5); **interactions**: Appendix 1 (lanthanum) **Contra-indications** bowel obstruction **Side-effects** gastro-intestinal disturbances; very rarely intestinal obstruction

**Dose**
- **ADULT** over 18 years, initially 2.4–4.8 g daily in 3 divided doses with meals, then adjusted according to plasma-phosphate concentration (usual dose range 2.4–12 g daily in 3 divided doses)

**Renagel** (Genzyme) Tablets, f/c, sevelamer 800 mg, net price 180-tab pack = £122.76. Label: 25, counselling, with meals

---

<table>
<thead>
<tr>
<th>9.5.2.2 Phosphate-binding agents</th>
</tr>
</thead>
</table>
| Aluminium-containing and calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Calcium-containing phosphate-binding agents are contra-indicated in hypercalcaemia or hypercalciuria. Phosphate-binding agents which contain aluminium may increase plasma aluminium in dialysis patients. Sevelamer is licensed for the treatment of hyperphosphataemia in patients on haemodialysis or peritoneal dialysis. The Scottish Medicines Consortium (p. 3) has advised (November 2007) that sevelamer (Renagel®) is not recommended for use within NHS Scotland for the control of hyperphosphataemia in adults receiving peritoneal dialysis. Lanthanum is licensed for the control of hyperphosphataemia in patients with chronic renal failure on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD).

**ALUMINIUM HYDROXIDE**

**Indications** hyperphosphataemia; dyspepsia (section 1.1) **Cautions** hyperaluminaemia; see also notes above; renal impairment (Appendix 3); **interactions**: Appendix 1 (antacids) **Side-effects** see section 1.1.1

**Alu-Cap® (3M)**
- **Capsules**, green/red, dried aluminium hydroxide 475 mg (low Na⁺). Net price 120-cap pack = £3.75

**Dose** phosphate-binding agent in renal failure, 4–20 capsules daily in divided doses with meals

**CALCIUM SALTS**

**Indications** hyperphosphataemia **Cautions** see notes above; **interactions**: Appendix 1 (antacids, calcium salts) **Side-effects** hypercalcaemia

**Adcal®** section 9.5.1.1

**Calcichew®** section 9.5.1.1

**Calcium-500** section 9.5.1.1

**Phossex® (Vitaline)**
- **Tablets**, yellow, calcium acetate 1 g (calcium 250 mg or Ca 6.2 mmol), net price 180-tab pack = £19.79. Label: 25, counselling, with meals

**Dose** phosphate-binding agent (with meals) in renal failure, according to the requirements of the patient

**LANTHANUM**

**Indications** hyperphosphataemia in patients on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD) **Cautions** acute peptic ulcer; ulcerative colitis; Crohn’s disease; bowel obstruction; hepatic impairment; breast-feeding (Appendix 5)
fluoride gels. Rinses may be used daily or weekly; daily use of a less concentrated rinse is more effective than weekly use of a more concentrated one. High-strength gels must be applied on a regular basis under professional supervision; extreme caution is necessary to prevent children from swallowing any excess. Less concentrated gels are available for home use. Varnishes are also available and are particularly valuable for young or disabled children since they adhere to the teeth and set in the presence of moisture.

Fluoride mouthwash, oral drops, tablets and toothpaste are prescribable on form FP10D (GP14 in Scotland, WP10D in Wales; for details see preparations, below).

There are also arrangements for health authorities to supply fluoride tablets in the course of pre-school dental schemes, and they may also be supplied in school dental schemes. Fluoride gels are not prescribable on form FP10D (GP14 in Scotland, WP10D in Wales).

## FLUORIDES

**Note** Sodium fluoride 2.2 mg provides approx. 1 mg fluoride ion

**Indications** prophylaxis of dental caries—see notes above

**Contra-indications** not for areas where drinking water is fluoridated

**Side-effects** occasional white flecks on teeth with recommended doses; rarely yellowish-brown discoloration if recommended doses are exceeded

**Dose**

**Note** Dose expressed as fluoride ion (F⁻)

- Water content less than F 300 micrograms/litre (0.3 parts per million), **CHILD** up to 6 months none; 6 months–3 years F 250 micrograms daily, 3–6 years F 500 micrograms daily, over 6 years F 1 mg daily
- Water content between F 300 and 700 micrograms/litre (0.3–0.7 parts per million), **CHILD** up to 3 years none, 3–6 years F 250 micrograms daily, over 6 years F 500 micrograms daily
- Water content above F 700 micrograms/litre (0.7 parts per million), supplements not advised

**Note** These doses reflect the recommendations of the British Dental Association, the British Society of Paediatric Dentistry and the British Association for the Study of Community Dentistry (*Br Dent J 1997; 182: 6–7*)

### Tablets

**Counselling** Tablets should be sucked or dissolved in the mouth and taken preferably in the evening

**En-De-Kay®** (Manx)

- Fluotabs 3–6 years, orange-flavoured, scored, sodium fluoride 1.1 mg (F 500 micrograms). Net price 200-tab pack = £2.38
- Fluotabs 6+ years, orange-flavoured, scored, sodium fluoride 2.2 mg (F 1 mg). Net price 200-tab pack = £2.38

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Tablets

**Fluor-a-day®** (Dental Health)

- Tablets, buff, sodium fluoride 1.1 mg (F 500 micrograms), net price 200-tab pack = £2.41; 2.2 mg (F 1 mg), 200-tab pack = £2.41

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Tablets

### Oral drops

**Note** Fluoride supplements not considered necessary below 6 months of age (see notes above)

**En-De-Kay®** (Manx)

- **Fludrops** (= paediatric drops), sugar-free, sodium fluoride 550 micrograms (F 250 micrograms)/0.15 mL. Net price 60 mL = £2.38

**Dental prescribing on NHS** Corresponds to Sodium Fluoride Oral Drops DPF 0.37% equivalent to sodium fluoride 80 micrograms (F 36 micrograms)/drop

### Mouthwashes

Rinse mouth for 1 minute and spit out

**Counselling** Avoid eating, drinking, or rinsing mouth for 15 minutes after use

**Duraphat®** (Colgate-Palmolive)

- **Weekly dental rinse** (= mouthwash), blue, sodium fluoride 0.2%. Net price 150 mL = £2.37. Counselling, see above

  - **Dose** **CHILD** 6 years and over, for **weekly use**, rinse with 10 mL

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Mouthwash 0.2%

**En-De-Kay®** (Manx)

- **Daily fluoride mouthrinse** (= mouthwash), blue, sodium fluoride 0.05%. Net price 250 mL = £1.51

  - **Dose** **CHILD** 6 years and over, for **daily use**, rinse with 10 mL

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Mouthwash 0.05%

**Fluorinse** (= mouthwash), red, sodium fluoride 2%. Net price 100 mL = £4.97. Counselling, see above

  - **Dose** **CHILD** 8 years and over, for **daily use**, dilute 5 drops to 10 mL of water, for **weekly use**, dilute 20 drops to 10 mL

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Mouthwash 2%

### Gels

**FluoriGard®** (Colgate-Palmolive)

- **Daily dental rinse** (= mouthwash), blue, sodium fluoride 0.05%. Net price 500 mL = £3.14. Counselling, see above

  - **Dose** **CHILD** 6 years and over, for **daily use**, rinse with 10 mL

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Mouthwash 0.05%

**Gel-Kam** (= gel), stannous fluoride 0.4% in glycerol basis. Net price 100 mL = £2.97. Counselling, see below

  - **Dose** **ADULT** and **CHILD** 3 years and over, for **daily use**, using a toothbrush, apply onto all tooth surfaces

**Counselling** Swish between teeth for 1 minute before spitting out. Avoid eating, drinking, or rinsing mouth for at least 30 minutes after use

**FluoriGard®** (Colgate-Palmolive)

- Tablets 0.5, purple, grape-flavoured, scored, sodium fluoride 1.1 mg (F 500 micrograms). Net price 200-tab pack = £1.91
- Tablets 1.0, orange, orange-flavoured, scored, sodium fluoride 2.2 mg (F 1 mg). Net price 200-tab pack = £1.91

**Dental prescribing on NHS** May be prescribed as Sodium Fluoride Tablets
9.5.4 Zinc

Zinc supplements should be given only when there is good evidence of deficiency (hypoproteinaemia spuriously lowers plasma-zinc concentration) or in zinc-losing conditions. Zinc deficiency can occur as a result of inadequate diet or malabsorption; excessive loss of zinc can occur in trauma, burns, and protein-losing conditions. A zinc supplement is given until clinical improvement occurs, but it may need to be continued in severe malabsorption, metabolic disease (section 9.8.1), or in zinc-losing states.

Parenteral nutrition regimens usually include trace amounts of zinc (section 9.3). If necessary, further zinc can be added to intravenous feeding regimens. A suggested dose for intravenous nutrition is elemental zinc 6.5 mg (Zn 100 micromol) daily.

9.5.5 Selenium

Selenium deficiency can occur as a result of inadequate diet or prolonged parenteral nutrition. A selenium supplement should be given only when there is good evidence of deficiency.

9.6 Vitamins

Vitamins are used for the prevention and treatment of specific deficiency states or where the diet is known to be inadequate; they may be prescribed in the NHS to prevent or treat deficiency but not as dietary supplements.

Their use as general ‘pick-me-ups’ is of unproven value and, in the case of preparations containing vitamin A or D, may actually be harmful if patients take more than the prescribed dose. The ‘fad’ for mega-vitamin therapy with water-soluble vitamins, such as ascorbic acid and pyridoxine, is unscientific and can be harmful.

Dietary reference values for vitamins are available in the Department of Health publication:


Dental patients It is unjustifiable to treat stomatitis or glossitis with mixtures of vitamin preparations; this delays diagnosis and correct treatment. Most patients who develop a nutritional deficiency despite an adequate intake of vitamins have malabsorption and if this is suspected the patient should be referred to a medical practitioner.

9.6.1 Vitamin A

Deficiency of vitamin A (retinol) is associated with ocular defects (particularly xerophthalmia) and an increased susceptibility to infections, but deficiency is rare in the UK (even in disorders of fat absorption). Massive overdose can cause rough skin, dry hair, an enlarged liver, and a raised erythrocyte sedimentation...
rate and raised serum calcium and serum alkaline phosphatase concentrations.

In view of evidence suggesting that high levels of vitamin A may cause birth defects, women who are (or may become) pregnant are advised not to take vitamin A supplements (including tablets and fish-liver oil drops), except on the advice of a doctor or an antenatal clinic; nor should they eat liver or products such as liver pâté or liver sausage.

**VITAMIN A**

**Indications** see notes above

**Cautions** see notes above; interactions: Appendix 1 (vitamins)

**Side-effects** see notes above

- See notes above and under preparations

**Vitamins A and D**

**Halibut-liver Oil** (Non-proprietary)

- **Capsules**, vitamin A 4000 units [also contains vitamin D]. Net price 100-cap pack = 93p

**Vitamins A and D** (Non-proprietary)

- **Capsules**, vitamin A 4000 units, vitamin D 400 units. Net price 84-cap pack = £3.14

**Note** May be difficult to obtain

**Halycitrol** (LAB)

- **Emulsion**, vitamin A 4600 units, vitamin D 380 units/5 mL. Net price 114 mL = £1.77

**Note** May be difficult to obtain

**Vitamins A, C and D**

**Healthy Start Children’s Vitamin Drops** (Non-proprietary)

- **Oral drops**, vitamin A 5000 units, vitamin D 2000 units, ascorbic acid 150 mg/mL.

Available free of charge to children under 4 years through the Healthy Start Scheme; otherwise available direct to the public from maternity and child health clinics; community pharmacists may have difficulty obtaining supplies

**Dose** prevention of vitamin deficiency. **CHILD** 1 month–5 years, 5 drops daily (5 drops contain vitamin A approx. 700 units, vitamin D approx. 300 units, ascorbic acid approx. 20 mg)

**Note** Healthy Start Vitaminas for women (containing ascorbic acid, vitamin D, and folic acid) are also available to women during pregnancy and until their baby is one year old, through the Healthy Start Scheme

**RIBOFLAVIN**

(Riboflavine, vitamin B)

**Indications** see notes above

**Preparations**

- Injections of vitamins B and C, see under Thiamine

**Oral vitamin B complex preparations**

See p. 540

**THIAMINE**

(Vitamin B)

**Indications** see notes above

**Cautions** anaphylactic shock may occasionally follow injection (see MHRA/CHM advice above); breastfeeding (Appendix 5)

**Dose**

- Mild chronic deficiency, 10–25 mg daily; severe deficiency, 200–300 mg daily

**Thiamine** (Non-proprietary)

- **Tablets**, thiamine hydrochloride 50 mg. net price 20 = £1.31; 100 mg, 20 = £1.50

Brands include *Benerva*
Nutrition and blood

Pabrinex® (Link) (NH)

I/M High potency injection, for intramuscular use only, ascorbic acid 500 mg, nicotinamide 160 mg, pyridoxine hydrochloride 50 mg, riboflavin 4 mg, thiamine hydrochloride 250 mg/7 mL. Net price 7 mL (in 2 amps) = £1.96

I/V High potency injection, for intravenous use only, ascorbic acid 500 mg, anhydrous glucose 1 g, nicotinamide 160 mg, pyridoxine hydrochloride 50 mg, riboflavin 4 mg, thiamine hydrochloride 250 mg/10 mL. Net price 10 mL (in 2 amps) = £1.96

Parenteral vitamins B and C for rapid correction of severe depletion or malabsorption (e.g. in alcoholism, after acute infections, postoperatively or in psychiatric states), maintenance of vitamins B and C in chronic intermittent haemodialysis

Dose see MHRA/CHM advice above

Coma or delirium from alcohol, from opioids, or from barbiturates, collapse following narcosis, psychosis following narcosis or electroconvulsive therapy, toxicity from acute infections, by intravenous infusion of I/V High potency or by deep intramuscular injection into the gluteal muscle of I/M High potency, 1 pair twice daily for up to 7 days

Haemodialysis, by intravenous infusion of I/V High potency (in sodium chloride intravenous infusion 0.9%) 1 pair every 2 weeks

Oral vitamin B complex preparations

See below

PYRIDOXINE HYDROCHLORIDE

(Vitamin B )

Indications see under Dose

Cautions interactions: Appendix 1 (vitamins)

Side-effects sensory neuropathy reported with high doses given for extended periods

Dose

• Deficiency states, 20–50 mg up to 3 times daily

• Isoniazid neuropathy, prophylaxis 10 mg daily [or 20 mg daily if suitable product not available]; therapeutic, 50 mg three times daily

• Idiopathic sideroblastic anaemia, 100–400 mg daily in divided doses

• Premenstrual syndrome, 50–100 mg daily (see notes above)

Prolonged use of pyridoxine in a dose of 10 mg daily is considered safe but the long-term use of pyridoxine in a dose of 200 mg or more daily has been associated with neuropathy. The safety of long-term pyridoxine supplementation with doses above 10 mg daily has not been established.

Pyridoxine (Non-proprietary)

Tablets, pyridoxine hydrochloride 10 mg, net price 20 = 34p; 20 mg, 20 = 34p; 50 mg, 28 = 84p

Injections of vitamins B and C

See under Thiamine

NICOTINAMIDE

Indications see notes above; acne vulgaris, see section 13.8.1

Nicotinamide (Non-proprietary)

Tablets, nicotinamide 50 mg. Net price 20 = £1.37

Injections of vitamins B and C

See under Thiamine

Oral vitamin B complex preparations

Note Other multivitamin preparations are in section 9.6.7.

Vitamin B Tablets, Compound

Tablets, nicotinamide 15 mg, riboflavin 1 mg, thiamine hydrochloride 1 mg. Net price 20 = £0.76

Dose prophylactic, 1–2 tablets daily

Vitamin B Tablets, Compound, Strong

Tablets, brown, f/c or s/c, nicotinamide 20 mg, pyridoxine hydrochloride 2 mg, riboflavin 2 mg, thiamine hydrochloride 5 mg. Net price 28-tab pack = £2.00

Dose treatment of vitamin-B deficiency, 1–2 tablets 3 times daily

Vigranon B® (Wallace Mfg)

Syrup, thiamine hydrochloride 5 mg, riboflavin 2 mg, nicotinamide 20 mg, pyridoxine hydrochloride 2 mg, panthenol 3 mg/5 mL. Net price 150 mL = £2.41

Other compounds

Potassium aminobenzoate has been used in the treatment of various disorders associated with excessive fibrosis such as scleroderma but its therapeutic value is doubtful.

Potaba® (Glenwood)

Capsules, potassium aminobenzoate 500 mg. Net price 20 = £1.59. Label: 21

Tablets, potassium aminobenzoate 500 mg. Net price 20 = £1.12. Label: 21

Envules® (= powder in sachets), potassium aminobenzoate 3 g. Net price 40 sachets = £17.21. Label: 13, 21

Dose Peyronie’s disease, scleroderma, 12 g daily in divided doses after food

Vitamin C

Vitamin C therapy is essential in scurvy, but less florid manifestations of vitamin C deficiency are commonly found, especially in the elderly. It is rarely necessary to prescribe more than 100 mg daily except early in the treatment of scurvy.

Severe scurvy causes gingival swelling and bleeding margins as well as petechiae on the skin. This is, however, exceedingly rare and a patient with these signs is more likely to have leukaemia. Investigation should not be delayed by a trial period of vitamin treatment.

Claims that vitamin C ameliorates colds or promotes wound healing have not been proved.

ASCORBIC ACID

Indications prevention and treatment of scurvy

Cautions interactions: Appendix 1 (vitamins)

Dose

• Prophylactic, 25–75 mg daily; therapeutic, not less than 250 mg daily in divided doses

Ascorbic Acid (Non-proprietary)

Tablets, ascorbic acid 50 mg, net price 28 = £1.21; 100 mg, 28 = £1.26; 200 mg, 28 = £1.27; 500 mg (label: 24), 28 = £3.12

Brands include Redoxon
9.6.4 Vitamin D

Note: The term Vitamin D is used for a range of compounds which possess the property of preventing or curing rickets. They include ergocalciferol (calciferol, vitamin D), colecalciferol (vitamin D), dihydrocholesterol, alfacalcidol (1α,25-dihydroxycholecalciferol), and calcitriol (1,25-dihydroxycholecalciferol).

Simple vitamin D deficiency can be prevented by taking an oral supplement of only 10 micrograms (400 units) of ergocalciferol (calciferol, vitamin D) or colecalciferol (vitamin D) daily. Vitamin D deficiency can occur in people whose exposure to sunlight is limited and in those whose diet is deficient in vitamin D. In these individuals, ergocalciferol or colecalciferol in a dose of 20 micrograms (800 units) daily by mouth can prevent vitamin D deficiency. Since there is no plain tablet of this strength available, calcium and ergocalciferol tablets can be given (although the calcium is unnecessary).

Preparations containing calcium with colecalciferol are available for the management of combined calcium and vitamin D deficiency, or for those at high risk of deficiency (see also Osteoporosis, p. 414 and Calcium Supplements, p. 532).

Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease usually requires vitamin D in pharmacological doses, such as ergocalciferol tablets up to 1 mg (40 000 units) daily; the hypocalcaemia of hypoparathyroidism often requires doses of up to 2.5 mg (100 000 units) daily in order to achieve normocalcaemia.

Vitamin D requires hydroxylation by the kidney to its active form, therefore the hydroxylated derivatives alfacalcidol or calcitriol should be prescribed if patients with severe renal impairment require vitamin D therapy. Calcitriol is also licensed for the management of post-menopausal osteoporosis.

Paricalcitol, a synthetic vitamin D analogue, is licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure (section 9.5.1.2).

Important. All patients receiving pharmacological doses of vitamin D and its analogues should have their plasma-calcium concentration checked at intervals (initially once or twice weekly) and whenever nausea or vomiting occur. Breast milk from women taking pharmacological doses of vitamin D can cause hypercalcaemia if given to an infant.

ERGOCALCIFEROL
(Calciferol, Vitamin D)

Indications: see notes above

Caution: take care to ensure correct dose in infants; monitor plasma calcium in patients receiving high doses and in renal impairment; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (vitamins)

Contra-indications: hypercalcaemia; metastatic calcification

Side-effects: symptoms of overdosage include anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine

Dose: See notes above

Daily supplements: See notes above

Note: There is no plain vitamin D tablet available for treating simple deficiency (see notes above). Alternatives include vitamins capsules (section 9.6.7), preparations of vitamins A and D (section 9.6.1), and calcium and ergocalciferol tablets (see below).

For cautions, contra-indications, and side-effects of calcium, see section 9.5.1.1

Calcium and Ergocalciferol (Non-proprietary)
(Calcium and Vitamin D)

Tablets, calcium lactate 300 mg, calcium phosphate 150 mg (calcium 97 mg or Ca 2 mmol), ergocalciferol 10 micrograms (400 units). Net price 28-tab pack = £2.38. Counselling, crush before administration or may be chewed.

Pharmacological strengths: See notes above

Note: The BP directs that when calciferol is prescribed or demanded, colecalciferol or ergocalciferol should be dispensed or supplied.

Ergocalciferol (Non-proprietary)

Tablets, ergocalciferol 250 micrograms (10 000 units), net price 20 = £4.40; 1.25 mg (50 000 units)

Note: May be difficult to obtain

Important: When the strength of the tablets ordered or prescribed is not clear, the intention of the prescriber with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

Injection, ergocalciferol, 7.5 mg (300 000 units)/mL in oil, net price 1-mL amp = £7.44, 2-mL amp = £8.93

ALFACALCIDOL
(1α-Hydroxycholecalciferol)

Indications: see notes above

Cautions: see under Ergocalciferol; also nephrolithiasis

Contra-indications: see under Ergocalciferol

Side-effects: see under Ergocalciferol; also rarely nephrocalcinosis, pruritus, rash, urticaria

Dose: By mouth or by intravenous injection over 30 seconds, ADULT and CHILD over 20 kg, initially 1 microgram daily (elderly 500 nanograms), adjusted to avoid hypercalcaemia; maintenance, usually 0.25–1 microgram daily; NEONATE and PRETERM NEONATE initially 50–100 nanograms/kg daily, CHILD under 20 kg initially 50 nanograms/kg daily

Alfacalcidol (Non-proprietary) FR
Capsules, alfacalcidol 250 nanograms, net price 30-cap pack = £5.08; 500 nanograms 30-cap pack = £9.99; 1 microgram 30-cap pack = £13.89

One-Alpha® (LEO) FR
Capsules, alfacalcidol 250 nanograms (white), net price 30-cap pack = £3.37; 500 nanograms (red), 30-cap pack = £6.27; 1 microgram (brown), 30-cap pack = £8.75

Excipients: include sesame oil
Oral drops, sugar-free, alfacalcidol 2 micrograms/mL (1 drop contains approx. 100 nanograms), net price 10 mL = £22.49

Excipients include alcohol

Note The concentration of alfacalcidol in One-Alpha drops is 10 times greater than that of the former presentation One-Alpha solution.

Injection, alfacalcidol 2 micrograms/mL, net price 0.5-mL amp = £2.16, 1-mL amp = £4.11

Note Contains propylene glycol and should be used with caution in small preterm neonates

CALCITRIOL
(1,25-Dihydroxycholecalciferol)

Indications see notes above

Cautions see under Ergocalciferol

Contra-indications see under Ergocalciferol

Side-effects see under Ergocalciferol

Dose

\- By mouth, renal osteodystrophy, initially 250 nanograms daily, or on alternate days (in patients with normal or only slightly reduced plasma-calcium concentration), increased if necessary in steps of 250 nanograms at intervals of 2–4 weeks; usual dose 0.5–1 microgram daily; CHILD not established

Established postmenopausal osteoporosis, 250 nanograms twice daily (monitor plasma-calcium concentration and creatinine, consult product literature)

\- By intravenous injection (or injection through catheter after haemodialysis), hypocalcaemia in dialysis patients with chronic renal failure, initially 500 nanograms (approx. 10 nanograms/kg) 3 times a week, increased if necessary in steps of 250–500 nanograms at intervals of 2–4 weeks; usual dose 0.5–3 micrograms 3 times a week; CHILD see BNF for Children

Moderate to severe secondary hyperparathyroidism in dialysis patients, initially 0.5–4 micrograms 3 times a week, increased if necessary in steps of 250–500 nanograms at intervals of 2–4 weeks; max. 8 micrograms 3 times a week

Calcitriol (Non-proprietary)

Capsules, calcitriol 250 nanograms, net price 30-cap pack = £5.87, 100-cap pack = £19.15; 500 nanograms, 30-cap pack = £10.50, 100-cap pack = £34.24

Rocaltril™ (Roche)

Capsules, calcitriol 250 nanograms (red/white), net price 20 = £3.83; 500 nanograms (red), 20 = £6.85

Calcijex® (Abbott)

Injection, calcitriol 1 microgram/mL, net price 1-mL amp = £5.14; 2 micrograms/mL, 1-mL amp = £10.28

With calcium

For cautions, contra-indications, and side-effects of calcium, see section 9.5.1.1

Adcal-D™ (ProStrak)

Tablets (chewable) (lemon or tutti-frutti flavour), calcium carbonate 1.5 g (calcium 600 mg or Ca 15 mmol), colecalciferol 10 micrograms (400 units), net price 56-tab pack = £4.06, 112-tab pack = £7.99. Label: 24

Dissolve (effervescent tablets), lemon flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca 15 mmol), colecalciferol 10 micrograms (400 units), net price 56-tab pack = £4.99. Label: 13

Cacit® D3 (Procter & Gamble Pharm.)

Granules, effervescent, lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca 12.5 mmol), colecalciferol 11 micrograms (440 units)/sachet, net price 30-sachet pack = £43.11. Label: 13

Calceos® (Galeni)

Tablets (chewable), lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £3.84. Label: 24

Calchew-D® (Shire)

Tablets (chewable), orange flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca 12.5 mmol), colecalciferol 5 micrograms (200 units), net price 100-tab pack = £15.02. Label: 24

Excipients include aspartame (section 9.4.1)

Calchew-D® Forte (Shire)

Tablets (chewable), lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £4.50, 100-tab pack = £7.50. Label: 24

Excipients include aspartame (section 9.4.1)

Calvotr D3® (Menarini)

Powder, lemon flavour, calcium phosphate 3.1 g (calcium 1.2 g or Ca 30 mmol), colecalciferol 20 micrograms (800 units), net price 30-sachet pack = £4.32. Label: 13, 21

Natalc D3® (Trinity-Chiesi)

Tablets, (aniseed, peppermint, and molasses flavour), calcium carbonate 1.5 g (calcium 600 mg or Ca 15 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £3.85. Label: 24

Excipients include aspartame (section 9.4.1)

With alendronic acid

Section 6.6.2

With risedronate sodium and calcium

Section 6.6.2

DIHYDROTACHYSTEROL

Indications see notes above

Cautions see under Ergocalciferol

Contra-indications see under Ergocalciferol

Side-effects see under Ergocalciferol

AT 10® (Intrapharm)

Oral solution, dihydrotachysterol 250 micrograms/mL. Net price 15-mL dropper bottle = £22.87

Excipients include arachis (peanut) oil

Dose acute, chronic, and latent forms of hypocalcaemic tetany due to hypoparathyroidism, consult product literature
**Vitamin E**

**Indications**  see under preparations below

**Cautions**  monitor plasma calcium and phosphate during dose titration and at least monthly when stabilised; monitor parathyroid hormone concentration; pregnancy (Appendix 4); breastfeeding (Appendix 5); interactions: Appendix 1 (vitamins)

**Contra-indications**  see under Ergocalciferol

**Side-effects**  see under Ergocalciferol; also dyspepsia, taste disturbance, breast tenderness, acne, pruritus, and rash

**Dose**
- Consult product literature

**Zemplar®** (Abbott) ▼ 

- **Capsules**
  - paricalcitol 1 microgram (grey), net price 28-cap pack = £69.44; 2 micrograms (orange-brown), 28-cap pack = £138.88; 4 micrograms (gold), 28-cap pack = £277.76
  - For prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure

- **Injection**
  - paricalcitol 5 micrograms/mL, net price 5 × 1-mL amp = £62.00, 5 × 2-mL amp = £124.00.
  - For injection via haemodialysis access

**Excipients** include propylene glycol, see Excipients, p. 2

- For prevention and treatment of secondary hyperparathyroidism associated with chronic renal failure in patients on haemodialysis

**Vitamin K**

**Indications**  see notes above

**Cautions**  G6PD deficiency (section 9.1.5) and vitamin E deficiency (risk of haemolysis); interactions: Appendix 1 (vitamins)

**Contra-indications**  neonates and infants, late pregnancy

**Dose**
- 10–40 mg daily, adjusted as necessary; **CHILD** 1–12 years, 5–10 mg daily, adjusted as necessary, 12–18 years, 10–20 mg daily, adjusted as necessary

**Menadiol Phosphate** (Cambridge)

- **Tablets**, menadiol sodium phosphate equivalent to 10 mg of menadiol phosphate. Net price 100-tab pack = £48.25

**Phytonadione** (Vitamin K)

**Indications**  see notes above

**Cautions**  intravenous injections should be given very slowly (see also below); pregnancy (Appendix 4); interactions: Appendix 1 (vitamins)

**ALPHA TOCOPHERYL ACETATE**

**Indications**  see notes above

**Cautions**  predisposition to thrombosis; increased risk of necrotising enterocolitis in neonate weighing less than 1.5 kg; interactions: Appendix 1 (vitamins)

**Side-effects**  diarrhoea and abdominal pain with doses more than 1 g daily

**Vitamin E Suspension** (Cambridge)

- **Suspension**, alpha tocopheryl acetate 500 mg/5 mL
  - Net price 100 mL = £25.08

- **Dose**
  - Malabsorption in cystic fibrosis, 100–200 mg daily; **CHILD** 1 month–1 year 50 mg daily; 1–12 years, 100 mg daily
  - Malabsorption in abetalipoproteinaemia, **ADULT** and **CHILD** 50–100 mg/kg daily
  - Malabsorption in chronic cholestasis and severe liver disease, **CHILD** see **BNF for Children**

**Note**

- Tablets containing tocopheryl acetate are available from ‘special-order’ manufacturers or specialist importing companies, see p. 939
9.6.7 Multivitamin preparations

Vitamins
Capsules, ascorbic acid 15 mg, nicotinamide 7.5 mg, riboflavin 500 micrograms, thiamine hydrochloride 1 mg, vitamin A 2500 units, vitamin D 300 units, net price 20 = 22p

Abidex (Chefaro UK)
Drops, vitamins A, B group, C, and D, net price 25 mL (with dropper) = £2.08
Excipients include arachis (peanut) oil
Note Contains 1333 units of vitamin A (as palmitate) per 0.6-mL dose

Dalivit (LPC)
Oral drops, vitamins A, B group, C, and D, net price 25 mL = £2.98, 50 mL = £4.85
Note Contains 5000 units of vitamin A (as palmitate) per 0.6-mL dose

Junior capsules, brown, vitamins (ascorbic acid 25 mg, biotin 50 micrograms, cyanocobalamin 2 micrograms, folic acid 100 micrograms, nicotinamide 7.5 mg, pantothenic acid 2 mg, pyridoxine 1 mg, riboflavin 1 mg, thiamine 1.5 mg, vitamin A 1250 units, vitamin D 200 units, vitamin E 5 mg, vitamin K 25 micrograms), minerals and trace elements (chromium 50 micrograms, copper 1 mg, iodine 75 micrograms, iron 5 mg, magnesium 1 mg, manganese 1.25 mg, molybdenum 50 micrograms, selenium 25 micrograms, zinc 5 mg), net price 30-cap pack = £3.52, 60-cap pack = £6.69
Dose vitamin and mineral deficiency and as adjunct in synthetic diets, CHILD over 5 years, 2 junior capsules daily

Ketovite (Paines & Byrne)
Tablets, yellow, ascorbic acid 16.6 mg, riboflavin 1 mg, thiamine hydrochloride 1 mg, pyridoxine hydrochloride 330 micrograms, nicotinamide 3.3 mg, calcium pantothenate 1.16 mg, alpha tocopheryl acetate 5 mg, inositol 50 mg, biotin 170 micrograms, folic acid 230 micrograms, acetonethaphone 50 micrograms, net price 100-tab pack = £4.17
Dose prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism and adjunct in restricted, specialised, or synthetic diets, 1 tablet 3 times daily; use with Ketovite Liquid for complete vitamin supplementation

Liquid, pink, sugar-free, vitamin A 2500 units, ergocalciferol 400 units, choline chloride 150 mg, cyanocobalamin 12.5 micrograms/5 mL, net price 150-mL pack = £2.70
Dose prevention of vitamin deficiency in disorders of carbohydrate or amino-acid metabolism and adjunct in restricted, specialised, or synthetic diets, 5 mL daily; use with Ketovite Tablets for complete vitamin supplementation

9.7 Bitters and tonics

Mixtures containing simple and aromatic bitters, such as alkaline gentian mixture, are traditional remedies for loss of appetite. All depend on suggestion.

Gentian Mixture, Alkaline, BP
(Alkaline Gentian Oral Solution)
Mixture, concentrated compound gentian infusion 10%, sodium bicarbonate 5% in a suitable vehicle. Extemporaneous preparations should be recently prepared according to the following formula: concentrated compound gentian infusion 1 mL, sodium bicarbonate 500 mg, double-strength chloroform water 5 mL, water to 10 mL
Dose 10 mL 3 times daily in water before meals

Effico (Forest)
Tonic, orange-red, thiamine hydrochloride 180 micrograms, nicotinamide 2.1 mg, caffeine 20.2 mg, compound gentian infusion 0.31 mL/5 mL, net price 300-mL pack = £2.53, 500-mL pack = £3.20

Metatone (Chefaro UK)
Tonic, thiamine hydrochloride 500 micrograms, calcium glycerophosphate 1250 units, vitamin A 1250 units, vitamin D 200 units, vitamin E 5 mg, vitamin K 25 micrograms, minerals and trace elements (calcium glycerophosphate 45.6 mg, manganese glyceralenate 25 micrograms, zinc 5 mg), net price 300 mL = £2.79
9.8 Metabolic disorders

9.8.1 Drugs used in metabolic disorders

This section covers drugs used in metabolic disorders and not readily classified elsewhere.

9.8.2 Acute porphyrias

Wilson’s disease

Penicillamine (see also section 10.1.3) is used in Wilson’s disease (hepatolenticular degeneration) to aid the elimination of copper ions. See below for other indications.

Trientine is used for the treatment of Wilson’s disease only in patients intolerant of penicillamine; it is not an alternative to penicillamine for rheumatoid arthritis or cystinuria. Penicillamine-induced systemic lupus erythematosus may not resolve on transfer to trientine.

Zinc prevents the absorption of copper in Wilson’s disease. Symptomatic patients should be treated initially with a chelating agent because zinc has a slow onset of action. When transferring from chelating treatment to zinc maintenance therapy, chelating treatment should be co-administered for 2–3 weeks until zinc produces its maximal effect.

PENICILLAMINE

Indications see under Dose below

Cautions see section 10.1.3

Contra-indications see section 10.1.3

Side-effects see section 10.1.3

Dose

• Wilson’s disease, 1.5–2 g daily in divided doses before food; max. 2 g daily for 1 year; maintenance 0.75–1 g daily; ELDERLY 20 mg/kg daily in divided doses, adjusted according to response; CHILD up to 20 mg/kg daily in divided doses, minimum 500 mg daily

• Autoimmune hepatitis (used rarely; after disease controlled with corticosteroids), initially 500 mg daily in divided doses increased slowly over 3 months; usual maintenance dose 1.25 g daily; ELDERLY not recommended

• Cystinuria, therapeutic, 1–3 g daily in divided doses before food, adjusted to maintain urinary cystine below 200 mg/litre; prophylactic (maintain urinary cystine below 300 mg/litre) 0.5–1 g at bedtime; maintain adequate fluid intake (at least 3 litres daily); CHILD and ELDERLY minimum dose to maintain urinary cystine below 200 mg/litre

• Severe active rheumatoid arthritis, section 10.1.3

Preparations

Section 10.1.3

TRIENTINE DIHYDROCHLORIDE

Indications Wilson’s disease in patients intolerant of penicillamine

Cautions see notes above; pregnancy (Appendix 4); interactions: Appendix 1 (trientine)

Side-effects nausea, rash; rarely anaemia

Dose

• 1.2–2.4 g daily in 2–4 divided doses before food; CHILD initially 0.6–1.5 g daily in 2–4 divided doses before food, adjusted according to response

Trientine Dihydrochloride (Univar) Capsules, trientine dihydrochloride 300 mg. Label: 6, 22

ZINC ACETATE

Indications Wilson’s disease (initiated under specialist supervision)

Cautions portal hypertension (risk of hepatic decompensation when switching from chelating agent); monitor full blood count and serum cholesterol; pregnancy (Appendix 4); interactions: Appendix 1 (zinc)

Contra-indications breast-feeding

Side-effects gastric irritation (usually transient; may be reduced if first dose taken mid-morning or with a little protein); less commonly sideroblastic anaemia and leucopenia

Dose

Note Dose expressed as elemental zinc

• Wilson’s disease, 50 mg 3 times daily (max. 50 mg 5 times daily), adjusted according to response; CHILD 1–6 years, 25 mg twice daily; 6–16 years, body-weight under 57 kg, 25 mg 3 times daily, body-weight over 57 kg, 50 mg 3 times daily; ADOLESCENT 16–18 years, 50 mg 3 times daily

Wilzin® (Orphan Europe) Capsules, zinc (as acetate) 25 mg (blue), net price 250-cap pack = £132.00; 50 mg (orange), 250-cap pack = £242.00. Label: 23

Carnitine deficiency

Carnitine is available for the management of primary carnitine deficiency due to inborn errors of metabolism or of secondary deficiency in haemodialysis patients.

CARNITINE

Indications primary and secondary carnitine deficiency

Cautions diabetes mellitus; renal impairment; monitoring of free and acyl carnitine in blood and urine recommended; pregnancy (Appendix 4) and breast-feeding

Side-effects nausea, vomiting, abdominal pain, diarrhoea, body odour; side-effects may be dose-related—monitor tolerance during first week and after any dose increase
**Nutrition and blood**

**Dose**
- Primary deficiency, by mouth, up to 200 mg/kg daily in 2–4 divided doses; higher doses of up to 400 mg/kg daily occasionally required; by intravenous injection over 2–3 minutes, up to 100 mg/kg daily in 3–4 divided doses
- Secondary deficiency, by intravenous injection over 2–3 minutes, 20 mg/kg after each dialysis session (dosage adjusted according to carnitine concentration); maintenance, by mouth, 1 g daily

**Carnitor®** (Sigma-Tau) (Sigma-Tau)

- Oral liquid, L-carnitine 100 mg/mL (10%), net price $10 x 10-mL (1-g) single-dose bottle = £35.00
- Paediatric solution, L-carnitine 300 mg/mL (30%), net price 20 mL = £21.00
- Excipients include sorbitol
- Injection, L-carnitine 200 mg/mL. Net price 5-mL amp = £11.90

**Fabry’s disease**

Agalsidase alfa and agalsidase beta, enzymes produced by recombinant DNA technology, are licensed for long-term enzyme replacement therapy in Fabry’s disease (a lysosomal storage disorder caused by deficiency of alpha-galactosidase A).

**AGALSIDASE ALFA AND BETA**

**Indications** Fabry’s disease (specialist use only)

**Cautions** pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (agalsidase alfa and beta)

**Side-effects** gastrointestinal disturbances, taste disturbances; tachycardia, bradycardia, palpitation, hypertension, hypotension, chest pain, oedema, flushing; dyspnoea, cough, wheezing, hoarseness, rhinorrhea; headache, fatigue, dizziness, asthenia, paraesthesia, syncope, neuropathic pain, tremor, sleep disturbances; influenza-like symptoms, nasopharyngitis; pain in extremities; eye irritation; tinnitus, vertigo; hypersensitivity reactions, pruritus, urticaria, rash, acne; less commonly bronchospasm, angioedema, cold extremities, parosmia, ear pain and swelling, skin discoloration, and injection-site reactions

**Fabrazyme®** (Genzyme)

- Intravenous infusion, powder for reconstitution, agalsidase beta, net price 5-mg vial = £325.50; 35-mg vial = £2269.20
- Dose: By intravenous infusion, ADULT and CHILD over 8 years 1 mg/kg every 2 weeks

**Replagal®** (Shire)

- Concentrate for intravenous infusion, agalsidase alfa 1 mg/mL, net price 1-mL vial = £356.85; 3.5-mL vial = £1161.57
- Dose: By intravenous infusion, ADULT and CHILD over 7 years 200 micrograms/kg every 2 weeks

**Gaucher’s disease**

Imiglucerase, an enzyme produced by recombinant DNA technology, is administered as enzyme replacement therapy for non-neurological manifestations of type I or type III Gaucher’s disease, a familial disorder affecting principally the liver, spleen, bone marrow, and lymph nodes.

**Miglustat**, an inhibitor of glucosylceramide synthase, is licensed for the treatment of mild to moderate type I Gaucher’s disease in patients for whom imiglucerase is unsuitable; it is given by mouth.

**IMIGLUCERASE**

**Indications** (specialist use only) non-neurological manifestations of type I or type III Gaucher’s disease

**Cautions** pregnancy (Appendix 4); breast-feeding (Appendix 5); monitor for imiglucerase antibodies; when stabilised, monitor all parameters and response to treatment at intervals of 6–12 months

**Side-effects** hypersensitivity reactions (including urticaria, angioedema, hypotension, flushing, tachycardia); less commonly nausea, vomiting, diarrhea, abdominal cramps, headache, dizziness, paraesthesia, fatigue, fever, arthralgia, injection-site reactions

**Dose**
- By intravenous infusion, initially 60 units/kg once every 2 weeks (2.5 units/kg 3 times a week or 15 units/kg once every 2 weeks may improve haematological parameters and organomegaly, but not bone parameters); maintenance, adjust dose according to response

**Cerezyme®** (Genzyme)

- Intravenous infusion, powder for reconstitution, imiglucerase, net price 200-unit vial = £553.35; 400-unit vial = £1106.70
- Electrolytes Na 0.62 mmol/200-unit vial, 1.24 mmol/400-unit vial

**MIGLUSTAT**

**Indications** mild to moderate type I Gaucher’s disease (specialist supervision only)

**Cautions** hepatic impairment (Appendix 2); renal impairment (Appendix 3); monitor cognitive and neurological function

**Contra-indications** pregnancy (Appendix 4); men should not father a child during or within 3 months of treatment; breast-feeding (Appendix 5)

**Side-effects** diarrhoea, flatulence, abdominal pain, dyspepsia, constipation, nausea, vomiting, anorexia, weight changes; tremor, dizziness, headache, peripheral neuropathy, impaired coordination, hypoaesthesia, paraesthesia, insomnia, fatigue, asthenia; decreased libido; thrombocytopenia; muscle spasm

**Dose**
- ADULT over 18 years, 100 mg 3 times daily; reduced if not tolerated to 100 mg 1–2 times daily

**Zavesca®** (Actelion)

- Capsules, miglustat 100 mg, net price 84-cap pack = £4015.00 (hospital only)
Mucopolysaccharidosis

Laronidase, an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in the treatment of non-neurological manifestations of mucopolysaccharidosis I, a lysosomal storage disorder caused by deficiency of alpha-L-iduronidase.

Idursulfase, an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in mucopolysaccharidosis II (Hunter syndrome), a lysosomal storage disorder caused by deficiency of iduronate-2-sulfatase.

Galsulfase, a recombinant form of human N-acetylgalactosamine-4-sulfatase, is licensed for long-term replacement therapy in mucopolysaccharidosis VI (Maroteaux-Lamy syndrome).

Infusion-related reactions often occur with administration of laronidase, idursulfase, and galsulfase; they can be managed by slowing the infusion rate or interrupting the infusion, and can be minimised by pre-treatment with an antihistamine and an antipyretic. Recurrent infusion-related reactions may require pre-treatment with a corticosteroid—consult product literature for details.

**GALSULFASE**

**Indications** (specialist use only) mucopolysaccharidosis VI

**Cautions** respiratory disease; acute febrile or respiratory illness (consider delaying treatment); pregnancy (Appendix 4)

**Infusion-related reactions** See notes above

**Contra-indications** breast-feeding (Appendix 5)

**Side-effects** abdominal pain, umbilical hernia, gastroenteritis; chest pain, hypertension; dyspnoea, apnoea, nasal congestion; rashes, malaise, areflexia; pharyngitis; conjunctivitis, corneal opacity; ear pain; facial oedema

**Dose**

- By intravenous infusion, ADULT and CHILD over 5 years, 1 mg/kg once weekly

**Naglazyme** (BioMarin)

Concentrate for intravenous infusion, galsulfase 1 mg/mL, net price 5-mL vial = £982.00

**LARONIDASE**

**Indications** (specialist use only) non-neurological manifestations of mucopolysaccharidosis I

**Cautions** monitor immunoglobulin G (IgG) antibody concentration; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (laronidase)

**Infusion-related reactions** See notes above

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain; cold extremities, pallor, flushing, tachycardia, blood pressure changes; dyspnoea, cough, angioedema, anaphylaxis; headache, paraesthesia, dizziness, fatigue, restlessness; influenza-like symptoms; musclekeletal pain, pain in extremities; rash, pruritus, urticaria, alopecia, infusion-site reactions; bronchospasm and respiratory arrest also reported

**Dose**

- By intravenous infusion, ADULT and CHILD over 5 years, 100 units/kg once weekly;

**Aldurazyme** (Genzyme)

Concentrate for intravenous infusion, laronidase 100 units/mL, net price 5-mL vial = £460.35

Electrolytes Na 1.29 mmol/5-mL vial

Nephropathic cystinosis

Mercaptamine (cysteamine) is available for the treatment of nephropathic cystinosis.

**MERCAPTAMINE** (Cysteamine)

**Indications** (specialist use only) nephropathic cystinosis

**Cautions** leucocyte-cystine concentration and haematological monitoring required—consult product literature; dose of phosphate supplement may need to be adjusted

**Contra-indications** pregnancy and breast-feeding; hypersensitivity to mercaptamine or penicillamine

**Side-effects** breath and body odour, nausea, vomiting, diarrhoea, anorexia, lethargy, fever, rash; also reported dehydration, hypertension, abdominal discomfort, gastroenteritis, drowsiness, encephalopathy, headache, nervousness, depression; anaemia, leuco-
penia; rarely gastro-intestinal ulceration and bleeding, seizures, hallucinations, urticaria, interstitial nephritis

**Dose**
- Initial doses should be one-sixth to one-quarter of the expected maintenance dose, increased gradually over 4–6 weeks
- Maintenance, **ADULT** and **CHILD** over 50 kg body-weight, 2 g daily in 4 divided doses
  - **CHILD** up to 12 years, 1.3 g/m (approx. 50 mg/kg) daily in 4 divided doses

**Cystagon** (Orphan Europe) [\[\]]

- **Capsules**, mercaptamine (as bitartrate) 50 mg, net price 100-cap pack = £59.00; 150 mg, 100-cap pack = £162.00
- **Note** **CHILD** under 6 years at risk of aspiration, capsules can be opened and contents sprinkled on food (at a temperature suitable for eating); avoid adding to acidic drinks (e.g. orange juice)

**Pompe disease**

Alglucosidase alfa, an enzyme produced by recombinant DNA technology, is licensed for long-term replacement therapy in Pompe disease, a lysosomal storage disorder caused by deficiency of acid alpha-glucosidase.

The Scottish Medicines Consortium (p. 3) has advised (February 2007) that alglucosidase alfa (*Myozyme*) is not recommended for use within NHS Scotland for the treatment of Pompe disease.

**ALGLUCOSIDASE ALFA**

- **Indications** (specialist use only) Pompe disease
- **Cautions** cardiac and respiratory dysfunction—monitor closely; monitor immunoglobulin G (IgG) antibody concentration; pregnancy (Appendix 4)
- **Infusion-related reactions** Infusion-related reactions very common, calling for use of antihistamine, antipyretic or corticosteroid; consult product literature for details
- **Contra-indications** breast-feeding (Appendix 5)
- **Side-effects** nausea, vomiting; flushing, tachycardia, blood pressure changes, cold extremities, cyanosis, facial oedema; cough, tachypnoea, bronchospasm; headache, agitation, tremor, irritability, restlessness, paraesthesia, dizziness; pyrexia, rigors; antibody formation; sweating, rash, pruritus, and urticaria; anaphylaxis

**Dose**
- **By intravenous infusion**, 20 mg/kg every 2 weeks

*Myozyme* (Genzyme) [\[\]]

- **Intravenous infusion**, powder for reconstitution, alglucosidase alfa, net price 50-mg vial = £368.59

**Urea cycle disorders**

Sodium phenylbutyrate is used in the management of urea cycle disorders. It is indicated as adjunctive therapy in all patients with neonatal-onset disease and in those with late-onset disease who have a history of hyperammonaemic encephalopathy.

Carglumic acid is licensed for the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.

**CARGLUMIC ACID**

- **Indications** hyperammonaemia due to *N*-acetylglutamate synthase deficiency (initiated under specialist supervision)
- **Cautions** pregnancy (Appendix 4)
- **Contra-indications** breast-feeding (Appendix 5)
- **Side-effects** sweating

**Dose**
- **ADULT** and **CHILD** initially 100 mg/kg daily in 2–4 divided doses immediately before food (max. 250 mg/kg daily), adjusted according to plasma–ammonia concentration; maintenance 10–100 mg/kg daily in 2–4 divided doses

*Carbaglu* (Orphan Europe) [\[\]]

- **Dispersible tablets**, carglumic acid 200 mg, net price 5-tab pack = £243.00, 60-tab pack = £2914.00
- **Label**: 13

**Tyrosinaemia type I**

Nitisinone is licensed for the treatment of hereditary tyrosinaemia type I in combination with dietary restriction of tyrosine and phenylalanine.
**SODIUM PHENYLButyRATE**

**Indications** adjunct in long-term treatment of urea cycle disorders (under specialist supervision)

**Cautions** congestive heart failure, hepatic and renal impairment; **interactions**: Appendix 1 (sodium phenylbutyrate)

**Contra-indications** pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** amenorrhoea and irregular menstrual cycles, decreased appetite, body odour, taste disturbances; less commonly nausea, vomiting, abdominal pain, peptic ulcer, pancreatitis, rectal bleeding, arrhythmia, oedema, syncope, depression, headache, rash, weight gain, renal tubular acidosis, aplastic anaemia, ecchymoses

**Dose**
- **ADULT** and **CHILD** over 20 kg, 9.9–13 g/m² daily in divided doses with meals (max. 20 g daily); **CHILD** less than 20 kg, 450–600 mg/kg daily in divided doses with meals

**Ammonaps®** (Swedish Orphan) pH

**Tablets**, sodium phenylbutyrate 500 mg. Contains Na⁺ 2.7 mmol/tablet. Net price 250-tab pack = £493.00

**Granules**, sodium phenylbutyrate 940 mg/g. Contains Na⁺ 5.4 mmol/g. Net price 266-g pack = £860.00

Note Granules should be mixed with food before taking

**Homocystinuria**

**Betaine** is licensed for the adjunctive treatment of homocystinuria involving deficiencies or defects in cystathionine beta-synthase, 5,10-methylene-tetrahydrofolate reductase, or cobalamin cofactor metabolism. Betaine should be used in conjunction with dietary restrictions and may be given with supplements of Vitamin B, pyridoxine, and folate under specialist advice.

The **Scottish Medicines Consortium** (p. 3) has advised (September 2007) that betaine anhydrous oral powder (**Cystadane®**) is not recommended for use within NHS Scotland as adjunctive treatment of homocystinuria.

**BETAINe**

**Indications** (specialist use only) adjunctive treatment of homocystinuria

**Cautions** monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** less commonly gastro-intestinal disorders, anorexia, reversible cerebral oedema (see Cautions), agitation, depression, personality disorder, sleep disturbances, urinary incontinence, alopecia, and urticaria

**Dose**
- **ADULT** and **CHILD** over 10 years, 3 g twice daily, adjusted according to response; max. 20 g/day; **CHILD** under 10 years 50 mg/kg twice daily, dose and frequency adjusted according to response; max. 75 mg/kg twice daily

**Cystadane®** (Orphan Europe) pH

**Powder**, betaine (anhydrous), net price 180 g = £314.00

Note Powder should be mixed with water, juice, milk, formula, or food until completely dissolved and taken immediately; measuring spoons are provided to measure 1 g, 150 mg, and 100 mg of powder

**9.8.2 Acute porphyrias**

The acute porphyrias (acute intermittent porphyria, variegate porphyria, hereditary coproporphyria, and 5-aminolaevulinic acid dehydratase deficiency porphyria) are hereditary disorders of haem biosynthesis; they have a prevalence of about 1 in 10 000 of the population.

Great care must be taken when prescribing for patients with acute porphyria, since certain drugs can induce acute porphyrin crises. Since acute porphyrias are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs.

Treatment of serious or life-threatening conditions should not be withheld from patients with acute porphyria. When there is no safe alternative, urinary porphobilinogen excretion should be measured regularly; if it increases or symptoms occur, the drug can be withdrawn and the acute attack treated. If an acute porphyrin attack occurs during pregnancy, contact an expert porphyria service for further advice.

**Haem arginate** is administered by short intravenous infusion as haem replacement in moderate, severe, or unremitting acute porphyrin crises. Since acute porphyrias are hereditary, relatives of affected individuals should be screened and advised about the potential danger of certain drugs.

Supplies of haem arginate may be obtained outside office hours from the on-call pharmacist at: St Thomas’ Hospital, London (020) 7188 7188

**HAEM ARGINATE**

(Human hemin)

**Indications** acute porphyrias (acute intermittent porphyria, porphyria variegata, hereditary coproporphyria)

**Cautions** pregnancy (Appendix 4); breast feeding (Appendix 5)

**Side-effects** rarely hypersensitivity reactions and fever; pain and thrombophlebitis at injection site

**Dose**
- **ADULT** and **CHILD** 3 mg/kg once daily (max. 250 mg daily) for 4 days; if response inadequate, repeat 4-day course with close biochemical monitoring

**Normosang®** (Orphan Europe) pH

Concentrate for intravenous infusion, haem arginate 25 mg/mL, net price 10-mL amp = £338.50

---

**BNF 57**

9 Nutrition and blood
Drugs unsafe for use in acute porphyrias

The following list contains drugs on the UK market that have been classified as ‘unsafe’ in porphyria because they have been shown to be porphyrinogenic in animals or in vitro, or have been associated with acute attacks in patients. Absence of a drug from the following lists does not necessarily imply that the drug is safe. For many drugs no information about porphyria is available.

An up-to-date list of drugs considered safe in acute porphyria is available at www.wmmic.wales.nhs.uk/porphyria_info.php

Further information may be obtained from: www.porphyria-europe.org

and also from:
Welsh Medicines Information Centre
University Hospital of Wales
Cardiff, CF14 4XW
Tel: (029) 2074 2979/3877

Note Quite modest changes in chemical structure can lead to changes in porphyrinogenicity but where possible general statements have been made about groups of drugs; these should be checked first.

Unsafe Drug Groups (check first)

<table>
<thead>
<tr>
<th>Amphetamines</th>
<th>Anabolic steroids</th>
<th>Antidepressants</th>
<th>Antihistamines</th>
<th>Barbiturates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Contraceptives, hormonal</td>
<td>Ergot derivatives</td>
<td>Gold salts</td>
<td>Hormone Replacement Therapy</td>
</tr>
</tbody>
</table>

Unsafe Drugs (check groups above first)

1. Includes tricyclic (and related) antidepressants and MAOIs; fluoxetine and mianserin thought to be safe.
2. Alimemazine (trimeprazine), chlorphenamine, desloratadine, fexofenadine, ketotifen, loratadine, and promethazine thought to be safe.
3. Includes primidone and thiopental.
4. Diltiazem may be used with caution if safer alternative not available.
5. Progestogens are more porphyrinogenic than oestrogens; oestrogens may be safe at least in replacement doses. Progestogens should be avoided whenever possible by all women susceptible to acute porphyria; however, when non-hormonal contraception is inappropriate, progestogens may be used with extreme caution if the potential benefit outweighs risk. The risk of an acute attack is greatest in women who have had a previous attack or are aged under 30 years. Long-acting contraceptives, hormonal and also from:
6. Includes co-trimoxazole and sulfasalazine.
7. Rosuvastatin is thought to be safe.
8. Contact Welsh Medicines Information Centre for further advice.
9. Although evidence of hazard is uncertain, manufacturer advises avoid.
10. Small amounts in medicines probably safe.
11. Ergometrine (oxytocin probably safe) and pergolide.
12. Progestogen preparations should never be used in those at risk of acute porphyria.
13. Status epilepticus has been treated successfully with intravenous diazepam.
14. When used for local anaesthesia, bupivacaine, lidocaine (lignocaine), procaine, prilocaine, and tetracaine are thought to be safe.
15. Buprenorphine, codeine, diamorphine, dihydrocodeine, fentanyl, methadone, morphine, and pethidine are thought to be safe.
16. Rifamycins have been used in a few patients without evidence of harm—use with caution if safer alternative not available.
17. Includes aminophylline.
Rheumatoid arthritis and other inflammatory disorders

A non-steroidal anti-inflammatory drug (NSAID) is indicated for pain and stiffness resulting from inflammatory rheumatic disease. Drugs are also used to influence the disease process itself (section 10.1.3). For rheumatoid arthritis these disease-modifying antirheumatic drugs (DMARDs) include penicillamine, gold salts, antimalarials (chloroquine and hydroxychloroquine), drugs that affect the immune response, and sulfasalazine; corticosteroids may also be of value (section 10.1.2.1). Drugs which may affect the disease process in psoriatic arthritis include sulfasalazine, gold salts, azathioprine, methotrexate (section 10.1.3), and etanercept. For long-term control of gout uricosuric drugs and allopurinol (section 10.1.4) can be used.

Osteoarthritis and soft-tissue disorders

In osteoarthritis (sometimes called degenerative joint disease or osteoarthrosis) non-drug measures, such as weight reduction and exercise, should be encouraged. For pain relief in osteoarthritis and soft-tissue disorders, paracetamol (section 4.7.1) should be used first and may need to be taken regularly. A topical NSAID (section 10.3.2) should also be considered, particularly in knee or hand osteoarthritis. If further pain relief is required, then an oral NSAID (section 10.1.1), selective inhibitor of cyclo-oxygenase-2, or opioid (section 4.7.2) should be considered; a proton pump inhibitor (section 1.3.5) should be taken with a NSAID or selective inhibitor of cyclo-oxygenase-2. An opioid should be considered before a NSAID or selective inhibitor of cyclo-oxygenase-2 in patients taking low-dose aspirin.
Topical capsaicin 0.025% (section 10.3.2) should be considered as an adjunct in hand or knee osteoarthritis.

Intra-articular corticosteroid injections (section 10.1.2.2) may produce temporary benefit in osteoarthritis, especially if associated with soft-tissue inflammation.

Glucosamine (section 10.1.5) is licensed for symptomatic relief of mild to moderate osteoarthritis of the knee.

10.1.1 Non-steroidal anti-inflammatory drugs

In single doses non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic activity comparable to that of paracetamol (section 4.7.1), but paracetamol is preferred, particularly in the elderly (see also Prescribing for the Elderly, p. 20).

In regular full dosage NSAIDs have both a lasting analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of continuous or regular pain associated with inflammation. Therefore, although paracetamol often gives adequate pain control in osteoarthritis, NSAIDs are more appropriate than paracetamol or the opioid analgesics in the inflammatory arthritides (e.g. rheumatoid arthritis) and in some cases of advanced osteoarthritis. NSAIDs can also be of benefit in the less well defined conditions of back pain and soft-tissue disorders.

Choice

Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individuals’ tolerance to these drugs and their response to them. About 60% of patients will respond to any NSAID; of the others, those who do not respond to one may well respond to another. Pain relief starts soon after taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks. If appropriate responses are not obtained within these times, another NSAID should be tried.

NSAIDs reduce the production of prostaglandins by inhibiting the enzyme cyclo-oxygenase. They vary in their selectivity for inhibiting different types of cyclo-oxygenase; selective inhibition of cyclo-oxygenase-2 reduces gastro-intestinal intolerance. Several other factors also influence susceptibility to gastro-intestinal effects, and a NSAID should be chosen on the basis of the incidence of gastro-intestinal and other side-effects.

Ibuprofen is a propionic acid derivative with anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other non-selective NSAIDs but its anti-inflammatory properties are weaker. Doses of 1.6 to 2.4 g daily are needed for rheumatoid arthritis and it is unsuitable for conditions where inflammation is prominent, such as acute gout. Dextibuprofen is the active enantiomer of ibuprofen. It has similar properties to ibuprofen and is licensed for the relief of mild to moderate pain and inflammation.

Other propionic acid derivatives:

- Naproxen is one of the first choices because it combines good efficacy with a low incidence of side-effects (but more than ibuprofen, see CSM comment below).
- Fenbufen is claimed to be associated with less gastrointestinal bleeding, but there is a high risk of rash (see p. 557).
- Feno profen is as effective as naproxen, and flurbiprofen may be slightly more effective. Both are associated with slightly more gastro-intestinal side-effects than ibuprofen.
- Ketoprofen has anti-inflammatory properties similar to ibuprofen and has more side-effects (see also CSM advice below). Dextketoprofen, an isomer of ketoprofen, has been introduced for the short-term relief of mild to moderate pain.
- Tiaprofenic acid is as effective as naproxen; it has more side-effects than ibuprofen (important: reports of severe cystitis, see CSM advice on p. 561).

Drugs with properties similar to those of propionic acid derivatives:

- Azapropazone is similar in effect to naproxen; it has a tendency to cause rashes and is associated with an increased risk of severe gastro-intestinal toxicity (important: see CSM restrictions on p. 554).
- Diclofenac and aceclofenac have actions and side-effects similar to those of naproxen.
- Etodolac is comparable in efficacy to naproxen; it is licensed for symptomatic relief of osteoarthritis and rheumatoid arthritis.
- Indometacin (indomethacin) has an action equal to or superior to that of naproxen, but with a high incidence of side-effects including headache, dizziness, and gastrointestinal disturbances (see also CSM advice below).
- Mefenamic acid has minor anti-inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinuation of treatment.
- Meloxicam is licensed for the short-term relief of pain in osteoarthritis and for long-term treatment of rheumatoid arthritis and ankylosing spondylitis.
- Nabumetone is comparable in effect to naproxen.
- Piroxicam is as effective as naproxen and has a long duration of action which permits once-daily administration. However, it has more gastro-intestinal side-effects than most other NSAIDs, and is associated with more frequent serious skin reactions (important: see CHMP advice, p. 560).
Sulindac is similar in tolerance to naproxen.

Tenoxicam is similar in activity and tolerance to naproxen. Its long duration of action allows once-daily administration.

Toltenamic acid is licensed for the treatment of migraine (section 4.7.4.1).

Ketorolac and the selective inhibitor of cyclo-oxygenase-2, parecoxib, are licensed for the short-term management of postoperative pain (section 15.1.4.2).

The selective inhibitors of cyclo-oxygenase-2, etoricoxib and celecoxib, are as effective as non-selective NSAIDs such as diclofenac and naproxen. Short-term data indicate that the risk of serious upper gastro-intestinal events is lower with selective inhibitors compared to non-selective NSAIDs; this advantage may be lost in patients who require concomitant low-dose aspirin. There are concerns about the cardiovascular safety of cyclo-oxygenase-2 selective inhibitors (see below).

Celecoxib and etoricoxib are licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; etoricoxib is also licensed for the relief of pain from acute gout.

Dental and orofacial pain Most mild to moderate dental pain and inflammation is effectively relieved by NSAIDs. Those used for dental pain include ibuprofen and diclofenac.

In an appraisal of the relative safety of 7 non-selective NSAIDs, the CSM assessed ibuprofen to have the lowest risk of serious gastro-intestinal side-effects (see p. 554).

For further information on the management of dental and orofacial pain, see p. 229.

Cautions and contra-indications NSAIDs should be used with caution in the elderly (risk of serious side-effects and fatalities, see also Prescribing for the Elderly p. 20), in allergic disorders (they are contra-indicated in patients with a history of hypersensitivity to aspirin or any other NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by aspirin or any other NSAID), during pregnancy and breast-feeding (see Appendix 4 and Appendix 5), and in coagulation defects. Long-term use of some NSAIDs is associated with reduced female fertility, which is reversible on stopping treatment.

In patients with renal, cardiac, or hepatic impairment caution is required since NSAIDs may impair renal function (see also Under-side-effects, below and Appendix 2 and Appendix 3); the dose should be kept as low as possible and renal function should be monitored.

All NSAIDs are contra-indicated in severe heart failure. The selective inhibitors of cyclo-oxygenase-2 (celecoxib, etoricoxib, and parecoxib) are contra-indicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and moderate or severe heart failure. The selective inhibitors of cyclo-oxygenase-2 should be used with caution in patients with a history of cardiac failure, left ventricular dysfunction, hyper-tension, in patients with oedema for any other reason, and in patients with risk factors for heart disease.

NSAIDs and cardiovascular events Cyclo-oxygenase-2 selective inhibitors are associated with an increased risk of thrombotic events (e.g. myocardial infarction and stroke) and should not be used in preference to non-selective NSAIDs except when specifically indicated (i.e. for patients at a particularly high risk of developing gastroduodenal ulceration or bleeding) and after assessing their cardiovascular risk.

Non-selective NSAIDs may also be associated with a small increased risk of thrombotic events particularly when used at high doses and for long-term treatment. Diclofenac (150 mg daily) and ibuprofen (2.4 g daily) are associated with an increased risk of thrombotic events. The increased risk for diclofenac is similar to that of licensed doses of etoricoxib. Naproxen (1 g daily) is associated with a lower thrombotic risk, and low doses of ibuprofen (1.2 g daily or less) have not been associated with an increased risk of myocardial infarction. A small increased thrombotic risk cannot be excluded for other NSAIDs.

The CHM has advised (October 2006) that the lowest effective dose of NSAID or cyclo-oxygenase-2 selective inhibitor should be prescribed for the shortest period to control symptoms and that the need for long-term treatment should be reviewed periodically.

The CSM has advised that non-selective NSAIDs are contra-indicated in patients with previous or active peptic ulceration and that selective inhibitors of cyclo-oxygenase-2 are contra-indicated in active peptic ulceration (see also CSM advice below). While it is preferable to avoid NSAIDs in patients with active or previous gastro-intestinal ulceration or bleeding, and to withdraw them if gastro-intestinal lesions develop, nevertheless patients with serious rheumatic diseases (e.g. rheumatoid arthritis) are usually dependent on NSAIDs for effective relief of pain and stiffness. For advice on the prophylaxis and treatment of NSAID-associated peptic ulcers, see section 1.3.

For interactions of NSAIDs, see Appendix 1 (NSAIDs).

Side-effects Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration occur (see also CSM advice below). Systemic as well as local effects of NSAIDs contribute to gastro-intestinal damage; taking oral formulations with milk or food, or using enteric-coated formulations, or changing the route of administration may only partially reduce symptoms such as dyspepsia. Those at risk of duodenal or gastric ulceration (including the elderly) who need to continue NSAID treatment should receive either a selective inhibitor of cyclo-oxygenase-2 alone, or a non-selective NSAID with gastroprotective treatment (section 1.3).

Other side-effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm—see CSM advice below), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivitv, and haematuria. Blood disorders have also occurred. Fluid retention may occur (rarely precipitating congestive heart failure); blood pressure may be raised.
Renal failure may be provoked by NSAIDs, especially in patients with renal impairment (important, see also under Cautions above). Rarely, papillary necrosis or interstitial fibrosis associated with NSAIDs can lead to renal failure.

Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, eye changes, Stevens-Johnson syndrome and toxic epidermal necrolysis are other rare side-effects. Induction of or exacerbation of colitis has been reported. Aseptic meningitis has been reported rarely with NSAIDs; patients with connective-tissue disorders such as systemic lupus erythematosus may be especially susceptible.

Overdosage: see Emergency Treatment of Poisoning, p. 29.

**CSM advice (gastro-intestinal side-effects)**

All NSAIDs are associated with serious gastro-intestinal toxicity; the risk is higher in the elderly. Evidence on the relative safety of 7 non-selective NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects. Azapropazone is associated with the highest risk (important: see also CSM restrictions, below) and ibuprofen with the lowest; piroxicam, ketoprofen, indometacin, naproxen and diclofenac are associated with intermediate risks (possibly higher in the case of piroxicam, see also CHMP advice, p. 560). Selective inhibitors of cyclo-oxygenase-2 are associated with a lower risk of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Recommendations are that NSAIDs associated with a low risk e.g. ibuprofen are generally preferred, to start at the lowest recommended dose, not to use more than one oral NSAID at a time, and to remember that all NSAIDs (including selective inhibitors of cyclo-oxygenase-2) are contra-indicated in patients with active peptic ulceration. The CSM also contra-indicates non-selective NSAIDs in patients with a history of peptic ulceration.

The combination of a NSAID and low-dose aspirin can increase the risk of gastro-intestinal side-effects; this combination should be used only if absolutely necessary and the patient should be monitored closely.

**CSM warning (asthma)**

Any degree of worsening of asthma may be related to the ingestion of NSAIDs, either prescribed or (in the case of ibuprofen and others) purchased over the counter.

**ACECLOFENAC**

**Indications** pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis

**Cautions** see notes above; avoid in acute porphyria (section 9.8.2); breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- 100 mg twice daily; CHILD not recommended

**Preservex®** (UCB Pharma) [TH]

Tablets, f/c, aceclofenac 100 mg, net price 60-tab pack = £9.45. Label: 21

**ACEMETACIN**

(Glycolic acid ester of indometacin)

**Indications** pain and inflammation in rheumatic disease and other musculoskeletal disorders; postoperative analgesia

**Cautions** see under Indometacin and notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Driving** Dizziness may affect performance of skilled tasks (e.g. driving)

**Contra-indications** see notes above

**Side-effects** see under Indometacin and notes above

**Dose**

- 120 mg daily in divided doses with food, increased if necessary to 180 mg daily; CHILD not recommended

**Emflex®** (Merck) [TH]

Capsules, yellow/orange, acemetacin 60 mg, net price 90-cap pack = £28.20. Label: 21, counselling, driving

**AZAPROPAZONE**

**Indications** see under CSM restrictions

**CSM restrictions** CSM has restricted azapropazone to use in rheumatoid arthritis, ankylosing spondylitis, and acute gout only when other NSAIDs have been tried and failed, has contra-indicated it in patients with a history of peptic ulceration, and has reduced the maximum daily dose to 600 mg for rheumatoid arthritis and ankylosing spondylitis in patients over 60 years, and those with impaired renal function

**Cautions** see notes above; interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above; also acute porphyria (section 9.8.2); history of inflammatory bowel disease or blood disorder

**Side-effects** see notes above; also photosensitivity; see CSM advice below

**Photosensitivity** CSM has reminded of the need to advise patients taking azapropazone to avoid direct exposure to sunlight (or to use sunscreen preparations)

**Dose**

- Rheumatoid arthritis and ankylosing spondylitis, 1.2 g daily in 2 or 4 divided doses; ELDERLY over 60 years, 300 mg twice daily; CHILD not recommended

- Acute gout, 1.8 g daily in divided doses until acute symptoms subside (usually by day 4) then 1.2 g daily in divided doses until symptoms resolve—consider alternative therapy if symptoms persist; ELDERLY over 60 years, 1.8 g daily in divided doses for the first 24 hours then 1.2 g daily in divided doses, reduced to 600 mg daily in divided doses as soon as possible (preferably by day 4) until acute symptoms resolve—consider alternative therapy if symptoms persist; CHILD not recommended

**Rheumox®** (Goldshield) [TH]

Capsules, orange, azapropazone 300 mg, net price 100-cap pack = £15.50. Label: 11, 21, counselling, photosensitivity (see above)
CELECOXIB

Indications  pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis

Cautions  see notes above; monitor blood pressure before treatment and during treatment; interactions: Appendix 1 (NSAI ds)

Contra-indications  see notes above; sulphonamide sensitivity; inflammatory bowel disease

Side-effects  see notes above; flatulence, insomnia; less commonly stomatitis, constipation, palpitation, fatigue, paraesthesia, muscle cramps; rarely taste disturbance, alopecia; very rarely aggravation of epilepsy

Dose  
- Osteoarthritis, 200 mg daily in 1–2 divided doses, increased if necessary to max. 200 mg twice daily; CHILD not recommended
- Rheumatoid arthritis, 100 mg twice daily, increased if necessary to 200 mg twice daily; CHILD not recommended
- Ankylosing spondylitis, 200 mg daily in 1–2 divided doses, increased if necessary to max. 400 mg daily in 1–2 divided doses; CHILD not recommended

Note  Discontinue if no improvement after 2 weeks on max. dose

Celebrex® (Pharmacia)  Capsules, celecoxib 100 mg (white/blue), net price 60-cap pack = £21.55; 200 mg (white/gold), 30-cap pack = £21.55

DEXIBuprofen

Indications  pain and inflammation associated with osteoarthritis and other musculoskeletal disorders; mild to moderate pain and inflammation including dysmenorrhoea and dental pain

Cautions  see notes above; systemic lupus erythematosus and other connective tissue disorders; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAI ds)

Contra-indications  see notes above

Side-effects  see notes above

Dose  
- 600–900 mg daily in up to 3 divided doses; increased if necessary to max. 1.2 g daily (900 mg daily for dysmenorrhoea); max. single dose 400 mg (300 mg for dysmenorrhoea); CHILD not recommended

Seractil® (Genus)  Tablets, f/c, dexibuprofen 300 mg, net price 60–tab pack = £9.47; 400 mg (scored) 60–tab pack = £9.47. Label: 21

DESKETOPROFEN

Indications  short-term treatment of mild to moderate pain including dysmenorrhoea

Cautions  see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAI ds)

Contra-indications  see notes above

Side-effects  see notes above

Dose  
- 12.5 mg every 4–6 hours or 25 mg every 8 hours; max. 75 mg daily; ELDERLY initially max. 50 mg daily; CHILD not recommended

Keral® (Menarini)  Tablets, f/c, scored, dexketoprofen (as trometamol) 25 mg, net price 20-tab pack = £3.67, 50-tab pack = £9.18. Label: 22

DICLOFENAC SODIUM

Indications  pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders; acute gout; postoperative pain

Cautions  see notes above; interactions: Appendix 1 (NSAI ds)

Contra-indications  see notes above; acute porphyria (section 9.8.2); avoid injections containing benzyl alcohol in neonates (see preparations below)

Intravenous use  Additional contra-indications include concomitant NSAID or anticoagulant use (including low-dose heparin), history of haemorrhagic diathesis, history of confirmed or suspected cerebrovascular bleeding, operations with high risk of haemorrhage, history of asthma, moderate or severe renal impairment, hypovolaemia, dehydration

Side-effects  see notes above; suppositories may cause rectal irritation; injection site reactions

Dose  
- By mouth, 75–150 mg daily in 2–3 divided doses
- By rectum in suppositories, 75–150 mg daily in divided doses
- CHILD 1–12 years, juvenile arthritis, by mouth or by rectum, 1–3 mg/kg (max. 150 mg) daily in divided doses (25 mg e/c tablets, 12.5 mg and 25 mg suppositories only)
- CHILD 6–12 years, postoperative pain, by rectum, 1–2 mg/kg (max. 150 mg) daily in divided doses (12.5 mg and 25 mg suppositories only) for max. 4 days

Diclofenac Sodium (Non-proprietary)  Tablets, e/c, diclofenac sodium 25 mg, net price 84–tab pack = £1.19; 50 mg, 84-tab pack = £1.36. Label: 5, 25

Brands include Defenc®, Dicloflex®, Diclozap®, Fenacot®, Flamrase

Dental prescribing on NHS Diclofenac Sodium Tablets may be prescribed

Suppositories, diclofenac sodium 100 mg, net price 10 = £3.06

Brands include Econac

Dyloject® (Javelin)  Injection, diclofenac sodium 37.5 mg/mL, net price 2-mL vial = £4.80

Dose  by deep intramuscular injection into the gluteal muscle, acute exacerbations of pain and postoperative pain, 75 mg once daily (twice daily in severe cases) for max. 2 days

Urteretic colic, 75 mg then a further 75 mg after 30 minutes if necessary

By intravenous injection (in supervised settings), acute postoperative pain, 75 mg repeated after 4–6 hours if necessary; max. 150 mg in 24 hours for 2 days

Prevention of postoperative pain, 25–50 mg after surgery; further doses given after 4–6 hours if necessary; max. 150 mg in 24 hours for 2 days

Note  The Scottish Medicines Consortium (p. 3) has advised (Feb 2008) that Dyloject® is accepted for restricted use within NHS Scotland for the treatment or prevention of postoperative pain by intravenous injection in supervised healthcare settings

Voltarol® (Novartis)  Tablets, e/c, diclofenac sodium 25 mg (yellow), net price 84-tab pack = £3.67; 50 mg (brown), 84-tab pack = £5.71. Label: 5, 25
Dispersible tablets, sugar-free, pink, diclofenac, equivalent to diclofenac sodium 50 mg, net price 21-tab pack = £6.19. Label: 13, 21

Note Voltarol Dispersible tablets are more suitable for short-term use in acute conditions for which treatment required for no more than 3 months (no information on use beyond 3 months)

Injection, diclofenac sodium 25 mg/mL, net price 3-mL amp = £8.3p

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 2), propylene glycol

Dose by deep intramuscular injection into the gluteal muscle, acute exacerbations of pain and postoperative pain, 75 mg once daily (twice daily in severe cases) for max. 2 days

Ureteric colic, 75 mg then a further 75 mg after 30 minutes if necessary

By intravenous infusion (in hospital setting), acute postoperative pain, 75 mg repeated if necessary after 4–6 hours, max. 150 mg in 24 hours for 2 days

Prevention of postoperative pain, initially after surgery 25–50 mg over 15–60 minutes then 5 mg/hour, max. 150 mg in 24 hours for 2 days

Suppositories, diclofenac sodium 12.5 mg, net price 10 = £1.71; 25 mg, 10 = £1.26; 50 mg, 10 = £2.07; 100 mg, 10 = £3.70

Diclofenac potassium

Voltarol® Rapid (Novartis) (PHV)

Tablets, s/c, diclofenac potassium 25 mg (red), net price 30-tab pack = £4.33; 50 mg (brown), 30-tab pack = £8.28

Dose rheumatic disease, musculoskeletal disorders, acute gout, postoperative pain, 75–150 mg daily in 2–3 divided doses; CHILD over 14 years, 75–100 mg daily in 2–3 divided doses

Migraine, 50 mg at onset, repeated after 2 hours if necessary then over 15–60 minutes then 5 mg/hour; max. 150 mg in 24 hours for 2 days

Contra-indications see notes above; also dehydration; monitor blood pressure before treatment, 2 weeks after

Topical preparations

Section 10.3.2

ETODOLAC

Indications pain and inflammation in rheumatoid arthritis and osteoarthritis

Cautions see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

Contra-indications see above

Side-effects see notes above; also flatulence, constipation, vomiting, ulcerative stomatitis, gastritis, vasculitis, palpitation, dyspnoea, confusion, fatigue, paraesthesia, tremor, urinary frequency, dysuria, pyrexia, and pruritus

Dose

ADULT over 18 years, 600 mg daily in 1–2 divided doses

Etodolac (Non-proprietary) (PHV)

Capsules, etodolac 300 mg, net price 60-cap pack = £8.14

Brands include Eccoxolac

Modified release

Etopan XL® (Taro) (PHV)

Tablets, m/r, f/c, grey, etodolac 600 mg, net price 30-tab pack = £15.50. Label: 25

Dose 1 tablet daily; CHILD not recommended

Lodine SR® (Shire) (PHV)

Tablets, m/r, f/c, light-grey, etodolac 600 mg, net price 30-tab pack = £15.50. Label: 25

Dose 1 tablet daily; CHILD not recommended

ETORICOXIB

Indications pain and inflammation in osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis; acute gout

Cautions see notes above; also dehydration; monitor blood pressure before treatment, 2 weeks after
initiation and periodically during treatment; hepatic impairment (avoid if severe; Appendix 2); renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above; inflammatory bowel disease; uncontrolled hypertension (persistently above 140/90 mmHg); breast-feeding (Appendix 5)

**Side-effects** see notes above; also flatulence, palpitation, fatigue, influenza-like symptoms, eczema, less commonly dry mouth, taste disturbance, mouth ulcer, constipation, appetite and weight change, atrial fibrillation, transient ischaemic attack, chest pain, flushing, cough, dyspnoea, epistaxis, anxiety, mental acuity impaired, paraesthesia, electrolyte disturbance, myalgia and arthralgia; very rarely confusion and hallucinations

**Dose**
- Osteoarthritis, ADULT and CHILD over 16 years, 30 mg once daily, increased if necessary to 60 mg once daily
- Rheumatoid arthritis and ankylosing spondylitis, ADULT and CHILD over 16 years, 90 mg once daily
- Acute gout, ADULT and CHILD over 16 years, 120 mg once daily for max. 8 days

**Fenoprofen**

**Indications** pain and inflammation in rheumatic disease and other musculoskeletal disorders

**Cautions** see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above

**Side-effects** see notes above; upper respiratory-tract infection, nasopharyngitis, and cystitis also reported

**Dose**
- 300–600 mg 3–4 times daily with food; max. 3 g daily
- CHILD not recommended

**Fenopron** (Typharm) Tablets, both orange, fenoprofen (as calcium salt) 300 mg (Fenopron 300), net price 100-tab pack = £9.45; 600 mg (Fenopron 600, scored), 100-tab pack = £18.29. Label: 21

**FLURBIPROFEN**

**Indications** pain and inflammation in rheumatic disease and other musculoskeletal disorders; mild to moderate pain including dysmenorrhoea; migraine; postoperative analgesia; sore throat (section 12.3.1)

**Cautions** see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above

**Side-effects** see notes above; also vomiting, ulcerative stomatitis; less commonly gastritis, paraesthesia, confusion, hallucinations, and fatigue

**Dose**
- ADULT and CHILD over 12 years, 150–200 mg daily in 2–4 divided doses, increased in acute conditions to 300 mg daily
- Dysmenorrhoea, ADULT and CHILD over 12 years, initially 100 mg, then 50–100 mg every 4–6 hours; max. 300 mg daily

**Flurbiprofen** (Non-proprietary) Tablets, flurbiprofen 50 mg, net price 20 = £2.54; 100 mg, 20 = £5.16. Label: 21

**Froben** (Abbott) Tablets, yellow, s/c, flurbiprofen 50 mg, net price 20 = £2.18; 100 mg, 20 = £4.13. Label: 21

**Modified release**

**Froben SR** (Abbott) Capsules, m/r, yellow, flurbiprofen 200 mg, net price 30-cap pack = £7.84. Label: 21, 25

**Dose**
- ADULT and CHILD over 12 years, 1 capsule daily, preferably in the evening

**IBUPROFEN**

**Indications** pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders; mild to moderate pain including dysmenorrhoea; postoperative analgesia; migraine; dental pain; fever and pain in children; post-immunisation pyrexia (section 14.1)

**Cautions** see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above

**Side-effects** see notes above; overdosage: see Emergency Treatment of Poisoning, p. 29

**Dose**
- ADULT and CHILD over 12 years, initially 300–400 mg 3–4 times daily; increased if necessary to max. 2.4 g daily; maintenance dose of 0.6–1.2 g daily may be adequate
Musculoskeletal and joint diseases

Suspension Sugar-free may be prescribed

10.1.1 Non-steroidal anti-inflammatory drugs

BNF 57

- Pain and fever in children, CHILD 1–3 months, see BNF for Children, CHILD 3–6 months (body-weight over 5 kg), 50 mg 3 times daily (max. 30 mg/kg daily in 3–4 divided doses); CHILD 6 months–1 year, 50 mg 3–4 times daily (max. 30 mg/kg daily in 3–4 divided doses); CHILD 1–4 years, 100 mg 3 times daily (max. 30 mg/kg daily in 3–4 divided doses); CHILD 4–7 years, 150 mg 3 times daily (max. 30 mg/kg daily in 3–4 divided doses); CHILD 7–10 years, 200 mg 3 times daily (up to 30 mg/kg daily (max. 2.4 g) in 3–4 divided doses); CHILD 10–12 years, 300 mg 3 times daily (up to 30 mg/kg daily (max. 2.4 g) in 3–4 divided doses)

- Rheumatic disease in children (including juvenile idiopathic arthritis), CHILD 3 months–18 years (body-weight over 5 kg), 30–40 mg/kg (max. 2.4 g) daily in 3–4 divided doses; in systemic juvenile idiopathic arthritis up to 60 mg/kg (max. 2.4 g) daily (unlicensed) in 4–6 divided doses

1 Ibuprofen (Non-proprietary) PbM

- Tablets, coated, ibuprofen 200 mg, net price 84-tab pack = £2.07; 400 mg, 84-tab pack = £2.31; 600 mg, 84-tab pack = £3.96. Brand: Label: 21
- Brands include Arthritis , Eufaft , Rimafen

- Oral suspension, ibuprofen 100 mg/5 mL, net price 100 mL = £1.44, 150 mL = £2.71, 500 mL = £8.88. Label: 21
- Note Sugar-free versions are available and can be ordered by specifying ‘sugar-free’ on the prescription
- Brands include Culprofen , Fenpaed , Feverfen , Nurofen for Children , Orfifen for Children

- Dental prescribing on NHS Ibuprofen Tablets and Ibuprofen Oral Suspension Sugar-free may be prescribed

Brufen® (Abbott) PbM

- Tablets, f/c, ibuprofen 200 mg, net price 100-tab pack = £4.08; 400 mg, 100-tab pack = £8.16; 600 mg, 100-tab pack = £12.24. Label: 21
- Syrup, orange, ibuprofen 100 mg/5 mL, net price 500 mL (orange-flavoured) = £8.88. Label: 21
- Granules, effervescent, ibuprofen 600 mg/sachet, net price 20-sachet pack = £6.80. Label: 13, 21
- Electrolytes Na approx. 9 mmol/sachet

- Modified release
- Brufen Retard® (Abbott) PbM
- Tablets, m/r, ibuprofen 800 mg, net price 56-tab pack = £6.74. Label: 25, 27
- Dose ADULT and CHILD over 12 years, 2 tablets daily as a single dose, preferably in the early evening, increased in severe cases to 3 tablets daily in 2 divided doses

- Fenbid® (Goldshield) PbM
- Spansule® (= capsule m/r), maroon/pink, enclosing off-white pellets, ibuprofen 300 mg, net price 120-cap pack = £9.64. Label: 25
- Dose ADULT and CHILD over 12 years, initially 2 capsules twice daily, increased in severe cases to 3 capsules twice daily; then 1–2 capsules twice daily

- Topical preparations
- Section 10.3.2

1. Can be sold to the public in certain circumstances; for exemptions see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available)

INDOMETACIN (Indomethacin)

Indications pain and moderate to severe inflammation in rheumatic disease and other acute musculoskeletal disorders; acute gout; dysmenorrhoea; closure of ductus arteriosus (section 7.1.1.1); premature labour (section 7.1.3)

Cautions see notes above; also epilepsy, parkinsonism, psychiatric disturbances; during prolonged therapy ophthalmic and blood examinations particularly advisable; avoid rectal administration in proctitis and haemorrhoids; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

Driving Dizziness may affect performance of skilled tasks (e.g. driving)

Contra-indications see notes above

Side-effects see notes above; frequently gastro-intestinal disturbances (including diarrhoea), headache, dizziness, and light-headedness; also gastro-intestinal ulceration and bleeding; rarely, drowsiness, confusion, insomnia, convulsions, psychiatric disturbances, depression, syncope, blood disorders (particularly thrombocytopenia), hypertension, hyperglycaemia, blurred vision, corneal deposits, peripheral neuropathy, and intestinal strictures; suppositories may cause rectal irritation and occasional bleeding

Dose
- By mouth, rheumatic disease, 50–200 mg daily in divided doses; CHILD not recommended
- Acute gout, 150–200 mg daily in divided doses
- Dysmenorrhoea, up to 75 mg daily
- By rectum in suppositories, 100 mg at night and in the morning if required; CHILD not recommended
- Combined oral and rectal treatment, max. total daily dose 150–200 mg

Indometacin (Non-proprietary) PbM

- Capsules, indometacin 25 mg, net price 28-cap pack = £1.59; 50 mg, 28-cap pack = £1.93. Label: 21, counselling, driving, see above
- Suppositories, indometacin 100 mg, net price 10 = £14.46. Counselling, driving, see above

- Modified release
- Indometacin m/r preparations PbM
- Capsules, m/r, indometacin 75 mg. Label: 21, 25, counselling, driving, see above
- Brands include Indolar SR , Pareldrin , Solo-Indo
- Dose 1 capsule 1–2 times daily, CHILD not recommended

KETOPROFEN

Indications pain and mild inflammation in rheumatic disease and other musculoskeletal disorders, and after orthopaedic surgery; acute gout; dysmenorrhoea

Cautions see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

Contra-indications see notes above

Side-effects see notes above; pain may occur at injection site (occasionally tissue damage); suppositories may cause rectal irritation

Dose
- By mouth, rheumatic disease, 100–200 mg daily in 2–4 divided doses; CHILD not recommended
- Pain and dysmenorrhoea, 50 mg up to 3 times daily; CHILD not recommended
**MEFENAMIC ACID**

**Indications** pain and inflammation in rheumatoid arthritis and osteoarthritis; postoperative pain, mild to moderate pain; dysmenorrhoea and menorrhagia

**Cautions** see notes above; epilepsy; breast-feeding (Appendix 5); acute porphyria (section 9.8.2); in proctitis or haemorrhoids; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above; renal failure (unless receiving dialysis); severe heart failure

**Side-effects** see notes above

**Dose**
- **Adult** over 18 years, 500 mg 3 times daily
- **Child** 12–18 years, acute pain including dysmenorrhoea, menorrhagia, 500 mg 3 times daily
- **Child** under 12 years not recommended

**Mefenamic Acid**

**Capsules**
- Mefenamic acid 250 mg, net price 100-cap pack = £3.97. Label: 21
- Tablets, mefenamic acid 500 mg, net price 28-tab pack = £1.97. Label: 21
- Suspension, mefenamic acid 50 mg/5 mL, net price 125 mL = £79.99. Label: 21

**Excipients** include ethanol

**MELOXICAM**

**Indications** pain and inflammation in rheumatic disease; exacerbation of osteoarthritis (short-term); ankylosing spondylitis

**Cautions** see notes above; avoid rectal administration in proctitis or haemorrhoids; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above; renal failure (unless receiving dialysis); severe heart failure

**Side-effects** see notes above

**Dose**
- **By mouth**, osteoarthritis, 7.5 mg daily, increased if necessary to max. 15 mg once daily
- **Rheumatoid arthritis, ankylosing spondylitis, 15 mg once daily, may be reduced to 7.5 mg daily; Elderly 7.5 mg daily**
- **By rectum**, in suppositories, osteoarthritis, 7.5 mg daily, increased if necessary to max. 15 mg once daily
- **Rheumatoid arthritis, ankylosing spondylitis, 15 mg once daily, may be reduced to 7.5 mg daily; Elderly 7.5 mg daily**
- **Child** under 15 years not recommended

**Meloxicam**

**Tablets**
- Meloxicam 7.5 mg, net price 30-tab pack = £2.85; 15 mg, 30-tab pack = £3.52. Label: 21

**Mobic**

**Tablets**
- yellow, scored, meloxicam 7.5 mg, net price 30-tab pack = £9.30; 15 mg, 30-tab pack = £12.93. Label: 21

**Note** Tablets may be dispersed in water

**Suppositories**
- meloxicam 7.5 mg, net price 12 = £3.72; 15 mg, 12 = £5.58

**NABUMETONE**

**Indications** pain and inflammation in osteoarthritis and rheumatoid arthritis

**Cautions** see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- **1 g at night; severe or persistent symptoms 0.5–1 g in morning and 1 g at night; Elderly 0.5–1 g daily; Child not recommended**

**Nabumetone**

**Tablets**
- Nabumetone 500 mg, net price 56-tab pack = £7.29. Label: 21

**Relifex**

**Tablets**
- red, f/c, nabumetone 500 mg. Net price 56-tab pack = £6.18. Label: 21

**Suspension**
- sugar-free, nabumetone 500 mg/5 mL. Net price 300-mL pack = £24.08. Label: 21
NAPROXEN

Indications
pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders; dysmenorrhoea; acute gout

Cautions
see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

Contra-indications
see notes above

Side-effects
see notes above

Dose

- Rheumatic disease, 0.5–1 g daily in 1–2 divided doses; CHILD 2–18 years, juvenile idiopathic arthritis, 5 mg/kg twice daily [max. 1 g daily] [unlicensed]

- Acute musculoskeletal disorders and dysmenorrhoea, 500 mg initially, then 250 mg every 6–8 hours as required; max. dose after first day 1.25 g daily; CHILD under 18 years, see BNF for Children

- Acute gout, 750 mg initially, then 250 mg every 8 hours until attack has passed; CHILD under 16 years not recommended

<table>
<thead>
<tr>
<th>Naproxen (Non-proprietary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets, naproxen 250 mg, net price 28-tab pack = £1.29; 500 mg, 28-tab pack = £1.71. Label: 21</td>
</tr>
<tr>
<td>Brands include Ardrexone</td>
</tr>
<tr>
<td>Tablets, e/c, naproxen 250 mg, net price 56-tab pack = £4.99; 375 mg, 56-tab pack = £6.96; 500 mg, 56-tab pack = £6.88. Label: 5, 25</td>
</tr>
</tbody>
</table>

1 Can be sold to the public for the treatment of primary dysmenorrhoea in women aged 15–50 years subject to max. single dose of 500 mg, max. daily dose of 750 mg for max. 3 days, and a max. pack size of 9 × 250 mg tablets

<table>
<thead>
<tr>
<th>Naprosyn® (Roche)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets, yellow, scored, naproxen 250 mg, net price 56-tab pack = £4.55; 500 mg, 56-tab pack = £9.09. Label: 21</td>
</tr>
<tr>
<td>Tablets, e/c. (Naprosyn EC®), naproxen 250 mg, net price 56-tab pack = £4.55; 375 mg, 56-tab pack = £6.82; 500 mg, 56-tab pack = £9.09. Label: 5, 25</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Synflex® (Roche)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets, blue, naproxen sodium 275 mg, net price 60-tab pack = £7.54. Label: 21</td>
</tr>
<tr>
<td>Note 275 mg naproxen sodium = 250 mg naproxen</td>
</tr>
<tr>
<td>Dose musculoskeletal disorders, postoperative analgesia, 550 mg twice daily when necessary, preferably after food; max. 1.1 g daily; CHILD under 16 years not recommended</td>
</tr>
<tr>
<td>Dysmenorrhoea and acute gout, initially 550 mg then 275 mg every 6–8 hours as required, max. of 1.375 g on first day and 1.1 g daily thereafter; CHILD under 16 years not recommended</td>
</tr>
<tr>
<td>Migraine, 825 mg at onset, then 275–550 mg at least 30 minutes after initial dose; max. 1.375 g in 24 hours; CHILD under 16 years not recommended</td>
</tr>
</tbody>
</table>

- With misoprostol

For cautions, contra-indications, and side-effects of misoprostol, see section 1.3.4

<table>
<thead>
<tr>
<th>Napratec® (Pharmacia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination pack, 56 yellow scored tablets, naproxen 500 mg; 56 white scored tablets, misoprostol 200 micrograms. Net price = £23.76. Label: 21</td>
</tr>
<tr>
<td>Dose patients requiring naproxen for rheumatoid arthritis, osteoarthritis, or ankylosing spondylitis, with prophylaxis against NSAID-induced gastrointestinal ulceration, 1 naproxen 500-mg tablet and 1 misoprostol 200-microgram tablet taken together twice daily with food; CHILD not recommended</td>
</tr>
</tbody>
</table>

PIROXICAM

Indications
pain and inflammation in rheumatic disease (including juvenile idiopathic arthritis) and other musculoskeletal disorders; acute gout

Cautions
see notes above and CHMP advice below; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

Contra-indications
see notes above

Side-effects
see notes above; pain at injection site (occasionally tissue damage)

Dose

- By mouth, rheumatic disease, initially 20 mg daily, increased if necessary to 30 mg daily in single or divided doses; CHILD (over 6 years), juvenile idiopathic arthritis, under 15 kg, 5 mg daily; 16–25 kg, 10 mg; 26–45 kg, 15 mg; over 46 kg, 20 mg (but see CHMP advice below)

Acute musculoskeletal disorders, 40 mg daily in single or divided doses for 2 days, then 20 mg daily for 7–14 days (but see CHMP advice below); CHILD not recommended

Acute gout, 40 mg initially, then 40 mg daily in single or divided doses for 4–6 days (but see CHMP advice below); CHILD not recommended

- By deep intramuscular injection into gluteal muscle, for initial treatment of acute conditions (but see CHMP advice below), as dose by mouth (on short-term basis); CHILD not recommended

CHMP advice

Piroxicam (June 2007)

The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastrointestinal side effects and serious skin reactions. The CHMP has advised that:

- piroxicam should be initiated only by physicians experienced in treating inflammatory or degenerative rheumatic diseases
- piroxicam should not be used as first-line treatment
- in adults, use of piroxicam should be limited to the symptomatic relief of osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis
- piroxicam dose should not exceed 20 mg daily
- piroxicam should no longer be used for the treatment of osteoarthritis, rheumatic disease, initially 20 mg daily, increased if necessary to 30 mg daily in single or divided doses; CHILD (over 6 years), juvenile idiopathic arthritis, under 15 kg, 5 mg daily; 16–25 kg, 10 mg; 26–45 kg, 15 mg; over 46 kg, 20 mg (but see CHMP advice below)

Acute musculoskeletal disorders, 40 mg daily in single or divided doses for 2 days, then 20 mg daily for 7–14 days (but see CHMP advice below); CHILD not recommended

Acute gout, 40 mg initially, then 40 mg daily in single or divided doses for 4–6 days (but see CHMP advice below); CHILD not recommended

- By deep intramuscular injection into gluteal muscle, for initial treatment of acute conditions (but see CHMP advice below), as dose by mouth (on short-term basis); CHILD not recommended

Note
Topical preparations containing piroxicam are not affected by these restrictions

Piroxicam (Non-proprietary)

| Capsules, piroxicam 10 mg, net price 56-cap pack = £2.07; 20 mg, 28-cap pack = £1.99. Label: 21 |
| Dispersible tablets, piroxicam 10 mg, net price 56-tab pack = £9.96; 20 mg, 28-tab pack = £35.07. Label: 13, 21 |
| Brexido® (Trinity) |
| Tablets, yellow, scored, piroxicam (as betadex) 20 mg, net price 30-tab pack = £14.66. Label: 21 |
| Dose osteoarthritis, rheumatic disease and acute musculoskeletal disorders, 1 tablet daily (may be halved in elderly); CHILD not recommended |
| Feldene® (Pfizer) |
| Capsules, piroxicam 10 mg (red/blue), net price 56-cap pack = £7.20; 20 mg (white), 28-cap pack = £7.20. Label: 21 |
**Corticosteroids**

The general actions, uses, and cautions of corticosteroids are described in section 6.3. Treatment with corticosteroids in rheumatic diseases should be reserved for specific indications, e.g. when other anti-inflammatory drugs are unsuccessful. Corticosteroids can induce osteoporosis, and prophylaxis should be considered on long-term treatment (section 6.6).

In severe, possibly life-threatening, situations a high initial dose of corticosteroid is given to induce remission and the dose is then reduced gradually and discontinued altogether. Relapse may occur as the dose of corticosteroid is reduced, particularly if the reduction is too rapid. The tendency is therefore to increase the maintenance dose and consequently the patient becomes dependent on corticosteroids. For this reason pulse doses of corticosteroids (e.g. methylprednisolone up to 1 g intravenously on 3 consecutive days) are used to suppress highly active inflammatory disease while longer-term treatment with a disease-modifying drug is commenced.

Prednisolone 7.5 mg daily may reduce the rate of joint destruction in moderate to severe rheumatoid arthritis of less than 2 years' duration. The reduction in joint destruction must be distinguished from mere symptomatic improvement (which lasts only 6 to 12 months at this dose) and care should be taken to avoid increasing the dose above 7.5 mg daily. Evidence supports maintenance of this anti-erosive dose for 2–4 years only after which treatment should be tapered off to reduce long-term adverse effects.

---

**Aspirin**

Aspirin (section 4.7.1) has been used in high doses to treat rheumatoid arthritis, but other NSAIDs are now preferred.

---

**SULINDAC**

**Indications** pain and inflammation in rheumatic disease and other musculoskeletal disorders; acute gout

**Cautions** see notes above; also renal stones

**Contra-indications** see notes above; breast-feeding (Appendix 1); jaundice with fever

**Side-effects** see notes above; jaundice with fever, cholestasis, hepatitis, hepatic failure; also urine discoloration occasionally reported

**Dose**

- 200 mg twice daily (may be reduced according to response); max. 400 mg daily; acute gout should respond within 7 days; limit treatment of peri-articular disorders to 7–10 days; CHILD not recommended

**Sulindac** (Non-proprietary)

**Tablets**, sulindac 100 mg, net price 56-tab pack = £17.51; 200 mg, 56-tab pack = £35.48. Label: 21

---

**TENOXICAM**

**Indications** pain and inflammation in rheumatic disease and other musculoskeletal disorders

**Cautions** see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- By mouth, rheumatic disease, 20 mg daily; CHILD not recommended
- Acute musculoskeletal disorders, 20 mg daily for 7 days; max. duration of treatment 14 days (including treatment by intravenous or intramuscular injection); CHILD not recommended
- By intravenous or intramuscular injection, initial treatment for 1–2 days if oral administration not possible, 20 mg once daily; CHILD not recommended

**Tenoxicam** (Non-proprietary)

**Injection**, powder for reconstitution, tenoxicam, net price 20-mg vial = £3.98

**Mobiflex** (Roche)

**Tablets**, yellow, f/c, tenoxicam 20 mg, net price 30-tab pack = £12.92. Label: 21

---

**TIAPROFENIC ACID**

**Indications** pain and inflammation in rheumatic disease and other musculoskeletal disorders

**Cautions** see notes above; breast-feeding (Appendix 5); interactions: Appendix 1 (NSAIDs)

**Contra-indications** see notes above; also active bladder or prostate disease (or symptoms) and history of recurrent urinary-tract disorders—i.e. urinary symptoms develop discontinue immediately and perform urine tests and culture; see also CSM advice below

**CSM advice**

Following reports of severe cystitis the CSM has recommended that tiaprofenic acid should not be given to patients with urinary-tract disorders and should be stopped if urinary symptoms develop. Patients should be advised to stop taking tiaprofenic acid and to report to their doctor promptly if they develop urinary-tract symptoms (such as increased frequency, nocturia, urgency, pain on urinating, or blood in urine)

**Side-effects** see notes above

**Dose**

- 300 mg twice daily; CHILD not recommended

**Surgam** (Sanofi-Aventis)

**Tablets**, tiaprofenic acid 300 mg, net price 56-tab pack = £15.56. Label: 21

---

**Aspirin**

Aspirin (section 4.7.1) has been used in high doses to treat rheumatoid arthritis, but other NSAIDs are now preferred.

---

**10.1.2.1 Systemic corticosteroids**

The general actions, uses, and cautions of corticosteroids are described in section 6.3. Treatment with corticosteroids in rheumatic diseases should be reserved for specific indications, e.g. when other anti-inflammatory drugs are unsuccessful. Corticosteroids can induce osteoporosis, and prophylaxis should be considered on long-term treatment (section 6.6).

In severe, possibly life-threatening, situations a high initial dose of corticosteroid is given to induce remission and the dose is then reduced gradually and discontinued altogether. Relapse may occur as the dose of corticosteroid is reduced, particularly if the reduction is too rapid. The tendency is therefore to increase the maintenance dose and consequently the patient becomes dependent on corticosteroids. For this reason pulse doses of corticosteroids (e.g. methylprednisolone up to 1 g intravenously on 3 consecutive days) are used to suppress highly active inflammatory disease while longer-term treatment with a disease-modifying drug is commenced.

Prednisolone 7.5 mg daily may reduce the rate of joint destruction in moderate to severe rheumatoid arthritis of less than 2 years’ duration. The reduction in joint destruction must be distinguished from mere symptomatic improvement (which lasts only 6 to 12 months at this dose) and care should be taken to avoid increasing the dose above 7.5 mg daily. Evidence supports maintenance of this anti-erosive dose for 2–4 years only after which treatment should be tapered off to reduce long-term adverse effects.
Polymyalgia rheumatica and giant cell (temporal) arteritis are always treated with corticosteroids. The usual initial dose of prednisolone in polymyalgia rheumatica is 10–15 mg daily and in giant cell arteritis 40–60 mg daily (the higher dose being used if visual symptoms occur). Treatment should be continued until remission of disease activity and doses are then reduced gradually to about 7.5–10 mg daily for maintenance. Relapse is common if therapy is stopped prematurely. Many patients require treatment for at least 2 years and in some patients it may be necessary to continue long-term low-dose corticosteroid treatment.

Polyparasitis nodosa and polymyositis are usually treated with corticosteroids. An initial dose of 60 mg of prednisolone daily is often used and reduced to a maintenance dose of 10–15 mg daily.

Systemic lupus erythematosus is treated with corticosteroids when necessary using a similar dosage regimen to that for polyparasitis nodosa and polymyositis (above). Patients with pleurisy, pericarditis, or other systemic manifestations will respond to corticosteroids. It may then be possible to reduce the dosage; alternate-day treatment is sometimes adequate, and the drug may be gradually withdrawn. In some mild cases corticosteroid treatment may be stopped after a few months. Many mild cases of systemic lupus erythematosus do not require corticosteroid treatment. Alternative treatment with anti-inflammatory analgesics, and possibly chloroquine or hydroxychloroquine, should be considered.

Ankylosing spondylitis should not be treated with long-term corticosteroids; rarely, pulse doses may be needed and may be useful in extremely active disease that does not respond to conventional treatment.

### 10.1.2 Local corticosteroid injections

Corticosteroids are injected locally for an anti-inflammatory effect. In inflammatory conditions of the joints, particularly in rheumatoid arthritis, they are given by intra-articular injection to relieve pain, increase mobility, and reduce deformity in one or a few joints. Full aseptic precautions are essential; infected areas should be avoided. Occasionally an acute inflammatory reaction develops after an intra-articular or soft-tissue injection of a corticosteroid. This may be a reaction to the microcrystalline suspension of the corticosteroid used, but must be distinguished from sepsis introduced into the injection site.

Smaller amounts of corticosteroids may also be injected directly into soft tissues for the relief of inflammation in conditions such as tennis or golfer’s elbow or compression neuropathies. In tendinitis, injections should be made into the tendon sheath and not directly into the tendon (due to the absence of a true tendon sheath, the Achilles tendon should not be injected). A soluble preparation (e.g. containing betamethasone or dexamethasone sodium phosphate) is preferred for injection into the carpal tunnel.

Hydrocortisone acetate or one of the synthetic analogues is generally used for local injection. Intra-articular corticosteroid injections can cause flushing and may affect the hyaline cartilage. Each joint should usually be treated no more than 3 times in one year.

Corticosteroid injections are also injected into soft tissues for the treatment of skin lesions (see section 13.4).

### LOCAL CORTICOSTEROID INJECTIONS

**Indications**  local inflammation of joints and soft tissues (for details, consult product literature)

**Cautions** see notes above and consult product literature; see also section 6.3.2

**Contra-indications** see notes above and consult product literature; avoid injections containing benzyl alcohol in neonates (see preparations below)

**Side-effects** see notes above and consult product literature

**Dose**

- See under preparations

#### Betamethasone

**Betnesol** (UCB Pharma) [\(\text{\textregistered}\)]

*Injection*, betamethasone (as sodium phosphate) 4 mg/mL, net price 1-mL amp = £1.22.

#### Dose calculated as dexamethasone

**Dexamethasone** (Organon) [\(\text{\textregistered}\)]

*Injection*, dexamethasone 4 mg/mL (as sodium phosphate) (\(=\) dexamethasone sodium phosphate 5.2 mg/mL \(=\) dexamethasone phosphate 4.8 mg/mL), net price 1-mL amp = £0.83; 2-mL vial = £1.27

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 0.4–4 mg (calculated as dexamethasone) according to size; where appropriate may be repeated at intervals of 3–21 days according to response

#### Dose calculated as dexamethasone phosphate

**Dexamethasone** (Hospira) [\(\text{\textregistered}\)]

*Injection*, dexamethasone phosphate 4 mg/mL (as sodium phosphate) (\(=\) dexamethasone 3.3 mg/mL \(=\) dexamethasone sodium phosphate 4.4 mg/mL), net price 1-mL amp = £1.00; 2-mL vial = £1.98

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 0.4–4 mg (calculated as dexamethasone phosphate) according to size (by soft-tissue infiltration 2–4 mg), where appropriate may be repeated at intervals of 3–21 days

#### Hydrocortisone acetate

**Hydrocortistab** (Sovereign) [\(\text{\textregistered}\)]

*Injection* (aqueous suspension), hydrocortisone acetate 25 mg/mL, net price 1-mL amp = £5.72

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 5–50 mg according to size, where appropriate may be repeated at intervals of 21 days; not more than 3 joints should be treated on any one day; CHILD 5–30 mg (divided)

#### Methylprednisolone acetate

**Depo-Medrone** (Pharmacia) [\(\text{\textregistered}\)]

*Injection* (aqueous suspension), methylprednisolone acetate 40 mg/mL, net price 1-mL vial = £2.87; 2-mL vial = £5.15; 3-mL vial = £7.47

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 4–80 mg, according to size, where appropriate may be repeated at intervals of 7–35 days; also for intralesional injection

**Depo-Medrone** with **Lidocaine** (Pharmacia) [\(\text{\textregistered}\)]

*Injection* (aqueous suspension), methylprednisolone acetate 40 mg, lidocaine hydrochloride 10 mg/mL, net price 1-mL vial = £3.28; 2-mL vial = £5.88

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 4–80 mg, according to size, where appropriate may be repeated at intervals of 7–35 days
10.1.3 Drugs that suppress the rheumatic disease process

Certain drugs such as those affecting the immune response can suppress the disease process in rheumatoid arthritis and psoriatic arthritis; gold, penicillamine, hydroxychloroquine, chloroquine, and sulfasalazine can also suppress the disease process in rheumatoid arthritis while sulfasalazine and possibly gold can suppress the disease process in psoriatic arthritis. Unlike NSAIDs, disease-modifying anti-rheumatic drugs (DMARDs) can affect the progression of disease but may require 2–6 months of treatment for a full therapeutic response. Since in the first few months of treatment, the course of rheumatoid arthritis is unpredictable and the diagnosis uncertain, it is usual to start treatment with an NSAID alone. However, disease-modifying anti-rheumatic drugs should be initiated by specialists as soon as diagnosis, progression, and severity of the disease have been confirmed. Response to a disease-modifying anti-rheumatic drug may allow the dose of the NSAID to be reduced.

Disease-modifying antirheumatic drugs can improve not only the symptoms of inflammatory joint disease but also extra-articular manifestations such as vasculitis. They reduce the erythrocyte sedimentation rate, C-reactive protein, and sometimes the titre of rheumatoid factor; some also retard erosive damage as judged radiologically.

### Prednisolone acetate

**Deltastab® (Sovereign)**

**Injection** (aqueous suspension), prednisolone acetate 25 mg/mL, net price 1-mL amp = £5.73

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 5–25 mg according to size; not more than 3 joints should be treated on any one day, where appropriate may be repeated when relapse occurs

For **intramuscular injection**, see section 6.3.2

### Triamcinolone acetonide

**Adcortyl® Intra-articular/Intradermal** (Squibb)

**Injection** (aqueous suspension), triamcinolone acetonide 10 mg/mL, net price 1-mL vial = £1.02; 5-mL vial = £4.14

**Excipients** include benzyl alcohol (avoid in neonates, see Excipients, p. 2)

**Dose** by intra-articular injection or intrasynovial injection (for details consult product literature), 2.5–15 mg according to size (for larger doses use Kenalog®); where appropriate may be repeated when relapse occurs

By **intradermal injection**, (for details consult product literature): 2–3 mg; max. 5 mg at any one site (total max. 30 mg); where appropriate may be repeated at intervals of 1–2 weeks

**CHILD under 6 years not recommended**

**Kenalog® Intra-articular/Intramuscular** (Squibb)

**Injection** (aqueous suspension), triamcinolone acetonide 40 mg/mL, net price 1-mL vial = £1.70; 1-mL prefilled syringe = £2.11; 2-mL prefilled syringe = £3.66

**Note** Intramuscular needle with prefilled syringe should be replaced for intra-articular injection

**Dose** by intra-articular or intrasynovial injection (for details consult product literature), 5–40 mg according to size; total max. 80 mg (for doses below 5 mg use Adcortyl Intra-articular/Intradermal), where appropriate may be repeated when relapse occurs. **CHILD under 6 years not recommended**

For **intramuscular injection**, see section 6.3.2

### Choice

The choice of a disease-modifying anti-rheumatic drug should take into account co-morbidity and patient preference. Sulfasalazine, methotrexate, intramuscular gold and penicillamine are similar in efficacy. However, sulfasalazine or methotrexate are often used first because they may be better tolerated.

Penicillamine and drugs that affect the immune response (‘immunomodulators’) are also sometimes used in rheumatoid arthritis where there are troublesome extra-articular features such as vasculitis, and in patients who are taking high doses of corticosteroids. Response to the drugs often produces a striking reduction in requirements of both corticosteroids and other drugs. Gold and penicillamine are effective in polidromic rheumatism. Systemic and discoid lupus erythematosus are sometimes treated with chloroquine or hydroxychloroquine.

If a disease-modifying anti-rheumatic drug does not lead to an objective benefit within 6 months (or within 3 months for inhibitors of tumour necrosis factor), it should be replaced by a different one.

In some circumstances, and under specialist supervision, combining two or more disease-modifying anti-rheumatic drugs can be considered.

### Juvenile idiopathic arthritis

Many children with juvenile idiopathic arthritis (juvenile chronic arthritis) do not require disease-modifying antirheumatic drugs. Methotrexate is effective [unlicensed indication]; sulfasalazine is an alternative [unlicensed indication] but it should be avoided in systemic-onset juvenile idiopathic arthritis. Gold and penicillamine are no longer used. For the role of adalimumab and etanercept in polyarticular juvenile idiopathic arthritis, see p. 569

### Gold

Gold can be given by intramuscular injection as sodium aurothiomalate or by mouth as auranofin.

**Sodium aurothiomalate** must be given by deep intramuscular injection and the area gently massaged. A test dose of 10 mg must be given followed by doses of 50 mg at weekly intervals until there is definite evidence of remission. Benefit is not to be expected until about 300–500 mg has been given; it should be discontinued if there is no remission after 1 g has been given. In patients who do respond, the interval between injections is then gradually increased to 4 weeks and treatment is continued for up to 5 years after complete remission. If relapse occurs the dosage frequency may be immediately increased to 50 mg weekly and only once control has been obtained again should the dosage frequency be decreased; if no response is seen within 2 months, alternative treatment should be sought. It is important to avoid complete relapse since second courses of gold are not usually effective. Children can be given 1 mg/kg weekly to a maximum of 50 mg weekly, the intervals being gradually increased to 4 weeks according to response; an initial test dose is given corresponding to one-tenth to one-fifth of the calculated dose.

**Auranofin** is given by mouth. If there is no response after 6 months treatment should be discontinued. Auranofin is less effective than parenteral gold.

Gold therapy should be discontinued in the presence of blood disorders, gastro-intestinal bleeding (associated with ulcerative enterocolitis), or unexplained proteinuria (associated with immune complex nephritis) which is
AURANOFIN
Indications active progressive rheumatoid arthritis
Cautions see under Sodium Aurothiomalate; inflammatory bowel disease; pregnancy (Appendix 4); breast-feeding (Appendix 5)
Blood counts Withdraw if platelet count falls below 100 000/mm³ or if signs and symptoms suggestive of thrombocytopenia occur, see also notes above
Counselling Patients should be advised to seek prompt medical attention if diarrhoea, rectal bleeding, sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, metallic taste, rash, breathlessness, or cough develop
Contra-indications see under Sodium Aurothiomalate
Side-effects see under Sodium Aurothiomalate; headache and dizziness
Dose • Administered on expert advice, 6 mg daily (initially in 2 divided doses then if tolerated as single dose), if response inadequate after 6 months, increase to 9 mg daily (in 3 divided doses), discontinue if no response after a further 3 months; CHILD not recommended

RIDURA® (Astellas) *(NM)
Tablets, yellow, f/c, auranofin 3 mg, net price 60-tab pack = £25.20. Label: 11, 21, counselling, blood disorder symptoms (see above)

SODIUM AUROTHIOMALATE
Indications active progressive rheumatoid arthritis, juvenile idiopathic arthritis
Cautions see notes above; elderly, history of urticaria, eczema, colitis; monitor for pulmonary fibrosis with annual chest X-ray; hepatic impairment (avoid if severe); renal impairment (avoid if severe); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (gold)
Counselling Patients should be advised to seek prompt medical attention if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, metallic taste, rash, breathlessness, or cough develop
Contra-indications history of blood disorders or bone marrow aplasia, exfoliative dermatitis, systemic lupus erythematosus, necrotising enterocolitis, pulmonary fibrosis; acute porphyria (section 9.8.2)
Side-effects see notes above; also severe anaphylactic reactions; stomatitis, taste disturbances, colitis, hepatotoxicity with cholestatic jaundice, pulmonary fibrosis, peripheral neuropathy, mouth ulcers, proteinuria, blood disorders (sometimes sudden and fatal), nephrotic syndrome, gold deposits in eye, alopecia, and skin reactions (including, on prolonged parenteral treatment, irreversible pigmentation in sun-exposed areas)

Dose • By deep intramuscular injection, administered on expert advice, see notes above

Myocrisin® (Sanofi-Aventis) *(NM)
Injection, sodium aurothiomalate 20 mg/mL, net price 0.5-mL (10-mg) amp = £3.80; 100 mg/mL, 0.5-mL (50-mg) amp = £11.23. Label: 11, counselling, blood disorder symptoms

Penicillamine
Penicillamine has a similar action to gold. More patients are able to continue treatment than with gold but side-effects are common.

Patients should be warned not to expect improvement for at least 6 to 12 weeks after treatment is initiated. Penicillamine should be discontinued if there is no improvement within 1 year.

Blood counts, including platelets, and urine examinations should be carried out before starting treatment and then every 1 or 2 weeks for the first 2 months then every 4 weeks to detect blood disorders and proteinuria (they should also be carried out in the week after any dose increase). A reduction in platelet count calls for discontinuation with subsequent re-introduction at a lower dosage and then, if possible, gradual increase. Proteinuria, associated with immune complex nephritis, occurs in up to 30% of patients, but may resolve despite continuation of treatment; treatment may be continued provided that renal function tests remain normal, oedema is absent, and the 24-hour urinary excretion of protein does not exceed 2 g.

Nausea may occur but is not usually a problem provided that penicillamine is taken before food or on retiring and that low initial doses are used and only gradually increased. Loss of taste can occur about 6 weeks after treatment is started but usually returns 6 weeks later irrespective of whether treatment is discontinued; mineral supplements are not recommended. Rashes are a common side-effect. Those that occur in the first few months of treatment disappear when the drug is stopped and treatment may then be re-introduced at a lower dose level and gradually increased. Late rashes are more resistant and often necessitate discontinuation of treatment.

Patients who are hypersensitive to penicillin may react rarely to penicillamine.

PENICILLAMINE
Indications see notes above and under Dose
Cautions see notes above; concomitant nephrotoxic drugs (increased risk of toxicity); gold treatment (avoid concomitant use if adverse reactions to gold); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (penicillamine)
Blood counts and urine tests See notes above. Longer intervals may be adequate in cystinuria and Wilson’s disease. Consider withdrawal if platelet count falls below 120 000/mm³ or white blood cells below 2500/mm³ or if 3 successive falls within reference range (can restart at reduced dose when counts return to within reference range but permanent withdrawal necessary if recurrence of leucopenia or thrombocytopenia)
Counselling Warn patient to tell doctor promptly if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop
Contra-indications lupus erythematosus
Side-effects (see also notes above) initially nausea, anorexia, fever, and skin reactions; taste loss (mineral supplements not recommended); blood disorders including thrombocytopenia, leucopenia, agranulocytosis and aplastic anaemia; proteinuria, rarely haematuria (withdraw immediately); haemolytic anaemia, nephrotic syndrome, lupus erythematosus-like syndrome, myasthenia gravis-like syndrome, polymyositis (rarely with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alopecia, bronchiolitis and pneumonitis, pempigus, Goodpasture's syndrome, and Stevens-Johnson syndrome also reported; male and female breast enlargement reported in non-rheumatoid conditions rheumatoid arthritis-like syndrome also reported; late rashes (consider withdrawing treatment)

Dose
- Severe active rheumatoid arthritis, administered on expert advice, ADULT initially 125–250 mg daily for 1 month increased by similar amounts at intervals of not less than 4 weeks to usual maintenance of 500–750 mg daily in divided doses; max. 1.5 g daily; if remission sustained for 6 months, reduction of daily dose by 125–250 mg every 12 weeks may be attempted; ELDERLY initially up to 125 mg daily for 1 month increased by similar amounts at intervals of not less than 4 weeks; max. 1 g daily; CHILD maintenance of 15–20 mg/kg daily (initial dose lower and increased at intervals of 4 weeks over a period of 3–6 months)
- Wilson's disease, autoimmune hepatitis, and cystinuria, section 9.8.1

Penicillamine (Non-proprietary) (CA)
Tablets, penicillamine 125 mg, net price 56-tab pack = £13.19; 250 mg, 56-tab pack = £16.96. Label: 6, 22, counselling, blood disorder symptoms (see above)

Distamine® (Alliance) (CA)
Tablets, f/c, penicillamine 125 mg, net price 100-tab pack = £6.82; 250 mg, 100-tab pack = £14.82. Label: 6, 22, counselling, blood disorder symptoms (see above)

Antimalariais
The antimalarial hydroxychloroquine is used to treat rheumatoid arthritis of moderate inflammatory activity; chloroquine is also licensed for treating inflammatory disorders but is used much less frequently and is generally reserved for use if other drugs have failed. Chloroquine and hydroxychloroquine are effective for mild systemic lupus erythematosus, particularly involving the skin and joints. These drugs should not be used for psoriatic arthritis.

Chloroquine and hydroxychloroquine are better tolerated than gold or penicillamine. Retinopathy (see below) rarely occurs provided that the recommended doses are not exceeded; in the elderly it is difficult to distinguish drug-induced retinopathy from changes of ageing. Mepacrine (section 5.4.4) is sometimes used in discoid lupus erythematosus [unlicensed].

Cautions Chloroquine and hydroxychloroquine should be used with caution in hepatic impairment (Appendix 2) and in renal impairment (Appendix 3). Manufacturers recommend regular ophthalmological examination but the evidence of practical value is unsatisfactory (see advice of the Royal College of Ophthalmologists, below). It is not necessary to withdraw an antimalarial drug during pregnancy (Appendix 4) if the rheumatic disease is well controlled. Chloroquine and hydroxychloroquine are present in breast milk and breast-feeding (Appendix 5) should be avoided when they are used to treat rheumatoid disease; chloroquine can, however, be used for malaria during pregnancy and breast-feeding (section 5.4.1). Both should be used with caution in neurological disorders (especially in those with a history of epilepsy), in severe gastro-intestinal disorders, in G6PD deficiency (section 9.1.3), in acute porphyria, and in the elderly (see also above). Chloroquine and hydroxychloroquine may exacerbate psoriasis and aggravate myasthenia gravis. Concurrent use of hepatotoxic drugs should be avoided; other interactions: Appendix 1 (chloroquine and hydroxychloroquine).

Screening for ocular toxicity
A review group convened by the Royal College of Ophthalmologists has updated guidelines for screening to prevent ocular toxicity on long-term treatment with chloroquine, hydroxychloroquine, and mepacrine (Ocular toxicity with hydroxychloroquine: guidelines for screening 2004). Chloroquine should be considered (for treating chronic inflammatory conditions) only if other drugs have failed. All patients taking chloroquine should receive ocular examination according to a protocol arranged locally between the prescriber and the ophthalmologist. Mepacrine has negligible ocular toxicity. The following recommendations relate to hydroxychloroquine, which is only rarely associated with toxicity.

Before treatment:
- Assess renal and liver function (adjust dose if impaired)
- Ask patient about visual impairment (not corrected by glasses). If impairment or eye disease present, assessment by an optometrist is advised and any abnormality should be referred to an ophthalmologist
- Record near visual acuity of each eye (with glasses where appropriate) using a standard reading chart
- Initiate hydroxychloroquine treatment if no abnormality detected (at a dose not exceeding hydroxychloroquine sulphate 6.5 mg/kg daily)

During treatment:
- Ask patient about visual symptoms and monitor visual acuity annually using the standard reading chart
- Refer to ophthalmologist if visual acuity changes or if vision blurred and warn patient to stop treatment and seek prescribing doctor’s advice
- A child treated for juvenile idiopathic arthritis should receive slit-lamp examination routinely to check for uveitis
- If long-term treatment is required (more than 5 years), individual arrangement should be agreed with the local ophthalmologist

Note To avoid excessive dosage in obese patients, the doses of hydroxychloroquine and chloroquine should be calculated on the basis of lean body weight. Ocular toxicity is unlikely if the dose of chloroquine phosphate does not exceed 4 mg/kg daily (equivalent to chloroquine base approx. 2.5 mg/kg daily)
Side-effects  The side-effects of chloroquine and hydroxychloroquine include gastro-intestinal disturbances, headache and skin reactions (rashes, pruritus); those occurring less frequently include ECG changes, convulsions, visual changes, retinal damage (see above), keratopathy, otoxicity, hair depigmentation, hair loss, and discoloration of skin, nails, and mucous membranes. Side-effects that occur rarely include blood disorders (including thrombocytopenia, agranulocytosis, and aplastic anaemia), mental changes (including emotional disturbances and psychosis), myopathy (including cardiomyopathy and neuromyopathy), acute generalised exanthematous pustulosis, exfoliative dermatitis, Stevens-Johnson syndrome, photosensitivity and hepatic damage. Important: very toxic in overdosage—immediate advice from poisons centres essential (see also p. 32).

CHLOROQUINE

Indications  active rheumatoid arthritis (including juvenile idiopathic arthritis), systemic and discoid lupus erythematosus; malaria (section 5.4.1)

Cautions  see notes above

Side-effects  see notes above

Dose  

- Administered on expert advice, by mouth, chloroquine (base) 150 mg daily; max. 2.5 mg/kg daily, see recommendations above; CHILD up to 3 mg/kg daily

Note  Chloroquine base 150 mg ≡ chloroquine sulphate 200 mg ≡ chloroquine phosphate 250 mg (approx.).

Preparations  

Section 5.4.1

HYDROXYCHLOROQUINE SULPHATE

Indications  active rheumatoid arthritis (including juvenile idiopathic arthritis), systemic and discoid lupus erythematosus; dermatological conditions caused or aggravated by sunlight

Cautions  see notes above

Side-effects  see notes above

Dose  

- Administered on expert advice, initially 400 mg daily in divided doses; maintenance 200–400 mg daily; max. 6.5 mg/kg daily (but not exceeding 400 mg daily), see recommendations above; CHILD up to 6.5 mg/kg daily (max. 400 mg daily)

Plaquenil® (Sanofi-Synthelabo) (pW)

Tablets, f/c. hydroxychloroquine sulphate 200 mg, net price 60-tab pack = £5.46. Label: 5, 21

Drugs affecting the immune response

Methotrexate is a disease-modifying antirheumatic drug suitable for moderate to severe rheumatoid arthritis. Azathioprine, ciclosporin, cyclophosphamide, leflunomide, and the cytokine modulators (adalimumab, anakinra, etanercept, and infliximab) are considered more toxic and they are used in cases that have not responded to other disease-modifying drugs.

Methotrexate is usually given in an initial dose of 7.5 mg by mouth once a week, adjusted according to response to a maximum of 15 mg once a week (occasionally 20 mg once a week). Regular full blood counts (including differential white cell count and platelet count), renal and liver function tests are required. In patients who experience mucosal or gastro-intestinal side-effects with methotrexate, folic acid 5 mg every week may help to reduce the frequency of such side-effects.

Azathioprine is usually given in a dose of 1.5 to 2.5 mg/kg daily in divided doses. Blood counts are needed to detect possible neutropenia or thrombocytopenia (usually resolved by reducing the dose). Nausea, vomiting, and diarrhoea may occur, usually starting early during the course of treatment, and may necessitate withdrawal of the drug; herpes zoster infection may also occur.

Leflunomide acts on the immune system as a disease-modifying antirheumatic drug. Its therapeutic effect starts after 4–6 weeks and improvement may continue for a further 4–6 months. Leflunomide, which is similar in efficacy to sulfasalazine and methotrexate, may be chosen when these drugs cannot be used. The active metabolite of leflunomide persists for a long period; active procedures to wash the drug out are required in case of serious adverse effects, or before starting treatment with another disease-modifying antirheumatic drug, or, in men or women, before conception. Side-effects of leflunomide include bone-marrow toxicity; its immunosuppressive effects increase the risk of infection and malignancy.

Ciclosporin (cyclosporin) is licensed for severe active rheumatoid arthritis when conventional second-line therapy is inappropriate or ineffective. There is some evidence that ciclosporin may retard the rate of erosive progression and improve symptom control in those who respond only partially to methotrexate.

Cyclophosphamide (section 8.1.1) may be used at a dose of 1 to 1.5 mg/kg daily by mouth for rheumatoid arthritis with severe systemic manifestations [unlicensed indication]; it is toxic and regular blood counts (including platelet counts) should be carried out. Cyclophosphamide can also be given intravenously in a dose of 0.5 to 1 g (with prophylactic mesna) for severe systemic rheumatoid arthritis and for other connective tissue diseases (especially with active vasculitis), repeated initially at fortnightly then at monthly intervals (according to clinical response and haematological monitoring).

Drugs that affect the immune response are also used in the management of severe cases of systemic lupus erythematosus and other connective tissue disorders. They are often given in conjunction with corticosteroids for patients with severe or progressive renal disease. They may be used in cases of polymyositis that are resistant to corticosteroids. They are used for their corticosteroid-sparing effect in patients whose corticosteroid requirements are excessive. Azathioprine is usually used.

Azathioprine and methotrexate are used in the treatment of psoriatic arthropathy [unlicensed indication] for severe or progressive cases that are not controlled with anti-inflammatory drugs.
AZATHIOPRINE

Indications  see notes above: inflammatory bowel disease [unlicensed indication] (section 1.5.3); transplantation rejection, see section 8.2.1
Cautions  see section 8.2.1
Contra-indications  see section 8.2.1
Side-effects  see section 8.2.1

Dose
- By mouth, initially, rarely more than 3 mg/kg daily, reduced according to response; maintenance 1–3 mg/kg daily; consider withdrawal if no improvement within 3 months

Preparations
Section 8.2.1

CICLOSPORIN
(Cyclosporin)

Indications  severe active rheumatoid arthritis when conventional second-line therapy inappropriate or ineffective; severe active ulcerative colitis [unlicensed indication] (section 1.5.3); graft-versus-host disease (section 8.2.2); atopic dermatitis and psoriasis (section 13.5.3).
Cautions  see section 8.2.2
Additional cautions in rheumatoid arthritis  Contra-indicated in abnormal renal function, uncontrolled hypertension (see also below), uncontrolled infections, and malignancy. Measure serum creatinine at least twice before treatment and monitor every 2 weeks for first 3 months; then every 4 weeks (or more frequently if dose increased or concomitant NSAIDs introduced or increased (see also interactions: Appendix 1 (cyclosporin)), reduce dose if serum creatinine increases more than 30% above baseline in more than 1 measurement; if above 90%, reduce dose by 50% (even if within normal range) and discontinue if reduction not successful within 1 month; monitor blood pressure (discontinue if hypertension develops that cannot be controlled by antihypertensive therapy); monitor hepatic function if concomitant NSAIDs given.
Side-effects  see section 8.2.2

Dose
- By mouth, administered in accordance with expert advice, initially 2.5 mg/kg daily in 2 divided doses, if necessary increased gradually after 6 weeks; max. 4 mg/kg daily (discontinue if response insufficient after 3 months); dose adjusted according to response for maintenance and treatment reviewed after 6 months (continue only if benefits outweigh risks); CHILD and under 18 years, not recommended Important For preparations and counselling and for advice on conversion between the preparations, see section 8.2.2

Preparations
Section 8.2.2

LEFLUNOMIDE

Indications  (specialist use only) moderate to severe active rheumatoid arthritis; active psoriatic arthritis
Caution renal impairment (avoid if moderate or severe; Appendix 3); impaired bone-marrow function including anaemia, leucopenia or thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis); recent treatment with other hepatotoxic or myelotoxic disease-modifying anti-rheumatic drugs; washout procedures recommended for serious adverse effects or before switching to other disease-modifying antirheumatic drugs (consult product literature and see Washout Procedure, below); history of tuberculosis; exclude pregnancy before treatment; effective contraception essential during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (plasma concentration monitoring required; waiting time before conception may be reduced with washout procedure—consult product literature and see Washout Procedure, below); monitor full blood count (including differential white cell count and platelet count) before treatment and every 2 weeks for 6 months then every 8 weeks; monitor liver function—see Hepatotoxicity, below; monitor blood pressure; interactions: Appendix 1 (leflunomide)

Hepatotoxicity  Potentially life-threatening hepatotoxicity reported usually in the first 6 months; monitor liver function before treatment and every 2 weeks for first 6 months then every 8 weeks. Discontinue treatment (and institute washout procedure—consult product literature and see Washout Procedure below) or reduce dose according to liver-function abnormality; if liver-function abnormality persists after dose reduction, discontinue treatment and institute washout procedure
Washout procedure  To aid drug elimination in case of serious adverse effect, or before starting another disease-modifying antirheumatic drug, or before conception (see also Appendix 4), stop treatment and give either colchicine 1 mg 3 times daily for 11 days or activated charcoal 50 g 4 times daily for 11 days; the concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception—consult product literature

Contra-indications  severe immunodeficiency; severe hypoproteinaemia; serious infection; hepatic impairment (Appendix 2); pregnancy (important teratogenic risk: see Cautions and Appendix 4); breastfeeding (Appendix 5)

Side-effects  diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders, abdominal pain; increased blood pressure; headache, dizziness, asthenia, paraesthesia, leucopenia; tenosynovitis; alopecia, rash, dry skin, pruritus; less commonly taste disturbance, anxiety, hypokalaemia, hypophosphataemia, anaemia, thrombocytopenia, and tendon rupture; rarely hepatitis, jaundice (see Hepatotoxicity, above), interstitial lung disease, severe infection, eosinophilia, and pancreatitis; very rarely pancreatitis, hepatic failure (see Hepatotoxicity, above), peripheral neuropathy, vasculitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis; hyperlipidaemia and renal failure also reported; important: discontinue treatment and institute washout procedure (see Washout Procedure under Caution) in case of serious side-effects

Dose
- Rheumatoid arthritis, ADULT over 18 years, initially 100 mg once daily for 3 days, then 10–20 mg once daily
- Psoriatic arthritis, ADULT over 18 years, initially 100 mg once daily for 3 days, then 20 mg once daily

Arava® (Sanofi-Aventis) Tablets, 5/c, leflunomide 10 mg (white), net price 30-tab pack = £51.13; 20 mg (yellow), 30-tab pack = £51.13; 100 mg (white), 3-tab pack = £25.56. Label: 4
METHOTREXATE

Indications moderate to severe active rheumatoid arthritis; Crohn’s disease [unlicensed indication] (section 1.5.3); malignant disease (section 8.1.3); psoriasis (section 13.5.3)

Cautions section 8.1; see CSM advice below (blood count, liver and pulmonary toxicity); extra caution in blood disorders (avoid if severe); peptic ulceration, ulcerative colitis, diarrhoea and ulcerative stomatitis (withdraw if stomatitis develops—may be first sign of gastro-intestinal toxicity); risk of accumulation in pleural effusion or ascites—drain before treatment; acute porphyria (section 9.8.2); renal impairment (avoid if creatinine clearance less than 20 mL/minute; Appendix 3); Interactions: see below and Appendix 1 (methotrexate)

CSM advice
In view of reports of blood dyscrasias (including fatalities) and liver cirrhosis with low-dose methotrexate, the CSM has advised:

- full blood count and renal and liver function tests before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months
- that patients should be advised to report all symptoms and signs suggestive of infection, especially sore throat

Treatment with folic acid (as calcium folinate, section 8.1) may be required in acute toxicity

Blood count Bone marrow suppression can occur abruptly; factors likely to increase toxicity include advanced age, renal impairment, and concomitant use with another anti-foolate drug. A clinically significant drop in white cell count or platelet count calls for immediate withdrawal of methotrexate and introduction of supportive therapy.

Liver toxicity Liver cirrhosis reported. Treatment should not be started or should be discontinued if any abnormality of liver function tests or liver biopsy is present or develops during therapy. Abnormalities can return to normal within 2 weeks after which treatment may be recommenced if judged appropriate.

Pulmonary toxicity Pulmonary toxicity may be a special problem in rheumatoid arthritis (patient to seek medical attention if dyspnoea, cough or fever); monitor for symptoms at each visit—discontinue if pneumonitis suspected.

Aspirin and other NSAIDs If aspirin or other NSAIDs are given concurrently the dose of methotrexate should be carefully monitored. Patients should be advised to avoid self-medication with over-the-counter aspirin or ibuprofen.

Contra-indications see Cautions above, hepatic impairment (Appendix 2), pregnancy (following administration to a woman or a man, avoid conception for at least 3 months after stopping—Appendix 4), breast-feeding (Appendix 5), active infection and immunodeficiency syndromes.

Side-effects section 8.1; also anorexia, abdominal discomfort, dyspepsia, gastro-intestinal ulceration and bleeding, diarrhoea, toxic megacolon, hepatotoxicity (see Cautions above); hypotension, pericarditis, pericardial tamponade; pulmonary oedema, pleuritic pain, pulmonary fibrosis, interstitial pneumonitis (see also Pulmonary Toxicity above); ana phylactic reactions, urticaria; dizziness, fatigue, chills, fever, drowsiness, malaise, headache, mood changes, neurotoxicity, confusion, paraesthesia; precipitation of diabetes; menstrual disturbances, vaginitis, cystitis, reduced libido, impotence; blood disorders; haemat uria, dysuria, renal failure; osteoporosis, arthralgia, myalgia, vasculitis; conjunctivitis, visual disturbance; rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, changes in nail and skin pigmentation, telangiectasia, acne, furunculosis, ecchymosis; injection-site reactions.

Dose
- Moderate to severe active rheumatoid arthritis, by mouth, 7.5 mg once weekly, adjusted according to response; max. weekly dose 20 mg
- Severe active rheumatoid arthritis, by subcutaneous or by intramuscular or by intravenous injection, 7.5 mg once weekly, increased according to response by 2.5 mg weekly; max. weekly dose 25 mg

Important
Note that the above dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:

- the patient is carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath)

Methotrexate (Non-proprietary) Tablets, yellow, methotrexate 2.5 mg, net price 28-tab pack = £3.27. Counselling, dose, NSAIDs

Brands include Mtxrex Tablets, yellow, methotrexate 10 mg, net price 20 (Hospira) = £11.44; (Pharmacia, Mtxrex*) = £9.03. Counselling, dose, NSAIDs

Parenteral preparations
See also section 8.1.3

Metobject* (Medac) Injection, prefilled syringe, methotrexate (as disodium salt) 10 mg/mL, net price 0.75 mL (7.5 mg) = £14.85, 1 mL (10 mg) = £15.29, 1.5 mL (15 mg) = £16.57, 2 mL (20 mg) = £17.84, 2.5 mL (25 mg) = £18.48

Cytokine modulators
Cytokine modulators should be used under specialist supervision.

Adalimumab, etanercept, and infliximab inhibit the activity of tumour necrosis factor alpha (TNF-α).

NICE guidance
Adalimumab for the treatment of psoriatic arthritis (August 2007)

Adalimumab is an option for the treatment of active and progressive psoriatic arthritis in adults with at least 3 tender joints and at least 3 swollen joints, who have not responded adequately to at least 2 standard disease-modifying antirheumatic drugs (used alone or in combination). Adalimumab should be used under specialist supervision and should be discontinued if there is an inadequate response after 12 weeks.
BNF 57

10.1.3 Drugs that suppress the rheumatic disease process

NICE guidance
Adalimumab, etanercept, and infliximab for the treatment of rheumatoid arthritis (October 2007)
The tumour necrosis factor alpha (TNF-\(\alpha\)) inhibitors adalimumab, etanercept, and infliximab are options for the treatment of adults with active rheumatoid arthritis who have failed to respond to at least 2 disease-modifying antirheumatic drugs (DMARDs), including methotrexate (unless contra-indicated). TNF-\(\alpha\) inhibitors should be given in combination with methotrexate; however, when methotrexate cannot be used because of intolerance or contra-indications, adalimumab or etanercept can be given as monotherapy.

Adalimumab, etanercept, and infliximab should be withdrawn if response is not adequate within 6 months. Response to treatment should be monitored at least every 6 months in patients who respond initially; treatment should be withdrawn if response is not maintained. An alternative TNF-\(\alpha\) inhibitor may be considered for patients in whom treatment is withdrawn because of intolerance before the initial 6-month assessment of efficacy.

Use of TNF-\(\alpha\) inhibitors for the treatment of severe, active, and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.

NICE guidance
Adalimumab, etanercept and infliximab for the treatment of ankylosing spondylitis (May 2008)
Adalimumab or etanercept are recommended as treatment options for adults with severe active ankylosing spondylitis whose disease satisfies specific criteria for diagnosis where there is confirmation of sustained active spinal disease, and where treatment with two or more NSAIDs taken sequentially at maximum tolerated or recommended doses for 4 weeks has failed to control symptoms. Response to adalimumab or etanercept treatment should be assessed at 12-week intervals and continued only if response is adequate. If response to treatment is not maintained, a repeat assessment should be made after a further 6 weeks and treatment discontinued if there is an inadequate response. Patients who are intolerant of adalimumab or etanercept during the initial 12 weeks may receive the alternative TNF-\(\alpha\) inhibitor (adalimumab or etanercept). However an alternative TNF-\(\alpha\) inhibitor is not recommended in patients who fail to respond initially or fail to maintain an adequate response. Infliximab is not recommended for the treatment of ankylosing spondylitis. Patients receiving infliximab for the treatment of ankylosing spondylitis can continue treatment until they and their specialist consider it appropriate to stop.

See full NICE guidance for specific criteria to diagnose severe active ankylosing spondylitis, confirm sustained active spinal disease, and assess response to treatment.

NICE guidance
Etanercept and infliximab for the treatment of adults with psoriatic arthritis (July 2006)
Etanercept is recommended for severe active psoriatic arthritis in adults with at least 3 tender joints and at least 3 swollen joints, and who have not responded adequately to 2 other disease-modifying antirheumatic drugs (used alone or in combination), infliximab [in combination with methotrexate, unless contra-indicated or not tolerated] is recommended for those intolerant of etanercept.

Etanercept or infliximab should be used under specialist supervision and should be withdrawn if inadequate response after 12 weeks.

NICE guidance
Adalimumab for the treatment of ankylosing spondylitis (October 2007)
Adalimumab is licensed for moderate to severe active rheumatoid arthritis when response to other disease-modifying antirheumatic drugs (including methotrexate) has been inadequate (see also NICE guidance, above); it can also be used for severe, active, and progressive disease in adults not previously treated with methotrexate. It is also licensed for active polyarticular juvenile idiopathic arthritis in adolescents who have not responded adequately to one or more disease-modifying antirheumatic drugs. In the treatment of rheumatoid arthritis and polyarticular juvenile idiopathic arthritis, adalimumab should be used in combination with methotrexate, but it can be given alone if methotrexate is inappropriate. Adalimumab is also licensed for the treatment of active and progressive psoriatic arthritis (see also NICE guidance, above) and severe active ankylosing spondylitis that have not responded adequately to other disease-modifying antirheumatic drugs. For the role of adalimumab in Crohn’s disease, see section 13.5.3. For the role of adalimumab in plaque psoriasis, see section 13.5.3.

Etanercept is licensed for the treatment of moderate to severe active rheumatoid arthritis either alone or in combination with methotrexate when the response to other disease-modifying antirheumatic drugs is inadequate (see also NICE guidance). It is also licensed for the treatment of active polyarticular juvenile idiopathic arth-
ritis in children who have not responded adequately to or are intolerant of methotrexate (see also NICE guidance), active and progressive psoriatic arthritis inadequately responsive to other disease-modifying antirheumatic drugs, and for severe ankylosing spondylitis inadequately responsive to conventional therapy. For the role of etanercept in plaque psoriasis, see section 13.5.3.

Infliximab is licensed for the treatment of active rheumatoid arthritis in combination with methotrexate when the response to other disease-modifying antirheumatic drugs is inadequate (see also NICE guidance). It is also licensed for the treatment of ankylosing spondylitis, in patients with severe axial symptoms who have not responded adequately to conventional therapy, and in combination with methotrexate (or alone if methotrexate is not tolerated or is contra-indicated) for the treatment of active and progressive psoriatic arthritis which has not responded adequately to disease-modifying antirheumatic drugs. For the role of infliximab in plaque psoriasis, see section 13.5.3.

Rituximab is licensed in combination with methotrexate for the treatment of severe active rheumatoid arthritis in patients whose condition has not responded adequately to other disease-modifying antirheumatic drugs (including one or more tumour necrosis factor inhibitors) or who are intolerant of them (see also NICE guidance, below). For the role of rituximab in malignant disease, see section 8.2.3.

NICE guidance

Rituximab for the treatment of rheumatoid arthritis (August 2007)

Rituximab, in combination with methotrexate, is an option for the treatment of severe active rheumatoid arthritis in adults who have not had an adequate response to, or are intolerant of, other disease-modifying antirheumatic drugs (DMARDs), including treatment with at least 1 tumour necrosis factor alpha (TNF-α) inhibitor. Treatment with rituximab plus methotrexate should be continued only if there is an adequate response to therapy; repeat courses should be given no more frequently than every 6 months.

Side-effects

Adalimumab, etanercept, infliximab, and rituximab have been associated with infections, sometimes severe, including tuberculosis, septicemia, and hepatitis B reactivation. Other side-effects include nausea, abdominal pain, worsening heart failure, hypersensitivity reactions, fever, headache, depression, antibody formation (including lupus erythematosus-like syndrome), pruritus, injection-site reactions, and blood disorders (including anaemia, leucopenia, thrombocytopenia, pancytopenia, and aplastic anaemia).

Anakinra inhibits the activity of interleukin-1. Anakinra (in combination with methotrexate) is licensed for the treatment of rheumatoid arthritis which has not responded to methotrexate alone; it is not, however, recommended for routine management of rheumatoid arthritis, see NICE guidance below.

The Scottish Medicines Consortium has advised (October 2003) that anakinra is not recommended for rheumatoid arthritis.

Abatacept prevents the full activation of T-lymphocytes. It is licensed for moderate to severe active rheumatoid arthritis in combination with methotrexate, in patients unresponsive or intolerant to other disease-modifying antirheumatic drugs (including at least one tumour necrosis factor (TNF) inhibitor). Abatacept is not recommended for use in combination with TNF inhibitors.

The Scottish Medicines Consortium has advised (August 2007) that abatacept is not recommended for the treatment of moderate to severe active rheumatoid arthritis.

**ABATACEPT**

**Indications** see under Cytokine Modulators, above

**Cautions** predisposition to infection (screen for latent tuberculosis and viral hepatitis); do not initiate until active infections are controlled; elderly (increased risk of side-effects); interactions: Appendix 1 (abatacept)

**Contra-indications** severe infection (see also Cautions); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** abdominal pain, diarrhoea, dyspepsia, nausea; flushing, hypertension; cough; dizziness, fatigue, headache; infection, rhinitis; rash; less commonly gastritis, stomatitis, tachycardia, bradycardia, palpitation, hypotension, dyspnoea, paraesthesia, weight gain, depression, anxiety, amenorrhoea, basal cell carcinoma, thrombocytopenia, leucopenia, arthralgia, pain in extremities, conjunctivitis, visual disturbance, vertigo, bruising, alopecia, and dry skin

**Dose**

- By intravenous infusion, ADULT over 18 years, body-weight less than 60 kg, 500 mg, repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks; body-weight 60–100 kg, 750 mg repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks; body-weight over 100 kg, 1 g repeated 2 weeks and 4 weeks after initial infusion, then every 4 weeks

**Note** Discontinue if no response within 6 months

**Orencia®** (Bristol-Myers Squibb) ▼ Intravenous infusion, powder for reconstitution, abatacept, net price 250-mg vial = £252.00

**Electrolytes** Na <0.5 mmol/vial
**ADALIMUMAB**

**Indications** see under Cytokine Modulators above; Crohn’s disease (section 1.5.3); psoriasis (section 13.5.3).

**Cautions** predisposition to infection; monitor for infections before, during, and for 5 months after treatment (see also Tuberculosis below); do not initiate until active infections are controlled; hepatitis B virus—monitor for active infection; children should be brought up to date with current immunisation schedule (section 14.1) before initiating therapy; mild heart failure (discontinue if symptoms develop or worsen—avoid in moderate or severe heart failure); demyelinating CNS disorders (risk of exacerbation); history of malignancy; monitor for non-melanoma skin cancer before and during treatment, especially in patients with a history of PUVA treatment for psoriasis or extensive immunosuppressant therapy; **interactions:** Appendix 1 (adalimumab)

**Tuberculosis** Patients should be evaluated for tuberculosis before treatment. Active tuberculosis should be treated with standard treatment (section 5.1.9) for at least 2 months before starting adalimumab. Patients who have previously received adequate treatment for tuberculosis can start adalimumab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemotherapy should ideally be completed before starting adalimumab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with adalimumab. Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop

**Contra-indications** pregnancy (Appendix 4); breast-feeding (Appendix 5); severe infection (see also Cautions)

**Side-effects** see under Cytokine Modulators above; infections, neutropenia (see also Cautions), and antibody formation; also reported pregnancy (Appendix 4); breast-feeding (Appendix 5); neutropenia

**Dose** 
- By subcutaneous injection, ADULT over 18 years, 40 mg on alternate weeks; if necessary increased to 40 mg weekly in patients receiving adalimumab alone; review treatment if no response within 12 weeks
- Polyarticular juvenile idiopathic arthritis, CHILD 13–17 years, 40 mg on alternate weeks; review treatment if no response within 12 weeks
- Psoriatic arthritis, ankylosing spondylitis, ADULT over 18 years, 40 mg on alternate weeks; discontinue treatment if no response within 12 weeks

**ADALIMUMAB Injection**
- adalimumab, net price 40-mg prefilled pen or prefilled syringe = £357.50. Counselling, tuberculosis

**ANAKINRA**

**Indications** see under Cytokine Modulators above

**Cautions** predisposition to infections; history of asthma (risk of serious infection); renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3); **interactions:** Appendix 1 (anakinra)

**Blood disorders** Neutropenia reported commonly. Monitor neutrophil count before treatment, then every month for 6 months, then every 3 months—discontinue if neutropenia develops. Patients should be instructed to seek medical advice if symptoms suggestive of neutropenia (such as fever, sore throat, infection) develop

**Contra-indications** pregnancy (Appendix 4); breast-feeding (Appendix 5); neutropenia

**Side-effects** injection-site reactions; headache; infections, neutropenia (see also Cautions), and antibody formation; also reported malignancy

**Dose** 
- By subcutaneous injection, ADULT over 18 years, 100 mg once daily

**Kinerei**

**Injection**
- anakinra, net price 100-mg prefilled syringe = £19.03. Counselling, blood disorder symptoms

**ETANERCEPT**

**Indications** see under Cytokine Modulators above; severe, active and progressive rheumatoid arthritis in patients not previously treated with methotrexate; psoriasis (section 13.5.3)

**Cautions** predisposition to infection (avoid if predisposition to septicaemia); significant exposure to herpes zoster virus—interrupt treatment and consider varicella–zoster immunoglobulin; hepatitis B virus—monitor for active infection; heart failure (risk of exacerbation); demyelinating CNS disorders (risk of exacerbation); history of blood disorders; **interactions:** Appendix 1 (etanercept)

**Tuberculosis** Patients should be evaluated for tuberculosis before treatment. Active tuberculosis should be treated with standard treatment (section 5.1.9) for at least 2 months before starting etanercept. Patients who have previously received adequate treatment for tuberculosis can start etanercept but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with etanercept. Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop

**Contra-indications** active infection; avoid injections containing benzyl alcohol in neonates (see preparations below); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see under Cytokine Modulators (p. 570); also interstitial lung disease, rash; rarely demyelinating disorders, seizures, Stevens-Johnson syndrome, and cutaneous vasculitis; very rarely toxic epidermal necrolysis; also reported appendicitis, cholecystitis, gastritis, gastro-intestinal haemorrhage, intestinal...
obstruction, liver damage, oesophagitis, pancreatitis, ulcerative colitis, vomiting, cerebral ischaemia, hypertension, hypotension, myocardial infarction, thrombophlebitis, thromboembolism, asthma, dyspnoea, asptic meningitis, confusion, paresis, paranoia, vertigo, lymphadenopathy, diabetes mellitus, haematuria, malignancy, renal calculi, renal impairment, bone fracture, bursitis, polyomyositis, scieritis, and cutaneous ulcer

### Dose
- **By subcutaneous injection**, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, **INFELIXIMAB** over 18 years, 25 mg twice weekly or 50 mg once weekly Polyarticular-course juvenile idiopathic arthritis, CHILD 4–17 years, 400 micrograms/kg (max. 25 mg) twice weekly, with an interval of 3–4 days between doses.

### Enbrel® (Wyeth) ▼ [link]
**Injection**, powder for reconstitution, etanercept, net price 25-mg vial (with solvent) = £98.39. Label: 10, alert card, counselling, tuberculosis and blood disorders.

**Paediatric injection**, powder for reconstitution, etanercept, net price 25-mg vial (with solvent) = £98.39. Label: 10, alert card, counselling, tuberculosis and blood disorders.

**Excipients** include benzyl alcohol (avoid in neonates, see Excipients, p. 2).

**Injection**, etanercept, net price 25-mg prefilled syringe = £98.39, 50-mg prefilled syringe = £178.75. Label: 10, alert card, counselling, tuberculosis and blood disorders.

### INFELIXIMAB

#### Indications
- see under Cytokine Modulators above; severe, active and progressive rheumatoid arthritis in patients not previously treated with methotrexate; inflammatory bowel disease (section 1.5.3); psoriasis (section 13.5.3).

#### Cautions
- predisposition to infection; monitor for infections before, during, and for 2 months after treatment (see also Tuberculosis below); hepatitis B virus—monitor for active infection; heart failure (discontinue if symptoms develop or worsen; avoid in moderate or severe heart failure); demyelinating CNS disorders (risk of exacerbation); history of malignancy (consider discontinuing treatment if malignancy develops); history of prolonged immunosuppressant or PUVA treatment in patients with psoriasis; inter- actions: Appendix 1 (infliximab).

#### Tuberculosis
- Patients should be evaluated for tuberculosis before treatment. Active tuberculosis should be treated with standard treatment (section 5.1.9) for at least 2 months before starting infliximab. Patients who have previously received adequate treatment for tuberculosis can start infliximab but should be monitored every 3 months for possible recurrence. In patients without active tuberculosis but who were previously not treated adequately, chemotherapy should ideally be completed before starting infliximab. In patients at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemotherapy can be given concurrently with infliximab. Patients should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop.

#### Hypersensitivity reactions
- Hypersensitivity reactions (including fever, chest pain, hypotension, hypertension, dyspnoea, pruritus, urticaria, serum sickness-like reactions, angioedema, anaphylaxis) reported during or within 1–2 hours after infusion (risk greatest during first or second infusion or in patients who discontinue other immuno- suppressants. All patients should be observed carefully for 1–2 hours after infusion and resuscitation equipment should be available for immediate use. Prophylactic antipyretics, anti- histamines, or hydrocortisone may be administered. Monitor for symptoms of delayed hypersensitivity if readministered after a prolonged period. Patients should be advised to keep Alert card with them at all times and seek medical advice if symptoms of delayed hypersensitivity develop.

#### Contra-indications
- severe infections (see also under Cautions); pregnancy (Appendix 4); breast-feeding (Appendix 5).

#### Side-effects
- see under Cytokine Modulators (p. 570) and under Cautions above; also diarrhoea, dyspepsia; flushing, chest pain; dyspnoea; dizziness, fatigue; sinusitis; rash, sweating, dry skin; less commonly con- stipation, gastro-oesophageal reflux, diverticulitis, cholecystitis, palpitation, arrhythmia, hypertension, hypotension, vasospasm, cyanosis, bradycardia, syn- copa, oedema, flushing, thrombophlebitis, epistaxis, bronchospasm, pleurisy, confusion, agitation, ner- vousness, amnesia, sleep disturbances, vaginitis, demyelinating disorders, antibody formation, pyelo- nephritis, myalgia, arthralgia, eye disorders, abnormal skin pigmentation, ecchymosis, cheilitis, and alopecia; rarely hepatitis, intestinal stenosis, intestinal perfora- tion, gastro-intestinal haemorrhage, pancreatitis, cir- culatory failure, meningitis, seizure, neuropathy, paraesthesia, lymphoma, and transverse myelitis; very rarely pericardial effusion, and skin reactions (includ- ing Stevens-Johnson syndrome, and toxic epidermal necrolysis); interstitial lung disease also reported.

#### Dose
- **By intravenous infusion**, rheumatoid arthritis (in combination with methotrexate), **ADULT** over 18 years, 3 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks; if response inadequate after 12 weeks, dose may be increased in steps of 1.5 mg/kg every 8 weeks, up to max. 7.5 mg/kg every 8 weeks; alternatively, 3 mg/kg may be given every 4 weeks; discontinue if no response by 12 weeks or no response by 12 weeks of initial infusion or after dose adjustment.

- Ankylosing spondylitis, **ADULT** over 18 years, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 6–8 weeks; discontinue if no response by 6 weeks of initial infusion.

- Psoriatic arthritis (in combination with methotrexate), **ADULT** over 18 years, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks.

- **Remicade®** (Schering-Plough) ▼ [link]
**Intravenous infusion**, powder for reconstitution, infliximab, net price 100-mg vial = £419.62. Label: 10, alert card, counselling, tuberculosis and hypersensi- tivity reactions.

#### RITUXIMAB

#### Indications
- see under Cytokine Modulators above; malignant disease (section 8.2.3).

#### Cautions
- section 8.2.3; predisposition to infection; hepatitis B virus—monitor for active infection.

#### Contra-indications
- section 8.2.3; severe infection.

#### Side-effects
- section 8.2.3 and under Cytokine Mod- ulators (p. 570); also dyspepsia; hypertension, hypo- tension; rhinitis, sore throat; asthma, paraesthesia, migraine; arthralgia, muscle spasm; urticaria
Acute attacks of gout

Acute attacks of gout are usually treated with high doses of NSAIDs such as diclofenac, etoricoxib, indometacin, ketoprofen, naproxen, or sulindac (section 10.1.1). Colchicine is an alternative in patients in whom NSAIDs are contra-indicated. Aspirin is not indicated in gout. Allopurinol and uricosurics are not effective in treating an acute attack and may prolong it indefinitely if started during the acute episode.

The use of colchicine is limited by the development of toxicity at higher doses, but it is of value in patients with heart failure since, unlike NSAIDs, it does not induce fluid retention; moreover, it can be given to patients receiving anticoagulants. Oral or parenteral corticosteroids are an effective alternative in those who cannot tolerate NSAIDs or who are resistant to other treatments. Intra-articular injection of a corticosteroid can be used in acute mono-articular gout [unlicensed indication]. A corticosteroid by intramuscular injection can be effective in podagra.

COLCHICINE

Indications acute gout, short-term prophylaxis during initial therapy with allopurinol and uricosuric drugs; prophylaxis of familial Mediterranean fever (recurrent polyserositis) [unlicensed]

Cautions elderly, gastro-intestinal disease, cardiac disease, hepatic impairment, renal impairment (avoid if creatinine clearance less than 10 mL/minute; Appendix 3); breast-feeding (Appendix 5); interactions: Appendix 1 (colchicine)

Contra-indications pregnancy (Appendix 4)

Side-effects most common are nausea, vomiting, and abdominal pain; excessive doses may also cause profuse diarrhoea, gastro-intestinal haemorrhage, rashes, renal and hepatic damage. Rarely peripheral neuritis, myopathy, alopecia, inhibition of spermato-genesis, and with prolonged treatment blood disorders

Dose

• Acute gout, 500 micrograms 2–4 times daily until symptoms relieved, max. 6 mg per course; course not to be repeated within 3 days
• Prevention of gout attacks during initial treatment with allopurinol or uricosuric drugs, 500 micrograms twice daily
• Prophylaxis of familial Mediterranean fever [unlicensed], 0.5–2 mg daily

Note BNF doses may differ from those in the product literature

Colchicine (Non-proprietary) (Pharmacia) Tablets, colchicine 500 micrograms, net price 20 = £5.06

10.1.4 Gout and cytotoxic-induced hyperuricaemia

It is important to distinguish drugs used for the treatment of acute attacks of gout from those used in the long-term control of the disease. The latter exacerbate and prolong the acute manifestations if started during an attack.

Sulfasalazine

Sulfasalazine (sulphasalazine) has a beneficial effect in suppressing the inflammatory activity of rheumatoid arthritis. Side-effects include rashes, gastro-intestinal intolerance and, especially in patients with rheumatoid arthritis, occasional leucopenia, neutropenia, and thrombocytopenia. These haematological abnormalities occur usually in the first 3 to 6 months of treatment and are reversible on cessation of treatment. Close monitoring of full blood counts (including differential white cell count and platelet count) is necessary initially, and at monthly intervals during the first 3 months (liver function tests also being performed at monthly intervals for the first 3 months). Although the manufacturer recommends renal function tests, evidence of practical value is unsatisfactory.

SULFASALAZINE (Sulphasalazine)

Indications active rheumatoid arthritis; inflammatory bowel disease, see section 15.1 and notes above

Cautions see section 15.1 and notes above

The CSM has recommended that patients should be advised to report any unexplained bleeding, bruising, purpura, sore throat, fever or malaise. A blood count should be performed and the drug stopped immediately if there is suspicion of a blood dyscrasia.

Contra-indications see section 15.1 and notes above

Side-effects see section 15.1 and notes above

Dose

• By mouth, administered on expert advice, as enteric-coated tablets, initially 500 mg daily, increased by 500 mg at intervals of 1 week to a max. of 2–3 g daily in divided doses

Sulfasalazine (Non-proprietary) (Pharmacia) Tablets, e/c, sulfasalazine 500 mg. Net price 112-tab pack = £21.52. Label: 5, 14, 25, counselling, blood disorder symptoms (see CSM recommendation above), contact lenses may be stained

Brands include Sulazine EC

Salazopyrin EN-Tabs® (Pharmacia) Tablets, e/c, yellow, t/c, sulfasalazine 500 mg. Net price 112-tab pack = £8.43. Label: 5, 14, 25, counselling, blood disorder symptoms (see CSM recommendation above), contact lenses may be stained

Note BNF 57 10.1.4 Gout and cytotoxic-induced hyperuricaemia 573
hyperuricaemia. These drugs should never be started during an acute attack; they are usually started 1–2 weeks after the attack has settled. The initiation of treatment may precipitate an acute attack, and therefore colchicine or an anti-inflammatory analgesic should be used as a prophylactic and continued for at least one month after the hyperuricaemia has been corrected. However, if an acute attack develops during treatment, then the treatment should continue at the same dosage and the acute attack treated in its own right.

Allopurinol is widely used and is especially useful in patients with renal impairment or urate stones when uricosuric drugs cannot be used; it is not indicated for the treatment of asymptomatic hyperuricaemia. It can cause rashes.

Sulfinpyrazone (sulfinpyrazone) can be used instead of allopurinol, or in conjunction with it in cases that are resistant to treatment.

Probenecid (available from ‘special-order’ manufacturers or specialist importing companies, see p. 939) is a uricosuric drug used to prevent nephrotoxicity associated with cidofovir (section 5.3.2.2).

Benzbromarone (available from ‘special-order’ manufacturers or specialist importing companies, see p. 939) is a uricosuric drug that can be used in patients with mild renal impairment.

Crystallisation of urate in the urine can occur with the uricosuric drugs and it is important to ensure an adequate urine output especially in the first few weeks of treatment. As an additional precaution the urine may be rendered alkaline. Aspirin and other salicylates antagonise the uricosuric drugs; they do not antagonise allopurinol but are nevertheless not indicated in gout.

**ALLOPURINOL**

**Indications** prophylaxis of gout and of uric acid and calcium oxalate renal stones; prophylaxis of hyperuricaemia associated with cancer chemotherapy

**Cautions** administer prophylactic colchicine (usually for first 3 months) or NSAID (not aspirin or salicylates) until at least 1 month after hyperuricaemia corrected; ensure adequate fluid intake (2–3 litres/day); for hyperuricaemia associated with cancer therapy, allopurinol treatment should be started before cancer therapy; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (allopurinol)

**Contra-indications** not a treatment for acute gout but continue if attack develops when already receiving allopurinol, and treat attack separately (see notes above)

**Side-effects** rashes (withdraw therapy; if rash mild re-introduce cautiously but discontinue promptly if recurrence—hypersensitivity reactions occur rarely and include exfoliation, fever, lymphadenopathy, arthralgia, and eosinophilia resembling Stevens-Johnson or Lyell’s syndrome, vasculitis, hepatitis, renal impairment, and very rarely seizures); gastrointestinal disorders; rarely malaise, headache, vertigo, drowsiness, visual and taste disturbances, hypertension, alopecia, hepatotoxicity, paraesthesia and neuropathy, gynaecomastia, blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia and aplastic anaemia)

**Dose**
- Initially 100 mg daily, preferably after food, then adjusted according to plasma or urinary uric acid concentration; usual maintenance dose in mild conditions 100–200 mg daily, in moderately severe conditions 300–600 mg daily, in severe conditions 700–900 mg daily; doses over 300 mg daily given in divided doses; CHILD under 15 years, (in neoplastic conditions, enzyme disorders) 10–20 mg/kg daily (max. 400 mg daily)

**Probenecid (Non-proprietary)**

**Tablets**, allopurinol 100 mg, net price 28-tab pack = £9.7p; 300 mg, 28-tab pack = £1.10. Label: 8, 21, 27

Brands include Caplenal, Cosuric, Rimapurinol

**Zyloric** (GSK)

**Tablets**, allopurinol 100 mg, net price 100-tab pack = £10.19; 300 mg, 28-tab pack = £7.31. Label: 8, 21, 27

**SULFINPYRAZONE** (Sulfinpyrazone)

**Indications** gout prophylaxis, hyperuricaemia

**Cautions** see under Probenecid; regular blood counts advisable; cardiac disease (may cause salt and water retention); renal impairment (avoid if creatinine clearance less than 30 mL/minute; Appendix 3)

**Side-effects** gastro-intestinal disturbances, urinary frequency, headache, flushing, dizziness, alopecia, anaemia, haemolytic anaemia, sore gums; hypersensitivity reactions including anaphylaxis, dermatitis, pruritus, urticaria, fever and Stevens-Johnson syndrome; rarely nephrotic syndrome, hepatic necrosis, leucopenia, aplastic anaemia; toxic epidermal necrolysis reported with concurrent colchicine

**Dose**
- Used with cidofovir, see section 5.3.2.2

**Probenecid (Non-proprietary)**

**Tablets**, probenecid 500 mg. Label: 12, 21, 27

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 939
Dose
- Initially 100–200 mg daily with food (or milk) increasing over 2–3 weeks to 600 mg daily (rarely 800 mg daily), continued until serum uric acid concentration normal then reduced for maintenance (maintenance dose may be as low as 200 mg daily)

Anturan® (Amdipharm)
Tablets, both yellow, s/c, sulfinpyrazone 100 mg, net price 84-tab pack = £5.66; 200 mg, 84-tab pack = £11.25. Label: 12, 21

Hyperuricaemia associated with cytotoxic drugs
Allopurinol is used to prevent hyperuricaemia associated with cytotoxic drugs—see section 8.1 (Hyperuricaemia) and Allopurinol above.

Rasburicase is licensed for the prophylaxis and treatment of acute hyperuricaemia, before and during initiation of chemotherapy, in patients with haematological malignancy and a high tumour burden at risk of rapid lysis.

**RASBURICASE**

**Indications** prophylaxis and treatment of acute hyperuricaemia with initial chemotherapy for haematological malignancy

**Cautions** monitor closely for hypersensitivity; atopic allergies; may interfere with test for uric acid—consult product literature

**Contra-indications** G6PD deficiency (section 9.1.5); pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** fever; less commonly nausea, vomiting, diarrhoea, constipation, rash, bronchospasm and anaphylaxis; haemolytic anaemia, methaemoglobinaemia

**Dose**
- **ADULT** over 18 years, 1.25 g once daily; review treatment if no benefit after 2–3 months

Alateris® (Pharmexx UK)
Tablets, glucosamine (as hydrochloride) 625 mg, net price 60-tab pack = £18.40

10.2 Drugs used in neuromuscular disorders

10.2.1 Drugs that enhance neuromuscular transmission

**Anticholinesterases** are used as first-line treatment in ocular myasthenia gravis and as an adjunct to immunosuppressant therapy for generalised myasthenia gravis.

Corticosteroids are used when anticholinesterases do not control symptoms completely. A second-line immunosuppressant such as azathioprine is frequently used to reduce the dose of corticosteroid.

Plasmapheresis or infusion of intravenous immunoglobulin [unlicensed indication] may induce temporary remission in severe relapses, particularly where bulbar or respiratory function is compromised or before thyromectomy.

**Anticholinesterases**

Glucosamine is a natural substance found in mucopolysaccharides, mucoproteins, and chitin. It is licensed for symptomatic relief of mild to moderate osteoarthritis of the knee, but the mechanism of action is not understood.

The Scottish Medicines Consortium (p. 3) has advised (May 2008) that glucosamine (Alateris®) is not recommended for use within NHS Scotland for the symptomatic relief of mild to moderate osteoarthritis of the knee.

**Anticholinesterases**

Anticholinesterase drugs enhance neuromuscular transmission in voluntary and involuntary muscle in myasthenia gravis. They prolong the action of acetylcholine by inhibiting the action of the enzyme acetylcholinesterase. Excessive dosage of these drugs can impair neuromuscular transmission and precipitate cholinergic crises by causing a depolarising block. This may be difficult to distinguish from a worsening myasthenic state.

Muscarinic side-effects of anticholinesterases include increased sweating, increased salivary and gastric secre-
tions, increased gastro-intestinal and uterine motility, and bradycardia. These parasympathomimetic effects are antagonised by atropine.

**Edrophonium** has a very brief action and it is therefore used mainly for the diagnosis of myasthenia gravis. However, such testing should be performed only by those experienced in its use; other means of establishing the diagnosis are available. A single test-dose usually causes substantial improvement in muscle power (lasting about 5 minutes) in patients with the disease (if respiration already impaired, *only* in conjunction with someone skilled at intubation).

Edrophonium can also be used to determine whether a patient with myasthenia is receiving inadequate or excessive treatment with cholinergic drugs. If treatment is excessive an injection of edrophonium will either have no effect or will intensify symptoms (if respiration already impaired, *only* in conjunction with someone skilled at intubation). Conversely, transient improvement may be seen if the patient is being inadequately treated. The test is best performed just before the next dose of anticholinesterase.

**Neostigmine** produces a therapeutic effect for up to 4 hours. Its pronounced muscarinic action is a disadvantage, and simultaneous administration of an anti-cholinergic drug such as atropine or propantheline may be required to prevent colic, excessive salivation, or diarrhoea. In severe disease neostigmine can be given every 2 hours. The maximum that most patients can tolerate is 180 mg daily.

**Pyridostigmine** is less powerful and slower in action than neostigmine but it has a longer duration of action. It is preferable to neostigmine because of its smoother action and the need for less frequent dosage. It is particularly preferred in patients whose muscles are weak on waking. It has a comparatively mild gastro-intestinal effect but an antimuscarinic drug may still be necessary (particularly with age). Pyridostigmine is preferable to neostigmine because of its smoother action and the need for less frequent dosage. Pyridostigmine is less powerful and slower in action than neostigmine but it has a longer duration of action.

**Distigmine** has the longest action but the danger of a cholinergic crisis caused by accumulation of the drug is greater than with shorter-acting drugs; it is rarely used in the management of myasthenia gravis.

Neostigmine and edrophonium are also used to reverse the actions of the non-depolarising neuromuscular blocking drugs (see section 15.1.6).

### Side-effects

- Nausea, vomiting, increased salivation, diarrhoea, abdominal cramps (more marked with higher doses); signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defaecation and micturition, miosis, nystagmus, bradycardia, heart block, arrhythmias, hypotension, agitation, excessive dreaming, and weakness eventually leading to fasciculation and paralysis.

### Dose

- **By mouth**, neostigmine bromide 15–30 mg at suitable intervals throughout day, total daily dose 75–300 mg (but see also notes above); **NEOSTIGMINE** 1–5 mg every 4 hours, half an hour before feeds; **CHILD** up to 6 years initially 7.5 mg, 6–12 years initially 15 mg, usual total daily dose 15–90 mg

- **By subcutaneous or intramuscular injection**, ADULT and **CHILD** over 12 years, neostigmine metilsulfate 1–2.5 mg at suitable intervals throughout day (usual total daily dose 5–20 mg); **NEOSTIGMINE** 150 micrograms/kg every 6–8 hours 30 minutes before feeds, increased to max. 300 micrograms/kg every 4 hours, if necessary [unlicensed]; **CHILD** 1 month–12 years 200–500 micrograms as required

**Neostigmine** (Non-proprietary) (PFI)

- Tablets, scored, neostigmine bromide 15 mg, net price 20 = £7.29

- **Injection**, neostigmine metilsulfate 2.5 mg/mL, net price 1 mL amp = 57p

### Distigmine Bromide

**Indications** myasthenia gravis (but rarely used); urinary retention and other indications (section 7.4.1)

**Cautions** see section 7.4.1

**Contra-indications** see section 7.4.1

**Side-effects** see section 7.4.1

**Dose**

- Initially 5 mg daily half an hour before breakfast, increased at intervals of 3–4 days if necessary to a max. of 20 mg daily; **CHILD** up to 10 mg daily according to age

**Preparations**

Section 7.4.1

### Edrophonium Chloride

**Indications** see under Dose and notes above; reversal of non-depolarising neuromuscular blockade and diagnosis of dual block (section 15.1.6)

**Cautions** see under Neostigmine; have resuscitation facilities; *extreme* caution in respiratory distress (see notes above) and in asthma

**Note** Severe cholinergic reactions can be counteracted by injection of atropine sulphate (which should always be available)

**Contra-indications** see under Neostigmine

**Side-effects** see under Neostigmine

**Dose**

- Diagnosis of myasthenia gravis, *by intravenous injection*, 2 mg followed after 30 seconds (if no adverse reaction has occurred) by 8 mg; in adults without suitable veins, *by intramuscular injection*, 10 mg

- Detection of overdosage or underdosage of cholinergic drugs, *by intravenous injection*, 2 mg (prefer-
ably just before next dose of anticholinesterase, see notes above)

- **CHILD** by intravenous injection, 20 micrograms/kg followed after 30 seconds (if no adverse reaction has occurred) by 80 micrograms/kg

**Edrophonium** (Cambridge) NW
Injection, edrophonium chloride 10 mg/mL, net price 1-mL amp = £7.86

### PYRIDOSTIGMINE BROMIDE

**Indications** myasthenia gravis

**Cautions** see under Neostigmine; weaker muscarinic action

**Contra-indications** see under Neostigmine

**Side-effects** see under Neostigmine

**Dose**

- **By mouth**, 30–120 mg at suitable intervals throughout day, total daily dose 0.3–1.2 g (but see also notes above); **NEONATE** 5–10 mg every 4 hours, 30–60 minutes before feeds; **CHILD** up to 6 years initially 30 mg, 6–12 years initially 60 mg, usual total daily dose 30–360 mg

**Mestinon®** (Valeant) SW
Tablets, scored, pyridostigmine (as bromide) 60 mg, net price 20 = £4.81

---

### Immunosuppressant therapy

**Corticosteroids** (section 6.3) are established as treatment for myasthenia gravis; although they are commonly given on alternate days there is little evidence of benefit over daily administration. Corticosteroid treatment is usually initiated under in-patient supervision and all patients should receive osteoporosis prophylaxis (section 6.6).

In **generalised myasthenia gravis** small initial doses of prednisolone (10 mg on alternate days) are increased in steps of 10 mg on alternate days to 1–1.5 mg/kg (max. 100 mg) on alternate days. When given daily, prednisolone is started at 5 mg daily and then increased in steps of 5 mg daily to 60 mg daily or occasionally up to 80 mg daily (0.75–1 mg/kg daily). About 10% of patients experience a transient but very serious worsening of symptoms in the first 2–3 weeks, especially if the corticosteroid is started at a high dose. However, ventilated patients may be started on 1.5 mg/kg (max. 100 mg) on alternate days. Smaller doses of corticosteroid are usually required in **ocular myasthenia**. Once clinical remission has occurred (usually after 2–6 months), the dose of prednisolone should be reduced slowly to the minimum effective dose (usually 10–40 mg on alternate days).

In **generalised myasthenia gravis** azathioprine (section 8.2.1) is usually started at the same time as the corticosteroid and it allows a lower maintenance dose of the corticosteroid to be used; azathioprine is initiated at a low dose, which is increased over 3–4 weeks to 2–2.5 mg/kg daily. Ciclosporin (section 8.2.2), methotrexate (section 8.1.3), or mycophenolate mofetil (section 8.2.1) can be used in patients unresponsive or intolerant to other treatments (unlicensed indications).

---

### BACLOFEN

**Indications** chronic severe spasticity resulting from disorders such as multiple sclerosis or traumatic partial section of spinal cord

**Cautions** psychiatric illness, Parkinson's disease, cerebrovascular disease, elderly; respiratory impairment, epilepsy; history of peptic ulcer (avoid oral route in active peptic ulceration); diabetes; hypertonic bladder sphincter; renal impairment (Appendix 3); pregnancy (Appendix 4); avoid abrupt withdrawal (risk of hyperactive state, may exacerbate spasticity, and precipitate autonomic dysfunction including hyperthermia, psychiatric reactions and convulsions, see also under Withdrawal below); **interactions**: Appendix 1 (muscle relaxants)

**Withdrawal** CSM has advised that serious side-effects can occur on abrupt withdrawal; to minimise risk, discontinue by gradual dose reduction over at least 1–2 weeks (longer if symptoms worsen)

**Side-effects** gastro-intestinal disturbances, dry mouth; hypotension, respiratory or cardiovascular depression; sedation, drowsiness, confusion, dizziness, ataxia, hallucinations, nightmares, headache, euphoria, insomnia, depression, anxiety, agitation, tremor; seizure; urinary disturbances; myalgia; nys-\n
---

### 10.2.2 Skeletal muscle relaxants

The drugs described below are used for the relief of chronic muscle spasm or spasticity associated with multiple sclerosis or other neurological damage; they are not indicated for spasm associated with minor injuries. They act principally on the central nervous system with the exception of dantrolene, which has a peripheral site of action. They differ in action from the muscle relaxants used in anaesthesia (section 15.1.5), which block transmission at the neuromuscular junction.

The underlying cause of spasticity should be treated and any aggravating factors (e.g. pressure sores, infection) remedied. Skeletal muscle relaxants are effective in most forms of spasticity except the rare alpha variety. The major disadvantage of treatment with these drugs is that reduction in muscle tone can cause a loss of splitting action of the spastic leg and trunk muscles and sometimes lead to an increase in disability.

**Dantrolene** acts directly on skeletal muscle and produces fewer central adverse effects making it a drug of choice. The dose should be increased slowly.

**Baclofen** inhibits transmission at spinal level and also depresses the central nervous system. The dose should be increased slowly to avoid the major side-effects of sedation and muscular hypotonia (other adverse events are uncommon).

**Diazepam** can also be used. Sedation and occasionally extensor hypotonus are disadvantages. Other benzodiazepines also have muscle-relaxant properties. Muscle-relaxant doses of benzodiazepines are similar to anxiolytic doses (section 4.1.2).

**Tizanidine** is an alpha -adrenoceptor agonist indicated for spasticity associated with multiple sclerosis or spinal cord injury.
tagmus; visual disorders; rash, hyperhidrosis; rarely taste disturbances, abdominal pain, paraesthesia, erectile dysfunction, dysarthria; very rarely hypothermia

**Dose**

- **By mouth**, 5 mg 3 times daily, preferably with or after food, gradually increased; max. 100 mg daily (discontinue if no benefit within 6 weeks); **CHILD** 0.75–2 mg/kg daily (over 10 years, max. 2.5 mg/kg daily) or 2.5 mg 4 times daily increased gradually according to age to maintenance: 1–2 years 10–20 mg daily, 2–6 years 20–30 mg daily, 6–10 years 30–60 mg daily

- **By intrathecal injection**, see preparation below

**Baclofen** (Non-proprietary) Tablets, baclofen 10 mg, net price 84-tab pack = £1.65. Label: 2, 8 Oral solution, baclofen 5 mg/5 mL, net price 300 mL = £8.95. Label: 2, 8 Brands include Lylex (sugar-free)

**Lioresal** (Novartis) Tablets, scored, baclofen 10 mg, net price 84-tab pack = £10.84. Label: 2, 8 Excipients include gluten Liquid, sugar-free, raspberry-flavoured, baclofen 5 mg/5 mL, net price 300 mL = £8.95. Label: 2, 8

**By intrathecal injection**

**Lioresal** (Novartis) Intrathecal injection, baclofen, 50 micrograms/mL, net price 1-mL amp (for test dose) = £2.74; 50 micrograms/mL, 20-mL amp (for use with implantable pump) = £60.77; 2 mg/mL, 5-mL amp (for use with implantable pump) = £60.77 Important Consult product literature for details on test dose and titration—important to monitor patients closely in appropriately equipped and staffed environment during screening and immediately after pump implantation. Resuscitation equipment must be available for immediate use

Dose by intrathecal injection, specialist use only, severe chronic spasticity unresponsive to oral antispastic drugs (or where side-effects of oral therapy unacceptable) or as alternative to ablative neurosurgical procedures, initial test dose 25–50 micrograms over at least 1 minute via catheter or lumbar puncture, increased in 25-microgram steps (not more often than every 24 hours) to max. 100 micrograms to determine appropriate dose then dose-adjustment phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 12 micrograms to 2 mg daily for spasticity of spinal origin or 22 micrograms to 1 mg daily for spasticity of cerebral origin) retaining some spasticity to avoid sensation of paralysis; **CHILD** 4–18 years (spasticity of cerebral origin only), initial test dose 25 micrograms then titrated as for **ADULT** to maintenance dose (ranging from 24 micrograms to 1.2 mg daily in children under 12 years)

**DANTROLENE SODIUM**

**Indications** chronic severe spasticity of voluntary muscle; malignant hyperthermia (section 15.1.8)

**Caution** impaired cardiac and pulmonary function; therapeutic effect may take a few weeks to develop—discontinue if no response within 45 days; **Interactions**: Appendix 1 (muscle relaxants). **Hepatotoxicity** Potentially life-threatening hepatotoxicity reported, usually if doses greater than 400 mg daily used, in females, patients over 30 years, if history of liver disorders, or concomitant use of hepatotoxic drugs; test liver function before and at intervals during therapy—discontinue if abnormal liver function tests or symptoms of liver disorder (counselling, see below); re-introduce only if complete reversal of hepatotoxicity

**Counselling** Patients should be told how to recognise signs of liver disorder and advised to seek prompt medical attention if symptoms such as anorexia, nausea, vomiting, fatigue, abdominal pain, dark urine, or pruritus develop. **Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-Indications** hepatic impairment (may cause severe liver damage); acute muscle spasm; avoid when spasticity is useful, for example, locomotion; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-Effects** diarrhoea (withdraw if severe, discontinue treatment if recurs on re-introduction), nausea, vomiting, anorexia, hepatotoxicity (see above), abdominal pain; pericarditis; pleural effusion, respiratory depression; headache, drowsiness, dizziness, asthenia, fatigue, seizures, fever, chills; speech and visual disturbances; rash; less commonly dysphagia, constipation, exacerbation of cardiac insufficiency, tachycardia, erratic blood pressure, dysphonia, depression, confusion, nervousness, insomnia, increased urinary frequency, urinary incontinence or retention, haematuria, crystalluria, and increased sweating

**Dose**

- Initially 25 mg daily, may be increased at weekly intervals to max. 100 mg 4 times daily; usual dose 75 mg 3 times daily; **CHILD** 5–18 years see **BNF** for Children

Dant瑞m® (Procter & Gamble Pharm.) Capsules, orange/brown, dantrolene sodium 25 mg, net price 20 = £2.46; 100 mg, 20 = £8.61. Label: 2, counselling, driving, hepatotoxicity

**DIAZEPAM**

**Indications** muscle spasm of varied aetiology, including tetanus; other indications (section 4.1.2, section 4.8, section 15.1.4.1)

**Cautions** see section 4.1.2; special precautions for intravenous injection (section 4.8.2)

**Contra-Indications** see section 4.1.2

**Side-Effects** see section 4.1.2; also hypotonia

**Dose**

- Muscle spasm, by mouth, 2–15 mg daily in divided doses, increased if necessary in spastic conditions to 60 mg daily according to response

Cerebral spasticity in selected cases, **CHILD** 2–40 mg daily in divided doses

By intramuscular or by slow intravenous injection (into a large vein at a rate of not more than 5 mg/minute), in acute muscle spasm, 10 mg repeated if necessary after 4 hours

**Note** Only use intramuscular route when oral and intravenous routes not possible; special precautions for intravenous injection see section 4.8.2

- **Tetanus**, **ADULT** and **CHILD**, by intravenous injection, 100–300 micrograms/kg repeated every 1–4 hours; by intravenous infusion (or by nasoduodenal tube), 3–10 mg/kg, over 24 hours, adjusted according to response

**Preparations** Section 4.1.2

**TIZANIDINE**

**Indications** spasticity associated with multiple sclerosis or spinal cord injury or disease

**Caution** elderly; monitor liver function monthly for first 4 months and in those who develop unexplained nausea, anorexia or fatigue; concomitant administra-
Cautions hepatic impairment (Appendix 2); renal short-term symptomatic relief of muscle Carisoma.

Dose see under Meprobamate (section 4.1.2); Side-effects see under Meprobamate (section Contra-indications see under Meprobamate (section 4.1.2); Cautions see under Meprobamate (section Indications short-term symptomatic relief of muscle spasms but see notes above)

Cautions hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); breast-feathering (Appendix 5); Interactions Appendix 1 (muscle relaxants)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Contra-indications severe hepatic impairment Side-effects drowsiness, fatigue, dizziness, dry mouth, nausea, gastro-intestinal disturbances, hypotension; also reported, bradycardia, insomnìa, hallucinations and altered liver enzymes (discontinue if persistently raised—consult product literature); rarely acute hepatitis

Dose Adults over 18 years, initially 2 mg daily as a single dose increased according to response at intervals of at least 3–4 days in steps of 2 mg daily (and given in divided doses) usually up to 24 mg daily in 3–4 divided doses; max. 36 mg daily

Tizanidine (Non-proprietary) Tablets, tizanidine (as hydrochloride) 2 mg net price 120-tab pack = £14.97; 4 mg, 120-tab pack = £21.76. Label: 2

Zanaflex® (Cephalon) Tablets, scored, tizanidine (as hydrochloride) 2 mg, net price 120-tab pack = £63.00; 4 mg, 120-tab pack = £80.00. Label: 2

Other muscle relaxants

The clinical efficacy of carisoprodol, meprobamate (section 4.1.2), and methocarbamol as muscle relaxants is not well established, although they have been included in compound analgesic preparations.

Carisoprodol is to be withdrawn from the market and the MHRA/CHM have advised that treatment with carisoprodol should no longer be started; patients who are already receiving it should have their treatment reviewed. However, carisoprodol should not be stopped abruptly because a withdrawal syndrome may occur.

CARISOPRODOL

Indications short-term symptomatic relief of muscle spasm (but see notes above)

Cautions see under Meprobamate (section 4.1.2); breast-feeding (Appendix 5); Interactions Appendix 1 (muscle relaxants)

Contra-indications see under Meprobamate (section 4.1.2)

Side-effects seen under Meprobamate (section 4.1.2); drowsiness is common

Dose see notes above; 350 mg 3 times daily; Elderly half adult dose or less

Carisoma® (Forest) Tablets, carisoprodol 125 mg, net price 100 = £6.65; 350 mg, 100 = £7.45. Label: 2

METHOCARBAMOL

Indications short-term symptomatic relief of muscle spasm (but see notes above)

Cautions hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); severe hepatic impairment

Side-effects nausea, vomiting, dyspepsia; hyper-sensitivity reactions (including urticaria, angioedema, anaphylaxis); fever, headache, drowsiness, dizziness, confusion, amnesia, restlessness, anxiety, tremor, seizures; blurred vision, nasal congestion; rash, pru- ritus; leucopenia, cholestatic jaundice

Dose 1.5 g 4 times daily; may be reduced to 750 mg 3 times daily; Elderly up to 750 mg 4 times daily may be sufficient; Child not recommended

Robaxin® (Shire) Tablets 750 Tablets, f/c, scored, methocarbamol 750 mg, net price 20 = £2.53. Label: 2

Nocturnal leg cramps

Quinine salts (section 5.4.1) 200–300 mg at bedtime are effective in reducing the frequency of nocturnal leg cramps by about 25% in ambulatory patients. It may take up to 4 weeks for improvement to become apparent; if there is benefit, quinine treatment can be continued. Patients should be monitored closely during the early stages for adverse effects as well as for benefit. Treatment should be interrupted at intervals of approximately 3 months to assess the need for further quinine treatment. Quinine is toxic in overdosage and accidental fatalities have occurred in children (see also below).

QUININE

Indications see notes above; malaria (section 5.4.1)

Cautions see section 5.4.1 and notes above

Contra-indications see section 5.4.1

Side-effects see section 5.4.1; important: very toxic in overdosage—immediate advice from poison centres essential (see also p. 32)

Dose see notes above

Preparations Section 5.4.1

10.3 Drugs for the relief of soft-tissue inflammation

10.3.1 Enzymes Rubefacients and other topical antirheumatics

Extravasation

Local guidelines for the management of extravasa- tion should be followed where they exist or specialist advice sought.

Extravasation injury follows leakage of drugs or intra- venous fluids from the veins or inadvertent administra-
tation into the subcutaneous or subdermal tissue. It must be dealt with promptly to prevent tissue necrosis. Acidic or alkaline preparations and those with an osmolality greater than that of plasma can cause extravasation injury; excipients including alcohol and polyethylene glycol have also been implicated. Cytotoxic drugs commonly cause extravasation injury. In addition, certain patients such as the very young and the elderly are at increased risk. Those receiving anti-coagulants are more likely to lose blood into surrounding tissues if extravasation occurs, while those receiving sedatives or analgesics may not notice the early signs or symptoms of extravasation.

**Prevention of extravasation** Precautions should be taken to avoid extravasation; ideally, drugs likely to cause extravasation injury should be given through a central line and patients receiving repeated doses of hazardous drugs peripherally should have the cannula resited at regular intervals. Attention should be paid to the manufacturers’ recommendations for administration. Placing a glyceryl trinitrate patch (section 2.6.1) distal to the cannula may improve the patency of the vessel in patients with small veins or in those whose veins are prone to collapse. Patients should be asked to report any pain or burning at the site of injection immediately.

**Management of extravasation** If extravasation is suspected the infusion should be stopped immediately but the cannula should not be removed until after an attempt has been made to aspirate the area (through the cannula) in order to remove as much of the drug as possible. Aspiration is sometimes possible if the extravasation presents with a raised bleb or blister at the injection site and is surrounded by hardened tissue, but it is often unsuccessful if the tissue is soft or soggy. **Corticosteroids** are usually given to treat inflammation, although there is little evidence to support their use in extravasation. Hydrocortisone or dexamethasone (section 6.3.2) can be given either locally by subcutaneous injection or intravenously at a site distant from the injury. **Antihistamines** (section 3.4.1) and **analgesics** (section 4.7) may be required for symptom relief.

The management of extravasation beyond these measures is not well standardised and calls for specialist advice. Treatment depends on the nature of the offending substance; one approach is to localise and neutralise the substance whereas another is to spread and dilute it. **Rubefacients** (e.g. capsaicin, ibuprofen, ketoprofen, and piroxicam) may provide some relief of pain in musculoskeletal conditions; they act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method which itself produces irritation of the skin. Counter-irritation is comforting in painful lesions of the muscles, tendons, and joints, and in non-articular rheumatism. Rubefacients probably all act through the same essential mechanism and differ mainly in intensity and duration of action.

**Hyaluronidase**

**Indications** enhance permeation of subcutaneous or intramuscular injections, local anaesthetics and subcutaneous infusions; promote resorption of excess fluids and blood

**Cautions** infants or elderly (control speed and total volume and avoid overhydration especially in renal impairment)

**Contra-indications** do not apply direct to cornea; avoid sites where infection or malignancy; not for anaesthesia in unexplained premature labour; not to be used to reduce swelling of bites or stings; not for intravenous administration

**Side-effects** oedema; rarely local irritation, infection, bleeding, bruising; occasional severe allergy (including anaphylaxis)

**Dose**
- With subcutaneous or intramuscular injection, 1500 units dissolved directly in solution to be injected (ensure compatibility)
- With local anaesthetics, 1500 units mixed with local anaesthetic solution (ophthalmology, 15 units/mL)
- Hypodermoclysis, 1500 units dissolved in 1 mL water for injections or 0.9% sodium chloride injection, administered before start of 500–1000 mL infusion fluid
- Extravasation (see notes above) or haematoma, 1500 units dissolved in 1 mL water for injections or 0.9% sodium chloride injection, infiltrated into affected area (as soon as possible after extravasation)

**Hyalase** (CP) (HAI)

**Injection**, powder for reconstitution, hyaluronidase (ovine). Net price 1500-unit amp = £7.60

**Rubefacients and other topical antirheumatics**

Rubefacients act by counter-irritation. Pain, whether superficial or deep-seated, is relieved by any method which itself produces irritation of the skin. Counter-irritation is comforting in painful lesions of the muscles, tendons, and joints, and in non-articular rheumatism. Rubefacients probably all act through the same essential mechanism and differ mainly in intensity and duration of action.

The use of a NSAID by mouth is effective for relieving musculoskeletal pain. **Topical NSAIDs** (e.g. felbinac, ibuprofen, ketoprofen, and piroxicam) may provide some relief of pain in musculoskeletal conditions; they can be considered as an adjunctive treatment in knee or hand osteoarthritis (see section 10.1).

A preparation containing capsaicin 0.025% is licensed for the symptomatic relief of osteoarthritis. It may need to be used for 1–2 weeks before pain is relieved. A
higher strength of capsaicin 0.075% cream is licensed for the symptomatic relief of postherpetic neuralgia (section 4.7.3) after lesions have healed, and for the relief of painful diabetic neuropathy (section 6.1.5).

**Topical NSAIDs and counter-irritants**

**Cautions** Apply with gentle massage only. Avoid contact with eyes, mucous membranes, and inflamed or broken skin; discontinue if rash develops. Hands should be washed immediately after use. Not for use with occlusive dressings. Topical application of large amounts can result in systemic effects, including hypersensitivity and asthma (renal disease has also been reported). Not generally suitable for children. Patient packs carry a warning to avoid during pregnancy or breast-feeding.

**Hypersensitivity** For NSAID hypersensitivity and asthma warning, see p. 553 and p. 554

**Photosensitivity** Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity

**Ketoprofen** (Non-proprietary) (£W)

- **Gel**, ketoprofen 2.5%, net price 30 g = £2.42, 50 g = £3.06, 100 g = £2.60.
- **Dose** apply 2–4 times daily for up to 7 days (usual max. 15 g daily).

**Piroxicam** (Non-proprietary) (£W)

- **Gel**, piroxicam 0.5%, net price 60 g = £1.65; 112 g = £2.65.
- **Dose** apply 3–4 times daily.

**Proprietary preparations**

**Feldene** (Pfizer) (£W)

- **Gel**, piroxicam 0.5%. Net price 60 g = £6.00; 112 g = £9.41 (also 7.5 g starter pack, hosp. only).
- **Excipients** include benzyl alcohol, propylene glycol.
- **Dose** apply 3–4 times daily; therapy should be reviewed after 4 weeks.

**Fenbid** (Forté) (£W)

- **Foam**, ibuprofen 10%, net price 100 g = £6.50.
- **Excipients** include benzyl alcohol.
- **Dose** apply up to 4 times daily; therapy should be reviewed after 14 days.

1. **Smaller pack sizes available on sale to the public.

**Ibugel** (Dermal) (£W)

- **Gel**, ibuprofen 10%, net price 100 g = £6.05.
- **Excipients** none as listed in section 13.1.3
- **Dose** apply up to 3 times daily.

2. **Orravil** (Rhône-Poulenc Rorer) (£W)

- **Gel**, ketoprofen 2.5%, net price 100 g = £5.87.
- **Excipients** include fragrance.
- **Dose** apply 2–4 times daily for up to 7 days (usual recommended dose 15 g daily).

1. **Smaller pack sizes available on sale to the public.

**Tralam** (Goldshield) (£W)

- **Foam**, felbinac 3.17%. Net price 100 g = £7.30.
- **Label** 15.
- **Excipients** include cetostearyl alcohol.
- **Gel**, felbinac 3%. Net price 100 g = £7.00.
- **Excipients** none as listed in section 13.1.3
- **Dose** apply 2–4 times daily, max. 25 g daily; therapy should be reviewed after 14 days.
- **Note** Felbinac is an active metabolite of the NSAID fenbufen.

\*\*Votarol Emulgel\*\* (Novartis) (£W)

- **Gel**, diclofenac diethylammonium salt 1.16% (equivalent to diclofenac sodium 1%), net price 20 g (hosp. only) = £1.55; 100 g = £7.00.
- **Excipients** include propylene glycol, fragrance.
- **Dose** apply 3–4 times daily; therapy should be reviewed after 14 days (or after 28 days for osteoarthritis).

1. **Smaller pack sizes available on sale to the public.

**Votarol Gel Patch** (Novartis) (£W)

- **Gel patch**, diclofenac epolamine (equivalent to 140 mg diclofenac sodium per patch), net price 10-patch pack = £14.09.
- **Excipients** include hydroxybenzoates (parabens), propylene glycol.
- **Dose** **ADULT** and **CHILD** over 15 years, ankle sprain, apply 1 patch daily for up to 3 days, epicondylitis, apply 1 patch twice daily for up to 14 days.
- **Note** The Scottish Medicines Consortium has advised (September 2005) that Votarol Gel Patch is not recommended for the treatment of pain in epicondylitis and ankle sprain.

**Capsaicin**

**Cautions** Avoid contact with eyes, and inflamed or broken skin. Hands should be washed immediately after use. Not for use under tight bandages. Avoid taking a hot shower or bath just before or after applying capsaicin—burning sensation enhanced.

**Side-effects** Transient burning sensation can occur during initial treatment, particularly if too much cream is used, or if the frequency of administration is less than 3–4 times daily.

**Zacin** (Cephalon) (£W)

- **Cream**, capsaicin 0.025%. Net price 45 g = £15.04.
- **Excipients** include benzyl alcohol, cetyl alcohol.
- **Dose** symptomatic relief in osteoarthritis, apply a small amount 4 times daily.

**Axsaín** (Cephalon) (£W)

- **Cream**, capsaicin 0.075%. Net price 45 g = £12.15.
- **Excipients** include benzyl alcohol, cetyl alcohol.
- **Dose** post-herpetic neuralgia (important: after lesions have healed), apply a small amount up to 3–4 times daily; for painful diabetic neuropathy, under supervision of hospital consultant, apply 3–4 times daily for 8 weeks then review.

**Poultices**

**Kaolin Poultice** (£)

- **Poultice**, heavy kaolin 52.7%, thymol 0.05%, boric acid 4.5%, peppermint oil 0.05%, methyl salicylate 0.2%, glycerol 42.5%. Net price 200 g = £2.44.
- **Dose** warm and apply directly or between layers of muslin; avoid application of overheated poultice.

**Kaolin Poultice K/L Pack** (£/l) (£)

- **Kaolin poultice** Net price 4 × 100-g pouches = £6.40.
11 Eye

11.1 Administration of drugs to the eye

Drugs are most commonly administered to the eye by topical application as eye drops or eye ointments. Where a higher drug concentration is required within the eye, a local injection may be necessary.

Eye-drop dispenser devices are available to aid the instillation of eye drops from plastic bottles; they are particularly useful for the elderly, visually impaired, arthritic, or otherwise physically limited patients.

Eye drops and eye ointments

Eye drops are generally instilled into the pocket formed by gently pulling down the lower eyelid and keeping the eye closed for as long as possible after application; one drop is all that is needed. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it.

When two different eye-drop preparations are used at the same time of day, dilution and overflow may occur when one immediately follows the other. The patient should therefore leave an interval of at least 5 minutes between the two.

Systemic effects may arise from absorption of drugs into the general circulation from conjunctival vessels or from the nasal mucosa after the excess preparation has drained down through the tear ducts. The extent of systemic absorption following ocular administration is highly variable; nasal drainage of drugs is associated with eye drops much more often than with eye ointments. Pressure on the lacrimal punctum for at least a minute after applying eye drops reduces nasolacrimal drainage and therefore decreases systemic absorption from the nasal mucosa.

For warnings relating to eye drops and contact lenses, see section 11.9.

Eye lotions

These are solutions for the irrigation of the conjunctival sac. They act mechanically to flush out irritants or foreign bodies as a first-aid treatment. Sterile sodium chloride 0.9% solution (section 11.8.1) is usually used. Clean water will suffice in an emergency.

Other preparations

Subconjunctival injection may be used to administer anti-infective drugs, mydriatics, or corticosteroids for conditions not responding to topical therapy. The drug diffuses through the cornea and sclera to the anterior and posterior chambers and vitreous humour. However, because the dose-volume is limited (usually not more than 1 mL), this route is suitable only for drugs which are readily soluble.

Drugs such as antimicrobials and corticosteroids may be administered systemically to treat susceptible eye conditions.
11.2 Control of microbial contamination

Preparations for the eye should be sterile when issued. Eye drops in multiple-application containers include a preservative but care should nevertheless be taken to avoid contamination of the contents during use.

Eye drops in multiple-application containers for domiciliary use should not be used for more than 4 weeks after first opening (unless otherwise stated).

Eye drops for use in hospital wards are normally discarded 1 week after first opening. Individual containers should be provided for each patient. A separate bottle should be supplied for each eye only if there are special concerns about contamination. Containers used before an operation should be discarded at the time of the operation and fresh containers supplied. A fresh supply should also be provided upon discharge from hospital; in specialist ophthalmology units, it may be acceptable to issue eye-drop bottles that have been dispensed to the patient on the day of discharge.

In out-patient departments single-application packs should preferably be used; if multiple-application packs are used, they should be discarded at the end of each day. In clinics for eye diseases and in accident and emergency departments, where the dangers of infection are high, single-application packs should be used; if a multiple-application pack is used, it should be discarded after single use.

Diagnostic dyes (e.g., fluorescein) should be used only from single-application packs.

In eye surgery single-application containers should be used if possible; if a multiple-application pack is used, it should be discarded after single use. Preparations used during intra-ocular procedures and others that may penetrate into the anterior chamber must be isotonic and without preservatives and buffered if necessary to a neutral pH. Specially formulated fluids should be used for intra-ocular surgery; intravenous infusion preparations are not suitable for this purpose. For all surgical procedures, a previously unopened container is used for each patient.

11.3 Anti-infective eye preparations

11.3.1 Antibacterials

Bacterial infections are generally treated topically with eye drops and eye ointments. Systemic administration is sometimes appropriate in blepharitis.

Chloramphenicol has a broad spectrum of activity and is the drug of choice for superficial eye infections. Chloramphenicol eye drops are well tolerated and the recommendation that chloramphenicol eye drops should be avoided because of an increased risk of aplastic anaemia is not well founded.

Other antibacterials with a broad spectrum of activity include the quinolones, ciprofloxacin, levofloxacin, and ofloxacin; the aminoglycosides, gentamicin and neomycin [unlicensed] are also active against a wide variety of bacteria. Gentamicin, quinolones, and polymyxin B are effective for infections caused by Pseudomonas aeruginosa.

Ciprofloxacin eye drops are licensed for corneal ulcers; intensive application (especially in the first 2 days) is required throughout the day and night.

Trachoma which results from chronic infection with Chlamydia trachomatis can be treated with azithromycin by mouth [unlicensed indication].

Fusidic acid is useful for staphylococcal infections.

Propamidine isetionate is of little value in bacterial infections but is specific for the rare but potentially devastating condition of acanthamoeba keratitis (see also section 11.9).

With corticosteroids Many antibacterial preparations also incorporate a corticosteroid but such mixtures should not be used unless a patient is under close specialist supervision. In particular they should not be prescribed for undiagnosed ‘red eye’ which is sometimes caused by the herpes simplex virus and may be difficult to diagnose (section 11.4).

Administration Frequency of application depends on the severity of the infection and the potential for irre-
versible ocular damage; antibacterial eye preparations are usually administered as follows:

**Eye drops** Apply 1 drop at least every 2 hours then reduce frequency as infection is controlled and continue for 48 hours after healing.

**Eye ointment** Apply either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).

### CHLORAMPHENICOL

**Indications** see notes above

**Side-effects** transient stinging; see also notes above

**Dose**

1. **Chloramphenicol** (Non-proprietary) 
   - **Eye drops**, chloramphenicol 0.5%. Net price 10 mL = £1.39
   - **Eye ointment**, chloramphenicol 1%. Net price 4 g = £1.63

1. Chloramphenicol 0.5% eye drops (in max. pack size 10 mL) and 1% eye ointment (in max. pack size 4 g) can be sold to the public for treatment of acute bacterial conjunctivitis in adults and children over 2 years; max. duration of treatment 5 days

**Chloromycetin** (Goldshield) 
- **Redidrops** (= eye drops), chloramphenicol 0.5%. Net price 5 mL = £1.65; 10 mL = £1.85
- **Ophthalmic ointment** (= eye ointment), chloramphenicol 1%. Net price 4 g = £1.85

<table>
<thead>
<tr>
<th>Single use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minims® Chloramphenicol</strong> (Chauvin)</td>
</tr>
<tr>
<td><strong>Eye drops</strong>, chloramphenicol 0.5%. Net price 20 x 0.5 mL = £4.92</td>
</tr>
</tbody>
</table>

### CIPROFLOXACIN

**Indications** superficial bacterial infections, see notes above; corneal ulcers

**Cautions** not recommended for children under 1 year; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** transient ocular irritation, visual disturbances, lid margin crusting, lid or conjunctival oedema, hyperaemia, conjunctival follicles, pho-

**Dose**

1. **Ciprofloxacin** (Non-proprietary) 
   - **Ophthalmic solution** (= eye drops), ciprofloxacin (as hydrochloride) 0.3%. Net price 5 mL = £4.94
   - **Eye ointment**, ciprofloxacin (as hydrochloride) 0.3%. Net price 3.5 g = £5.49

### FUSIDIC ACID

**Indications** see notes above

**Dose**

- See under preparation below

**Fucithalmic** (LEO) 
- **Eye drops**, m/r, fusidic acid 1% in gel basis (liquifies on contact with eye). Net price 5 g = £2.09
- **Excipients** include benzalkonium chloride, disodium edetate

**Dose** apply twice daily

### GENTAMICIN

**Indications** see notes above

**Dose**

- See Administration in notes above

**Genticin** (Roche) 
- **Drops** (for ear or eye), gentamicin 0.3% (as sulphate). Net price 10 mL = £1.78
- **Excipients** include benzalkonium chloride

### LEVOFLOXACIN

**Indications** see notes above

**Cautions** not recommended for children under 1 year; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** transient ocular irritation, visual disturbances, lid margin crusting, lid or conjunctival oedema, hyperaemia, conjunctival follicles, photo-

**Dose**

1. **Ofaquix** (Kestrel Ophthalmics) 
   - **Eye drops**, levofloxacin 0.5%, net price 5 mL = £6.95
   - **Excipients** include benzalkonium chloride

1. Levofloxacin 0.5% eye drops (in max. pack size 20 mL) and 0.5% single use units = £17.95

### NEOMYCIN SULPHATE

**Indications** see notes above

**Dose**

- See Administration in notes above

**Neomycin** (Non-proprietary) 
- **Eye drops**, neomycin sulphate 0.5% (3500 units/mL). Net price 10 mL = £2.31
- **Available from specialist importing companies, p. 939**
- **Eye ointment**, neomycin sulphate 0.5% (3500 units/g). Net price 3 g = £2.44
- **Available from specialist importing companies, p. 939**

1. **With other antibacterials**
   - **Neosporin** (PL/VA) 
     - **Eye drops**, gramicidin 25 units, neomycin sulphate 1700 units, polymyxin B sulphate 5000 units/mL. Net price 5 mL = £4.86
     - **Excipients** include thiomersal
     - **Dose** apply 2–4 times daily or more frequently if required

1. **With hydrocortisone**
   - Section 12.1.1
OFLOXACIN

Indications see notes above
Cautions pregnancy (Appendix 4); breastfeeding (Appendix 5)
Side-effects local irritation including photophobia; dizziness, numbness, nausea and headache reported
Dose
- Apply every 2–4 hours for the first 2 days then reduce frequency to 4 times daily (max. 10 days treatment)
Exocop® (Allergan)  
Ophthalmic solution (= eye drops), ofloxacin 0.3%. Net price 5 mL = £2.17
Excipients include benzalkonium chloride

POLYMIXIN B SULPHATE

Indications see notes above
Side-effects local irritation and dermatitis
Dose
- See Administration in notes above
With other antibacterials Polyfax® (PLIVA)  
Eye ointment, polymyxin B sulphate 10 000 units, bacitracin zinc 500 units/g. Net price 4 g = £3.26

PROPAMIDINE ISETIONATE

Indications local treatment of infections (but see notes above)
Dose
- See preparations
Brolene® (Aventis Pharma)  
Eye drops, propamidine isetionate 0.1%. Net price 10 mL = £2.80
Excipients include benzalkonium chloride
Dose apply 4 times daily
Note Eye drops containing propamidine isetionate 0.1% also available from Typharm (Golden Eye Drops)
Eye ointment, dibromopropamidine isetionate 0.15%. Net price 5 g = £2.92
Dose apply 1–2 times daily
Note Eye ointment containing dibromopropamidine isetionate 0.15% also available from Typharm (Golden Eye Ointment)

11.4 Corticosteroids and other anti-inflammatory preparations

11.4.1 Corticosteroids

11.4.2 Other anti-inflammatory preparations

11.3.2 Antifungals

Fungal infections of the cornea are rare but can occur after agricultural injuries, especially in hot and humid climates. Orbital mycosis is rarer, and when it occurs it is usually because of a direct spread of infection from the paranasal sinuses. Increasing age, debility, or immunosuppression may encourage fungal proliferation. The spread of infection through blood occasionally produces a metastatic endophthalmitis.

Many different fungi are capable of producing ocular infection; they may be identified by appropriate laboratory procedures.

Antifungal preparations for the eye are not generally available. Treatment will normally be carried out at specialist centres, but requests for information about supplies of preparations not available commercially should be addressed to the Strategic Health Authority (or equivalent), or to the nearest hospital ophthalmology unit, or to Moorfields Eye Hospital, City Road, London EC1V 2PD (tel. (020) 7253 3411).

11.3.3 Antvirals

Hepatitis infections producing, for example, dendritic corneal ulcer can be treated with aciclovir. Slow-release ocular implants containing ganciclovir (available on a named-patient basis from specialist importing companies, see p. 924) may be inserted surgically to treat immediate sight-threatening CMV retinitis. Local treatments do not protect against systemic infection or infection in the other eye. For systemic treatment of CMV retinitis, see section 5.3.2.2.

ACICLOVIR  
(Acyclovir)

Indications local treatment of herpes simplex infections
Side-effects local irritation and inflammation, superficial punctate keratopathy; rarely blepharitis; very rarely hypersensitivity reactions including angioedema
Dose
- Apply 5 times daily (continue for at least 3 days after complete healing)
Zovirax® (GSK)  
Eye ointment, aciclovir 3%. Net price 4.5 g = £9.92
Tablets, section 5.3.2.1
Injection, section 5.3.2.1
Cream, section 13.10.3
surgery to reduce inflammation and prevent infection; use of combination products is otherwise rarely justified. Systemic corticosteroids (section 6.3.2) may be useful for ocular conditions. The risk of producing a ‘steroid cataract’ increases with the dose and duration of corticosteroid use.

The Scottish Medicines Consortium (p. 3) has advised (May 2008) that loteprednol etabonate 0.5% eye drops (Lotemax®) are not recommended for use within NHS Scotland.

### BETAMETHASONE

**Indications**  local treatment of inflammation (short-term)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- Apply eye drops every 1–2 hours until controlled then reduce frequency; apply eye ointment 2–4 times daily or at night when used with eye drops

**Betnesol®** (UCB Pharma) (**BN**)

**Drops** (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 10 mL = £2.32

**Exipients** include benzalkonium chloride, disodium edetate

**Eye ointment**, betamethasone sodium phosphate 0.1%. Net price 3 g = £1.41

**Vistamethasone®** (Martindale) (**BN**)

**Drops** (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 5 mL = £1.02; 10 mL = £1.16

**Exipients** include benzalkonium chloride

With neomycin

**Betnesol-N®** (UCB Pharma) (**BN**)

**Drops** (for ear, eye, or nose), see section 12.1.1

**Eye ointment**, betamethasone sodium phosphate 0.1%, neomycin sulphate 0.5%. Net price 3 g = £1.28

**Vistamethasone N®** (Martindale) (**BN**)

**Drops** (for ear, eye, or nose), see section 12.1.1

### DEXAMETHASONE

**Indications**  local treatment of inflammation (short-term)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- Apply eye drops every 30–60 minutes until controlled then reduce frequency to 4–6 times daily

**Maxidex®** (Alcon) (**BN**)

**Eye drops**, dexamethasone 0.1%, hypromellose 0.5%. Net price 5 mL = £1.49; 10 mL = £2.95

**Exipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Single use**

**Minims® Dexamethasone** (Chauvin) (**BN**)

**Eye drops**, dexamethasone sodium phosphate 0.1%. Net price 20 × 0.5 mL = £6.95

**Exipients** include disodium edetate

With antibacterials

**Maxitrol®** (Alcon) (**BN**)

**Eye drops**, dexamethasone 0.1%, neomycin 0.35% (as sulphate), polymyxin B sulphate 6000 units/mL. Net price 5 mL = £1.77

**Exipients** include benzalkonium chloride, polysorbate 20

**Eye ointment**, dexamethasone 0.1%, neomycin 0.35% (as sulphate), polymyxin B sulphate 6000 units/g. Net price 3.5 g = £1.52

**Exipients** include hydrocortisone (pamabrom), wool fat

**Dose** apply 3–4 times daily or at night when used with eye drops

**Sofradex®** (Sanofi-Aventis) (**BN**)

**Eye drops**, dexamethasone 0.1%, tobramycin 0.3%. Net price 5 mL = £5.65

**Exipients** include benzalkonium chloride, disodium edetate

### FLUOROMETHOLONE

**Indications**  local treatment of inflammation (short-term)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- Apply every hour for 24–48 hours then reduce frequency to 2–4 times daily

**FML®** (Allergan) (**BN**)

**Ophthalmic suspension** (= eye drops), fluorometholone 0.1%, polyvinyl alcohol (Liquifilm®) 1.4%. Net price 5 mL = £1.71; 10 mL = £2.95

**Exipients** include benzalkonium chloride, disodium edetate, polysorbate 80

### HYDROCORTISONE ACETATE

**Indications**  local treatment of inflammation (short-term)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- Apply eye drops every 30–60 minutes until controlled then reduce frequency to every 4 hours

**Hydrocortisone** (Non-proprietary) (**BN**)

**Eye drops**, hydrocortisone acetate 1%. Net price 10 mL = £8.61

**Eye ointment**, hydrocortisone acetate 0.5%, net price 3 g = £2.40; 1%, 3 g = £2.42; 2.5%, 3 g = £6.55

With neomycin

**Neo-Cortef®** (PLIVA) (**BN**)

**Ointment** (for ear or eye), see section 12.1.1

**Note** May be difficult to obtain

**Dose** apply 2–3 times daily

### LOTEPREDNOL ETABONATE

**Indications**  treatment of post-operative inflammation following ocular surgery

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- Apply 4 times daily starting 24 hours after surgery; max. duration of treatment 14 days
PREDNISOLONE

**Indications** local treatment of inflammation (short-term)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**
- Apply every 1–2 hours until controlled then reduce frequency

**Predsol®** (UCB Pharma) (£)
- **Drops** (for ear or eye), prednisolone sodium phosphate 0.5%. Net price 10 mL = £2.00
  - Excipients include benzalkonium chloride, disodium edetate

**Pred Forte®** (Allergan) (£)
- **Eye drops**, prednisolone acetate 1%. Net price 5 mL = £1.52; 10 mL = £3.05
  - Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

**Predsol-N®** (UCB Pharma) (£)
- **Drops** (for ear or eye), see section 12.1.1
  - Excipients include benzalkonium chloride, disodium edetate, polyvinylpyrrolidone

**Single use**

**Minims® Prednisolone Sodium Phosphate** (Chauvin) (£)
- **Eye drops**, prednisolone sodium phosphate 0.5%. Net price 20 × 0.5 mL = £5.75
  - Excipients include disodium edetate

**With neomycin**

**Predsol-N Emadine®** (Alcon) (£)
- **Opthalmic suspension** include benzalkonium chloride, disodium edetate

**AZELASTINE HYDROCHLORIDE**

**Indications** allergic conjunctivitis

**Side-effects** mild transient irritation; bitter taste reported

**Dose**
- Seasonal allergic conjunctivitis, **ADULT** and **CHILD** over 4 years, apply twice daily, increased if necessary to 4 times daily
- Perennial conjunctivitis, **ADULT** and **ADOLESCENT** over 12 years, apply twice daily, increased if necessary to 4 times daily; max. duration of treatment 6 weeks

**Optilast®** (Viatris) (£)
- **Eye drops**, azelastine hydrochloride 0.05%. Net price 8 mL = £6.40
  - Excipients include benzalkonium chloride, disodium edetate

**Note** Azelastine 0.05% eye drops can be sold to the public (in max. pack size of 6 mL) for treatment of seasonal and perennial allergic conjunctivitis in adults and children over 12 years

**EMEDASTINE**

**Indications** seasonal allergic conjunctivitis

**Side-effects** transient burning or stinging; blurred vision, local oedema, keratitis, irritation, dry eye, lacrimation, corneal infiltrates (discontinue) and staining; photophobia; headache, and rhinitis occasionally reported

**Dose**
- **ADULT** and **CHILD** over 3 years, apply twice daily

**Emedine®** (Alcon) (£)
- **Eye drops**, emedastine 0.05% (as difumarate), net price 5 mL = £7.69
  - Excipients include benzalkonium chloride

**EPINASTINE HYDROCHLORIDE**

**Indications** seasonal allergic conjunctivitis

**Side-effects** burning; less commonly dry mouth, taste disturbance; nasal irritation, rhinitis; headache, blepharoconjunctivitis, conjunctival oedema and hyperaemia.

Other preparations used for the topical treatment of inflammation and allergic conjunctivitis include antihistamines, lodoxamide, and sodium cromoglicate.

Eye drops of antihistamines such antazoline (with xylometazoline as Otrivine-Antistin®), azelastine, epinastine, ketotifen and olopatadine may be used for allergic conjunctivitis.

**Sodium cromoglicate** (sodium cromoglycate) and nedocromil sodium eye drops can be useful for vernal keratoconjunctivitis and other allergic forms of conjunctivitis.

Lodoxamide eye drops are used for allergic conjunctival conditions including seasonal allergic conjunctivitis.

Diclofenac eye drops (section 11.8.2) and emedastine eye drops are also licensed for seasonal allergic conjunctivitis.
dry eye, local irritation, photophobia, visual disturbance; pruritus

**Dose**
- **ADULT** and **preadolescent** over 12 years, apply twice daily; max. duration of treatment 8 weeks

**Relestat** (Allergan) **(F)***

*Eye drops*, epinastine hydrochloride 500 micrograms/mL, net price 5 mL = £9.90

**Excipients** include benzalkonium chloride, disodium edetate

**KETOTIFEN**

**Indications** seasonal allergic conjunctivitis

**Side-effects** burning or stinging, punctate corneal epithelial erosions; less commonly dry eye, subconjunctival haemorrhage, photophobia; headache, drowsiness, skin reactions, and dry mouth also reported

**Dose**
- **ADULT** and **CHILD** over 3 years, apply twice daily

**Zaditen** (Novartis) **(F)***

*Eye drops*, ketotifen (as fumarate) 250 micrograms/mL, net price 5 mL = £9.75

**Excipients** include benzalkonium chloride

**LODOXAMIDE**

**Indications** allergic conjunctivitis

**Side-effects** burning, stinging, itching, and lacrimation; flushing and dizziness reported

**Dose**
- **ADULT** and **CHILD** over 4 years, apply 4 times daily

**Alomide** (Alcon) **(F)***

*Ophthalmic solution* (= eye drops), lodoxamide 0.1% (as trometamol). Net price 10 mL = £5.48

**Excipients** include benzalkonium chloride, disodium edetate

**Note** Lodoxamide 0.1% eye drops can be sold to the public for the treatment of allergic conjunctivitis in adults and children over 4 years

**NEDOCROMIL SODIUM**

**Indications** allergic conjunctivitis; seasonal keratoconjunctivitis

**Side-effects** burning and stinging; distinctive taste reported

**Dose**
- Seasonal and perennial conjunctivitis, **ADULT** and **CHILD** over 6 years, apply twice daily increased if necessary to 4 times daily; max. 12 weeks treatment for seasonal allergic conjunctivitis
- Seasonal keratoconjunctivitis, **ADULT** and **CHILD** over 6 years, apply 4 times daily

**Rapitil** (Aventis Pharma) **(F)***

*Eye drops*, nedocromil sodium 2%. Net price 5 mL = £5.12

**Excipients** include benzalkonium chloride, disodium edetate

**OLOPATADINE**

**Indications** seasonal allergic conjunctivitis

**Side-effects** local irritation; less commonly keratitis, dry eye, local oedema, photophobia; headache, asthenia, dizziness; dry nose also reported

**Dose**
- **ADULT** and **CHILD** over 3 years, apply twice daily; max. duration of treatment 4 months

**Opatanol** (Alcon) **(F)***

*Eye drops*, olopatadine (as hydrochloride) 1 mg/mL, net price 5 mL = £4.11

**Excipients** include benzalkonium chloride

**SODIUM CROMOGLYCATE**

*(Sodium cromoglycate)*

**Indications** allergic conjunctivitis; seasonal keratoconjunctivitis

**Side-effects** burning and stinging

**Dose**
- **ADULT** and **CHILD** apply eye drops 4 times daily

**Sodium Cromoglicate** *(Non-proprietary)***

*Eye drops*, sodium cromoglicate 2%. Net price 13.5 mL = £2.01

**Brands** include Hay-Crom Aqueous, Opticrom Aqueous, Vioform

1. Sodium cromoglicate 2% eye drops can be sold to the public (in max. pack size of 10 mL) for treatment of acute seasonal and perennial allergic conjunctivitis

**11.5 Mydriatics and cycloplegics**

Antimuscarinics dilate the pupil and paralyse the ciliary muscle; they vary in potency and duration of action.

Short-acting, relatively weak mydriatics, such as tropicamide 0.5%, facilitate the examination of the fundus of the eye. Cyclopentolate 1% or atropine are preferable for producing cycloplegia for refraction in young children. Atropine ointment 1% is sometimes preferred for children aged under 5 years because the ointment formulation reduces systemic absorption. Atropine, which has a longer duration of action, is also used for the treatment of anterior uveitis mainly to prevent posterior synechiae, often with phenylephrine 10% eye drops (2.5% in children, the elderly, and those with cardiac disease). Homatropine 1% is also used in the treatment of anterior segment inflammation, and may be preferred for its shorter duration of action.

**Cautions** Darkly pigmented iris is more resistant to pupillary dilatation and caution should be exercised to avoid overdosage. Mydriasis can precipitate acute angle-closure glaucoma in a few patients, usually aged over 60 years and hypermetropic (long-sighted), who are predisposed to the condition because of a shallow anterior chamber. Phenylephrine may interact with systemically administered monoamine-oxidase inhibitors; other interactions: Appendix 1 (sympathomimetics).

**Driving** Patients should be warned not to drive for 1–2 hours after mydriasis.

**Side-effects** Ocular side-effects of mydriatics and cycloplegics include transient stinging and raised intra-ocular pressure; on prolonged administration, local irritation, hyperaemia, oedema and conjunctivitis can occur. Contact dermatitis can occur with the antimuscarinic mydriatic drugs, especially atropine.
Systemic side-effects of atropine and cyclopentolate can occur, particularly in children and the elderly; see section 1.2 for systemic side-effects of antimuscarinic drugs.

**Antimuscarinics**

**ATROPINE SULPHATE**

**Indications** refraction procedures in young children; anterior uveitis—see also notes above

**Cautions** risk of systemic effects with eye drops in infants under 3 months—eye ointment preferred; see also notes above

**Side-effects** see notes above

*Atropine* (Non-proprietary)

Eye drops, atropine sulphate 0.5%, net price 10 mL = £2.32; 1%, 10 mL = 98p

Eye ointment, atropine sulphate 1%. Net price 3 g = £2.97

**Single use**

Minims® Atropine Sulphate (Chauvin)

Eye drops, atropine sulphate 1%. Net price 20 x 0.5 mL = £4.92

**CYCLOPENTOLATE HYDROCHLORIDE**

**Indications** see notes above

**Cautions** see notes above

**Side-effects** see notes above

*Mydriolate* (Intrapharm)

Eye drops, cyclopentolate hydrochloride 0.5%, net price 5 mL = 97p; 1%, 5 mL = £1.19

Excipients include benzalkonium chloride

**Single use**

Minims® Cyclopentolate Hydrochloride (Chauvin)

Eye drops, cyclopentolate hydrochloride 0.5% and 1%. Net price 20 x 0.5 mL (both) = £4.92

**HOMATROPINE HYDROBROMIDE**

**Indications** see notes above

**Cautions** see notes above

**Side-effects** see notes above

*Homatropine* (Non-proprietary)

Eye drops, homatropine hydrobromide 1%, net price 10 mL = £2.14; 2%, 10 mL = £2.26

**TROPICAMIDE**

**Indications** see notes above

**Cautions** see notes above

**Side-effects** see notes above

*Mydriacyl* (Alcon)

Eye drops, tropicamide 0.5%, net price 5 mL = £1.36; 1%, 5 mL = £1.68

Excipients include benzalkonium chloride, disodium edetate

**Sympathomimetics**

**PHENYLEPHRINE HYDROCHLORIDE**

**Indications** mydriasis; see also notes above

**Cautions** children and elderly (avoid 10% strength); cardiovascular disease (avoid or use 2.5% strength only); tachycardia; hyperthyroidism; diabetes; see also notes above

**Side-effects** eye pain and stinging; blurred vision, photophobia; systemic effects include palpitations, arrhythmias, hypertension, coronary artery spasm; very rarely angle-closure glaucoma

*Phenylephrine* (Non-proprietary)

Eye drops, phenylephrine hydrochloride 10%. Net price 10 mL = £3.38

**Single use**

Minims® Phenylephrine Hydrochloride (Chauvin)

Eye drops, phenylephrine hydrochloride 2.5%, net price 20 x 0.5 mL (both) = £5.75

Excipients include disodium edetate, sodium metabisulphite

**11.6 Treatment of glaucoma**

Glaucoma describes a group of disorders characterised by a loss of visual field associated with cupping of the optic disc and optic nerve damage. While glaucoma is generally associated with raised intra-ocular pressure, it can occur when the intra-ocular pressure is within the normal range.

The commonest form of glaucoma is primary open-angle glaucoma (chronic simple glaucoma; wide-angle glaucoma), where the obstruction is in the trabecular meshwork. The condition is often asymptomatic and the patient may present with significant loss of visual-field. Primary angle closure glaucoma (acute closed-angle glaucoma, narrow-angle glaucoma) results from blockage of aqueous humour flow into the anterior chamber and is a medical emergency.

Drugs that reduce intra-ocular pressure by different mechanisms are available for managing glaucoma. A topical beta-blocker or a prostaglandin analogue is usually the drug of first choice. It may be necessary to combine these drugs or add others, such as miotics, sympathomimetics, or carbonic anhydrase inhibitors, to control intra-ocular pressure.

For urgent reduction of intra-ocular pressure and before surgery, mannitol 20% (up to 500 mL) is given by slow intravenous infusion until the intra-ocular pressure has been satisfactorily reduced. Acetazolamide by intravenous injection can also be used for the emergency management of raised intra-ocular pressure.

Standard antiglaucoma therapy is used if supplementary treatment is required after iridotomy, iridectomy, or a drainage operation in either primary open-angle or acute closed-angle glaucoma.
Beta-blockers

Topical application of a beta-blocker to the eye reduces intra-ocular pressure effectively in primary open-angle glaucoma, probably by reducing the rate of production of aqueous humour. Administration by mouth also reduces intra-ocular pressure but this route is not used since side-effects may be troublesome.

Beta-blockers used as eye drops include betaxolol, carteolol, levobunolol, metipranolol, and timolol.

Cautions, contraindications and side-effects

Systemic absorption may follow topical application to the eyes; therefore, eye drops containing a beta-blocker are contra-indicated in patients with bradycardia, heart block, or uncontrolled heart failure. Important: for a warning to avoid in asthma see CSM advice below. Consider also other cautions, contra-indications and side-effects of beta-blockers (p. 85). Local side-effects of eye drops include ocular stinging, burning, pain, itching, erythema, dry eyes and allergic reactions including anaphylaxis and blepharoconjunctivitis; occasionally corneal disorders have been reported.

CSM advice The CSM has advised that beta-blockers, even those with apparent cardioselectivity, should not be used in patients with asthma or a history of obstructive airways disease, unless no alternative treatment is available. In such cases the risk of inducing bronchospasm should be appreciated and appropriate precautions taken.

Interactions Since systemic absorption may follow topical application the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind. See also Appendix 1 (beta-blockers).

Betaxolol hydrochloride

Indications see notes above
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above
Dose
- Apply twice daily

Betoptic® (Alcon) (£)
Ophthalmic solution (= eye drops), betaxolol (as hydrochloride) 0.5%, net price 5 mL = £2.00
Excipients include benzalkonium chloride, disodium edetate
Ophthalmic suspension (= eye drops), betaxolol (as hydrochloride) 0.25%, net price 5 mL = £2.80
Excipients include benzalkonium chloride, disodium edetate

Unit dose eye drop suspension, m/t, betaxolol (as hydrochloride) 0.25%, net price 50 × 0.25 mL = £14.49

Carbotrol hydrochloride

Indications see notes above
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above
Dose
- Apply twice daily

Teoptic® (Novartis) (£)
Eye drops, carteolol hydrochloride 1%, net price 5 mL = £4.60; 2%, 5 mL = £5.40
Excipients include benzalkonium chloride

LEVOBUNOLOL HYDROCHLORIDE

Indications see notes above
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above; anterior uveitis occasionally reported
Dose
- Apply once or twice daily

Levobunolol (Non-proprietary) (£)
Eye drops, levobunolol hydrochloride 0.5%. Net price 5 mL = £2.68
Betagan® (Allergan) (£)
Eye drops, levobunolol hydrochloride 0.5%, polyvinyl alcohol (Liquifilm®) 1.4%. Net price 5-mL = £1.85
Excipients include benzalkonium chloride, disodium edetate, sodium metabisulphite

Unit dose eye drops, levobunolol hydrochloride 0.5%, polyvinyl alcohol (Liquifilm®) 1.4%. Net price 30 × 0.4 mL = £9.98
Excipients include disodium edetate

Metipranolol

Indications see notes above but in chronic open-angle glaucoma restricted to patients allergic to preservatives or to those wearing soft contact lenses (in whom benzalkonium chloride should be avoided)
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above; granulomatous anterior uveitis reported (discontinue treatment)
Dose
- Apply twice daily

Minims® Metipranolol (Chauvin) (£)
Eye drops, metipranolol 0.1%, net price 20 × 0.5 mL = £10.19

Timolol maleate

Indications see notes above
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above
Dose
- Apply twice daily; long-acting preparations, see under preparations below

Timolol (Non-proprietary) (£)
Eye drops, timolol (as maleate) 0.25%, net price 5 mL = £2.30; 0.5%, 5 mL = £1.95

Timoptol® (MSD) (£)
Eye drops, in Ocumeter® metered-dose unit, timolol (as maleate) 0.25%, net price 5 mL = £3.12, 0.5%, 5 mL = £3.12
Excipients include benzalkonium chloride

Unit dose eye drops, timolol (as maleate) 0.25%, net price 30 × 0.2 mL = £8.45; 0.5%, 30 × 0.2 mL = £9.65

Once-daily preparations

Nygocil® (Novartis) (£)
Eye gel (= eye drops), timolol (as maleate) 0.1%, net price 5 g = £2.85
Excipients include benzalkonium chloride
Dose apply once daily
Timoptic®-LA (MSD) (INN) Ophthalmic gel-forming solution (= eye drops), timolol (as maleate) 0.25%, net price 2.5 mL = £3.12; 0.5%, 2.5 mL = £3.12
Excipients include benzododecinium bromide
Dose apply once daily

With bimatoprost
See under Rimatoprost

With brimonidine
See under Brimonidine

With dorzolamide
See under Dorzolamide

With latanoprost
See under Latanoprost

With travoprost
See under Travoprost

Prostaglandin analogues

Latanoprost and travoprost are prostaglandin analogues which increase uveoscleral outflow; bimatoprost is a related drug. They are used to reduce intra-ocular pressure in ocular hypertension or in open-angle glaucoma. Patients receiving prostaglandin analogues should be monitored for any changes to eye coloration since an increase in the brown pigment in the iris may occur; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only.

BIMATOPROST

Indications raised intra-ocular pressure in open-angle glaucoma; ocular hypertension

Cautions see under Latanoprost and notes above

Side-effects see under Latanoprost

Dose

• Apply once daily, preferably in the evening; CHILD and ADOLESCENT under 18 years, not recommended

Lumigan® (Allergan) (INN) Eye drops, bimatoprost 300 micrograms/mL, net price 3 mL = £11.46, triple pack (3 x 3 mL) = £32.66
Excipients include benzaalkonium chloride

With timolol

See under Timolol, contra-indications, and side-effects of timolol, see section 11.6, Beta-blockers

Ganfort® (Allergan) (INN) Eye drops, bimatoprost 300 micrograms/mL, timolol (as maleate) 5 mg/mL, net price 3 mL = £14.58
Excipients include benzaalkonium chloride

Dose for raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate; apply once daily, preferably in the morning

LATANOPROST

Indications raised intra-ocular pressure in open-angle glaucoma; ocular hypertension

Cautions before initiating treatment, advise patients of possible change in eye colour; monitor for eye colour change (see also notes above); aphakia, or pseudophakia with torn posterior lens capsule or anterior chamber lenses; risk factors for iritis, uveitis, and cystoid macular oedema; brittle or severe asthma; not to be used within 5 minutes of use of thiomersal-containing preparations; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects brown pigmentation particularly in those with mixed-colour irides; blepharitis, ocular irritation and pain; darkening, thickening and lengthening of eye lashes; conjunctival hyperaemia; transient punctate epithelial erosion; skin rash; less commonly eyelid oedema and rash; rarely dyspnœa, exacerbation of asthma, iritis, uveitis, local oedema, darkening of palpebral skin; very rarely chest pain, exacerbation of angina

Dose

• Apply once daily, preferably in the evening; CHILD not recommended

Xalatan® (Pharmacia) (INN) Eye drops, latanoprost 50 micrograms/mL, net price 2.5 mL = £13.14
Excipients include benzaalkonium chloride

With timolol

For cautions, contra-indications, and side-effects of timolol, see section 11.6, Beta-blockers

Xalacom® (Pharmacia) (INN) Eye drops, latanoprost 50 micrograms, timolol (as maleate) 5 mg/mL, net price 2.5 mL = £15.07
Excipients include benzaalkonium chloride

Dose for raised intra-ocular pressure in patients with open-angle glaucoma and ocular hypertension when beta-blocker alone not adequate; apply once daily

TRAVOPROST

Indications raised intra-ocular pressure in open-angle glaucoma; ocular hypertension

Cautions see under Latanoprost and notes above

Side-effects see under Latanoprost

Dose

• Apply once daily, preferably in the evening; CHILD and ADOLESCENT under 18 years, not recommended

Travatan® (Alcon) (INN) Eye drops, travoprost 40 micrograms/mL, net price 2.5 mL = £10.50
Excipients include benzaalkonium chloride

With timolol

For cautions, contra-indications, and side-effects of timolol, see section 11.6, Beta-blockers

DuoTrav® (Alcon) (INN) Eye drops, travoprost 40 micrograms, timolol (as maleate) 5 mg/mL, net price 2.5 mL = £13.20
Excipients include benzaalkonium chloride, disodium edetate

Dose for raised intra-ocular pressure in patients with open-angle glaucoma or ocular hypertension when beta-blocker or prostaglandin analogue alone not adequate; apply once daily, CHILD and ADOLESCENT under 18 years, not recommended
**Sympathomimetics**

Dipivefrine is a pro-drug of adrenaline (epinephrine). It is claimed to pass more rapidly than adrenaline through the cornea and is then converted to the active form. Adrenaline probably acts both by reducing the rate of production of aqueous humour and by increasing the outflow through the trabecular meshwork. Because it is a mydriatic, adrenaline should be used with caution in patients susceptible to angle-closure glaucoma, unless an iridectomy has been carried out. Side-effects include severe smarting and redness of the eye; adrenaline should be used with caution in patients with hypertension and heart disease.

**Brimonidine**, a selective alpha -adrenoceptor agonist, is licensed for the reduction of intra-ocular pressure in open-angle glaucoma or ocular hypertension in patients for whom beta-blockers are inappropriate; it may also be used as adjunctive therapy when intra-ocular pressure is inadequately controlled by other antiglaucoma therapy.

Apraclonidine (section 11.8.2) is another alpha -adrenoceptor agonist. Eye drops containing apraclonidine 0.5% are used for a short term to delay laser treatment or surgery for glaucoma in patients not adequately controlled by another drug; eye drops containing 1% are used for control of intra-ocular pressure after anterior segment laser surgery.

**BRIMONIDINE TARTRATE**

**Indications** raised intra-ocular pressure, see notes above

**Cautions** severe cardiovascular disease; cerebral or coronary insufficiency, Raynaud's syndrome, postural hypotension, depression, hepatic or renal impairment; pregnancy, breast-feeding; interactions: Appendix 1 (brimonidine)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving)

**Side-effects** ocular reactions including conjunctival hyperaemia, stinging, photophobia, corneal erosion, superficial punctuate keratitis, eye pain, discharge, dryness, and irritation, eyelid inflammation, oedema, pruritus conjunctivitis, photophobia; also, hypertension, headache, depression, dry mouth, fatigue, drowsiness; less commonly, taste disturbances, palpitation, dizziness, syncope, rhinitis, nasal dryness

**Dose**

- Apply twice daily

**Alphagan®** (Allergan) [Prescriber information]

**Eye drops**, brimonidine tartrate 0.2%, net price 5 mL = £26.85

**Excipients** include benzalkonium chloride

**With timolol**

For cautions, contra-indications, and side-effects of timolol, see section 11.6, Beta-blockers

**Combigan®** (Allergan) [Prescriber information]

**Eye drops**, brimonidine tartrate 0.2%, timolol (as maleate) 0.5%, net price 5-mL = £10.00

**Excipients** include benzalkonium chloride

**Dose** for raised intra-ocular pressure in open-angle glaucoma and for ocular hypertension when beta-blocker alone not adequate, apply twice daily

**Carbonic anhydrase inhibitors and systemic drugs**

The **carbonic anhydrase inhibitors**, acetazolamide, brinzolamide, and dorzolamide, reduce intra-ocular pressure by reducing aqueous humour production. Systemic use also produces weak diuresis.

Acetazolamide is given by mouth or by intravenous injection (intramuscular injections are painful because of the alkaline pH of the solution). It is used as an adjunct to other treatment for reducing intra-ocular pressure. Acetazolamide is a sulphonamide; blood disorders, rashes, and other sulphonamide-related side-effects occur occasionally. It is not generally recommended for long-term use; electrolyte disturbances and metabolic acidosis that occur may be corrected by administering potassium bicarbonate (as effervescent potassium tablets, section 9.2.1.3).

Dorzolamide and brinzolamide are topical carbonic anhydrase inhibitors. They are licensed for use in patients resistant to beta-blockers or those in whom beta-blockers are contra-indicated. They are used alone or as an adjunct to a topical beta-blocker. Systemic absorption may rarely give rise to sulphonamide-like side-effects and may require discontinuation if severe.

The **osmotic diuretics**, intravenous hypertonic mannitol (section 2.2.5), or glycerol by mouth, are useful short-term ocular hypotensive drugs.

**ACETAZOLAMIDE**

**Indications** reduction of intra-ocular pressure in open-angle glaucoma, secondary glaucoma, and peri-operatively in angle-closure glaucoma; diuresis (section 2.2.7); epilepsy

**Cautions** not generally recommended for prolonged use but if given monitor blood count and plasma electrolyte concentration; pulmonary obstruction (risk of acidosis); elderly; pregnancy (Appendix 4); avoid extravasation at injection site (risk of necrosis); interactions: Appendix 1 (diuretics)

**Contra-indications** hypokalaemia, hyponatraemia, hyperchloaraemic acidosis; severe hepatic impairment; renal impairment (Appendix 3); sulphonamide hypersensitivity

**Side-effects** nausea, vomiting, diarrhoea, taste disturbance; loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression; thirst, polyuria; reduced libido; metabolic acidosis and electrolyte disturbances on long-term therapy; occasionally, drowsiness, confusion, hearing disturbances, urticaria, melaena, glycosuria, haematuria, abnormal liver function, renal calculi, blood disorders including agranulocytosis and thrombocytopenia, rashes
including Stevens-Johnson syndrome and toxic epidermal necrolysis; rarely, photosensitivity, liver damage, flaccid paralysis, convulsions; transient myopia reported

**Dose**

- Glaucoma, by mouth or by intravenous injection, 0.25–1 g daily in divided doses
- Epilepsy, by mouth or by intravenous injection, 0.25–1 g daily in divided doses; CHILD 8–30 mg/kg daily, max. 750 mg daily

**Note** Dose by intramuscular injection, as for intravenous injection but preferably avoided because of alkalinity

**Diamox** (Goldshield) Tablets, acetazolamide 250 mg. Net price 112-tab pack = £12.68. Label: 3

**Sodium Parenteral** (= injection), powder for reconstitution, acetazolamide (as sodium salt). Net price 500-mg vial = £14.76

**BRINZOLAMIDE**

**Indications** adjunct to beta-blockers or used alone in raised intra-ocular pressure in ocular hypertension and in open-angle glaucoma if beta-blocker alone inadequate or inappropriate

**Cautions** hepatic impairment; pregnancy (Appendix 4); interactions: Appendix 1 (brinzolamide)

**Contra-indications** renal impairment (creatinine clearance less than 30 mL/minute), hyperchloremic acidosis; breast-feeding

**Side-effects** local irritation, taste disturbance; less commonly nausea, dyspepsia, dry mouth, chest pain, epistaxis, haemoptysis, rhinitis, pharyngitis, bronchitis, paraesthesia, depression, dizziness, headache, dermatitis, alopecia, corneal erosion

**Dose**

- Apply twice daily increased to 3 times daily if necessary
- Azopt (Alcon) Eye drops, brinzolamide 10 mg/mL, net price 5 mL = £6.90

**Contra-indications** renal impairment (Appendix 3); hyperchloremic acidosis; pregnancy and breast-feeding

**Side-effects** nausea, bitter taste, dry mouth; headache, asthenia; ocular irritation, blurred vision, lacrimation, conjunctivitis, superficial punctate keratitis, eyelid inflammation; less commonly iridocyclitis; rarely hypersensitivity reactions (including urticaria, angioedema, bronchospasms), dizziness, paraesthesia, urolithiasis, eyelid crusting, transient myopia, corneal oedema, epistaxis, throat irritation

**Dose**

- Used alone, apply 3 times daily
- With topical beta-blocker, apply twice daily

**Trusopt** (MSD) **Ophthalmic solution** (= eye drops), in Ocumeter Plus metered-dose unit, dorzolamide (as hydrochloride) 2%, net price 5 mL = £6.33

**Excipients** include benzalkonium chloride

**Unit dose eye drops**, dorzolamide (as hydrochloride) 2%, net price 60 × 0.2 mL = £24.18

**With timolol**

For cautions, contra-indications, and side-effects of timolol, see section 11.6, Beta-blockers

**Cosopt** (MSD) **Ophthalmic solution** (= eye drops), dorzolamide (as hydrochloride) 2%, timolol (as maleate) 0.5%, net price 5 mL = £10.05

**Excipients** include benzalkonium chloride

**Unit dose eye drops**, dorzolamide (as hydrochloride) 2%, timolol (as maleate) 0.5%, net price 60 × 0.2 mL = £28.59

**Miotics**

The small pupil is an unfortunate side-effect of these drugs (except when pilocarpine is used temporarily before an operation for angle-closure glaucoma). They act by opening up the inefficient drainage channels in the trabecular meshwork resulting from contraction or spasm of the ciliary muscle.

Miotics used in the management of raised intra-ocular pressure include pilocarpine.

**Cautions** A darkly pigmented iris may require higher concentration of the miotic or more frequent administration and care should be taken to avoid overdosage. Retinal detachment has occurred in susceptible individuals and those with retinal disease; therefore fundus examination is advised before starting treatment with a miotic. Care is also required in conjunctival or corneal damage. Intra-ocular pressure and visual fields should be monitored in those with chronic simple glaucoma and those receiving long-term treatment with a miotic.

Miotics should be used with caution in cardiac disease, hypertension, asthma, peptic ulceration, urinary-tract obstruction, and Parkinson’s disease.

**Counselling** Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting conditions.

**Contra-indications** Miotics are contra-indicated in conditions where pupillary constriction is undesirable such as acute iritis, anterior uveitis and some forms of secondary glaucoma. They should be avoided in acute inflammatory disease of the anterior segment.

**Side-effects** Ciliary spasm leads to headache and browache which may be more severe in the initial 2–4 weeks of treatment (a particular disadvantage in patients under 40 years of age). Ocular side-effects include burning, itching, smarting, blurred vision, conjunctival vascular congestion, myopia, lens changes
with chronic use, vitreous haemorrhage, and pupillary block. Systemic side-effects (see under Parasympathomimetics, section 7.4.1) are rare following application to the eye.

### PILOCARPINE

#### Indications
see notes above; dry mouth (section 12.3.5)

#### Cautions
see notes above

#### Contra-indications
see notes above

#### Side-effects
see notes above

#### Dose
- Apply up to 4 times daily; long-acting preparations, see under preparations below

### Pilocarpine Hydrochloride

#### (Non-proprietary)

#### Eye drops
- pilocarpine hydrochloride 0.5%, net price 10 mL = £1.39; 1%, 10 mL = £2.71; 2%, 10 mL = £2.59; 3%, 10 mL = £1.77; 4%, 10 mL = £3.46

#### Single use

- **Minims® Pilocarpine Nitrate (Chauvin)**
  - **Eye drops**, pilocarpine nitrate 2%, net price 20 × 0.5 mL = £4.92

#### Long acting

- **Pilogel® (Alcon)**
  - Ophthalmic gel, pilocarpine hydrochloride 4%, net price 5 g = £6.86
  - **Excipients** include benzalkonium chloride, disodium edetate
  - **Dose** apply 1–1.5 cm gel once daily at bedtime

### 11.7 Local anaesthetics

Oxybuprocaine and tetracaine (amethocaine) are probably the most widely used topical local anaesthetics. Proxymetacaine causes less initial stinging and is useful for children. Oxybuprocaine or a combined preparation of lidocaine (lignocaine) and fluorescein is used for tonometry. Tetracaine produces a more profound anaesthesia and is suitable for use before minor surgical procedures, such as the removal of corneal sutures. It has a temporary disruptive effect on the corneal epithelium. Lidocaine, with or without adrenaline (epinephrine), is injected into the eyelids for minor surgery, while retrobulbar or peribulbar injections are used for surgery of the globe itself. Local anaesthetics should never be used for the management of ocular symptoms.

Local anaesthetic eye drops should be avoided in preterm neonates because of the immaturity of the metabolising enzyme system.

### LIDOCAINE HYDROCHLORIDE

#### (Lignocaine hydrochloride)

#### Indications
local anaesthetic

- **Minims® Lignocaine and Fluorescein (Chauvin)**
  - **Eye drops**, lidocaine hydrochloride 4%, fluorescein sodium 0.25%. Net price 20 × 0.5 mL = £6.93

### OXYBUPROCAINE HYDROCHLORIDE

#### (Benoxinate hydrochloride)

#### Indications
local anaesthetic

- **Minims® Oxybuprocaine Hydrochloride (Chauvin)**
  - **Eye drops**, oxybuprocaine hydrochloride 0.4%. Net price 20 × 0.5 mL = £4.92

### PROXYMETACAINE HYDROCHLORIDE

#### Indications
local anaesthetic

- **Minims® Proxymetacaine (Chauvin)**
  - **Eye drops**, proxymetacaine hydrochloride 0.5%. Net price 20 × 0.5 mL = £6.95

- **With fluorescein**
  - **Minims® Proxymetacaine and Fluorescein (Chauvin)**
    - **Eye drops**, proxymetacaine hydrochloride 0.5%, fluorescein sodium 0.25%. Net price 20 × 0.5 mL = £7.95

### TETRACAINE HYDROCHLORIDE

#### (Amethocaine hydrochloride)

#### Indications
local anaesthetic

- **Minims® Amethocaine Hydrochloride (Chauvin)**
  - **Eye drops**, tetracaine hydrochloride 0.5% and 1%. Net price 20 × 0.5 mL (both) = £5.75

### 11.8 Miscellaneous ophthalmic preparations

#### 11.8.1 Tear deficiency, ocular lubricants, and astringents

- Chronic soreness of the eyes associated with reduced or abnormal tear secretion (e.g. in Sjögren’s syndrome) often responds to tear replacement therapy or pilocarpine given by mouth (section 12.3.5). The severity of the condition and patient preference will often guide the choice of preparation.

- **Hypromellose** is the traditional choice of treatment for tear deficiency. It may need to be instilled frequently (e.g. hourly) for adequate relief. Ocular surface mucin is often abnormal in tear deficiency and the combination
of hypromellose with a mucolytic such as acetylcysteine can be helpful.

The ability of carbomers to cling to the eye surface may help reduce frequency of application to 4 times daily.

Polyvinyl alcohol increases the persistence of the tear film and is useful when the ocular surface mucin is reduced.

Povidone and sodium hyaluronate eye drops are also used in the management of tear deficiency.

Sodium chloride 0.9% drops are sometimes useful in tear deficiency, and can be used as ‘comfort drops’ by contact lens wearers, and to facilitate lens removal. Special presentations of sodium chloride 0.9% and other irrigation solutions are used routinely for intraocular surgery.

Eye ointments containing a paraffin may be used to lubricate the eye surface, especially in cases of recurrent corneal epithelial erosion. They may cause temporary visual disturbance and are best suited for application before sleep. Ointments should not be used during contact lens wear.

Zinc sulphate is a traditional astringent that is now little used.

### ACETYLICYSTEINE

**Indications** tear deficiency, impaired or abnormal mucus production

**Dose**
- Apply 3–4 times daily

**Ilube®** (Alcon)
- **Eye drops**, acetylcysteine 5%, hypromellose 0.35%. Net price 10 mL = £4.63
  - **Excipients** include benzalkonium chloride, disodium edetate

### CARBOMERS

**(Polyacrylic acid)**

**Note** Synthetic high molecular weight polymers of acrylic acid cross-linked with either allyl ethers of sucrose or allyl ethers of pentaerythritol

**Indications** dry eyes including keratoconjunctivitis sicca, unstable tear film

**Dose**
- Apply 3–4 times daily or as required

**GelTears®** (Chauvin)
- **Gel** (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 10 g = £2.80
  - **Excipients** include benzalkonium chloride

**Liposic®** (Bausch & Lomb)
- **Gel** (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 10 g = £2.96
  - **Excipients** include cetrimide

**Liquivisc®** (Allergan)
- **Gel** (= eye drops), carbomer 974P (polyacrylic acid) 0.25%, net price 10 g = £1.99
  - **Excipients** include benzalkonium chloride
  - **Note** May be difficult to obtain

**Viscotears®** (Novartis)
- **Liquid gel** (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 10 g = £3.12
  - **Excipients** include cetrimide

### CARMELLOSE SODIUM

**Indications** dry eye conditions

**Dose**
- Apply as required

**Optive®** (Allergan)
- **Eye drops**, carmellose sodium 0.5%, glycerol, net price 10 mL = £7.49

**Single use**

**Celluvics®** (Allergan)
- **Eye drops**, carmellose sodium 0.5%, net price 30 x 0.4 mL = £7.59, 90 x 0.4 mL = £15.53; 1%, 30 x 0.4 mL = £7.59, 60 x 0.4 mL = £10.99

### HYDROXYETHYLCELLULOSE

**Indications** tear deficiency

**Minims® Artificial Tears** (Chauvin)
- **Eye drops**, hydroxyethylcellulose 0.44%, sodium chloride 0.35%. Net price 20 x 0.5 mL = £5.75

### HYPROMELLOSE

**Indications** tear deficiency

**Note** The Royal Pharmaceutical Society of Great Britain has stated that where it is not possible to ascertain the strength of hypromellose prescribed, the prescriber should be contacted to clarify the strength intended.

**Hypromellose** (Non-proprietary)
- **Eye drops**, hypromellose 0.3%, net price 10 mL = £1.63
  - **Brands** include Artelac

**Isopto Alkaline®** (Alcon)
- **Eye drops**, hypromellose 1%, net price 10 mL = 99p
  - **Excipients** include benzalkonium chloride

**Isopto Plain®** (Alcon)
- **Eye drops**, hypromellose 0.5%, net price 10 mL = 85p
  - **Excipients** include benzalkonium chloride

**Tears Naturale®** (Alcon)
- **Eye drops**, dextran '70' 0.1%, hypromellose 0.3%, net price 15 mL = £1.68
  - **Excipients** include benzalkonium chloride, disodium edetate

**Hypromellose** (Non-proprietary)
- **Eye drops**, hypromellose 0.3%, net price 30 x 0.4 mL = £5.75

**Artelac® SDU** (Pharma-Global)
- **Eye drops**, hypromellose 0.32%, net price 30 x 0.5 mL = £13.95

### LIQUID PARAFFIN

**Indications** dry eye conditions

**Lacri-Lube®** (Allergan)
- **Eye ointment**, white soft paraffin 57.3%, liquid paraffin 42.5%, wool alcohols 0.2%. Net price 3.5 g = £2.28, 5 g = £2.96
Lubri-Tears® (Alcon)

Eye ointment, white soft paraffin 60%, liquid paraffin 30%, wool fat 10%. Net price 5 g = £2.29

PARAFFIN, YELLOW, SOFT

Indications  see notes above

Simple Eye Ointment

Ointment, liquid paraffin 10%, wool fat 10%, in yellow soft paraffin. Net price 4 g = £3.03

POLYVINYL ALCOHOL

Indications  tear deficiency

Liquifilm Tears® (Allergan)

Ophthalmic solution (= eye drops), polyvinyl alcohol 1.4%. Net price 15 mL = £1.93

Excipients include benzalkonium chloride, disodium edetate

Ophthalmic solution (= eye drops), polyvinyl alcohol 1.4%, povidone 0.6%. Net price 30 x 0.4 mL = £5.35

Sno Tears® (Chauvin)

Eye drops, polyvinyl alcohol 1.4%. Net price 10 mL = £1.06

Excipients include benzalkonium chloride, disodium edetate

POVIDONE

Indications  dry eye conditions

Dose

• Apply 4 times daily or as required

Oculotect® (Novartis)

Eye drops, povidone 5%. Net price 20 x 0.4 mL = £3.40

SODIUM CHLORIDE

Indications  irrigation, including first-aid removal of harmful substances

Sodium Chloride 0.9% Solutions

See section 13.11.1

Balanced Salt Solution

Solution (sterile), sodium chloride 0.64%, sodium acetate 0.39%, sodium citrate 0.17%, calcium chloride 0.048%, magnesium chloride 0.03%, potassium chloride 0.075%

For intra-ocular or topical irrigation during surgical procedures

Brands include Iocare

□ Single use

Minims® Saline (Chauvin)

Eye drops, sodium chloride 0.9%. Net price 20 x 0.5 mL = £4.92

□ With local anaesthetic

Section 11.7

SODIUM HYALURONATE

Indications  dry eye conditions

Dose

• Apply as required

□ With local anaesthetic

Section 11.7

Hycosan® (Bausch & Lomb)

Eye drops, sodium hyaluronate 0.1%, net price 10 mL = 7.19

Oxyal® (Kestrel Ophthalmics)

Eye drops, sodium hyaluronate 0.15%, net price 10 mL = £4.15

Vismed® Multi (TRB Chemedica)

Eye drops, sodium hyaluronate 0.18%, net price 10 mL = £6.81

□ Single use

Clinitas® (Altacor)

Eye drops, sodium hyaluronate 0.4%, net price 30 x 0.5 mL = £5.70

Dose

Ocusan® (Agepha)

Eye drops, sodium hyaluronate 0.2%, net price 20 x 0.5 mL = £5.25

Vismed® (TRB Chemedica)

Eye drops, sodium hyaluronate 0.18%, net price 20 x 0.3 mL = £5.10

ZINC SULPHATE

Indications  see notes above

Cautions  see notes above

Zinc Sulphate (Non-proprietary)

Eye drops, zinc sulphate 0.25%. Net price 10 mL = £3.15

11.8.2 Ocular diagnostic and peri-operative preparations and photodynamic treatment

Ocular diagnostic preparations

Fluorescein sodium is used in diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

□ FLUORESCIN SODIUM

Indications  detection of lesions and foreign bodies

Minims® Fluorescein Sodium (Chauvin)

Eye drops, fluorescein sodium 1% or 2%. Net price 20 x 0.5 mL (both) = £4.92

11 Eye
Ocular peri-operative drugs

Drugs used to prepare the eye for surgery, drugs that are injected into the anterior chamber at the time of surgery, and those used after eye surgery, are included here.

Non-steroidal anti-inflammatory eye drops such as diclofenac, flurbiprofen, and ketorolac, are used for the prophylaxis and treatment of inflammation, pain, and other symptoms associated with ocular surgery or laser treatment of the eye. Diclofenac and flurbiprofen are also used to prevent miosis during ocular surgery.

Apraclonidine, an alpha-adrenoceptor agonist, reduces intra-ocular pressure possibly by reducing the production of aqueous humour. It is used to control increases in intra-ocular pressure associated with ocular surgery and as short-term treatment to reduce intra-ocular pressure prior to surgery.

Acetylcholine, instilled into the anterior chamber of the eye during surgery, rapidly produces miosis which lasts approximately 20 minutes. If prolonged miosis is required, it can be applied again.

Intra-ocular sodium hyaluronate and balanced salt solution (section 11.8.1) are used during surgical procedures on the eye.

ACETYLCHOLINE CHLORIDE

Indications cataract surgery, penetrating keratoplasty, iridectomy, and other anterior segment surgery requiring rapid complete miosis

Contra-indications pregnancy; breast-feeding

Side-effects rarely bradycardia, hypotension, breathing difficulty, sweating, flushing

Miochol-E® (Novartis) Intra-ocular irrigation, powder for reconstitution, acetylcholine chloride 10 mg/mL (1%) when reconstituted, net price 20-mg vial (with solvent) = £9.10

APRACLONIDINE

Note Apraclonidine is a derivative of clonidine

Indications control of intra-ocular pressure

Cautions history of angina, severe coronary insufficiency, recent myocardial infarction, heart failure, cerebrovascular disease, vasovagal attack, chronic renal failure; depression; pregnancy and breast-feeding; monitor intra-ocular pressure and visual fields; loss of effect may occur over time; suspend treatment if reduction in vision occurs in end-stage glaucoma; monitor for excessive reduction in intra-ocular pressure following peri-operative use; interactions: Appendix 1 (apraclonidine)

Driving Drowsiness may affect performance of skilled tasks (e.g. driving)

Contra-indications history of severe or unstable and uncontrolled cardiovascular disease

Side-effects dry mouth, taste disturbance; hyperaemia, ocular pruritus, discomfort and lacrimation (withdraw if ocular intolerance including oedema of lids and conjunctiva); headache, asthenia, dry nose; lid retraction, conjunctival blanching and mydriasis reported after peri-operative use; since absorption may follow topical application systemic effects (see Clonidine Hydrochloride, section 2.5.2) may occur

Dose • See under preparations below

Iopidine® (Alcon) Ophthalmic solution (= eye drops), apraclonidine 1% (as hydrochloride), net price 12 × 2 single use 0.25-mL units = £81.90

Dose control or prevention of postoperative elevation of intra-ocular pressure after anterior segment laser surgery; apply 1 drop 1 hour before laser procedure then 1 drop immediately after completion of procedure; CHILD not recommended

Iopidine 0.5% ophthalmic solution (= eye drops), apraclonidine 0.5% (as hydrochloride), net price 5 mL = £11.45

Excipients include benzalkonium chloride

Dose short-term adjunctive treatment of chronic glaucoma in patients not adequately controlled by another drug (see note below); apply 1 drop 3 times daily usually for max. 1 month; CHILD not recommended

Note May not provide additional benefit if patient already using two drugs that suppress the production of aqueous humour

DICLOFENAC SODIUM

Indications inhibition of intra-operative miosis during cataract surgery (but does not possess intrinsic mydriatic properties); postoperative inflammation in cataract surgery, strabismus surgery or argon laser trabeculoplasty; pain in corneal epithelial defects after photorefractive keratectomy, radial keratotomy or accidental trauma; seasonal allergic conjunctivitis (section 11.4.2)

Voltarol® Ophtha Multidose (Novartis) Eye drops, diclofenac sodium 0.1%, net price 5 mL = £6.68

Excipients include benzalkonium chloride, disodium edetate, propylene glycol

Single use Voltarol® Ophtha (Novartis) Eye drops, diclofenac sodium 0.1%, net price pack of 5 single-dose units = £4.00, 40 single-dose units = £32.00

FLURBIPROFEN SODIUM

Indications inhibition of intra-operative miosis (but does not possess intrinsic mydriatic properties); anterior segment inflammation following postoperative and post-laser trabeculoplasty when corticosteroids contra-indicated

Ocufen® (Allergan) Ophthalmic solution (= eye drops), flurbiprofen sodium 0.03%, polyvinyl alcohol (Liquifilm®) 1.4%, net price 40 × 0.4 mL = £37.15

KETOROLAC TROMETAMOL

Indications prophylaxis and reduction of inflammation and associated symptoms following ocular surgery

Acular® (Allergan) Eye drops, ketorolac trometamol 0.5%, net price 5 mL = £5.00

Excipients include benzalkonium chloride, disodium edetate

Subfoveal choroidal neovascularisation

Pegaptanib and ranibizumab are vascular endothelial growth factor inhibitors licensed for the treatment of neovascular (wet) age-related macular degeneration;
they are given by intravitreal injection by specialists experienced in the management of this condition.

### NICE guidance

#### Ranibizumab and pegaptanib for the treatment of wet age-related macular degeneration (August 2008)

Ranibizumab is recommended for the treatment of wet age-related macular degeneration if all of the following apply:

- the best corrected visual acuity is between 6/12 and 6/96;
- there is no permanent structural damage to the central fovea;
- the lesion size is less than or equal to 12 disc areas in greatest linear dimension;
- there is evidence of recent disease progression;
- the cost of ranibizumab beyond 14 injections is met by the manufacturer.

Ranibizumab should only be continued in patients who maintain adequate response to therapy. Pegaptanib is not recommended for the treatment of wet age-related macular degeneration; patients currently receiving pegaptanib for any lesion type can continue therapy until they and their specialist consider it appropriate to stop.

Verteporfin is licensed for use in the photodynamic treatment of age-related macular degeneration associated with predominantly classic subfoveal choroidal neovascularisation or with pathological myopia (see NICE guidance below). Following intravenous infusion, verteporfin is activated by local irradiation using non-thermal red light to produce cytotoxic derivatives. Only specialists experienced in the management of these conditions should use it.

### NICE guidance

#### Photodynamic therapy for wet age-related macular degeneration (September 2003)

Photodynamic therapy is recommended for wet age-related macular degeneration with a confirmed diagnosis of classic (no occult) subfoveal choroidal neovascularisation and best-corrected visual acuity of 6/60 or better.

Photodynamic therapy is not recommended for wet age-related macular degeneration with predominantly classic but partly occult subfoveal choroidal neovascularisation except in clinical studies.

#### PEGAPTANIB SODIUM

**Indications**
- see notes above—specialist use only

**Cautions**
- monitor intra-ocular pressure following injection; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications**
- ocular or pericocular infection

**Side-effects**
- rhinorrhoea; headache; eye pain, anterior chamber inflammation, raised intra-ocular pressure, punctate keratitis, vitreous floaters, cataract, conjunctival and retinal haemorrhage, local oedema, conjunctivitis, corneal dystrophy, dry eye, endophthalmitis, eye discharge, eye irritation, macular degeneration, mydriasis, peribulbar haematoma, photophobia, flashing lights, vitreous disorders; less commonly vomiting, dyspepsia, palpitation, chest pain, hypertension, aortic aneurysm, influenza-like symp-
toms, nightmares, depression, back pain, asthenopia, blepharitis, corneal deposits, vitreous haemorrhage, chalazion, retinal exudates, eyelid ptosis, decreased intra-ocular pressure, injection-site reactions, retinal detachment, occlusion of retinal blood vessels, ectropion, eye movement disorder, pupillary disorder, iritis, optic nerve cupping, nasopharyngitis, deafness, vertigo, eczema, changes in hair colour, rash, pruritus, night sweats

**Dose**
- By intravitreal injection, 300 micrograms once every 6 weeks into the affected eye

**Note**
- For further information on administration, consult product literature

**Macugen**® (Pfizer) [RW]

Solution for intravitreal injection, pegaptanib (as sodium salt), net price 300-microgram vial = £514.00

### RANIBIZUMAB

**Indications**
- see notes above—specialist use only

**Cautions**
- monitor intra-ocular pressure and for signs of ocular infection following injection; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Contra-indications**
- ocular or pericocular infection; severe intra-ocular inflammation

**Side-effects**
- nausea; headache; nasopharyngitis, cough; anxiety; anaemia; arthralgia; raised intra-ocular pressure, visual disturbance, conjunctival and vitreous disorders, eye inflammation and irritation, eye haemorrhage; allergic skin reactions; less commonly atrial fibrillation, blindness, corneal disorders, iris adhesion, injection site reactions

**Dose**
- By intravitreal injection, initially 500 micrograms once a month for 3 months into the affected eye, thereafter monitor visual acuity once a month; if necessary subsequent doses may be given at least 1 month apart

**Note**
- For further information on administration, consult product literature

**Antimicrobial eye drops should be administered into the affected eye for 3 days before and 3 days after each injection**

**Lucentis®** (Novartis) [RW]

Solution for intravitreal injection, ranibizumab 10 mg/mL, net price 0.23-mL vial = £761.20

### VERTEPORFIN

**Indications**
- see notes above—specialist use only

**Cautions**
- photosensitivity—avoid exposure of unprotected skin and eyes to bright light during infusion and for 48 hours afterwards; hepatic impairment (avoid if severe), biliary obstruction; avoid extravasation; pregnancy (Appendix 4)

**Contra-indications**
- acute porphyria; breast-feeding (Appendix 5)

**Side-effects**
- visual disturbances (including blurred vision, flashing lights, visual-field defects), nausea, back pain, asthenia, pruritus, hypercholesterolaemia, fever; rarely lacrimation disorder, subretinal or vitreous haemorrhage, hypersensitivity reactions (including chest pain, syncope, headache, dizziness, dyspnoea, urticaria, sweating, changes in blood pressure and in heart rate); injection-site reactions including pain, oedema, inflammation, haemorrhage, discoloration and blistering
**Dose**

*By intravenous infusion* over 10 minutes, 6 mg/m²

**Note** For information on administration and light activation, consult product literature

**Visudyne®** (Novartis)

**Injection**, powder for reconstitution, verteporfin, net price 15-mg vial = £850.00

---

**11.9 Contact lenses**

**Note** Some recommendations in this section involve non-licensed indications.

For cosmetic reasons many people prefer to wear contact lenses rather than spectacles; contact lenses are also sometimes required for medical indications. Visual defects are corrected by either rigid ('hard' or gas permeable) lenses or soft (hydrogel or silicone hydrogel) lenses; soft lenses are the most popular type, because they are the most comfortable, but they may not give the best vision. Lenses should usually be worn for a specified number of hours each day. Continuous (extended) wear involves much greater risks to eye health and is not recommended except where medically indicated.

Contact lenses require meticulous care. Poor compliance with directions for use, and with daily cleaning and disinfection, can result in complications including ulcerative keratitis and conjunctival problems (such as purulent or papillary conjunctivitis). One-day disposable lenses, which are worn only once and therefore require no maintenance or storage, are becoming increasingly popular.

**Acanthamoeba keratitis**, a sight-threatening condition, is associated with ineffective lens cleaning and disinfection or the use of contaminated lens cases. The condition is especially associated with the use of soft lenses (including frequently replaced lenses). **Acanthamoeba keratitis** is treated, by specialists, with intensive use of polihexanide (polyhexamethylene biguanide), propamidine isetionate (section 11.3.1), chlorhexidine, and neomycin (section 11.3.1) drops, sometimes used in combination.

**Contact lenses and drug treatment** Special care is required in prescribing eye preparations for contact lens users. Some drugs and preservatives in eye preparations can accumulate in hydrogel lenses and may induce toxic reactions. Therefore, unless medically indicated, the lenses should be removed before instillation and not worn during the period of treatment. Alternatively, unpreserved drops can be used. Eye drops may, however, be instilled over rigid corneal contact lenses. Ointment preparations should never be used in conjunction with contact lens wear; oily eye drops should also be avoided.

Many drugs given systemically can also have adverse effects on contact lens wear. These include oral contraceptives (particularly those with a higher oestrogen content), drugs which reduce blink rate (e.g. anxiolytics, hypnotics, antihistamines, and muscle relaxants), drugs which reduce lacrimation (e.g. antihistamines, antimuscarinics, phenothiazines and related drugs, some beta-blockers, diuretics, and tricyclic antidepressants), and drugs which increase lacrimation (including epinephrine and hydralazine). Other drugs that may affect contact lens wear are isotretinoin (can cause conjunctival inflammation), aspirin (salicylic acid appears in tears and can be absorbed by contact lenses—leading to irritation), and rifampicin and sulfasalazine (can discolor lenses).
12 Ear, nose, and oropharynx

12.1 Drugs acting on the ear 600
12.1.1 Otitis externa 600
12.1.2 Otitis media 603
12.1.3 Removal of ear wax 603
12.2 Drugs acting on the nose 604
12.2.1 Drugs used in nasal allergy 604
12.2.2 Topical nasal decongestants 606
12.2.3 Nasal preparations for infection 607
12.3 Drugs acting on the oropharynx 608
12.3.1 Drugs for oral ulceration and inflammation 608
12.3.2 Oropharyngeal anti-infective drugs 610
12.3.3 Lozenges and sprays 612
12.3.4 Mouthwashes, gargles, and dentifrices 612
12.3.5 Treatment of dry mouth 613

This chapter also includes advice on the drug management of the following:
- allergic rhinitis, p. 604
- nasal polyps, p. 604
- oropharyngeal infections, p. 610
- periodontitis, p. 609

12.1.1 Otitis externa

Otitis externa is an inflammatory reaction of the meatal skin. It is important to exclude an underlying chronic otitis media before treatment is commenced. Many cases recover after thorough cleansing of the external ear canal by suction or dry mopping. A frequent problem in resistant cases is the difficulty in applying lotions and ointments satisfactorily to the relatively inaccessible affected skin. The most effective method is to introduce a ribbon gauze dressing or sponge wick soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution. When this is not practical, the ear should be gently cleansed with a probe covered in cotton wool and the patient encouraged to lie with the affected ear uppermost for ten minutes after the canal has been filled with a liberal quantity of the appropriate solution.

If infection is present, a topical anti-infective which is not used systemically (such as neomycin or clioquinol) may be used, but for only about a week as excessive use may result in fungal infections; these may be difficult to treat and require expert advice. Sensitivity to the anti-infective or solvent may occur and resistance to antibacterials is a possibility with prolonged use. Aluminium acetate ear drops are also effective against bacterial infection and inflammation of the ear. Chloramphenicol may be used but the ear drops contain propylene glycol and cause hypersensitivity reactions in about 10% of patients. Solutions containing an anti-infective and a corticosteroid (such as Locorten-Vioform®) are used for treating cases where infection is present with inflammation and eczema.

In view of reports of ototoxicity in patients with a perforated tympanic membrane (eardrum), the CSM has stated that treatment with a topical aminoglycoside antibiotic is contra-indicated in those with a tympanic perforation. However, many specialists do use these drops cautiously in the presence of a perforation in patients with otitis media (section 12.1.2) and where other measures have failed for otitis externa.

A solution of acetic acid 2% acts as an antifungal and antibacterial in the external ear canal. It may be used to treat mild otitis externa but in severe cases an anti-inflammatory preparation with or without an anti-infective drug is required. A proprietary preparation containing acetic acid 2% (EarCalm® spray) is on sale to the public.
For severe pain associated with otitis externa, a simple analgesic, such as paracetamol (section 4.7.1) or ibuprofen (section 10.1.1), can be used. A systemic antibacterial (Table 1, section 5.1) can be used if there is spreading cellulitis or if the patient is systemically unwell. When a resistant staphylococcal infection (a boil) is present in the external auditory meatus, fluocinolone acetonide (or an aminoglycoside) may be needed in pseudomonal infections which may occur if the patient has diabetes or is immunocompromised.

The skin of the pinna adjacent to the ear canal is often affected by eczema. Topical corticosteroid creams and ointments (section 13.4) are then required, but prolonged use should be avoided.

### Astringent preparations

#### ALUMINIUM ACETATE

**Indications** inflammation in otitis externa (see notes above)

**Dose**

- Insert into meatus or apply on a ribbon gauze dressing or sponge wick which should be kept saturated with the ear drops

**Aluminium Acetate** (Non-proprietary)

- **Ear drops 13%**, aluminium sulphate 2.25 g, calcium carbonate 1 g, tartaric acid 450 mg, acetic acid (33%) 2.5 mL, purified water 7.5 mL

  - Available from manufacturers of ‘special order’ products

- **Ear drops 8%**, dilute 8 parts aluminium acetate ear drops (13%) with 5 parts purified water. Must be freshly prepared

### Anti-inflammatory preparations

#### Corticosteroids

Topical corticosteroids are used to treat inflammation and eczema in otitis externa.

**Cautions** Prolonged use of topical corticosteroid ear preparations should be avoided.

**Contra-indications** Corticosteroid ear preparations should be avoided in the presence of an untreated ear infection. If infection is present, the corticosteroid should be used in combination with a suitable anti-infective (see notes above).

**Side-effects** Local sensitivity reactions may occur.

### BETAMETHASONE SODIUM PHOSPHATE

**Indications** eczematous inflammation in otitis externa (see notes above)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

#### Betnesol® (UCB Pharma) **[Link]**

- **Drops** (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 10 mL = £2.32

  - **Excipients** include benzalkonium chloride, disodium edetate

  - **Dose** ear, apply 2–3 drops every 2–3 hours; reduce frequency when relief obtained; eye, section 11.4.1; nose, section 12.2.1

#### Vistamethasone® (Martindale) **[Link]**

- **Drops** (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 5 mL = £1.02; 10 mL = £1.16

  - **Excipients** include benzalkonium chloride, disodium edetate

  - **Dose** ear, apply 2–3 drops every 3–4 hours; reduce frequency when relief obtained; eye, section 11.4.1; nose, section 12.2.1

#### With antibacterial

**Betnesol-N®** (UCB Pharma)

- **Drops** (for eye, ear, or nose), betamethasone sodium phosphate 0.1%, neomycin sulphate 0.5%. Net price 10 mL = £2.39

  - **Excipients** include benzalkonium chloride, disodium edetate

  - **Dose** ear, apply 2–3 drops 3–4 times daily; eye, section 11.4.1; nose, section 12.2.3

### DEXAMETHASONE

**Indications** eczematous inflammation in otitis externa (see notes above)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

#### With antibacterial

**Otomize®** (GSK Consumer Healthcare) **[Link]**

- **Ear spray**, dexamethasone 0.1%, neomycin sulphate 3250 units/mL, glacial acetic acid 2%. Net price 5-mL pump-action aerosol unit = £4.24

  - **Excipients** include hydrocortisone (parabens)

  - **Dose** ear, apply 1 metered spray 3 times daily

**Sofradex®** (Sanofi-Aventis) **[Link]**

- **Drops** (for ear or eye), dexamethasone (as sodium metasulphobenzoate) 0.05%, framycetin sulphate 0.5%, framycetin sulphate 0.5%, gramicidin 0.005%. Net price 5 mL = £1.09; 10 mL = £1.20

  - **Excipients** include thiomersal

  - **Dose** ear, apply 2–3 drops every 3–4 hours; reduce frequency when relief obtained; eye, section 11.4.1; nose, section 12.2.3

### FLUMETASONE PIVALATE

(flumethasone pivalate)

**Indications** eczematous inflammation in otitis externa (see notes above)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

#### With antibacterial

**Locoten-Vioform®** (Amdipharm) **[Link]**

- **Ear drops**, flumetason pivalate 0.02%, ciprofloxacin 1%. Net price 7.5 mL = £1.47

  - **Dose** ADULT and CHILD over 2 years apply 2–3 drops into the ear twice daily for 7–10 days

  - **Note** Clioquinol stains skin and clothing
HYDROCORTISONE

Indications  eczematous inflammation in otitis externa (see notes above)

Cautions  see notes above

Contra-indications  see notes above

Side-effects  see notes above

With antibacterial

Gentisone® HC  (Amidipharm)  

Ear drops, hydrocortisone acetate 1%, gentamicin 0.3% (as sulphate). Net price 10 mL = £3.69

Excipients  include benzalkonium chloride, disodium edetate

Dose  ear, apply 2–4 drops 3–4 times daily and at night

Neo-Cortef®  (PLIVA)  

Ointment  (for ear or eye), hydrocortisone acetate 1.5%, neomycin sulphate 0.5%. Net price 3.9 g = £1.53

Excipients  include wool fat

Dose  ear, apply 1–2 times daily; eye, see section 11.4.1

Note  May be difficult to obtain

Otosporin®  (GSK)  

Ear drops, hydrocortisone 1%, neomycin sulphate 3400 units, polymyxin B sulphate 10 000 units/mL. Net price 5 mL = £2.00; 10 mL = £4.00

Excipients  include cetostearyl alcohol, hydroxybenzoates (parabens), polysorbate 20

Dose  ADULT and CHILD over 3 years, ear, apply 3 drops 3–4 times daily

PREDNISOLONE SODIUM PHOSPHATE

Indications  eczematous inflammation in otitis externa (see notes above)

Cautions  see notes above

Contra-indications  see notes above

Side-effects  see notes above

Predsol®  (UCB Pharma)  

Ear drops, hydrocortisone acetate 0.5%, neomycin sulphate 0.5%. Net price 10 mL = £2.00

Excipients  include benzalkonium chloride, disodium edetate

Dose  ear, apply 2–3 drops every 2–3 hours; reduce frequency when relief obtained, eye, section 11.4.1

With antibacterial

Predsol-N®  (UCB Pharma)  

Ear drops, hydrocortisone acetate 0.5%, neomycin sulphate 0.5%. Net price 10 mL = £2.36

Excipients  include benzalkonium chloride, disodium edetate

Dose  ear, apply 2–3 drops 3–4 times daily; eye, section 11.4.1

TRIAMCINOLONE ACETONIDE

Indications  eczematous inflammation in otitis externa (see notes above)

Cautions  see notes above

Contra-indications  see notes above

Side-effects  see notes above

With antibacterial

Tri-Adcortyl Otic®  (Squibb)  

Ear ointment, triamcinolone acetonide 0.1%, gramicidin 0.025%, neomycin 0.25% (as sulphate), nystatin 100 000 units/g in Plastibase®. Net price 10 g = £1.58

Dose  ear, ADULT and CHILD over 1 year, apply 2–3 times daily

Anti-infective preparations

CHLORAMPHENICOL

Indications  bacterial infection in otitis externa (but see notes above)

Cautions  avoid prolonged use (see notes above)

Side-effects  high incidence of sensitivity reactions to vehicle

Chloramphenicol  (Non-proprietary)  

Ear drops, chloramphenicol in propylene glycol, net price 5%, 10 mL = £1.83; 10%, 10 mL = £5.62

Dose  ear, apply 2–3 drops 2–3 times daily

CLOTRIMAZOLE

Indications  fungal infection in otitis externa (see notes above)

Side-effects  occasional local irritation or sensitivity

Canesten®  (Bayer Consumer Care)  

Solution, clotrimazole 1% in polyethylene glycol 400 (macrogol 400). Net price 20 mL = £2.43

Dose  ear, apply 2–3 times daily continuing for at least 14 days after disappearance of infection; skin, section 13.10.2

FRAMYCETIN SULPHATE

Indications  bacterial infection in otitis externa (see notes above)

Cautions  avoid prolonged use (see notes above)

Contra-indications  perforated tympanic membrane (see p. 600)

Side-effects  local sensitivity

With corticosteroid

Locorten-Vioform®  see Flumetasone, p. 601

GENTAMICIN

Indications  bacterial infection in otitis externa (see notes above)

Cautions  avoid prolonged use (see notes above)

Contra-indications  perforated tympanic membrane (but see also p. 600 and section 12.1.2)

Side-effects  local sensitivity

With corticosteroid

Gentisone® HC  see Hydrocortisone, above
12.1.2 Otitis media

Acute otitis media  Acute otitis media is the commonest cause of severe pain in small children. Many infections, especially those accompanying coryza, are caused by viruses. Most uncomplicated cases resolve without antibacterial treatment and a simple analgesic, such as paracetamol, may be sufficient. In children without systemic features, a systemic antibacterial may be started after 72 hours if there is no improvement, or earlier in immunocompromised patients, in children under 2 years, or if there is deterioration (Table 1, section 5.1). Topical treatment of acute otitis media is ineffective and there is no place for drops containing a local anaesthetic. Perforation of the tympanic membrane in patients with acute otitis media usually heals spontaneously without treatment; if there is no improvement, e.g. pain or discharge persists, a systemic antibacterial (Table 1, section 5.1) can be given.

Otitis media with effusion  Otitis media with effusion (‘glue ear’) occurs in about 10% of children and in 90% of children with cleft palate. Systemic antibiotics are not usually required. If ‘glue ear’ persists for more than a month or two, the child should be referred for assessment and follow up because of the risk of long-term hearing impairment which can delay language development. Untreated or resistant glue ear may be responsible for some types of chronic otitis media.

Chronic otitis media  Opportunistic organisms are often present in the debris, keratin, and necrotic bone of the middle ear and mastoid in patients with chronic otitis media. The mainstay of treatment is thorough cleansing with aural microsuction which may completely resolve long-standing infection. Local cleansing of the meatal skin is usually performed by treatment with a sponge wick or ribbon gauze dressing soaked with corticosteroid ear drops or with an astringent such as aluminium acetate solution; this is particularly beneficial for discharging ears or infections of the mastoid cavity. An antibacterial ear ointment may also be used. Acute exacerbations of chronic infection may also require systemic treatment with amoxicillin (or erythro-

mycin if penicillin-allergic); treatment is adjusted according to the results of sensitivity testing. Parenteral antibacterials are required if *Pseudomonas aeruginosa* and *Proteus* spp. are present.

The CSM has stated that topical treatment with ototoxic antibacterials is contra-indicated in the presence of a perforation (section 12.1.1). However, many specialists use ear drops containing aminoglycosides (e.g. neomycin) or polymyxins if the otitis media has failed to settle with systemic antibacterials; it is considered that the pus in the middle ear associated with otitis media carries a higher risk of ototoxicity than the drops themselves. Ciprofloxacin or ofloxacin ear drops [both unlicensed; available on named-patient basis from a specialist importing company] or eye drops used in the ear [unlicensed indication] are an effective alternative to aminoglycoside ear drops for chronic otitis media in patients with perforation of the tympanic membrane.

Wax may be removed by syringing with water (warmed to body temperature). If necessary, wax can be softened using simple remedies such as *olive oil* ear drops or *almond oil* ear drops; *sodium bicarbonate* ear drops are also effective but may cause dryness of the ear canal. If the wax is hard and impacted the drops may be used twice daily for a few days before syringing; otherwise the wax may be softened on the day of syringing. The patient should lie with the affected ear uppermost for 5 to 10 minutes after a generous amount of the softening remedy has been introduced into the ear. Some proprietary preparations containing organic solvents can irritate the meatal skin, and in most cases the simple remedies indicated above are just as effective and less likely to cause irritation. Docusate sodium or urea–hydrogen peroxide are ingredients in a number of proprietary preparations for softening ear wax.

**Almond Oil** (Non-proprietary)  
*Ear drops,* almond oil in a suitable container  
Allow to warm to room temperature before use

**Olive Oil** (Non-proprietary)  
*Ear drops,* olive oil in a suitable container  
Allow to warm to room temperature before use

**Sodium Bicarbonate** (Non-proprietary)  
*Ear drops,* sodium bicarbonate 5%, net price 10 mL = £1.25

**Cerumol** (LAB)  
*Ear drops,* chlorobutanol 5%, arachis (peanut) oil 57.3%. Net price 11 mL = £1.76

**Exterol** (Dermal)  
*Ear drops,* urea–hydrogen peroxide complex 5% in glycerol. Net price 8 mL = £1.83
Sometimes allergic rhinitis is accompanied by vasomotor rhinitis. In this situation, the addition of topical nasal ipratropium bromide (section 12.2.2) can reduce watery rhinorrhea.

Very disabling symptoms occasionally justify the use of systemic corticosteroids for short periods (section 6.3), for example, in students taking important examinations. They may also be used at the beginning of a course of treatment with a corticosteroid spray to relieve severe mucosal oedema and allow the spray to penetrate the nasal cavity.

Pregnancy If a pregnant woman cannot tolerate the symptoms of allergic rhinitis, treatment with nasal beclometasone, budesonide, fluticasone, or sodium cromoglicate may be considered.

### Antihistamines

#### AZELASTINE HYDROCHLORIDE

**Indications** allergic rhinitis

**Side-effects** irritation of nasal mucosa; bitter taste (if applied incorrectly)

**Rhinolast** (Viatris) £1.26

Nasal spray, azelastine hydrochloride 140 micrograms (0.14 mL)/metered spray. Net price 22 mL (with metered pump) = £11.09

**Excipients** include sodium edetate

**Dose** ADULT and CHILD over 5 years, 140 micrograms (1 spray) into each nostril twice daily

**Note** Preparations of azelastine hydrochloride can be sold to the public for nasal administration in aqueous form (other than by aerosol) if supplied for the treatment of seasonal allergic rhinitis or perennial allergic rhinitis in adults and children over 5 years, subject to max. single dose of 140 micrograms per nostril, max. daily dose of 280 micrograms per nostril, and a pack size limit of 36 doses

### Corticosteroids

Nasal preparations containing corticosteroids (beclometasone, betamethasone, budesonide, flunisolide, fluticasone, mometason, and triamcinolone) have a useful role in the prophylaxis and treatment of allergic rhinitis (see notes above).

**Cautions** Corticosteroid nasal preparations should be avoided in the presence of untreated nasal infections, and also after nasal surgery (until healing has occurred); they should also be avoided in pulmonary tuberculosis. Patients transferred from systemic corticosteroids may experience exacerbation of some symptoms. Systemic absorption may follow nasal administration particularly if high doses are used or if treatment is prolonged; for cautions and side-effects of systemic corticosteroids, see section 6.3.2. The risk of systemic effects may be greater with nasal drops than with nasal sprays; drops are administered incorrectly more often than sprays. The CSM recommends that the height of children receiving prolonged treatment with nasal corticosteroids is monitored; if growth is slowed, referral to a paediatrician should be considered.

**Side-effects** Local side-effects include dryness, irritation of nose and throat, epistaxis and rarely ulceration; nasal septal perforation (usually following nasal surgery)
and raised intra-ocular pressure or glaucoma may also occur rarely. Headache, smell and taste disturbances may also occur. Hypersensitivity reactions, including bronchospasm, have been reported.

### BECLOMETASONE DIPROPIONATE

**Indications**
- prophylaxis and treatment of allergic and vasomotor rhinitis

**Cautions**
- see notes above

**Side-effects**
- see notes above

**Dose**
- **ADULT** and **CHILD** over 6 years, 100 micrograms (2 sprays) into each nostril twice daily; max. total 400 micrograms (8 sprays) daily; when symptoms controlled, dose reduced to 50 micrograms (1 spray) into each nostril twice daily

**Beclometasone (Non-proprietary)**
- Nasal spray, beclometasone dipropionate 50 micrograms/metered spray. Net price 200-spray unit = £2.89

**Brands** include Nasonex, AstraZeneca, and Syntaris.

1. Can be sold to the public for nasal administration (other than by aerosol) if supplied for the prevention and treatment of seasonal allergic rhinitis in adults over 18 years subject to max. single dose of 200 micrograms per nostril, max. daily dose of 200 micrograms per nostril for max. period of 3 months, and a pack size of 10 mg

### RHINOCORT AQUA®

**Indications**
- prophylaxis and treatment of allergic rhinitis

**Cautions**
- see notes above

**Side-effects**
- see notes above

**Dose**
- **ADULT** over 12 years, 128 micrograms (2 sprays) into each nostril once daily in the morning or 64 micrograms (1 spray) into each nostril twice daily; when control achieved reduce to 64 micrograms (1 spray) into each nostril once daily, max. duration of treatment 3 months

**Brands** include Flixonase Nasule, AstraZeneca, and Budesonide.

### FLUNISOLIDE

**Indications**
- prophylaxis and treatment of allergic rhinitis

**Cautions**
- see notes above

**Side-effects**
- see notes above

**Dose**
- **ADULT** and **CHILD** over 12 years, 64 micrograms (1 spray) into each nostril twice daily for up to 3 months

### FLUTICASONE PROPIONATE

**Indications**
- prophylaxis and treatment of allergic rhinitis and perennial rhinitis; nasal polyps

**Cautions**
- see notes above; interactions: Appendix 1 (corticosteroids)

**Side-effects**
- see notes above

**Dose**
- **Rhinitis**, 100 micrograms (2 sprays) into each nostril once daily, preferably in the morning, increased to max. twice daily if required; when control achieved reduce to 50 micrograms (1 spray) into each nostril once daily; **CHILD** 4–11 years, 50 micrograms (1 spray) into each nostril once daily, preferably in the morning, increased to max. twice daily if required

- **Nasal polyps**, see Flixonase Nasule® below

### BUDESONIDE

**Indications**
- prophylaxis and treatment of allergic and vasomotor rhinitis; nasal polyps

**Cautions**
- see notes above; interactions: Appendix 1 (corticosteroids)

**Side-effects**
- see notes above

**Dose**
- See preparations
**12.2.2 Topical nasal decongestants**

The nasal mucosa is sensitive to changes in atmospheric temperature and humidity and these alone may cause slight nasal congestion. The nose and nasal sinuses produce a litre of mucus in 24 hours and much of this finds its way silently into the stomach via the nasopharynx. Slight changes in the nasal airway, accompanied by an awareness of mucus passing along the nasopharynx, may cause some patients to be inaccurately diagnosed as suffering from chronic sinusitis. These symptoms are particularly noticeable in the later stages of the common cold. **Sodium chloride** 0.9% given as nasal drops may relieve nasal congestion by helping to liquefy mucous secretions.

**Inhalation of warm moist air** is useful in the treatment of symptoms of acute infective conditions. The addition of volatile substances such as menthol and eucalyptus may encourage the use of warm moist air (section 3.8).

Symptoms of nasal congestion associated with vasomotor rhinitis and the common cold can be relieved by the short-term use (usually not longer than 7 days) of decongestant nasal drops and sprays. These all contain sympathomimetic drugs which exert their effect by vasoconstriction of the mucosal blood vessels which in turn reduces oedema of the nasal mucosa. They are of limited value because they can give rise to a rebound congestion (rhinitis medicamentosa) on withdrawal, due to a secondary vasodilation with a subsequent temporary increase in nasal congestion. This in turn tempts the further use of the decongestant, leading to a vicious cycle of events.

**Epinephrine nasal drops** is the safest sympathomimetic preparation and can give relief for several hours. The more potent sympathomimetic drugs oxymetazoline, and xylometazoline are more likely to cause a rebound effect. All of these preparations may cause a hypertensive crisis if used during treatment with a monoamine-oxidase inhibitor including moclobemide. The CHM/MHRA has stated that non-prescription cough and cold medicines containing epinephrine, oxymetazoline, or xylometazoline should not be used in children under 2 years of age (section 3.9.1). However, in special circumstances, some specialists prescribe nasal drops containing epinephrine or xylometazoline in children under 2 years of age for the short-term treatment of severe nasal obstruction that has not responded to sodium chloride 0.9% nose drops and inhalation of warm moist air.

Non-allergic wet cough rhinorrhea often responds well to treatment with the antimuscarinic **iropatripium bromide**.

Systemic nasal decongestants—see section 3.10.

---

**Nasal drops**, **trituration** 400 micrograms/unit dose, net price 28 x 0.4 mL units = £13.76. **Excipients** include polysorbate 20

**Nasal spray**, mometasone furoate 50 micrograms/metered spray. Net price 150-spray unit = £10.52. **Excipients** include benzalkonium chloride, polysorbate 80

**Aqueous nasal spray**, fluticasone propionate 50 micrograms/metered spray. Net price 150-spray unit = £10.52. **Excipients** include benzalkonium chloride, polysorbate 80

**Nasal drops**, **trituration** 400 micrograms/unit dose, net price 28 x 0.4 mL units = £13.76. **Excipients** include polysorbate 20

**Nasal spray**, mometasone furoate 50 micrograms/metered spray. Net price 150-spray unit = £7.83. **Excipients** include benzalkonium chloride, polysorbate 80

**Aqueous nasal spray**, fluticasone propionate 50 micrograms/metered spray. Net price 150-spray unit = £10.52. **Excipients** include benzalkonium chloride, polysorbate 80

**Nasal drops**, **trituration** 400 micrograms/unit dose, net price 28 x 0.4 mL units = £13.76. **Excipients** include polysorbate 20

**Nasal spray**, triamcinolone acetonide 55 micrograms/metered spray. Net price 120-spray unit = £7.39. **Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Nasal drops**, **trituration** 400 micrograms/unit dose, net price 28 x 0.4 mL units = £13.76. **Excipients** include polysorbate 20

**Aqueous nasal spray**, triamcinolone acetonide 55 micrograms/metered spray. Net price 150-spray unit = £7.39. **Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Nasal drops**, **trituration** 400 micrograms/unit dose, net price 28 x 0.4 mL units = £13.76. **Excipients** include polysorbate 20

**Aqueous nasal spray**, triamcinolone acetonide 55 micrograms/metered spray. Net price 150-spray unit = £7.83. **Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Aqueous nasal spray**, triamcinolone acetonide 55 micrograms/metered spray. Net price 150-spray unit = £7.83. **Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Aqueous nasal spray**, triamcinolone acetonide 55 micrograms/metered spray. Net price 150-spray unit = £7.83. **Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

---

**Mometasone furoate**

**Indications** see preparations

**Cautions** see notes above

**Side-effects** see notes above

---

**Nasonex** (Schering-Plough) **(A)W**

**Nasal spray**, mometasone furoate 50 micrograms/metered spray. Net price 140-spray unit = £7.83. **Excipients** include benzalkonium chloride, polysorbate 80

**Dose** nasal polyps, **ADULT** and **ADOLESCENT** over 12 years, 100 micrograms (2 sprays) into each nostril once daily, increased if necessary to max. 200 micrograms (4 sprays) into each nostril once daily, when control achieved reduce to 50 micrograms (1 spray) into each nostril once daily. **CHILD** 6–11 years, 50 micrograms (1 spray) into each nostril once daily.

**Nasal polyps, ADULT** over 18 years, 100 micrograms (2 sprays) into each nostril once daily, increased if necessary after 5–6 weeks to 100 micrograms (2 sprays) into each nostril twice daily (consider alternative treatment if no improvement after further 5–6 weeks); reduce to the lowest effective dose when control achieved

---

**Triamcinolone acetonide**

**Indications** prophylaxis and treatment of allergic rhinitis

**Cautions** see notes above

**Side-effects** see notes above

---

**Nasacort** (Aventis Pharma) **(A)W**

**Aqueous nasal spray**, triamcinolone acetonide 55 micrograms/metered spray. Net price 120-spray unit = £7.39. **Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Dose** **ADULT** and **CHILD** over 12 years 110 micrograms (2 sprays) into each nostril once daily, when control achieved, reduce to 55 micrograms (1 spray) into each nostril once daily. **CHILD** 6–12 years, 55 micrograms (1 spray) into each nostril once daily

**Note** Preparations of triamcinolone acetonide can be sold to the public for nasal administration as a non-presurised nasal spray if supplied for the symptomatic treatment of seasonal allergic rhinitis in adults over 18 years, subject to max. daily dose of 110 micrograms per nostril for max. 3 months, and a pack size of 3.575 mg

---

**Cromoglicate**

**Sodium Cromoglicate** (Sodium Cromoglicate)

**Indications** prophylaxis of allergic rhinitis

**Side-effects** local irritation; rarely transient bronchospasm

---

**Rynacrom** (Sanoﬁ-Aventis)

4% aqueous nasal spray, sodium cromoglicate 4% (5.2 mg/spray). Net price 22 mL with pump = £17.76. **Excipients** include benzalkonium chloride, disodium edetate

**Dose** **ADULT** and **CHILD**, 1 spray into each nostril 2–4 times daily

**Vividrin** (Pharma-Global)

**Nasal spray**, sodium cromoglicate 2%. Net price 15 mL = £10.35. **Excipients** include benzalkonium chloride, edetic acid, polysorbate 80

**Dose** **ADULT** and **CHILD**, 1 spray into each nostril 4–6 times daily

---

**Fixonase Nasule** (A&H)**(A)W**

**Nasal drops**, fluticasone propionate 400 micrograms/unit dose, net price 28 x 0.4 mL units = £13.76. **Excipients** include polysorbate 20

**Dose** nasal polyps, **ADULT** and **ADOLESCENT** over 16 years, 200 micrograms (approx. 6 drops) into each nostril once or twice daily; consider alternative treatment if no improvement after 4–6 weeks

---

**Nasofan** (IVAX) **(A)W**

**Aqueous nasal spray**, fluticasone propionate 50 micrograms/metered spray. Net price 150-spray unit = £10.52. **Excipients** include benzalkonium chloride, polysorbate 80

---

12 Ear, nose, and oropharynx

---
**Sinusitis and oral pain**  Sinusitis affecting the maxillary antrum can cause pain in the upper jaw. Where this is associated with blockage of the opening from the sinus into the nasal cavity, it may be helpful to relieve the congestion with inhalation of warm moist air (section 3.8) or with **epinephrine nasal drops** (see above). For antibacterial treatment of sinusitis, see Table 1, section 5.1.

### Sympathomimetics

#### Ephedrine Hydrochloride

**Indications** nasal congestion  
**Cautions** see notes above; also avoid excessive or prolonged use; caution in infants under 3 months (no good evidence of value—if irritation occurs might narrow nasal passage); **interactions:** Appendix 1  
**Side-effects** local irritation, nausea, headache; after excessive use tolerance with diminished effect, rebound congestion; cardiovascular effects also reported  
**Dose**  
- **Ephedrine** (Non-proprietary)  
  - **Nasal drops**, ephedrine hydrochloride 0.5%, net price 10 mL = £1.25; 1%, 10 mL = £1.31  
  - **Note** The BP directs that if no strength is specified 0.5% drops should be supplied  
  - **Dose** 1–2 drops into each nostril up to 4 times daily when required, **CHILD** 3 months–12 years (on a specialist’s advice only for **CHILD** 3 months–2 years), 1–2 drops of 0.5% solution into each nostril 3–4 times daily, max. duration 7 days  
  - **Dental prescribing on NHS** Ephedrine nasal drops may be prescribed  
  - **1. Can be sold to the public provided no more than 180 mg of ephedrine base (or salts) are supplied at one time, and pseudoephedrine salts are not supplied at the same time; for more details see Medicines, Ethics and Practice, No. 32, London Pharmaceutical Press, 2008 (and subsequent editions as available)**

#### Xylometazoline Hydrochloride

**Indications** nasal congestion  
**Cautions** see under Ephedrine Hydrochloride and notes above  
**Side-effects** see under Ephedrine Hydrochloride and notes above  
**Dose**  
- **Xylometazoline** (Non-proprietary)  
  - **Nasal drops**, xylometazoline hydrochloride 0.1%, net price 10 mL = £1.91  
  - **Dose** 2–3 drops into each nostril 2–3 times daily when required; max. duration 7 days; not recommended for children under 12 years  
  - **Brands include** Otradrone, Otrivine, Otraspray  
  - **Paediatric nasal drops**, xylometazoline hydrochloride 0.05%, net price 10 mL = £1.59  
  - **Dose** **CHILD** 2–12 years 1–2 drops into each nostril 1–2 times daily when required (on a specialist’s advice only for **CHILD** 3 months–2 years), max. duration 7 days  
  - **Brands include** Otradrone, Otrivine, Tinycolds

### Antimuscarinic

#### IPATROPIUM BROMIDE

**Indications** rhinorrhoea associated with allergic and non-allergic rhinitis  
**Cautions** see section 3.1.2; avoid spraying near eyes  
**Side-effects** epistaxis, nasal dryness, and irritation; less frequently nausea, headache, and pharyngitis; **very rarely** antimuscarinic effects such as gastrointestinal motility disturbances, palpitations, and urinary retention  
**Dose**  
- **ADULT** and **CHILD** over 12 years, 42 micrograms (2 sprays) into each nostril 2–3 times daily  
- **Rinatec** (Boehringer Ingelheim)  
  - **Nasal spray 0.03%**, ipratropium bromide 21 micrograms/metered spray. Net price 180-dose unit = £4.55  
  - **Excipients** include benzalkonium chloride, disodium edetate

### 12.2.3 Nasal preparations for infection

There is no evidence that topical anti-infective nasal preparations have any therapeutic value in rhinitis or sinusitis; for elimination of nasal staphylococci, see below.  
Systemic treatment of sinusitis—see Table 1 section 5.1

#### Betnesol-N® (UCB Pharma)  
**Drops** (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, neomycin sulphate 0.5%. Net price 10 mL = £2.39  
**Excipients** include benzalkonium chloride, disodium edetate  
**Dose** **nose**, 2–3 drops into each nostril 2–3 times daily; **eye**, section 11.4.1; **ear**, section 12.1.1

#### Vistarinasone N® (Martenstian)  
**Drops** (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, neomycin sulphate 0.5%. Net price 5 mL = £1.09, 10 mL = £1.20  
**Excipients** include thiomersal  
**Dose** **nose**, 2–3 drops into each nostril twice daily; **eye**, section 11.4.1; **ear**, section 12.1.1

### Nasal staphylococci

Elimination of organisms such as staphylococci from the nasal vestibule can be achieved by the use of a cream containing chlorhexidine and neomycin (Naseptin®), but re-colonisation frequently occurs. Coagulase-positive staphylococci are present in the noses of 40% of the population.  
A nasal ointment containing mupirocin is also available; it should probably be held in reserve for resistant cases. In hospital or in care establishments, mupirocin nasal ointment should be reserved for the eradication

---

**Nasal spray**, xylometazoline hydrochloride 0.1%, net price 10 mL = £1.91  
**Dose** 1 spray into each nostril 2–3 times daily when required; max. duration 7 days; not recommended for children under 12 years  
**Brands include** Otrasprr , Otrivine , Otraspray
Ulceration of the oral mucosa may be caused by trauma (physical or chemical), recurrent aphthae, infections, carcinoma, dermatological disorders, nutritional deficiencies, gastro-intestinal disease, haematopoietic disorders, and drug therapy (see also Chemotherapy-induced mucositis and myelosuppression, section 8.1). It is important to establish the diagnosis in each case as the majority of these lesions require specific management in addition to local treatment. Local treatment aims to protect the ulcerated area, to relieve pain, to reduce inflammation, or to control secondary infection. Patients with an unexplained mouth ulcer of more than 3 weeks’ duration require urgent referral to hospital to exclude oral cancer.

**Simple mouthwashes** A saline mouthwash (section 12.3.4) may relieve the pain of traumatic ulceration. The mouthwash is made up with warm water and used at frequent intervals until the discomfort and swelling subsides.

**Antiseptic mouthwashes** Secondary bacterial infection may be a feature of any mucosal ulceration; it can increase discomfort and delay healing. Use of chlorhexidine mouthwash (section 12.3.4) is often beneficial and may accelerate healing of recurrent aphthae.

**Mechanical protection** Carmellose gelatin paste may relieve some discomfort arising from ulceration by protecting the ulcer site. As the paste adheres to dry mucosa, it is difficult to apply it effectively to the tongue and oropharynx.

**Corticosteroids** Topical corticosteroid therapy may be used for some forms of oral ulceration. In the case of aphthous ulcers it is most effective if applied in the ‘prodromal’ phase. Thrush or other types of candidiasis are recognised complications of corticosteroid treatment.

**Hydrocortisone oromucosal tablets** are allowed to dissolve next to an ulcer and are useful in recurrent aphthae and erosive lichenoid lesions.

**Triamcinolone dental paste** is designed to keep the corticosteroid in contact with the mucosa for long enough to permit penetration of the lesion. As the paste adheres to dry mucosa, it is difficult to apply it effectively to the tongue and oropharynx.

**Beclometasone** inhaler 50–100 micrograms sprayed twice daily on the oral mucosa is used to manage oral ulceration [unlicensed indication]. Alternatively, betamethasone soluble tablets dissolved in water can be used as a mouthwash to treat oral ulceration [unlicensed indication].

**Systemic corticosteroid therapy** (section 6.3.2) is reserved for severe conditions such as pemphigus vulgaris.

**Local anaesthetics** Local anaesthetics have a limited role in the management of oral ulceration. When applied topically their action is of a relatively short duration so that anaesthesia cannot be maintained continuously throughout the day. The main indication for a topical local anaesthetic is to relieve the pain of otherwise intractable oral ulceration particularly when it is due to major aphthae. For this purpose lidocaine (lignocaine) 5% ointment or lozenges containing a local anaesthetic are applied to the ulcer. Lidocaine 10% solution as spray (section 15.2) can be applied thinly to the ulcer [unlicensed indication] using a cotton bud. When local anaesthetics are used in the mouth care must be taken not to produce anaesthesia of the pharynx before meals as this might lead to choking.

**Benzydamine** mouthwash or spray may be useful in reducing the discomfort associated with a variety of ulcerative conditions. It has also been found to be effective in reducing the discomfort of post-irradiation mucositis. Some patients find the full-strength mouthwash causes some stinging and, for them, it should be diluted with an equal volume of water.

**Flurbiprofen** lozenges are licensed for the relief of sore throat.

**Choline salicylate** gel has some analgesic action and may provide relief for recurrent aphthae, but excessive application or confinement under a denture irritates the mucosa and can itself cause ulceration. Benefit in teething may merely be due to pressure of application (comparable with biting a teething ring); excessive use can lead to salicylate poisoning.
Other preparations Doxycycline rinsed in the mouth may be of value for recurrent aphthous ulceration.

Periodontitis Low-dose doxycycline (Periostar®) is licensed as an adjunct to scaling and root planing for the treatment of periodontitis; a low dose of doxycycline reduces collagenase activity without inhibiting bacteria associated with periodontitis. For anti-infectives used in the treatment of destructive (refractory) forms of periodontal disease, see section 12.3.2 and Table 1, section 5.1. For mouthwashes used for oral hygiene and plaque inhibition, see section 12.3.4.

BENZYMADINE HYDROCHLORIDE
Indications painful inflammatory conditions of oropharynx
Side-effects occasional numbness or stinging; rarely hypersensitivity reactions

Difflam® (3M)
Oral rinse, green, benzydamine hydrochloride 0.15%, net price 200 mL (Difflam® Sore Throat Rinse) £2.63; 300 mL £4.01

Dose ADULT and ADOLESCENT over 12 years, rinse or gargle, using 15 mL (dilute with an equal volume of water if stinging occurs) every 1½–3 hours as required, usually for not more than 7 days

Dental prescribing on NHS May be prescribed as Benzydamine Mouthwash 0.15%

Spray, benzydamine hydrochloride 0.15%. Net price 30–mL unit = £3.17

Dose ADULT 4–8 sprays onto affected area every 1½–3 hours; CHILD under 6 years 1 spray per 4 kg body-weight to max. 4 sprays every 1½–3 hours; 6–12 years 4 sprays every 1½–3 hours

Dental prescribing on NHS May be prescribed as Benzydamine Oromucosal Spray 0.15%

CARMELLOSE SODIUM
Indications mechanical protection of oral and perioral lesions

Orabase® (Convatec)
Protective paste (= oral paste), carmellose sodium 16.7%, pectin 16.7%, gelatin 16.7%, in Plastibase®. Net price 30 g = £2.02; 100 g = £4.88

Dose apply a thin layer when necessary after meals

Dental prescribing on NHS May be prescribed as Carmellose Gelatin Paste

Orabhesive® (Convatec)
Powder, carmellose sodium, pectin, gelatin, equal parts. Net price 25 g = £2.33

Dose sprinkle on the affected area

CORTICOSTEROIDS
Indications oral and perioral lesions
Contra-indications untreated oral infection; manufacturer of triamcinolone contra-indicates use on tuberculous and viral lesions
Side-effects occasional exacerbation of local infection; thrush or other candidal infections

Adcortyl in Orabase® (Squibb) (SFH)
Oral paste, triamcinolone acetonide 0.1% in adhesive basis. Net price 10 g = £1.18

Dose ADULT and CHILD, apply a thin layer 2–4 times daily; do not rub in; use limited to 5 days for children and short-term use also advised for elderly

Dental prescribing on NHS May be prescribed as Triamcinolone Dental Paste

Note A 5-g tube is on sale to the public for the treatment of common mouth ulcers for max. 5 days

Betnesol® (Geltech) (SFH)
Soluble tablets, pink, scored, betamethasone 500 micrograms (as sodium phosphate). net price 100-pack = £5.17. Label: 10, steroid card, 13, 21

Dose oral ulceration, (unlicensed indication) ADULT and CHILD over 12 years, 500 micrograms dissolved in 20 mL water and rinsed around the mouth 4 times daily, not to be swallowed

Dental prescribing on the NHS May be prescribed as Betamethasone Soluble Tablets 500 micrograms

Coraln® (UCB Pharma)
Pellets (= oromucosal tablets), hydrocortisone 2.5 mg (as sodium succinate). Net price 20 = £2.54

Dose ADULT and CHILD over 12 years, 1 lozenge 4 times daily, allowed to dissolve slowly in the mouth in contact with the ulcer; CHILD under 12 years, only on medical advice

Dental prescribing on NHS May be prescribed as Hydrocortisone Oromucosal Tablets

DOXYCYCLINE
Indications see preparations; oral herpes (section 12.3.2); other indications (section 5.1.3)
Cautions section 5.1.3; monitor for superficial fungal infection, particularly, if predisposition to oral candidiasis
Contra-indications section 5.1.3
Side-effects section 5.1.3; fungal superinfection
Dose

Note Doxycycline stains teeth; avoid in children under 12 years of age

Periodostat® (Alliance) (SFH)
Tablets, H.c, doxycycline (as hyclate) 20 mg, net price 56-tab pack = £16.50. Label: 6, 11, 27, counselling, posture

Dose periodontitis (as an adjunct to gingival scaling and root planing), 20 mg twice daily for 3 months; CHILD under 12 years not recommended

Counselling Tablets should be swallowed whole with plenty of fluid (at least 100 mL), while sitting or standing

Dental prescribing on NHS May be prescribed as Doxycycline Tablets 20 mg

Local application

For recurrent aphthous ulceration, the contents of a 100 mg doxycycline capsule can be stirred into a small amount of water then rinsed around the mouth for 2–3 minutes 4 times daily usually for 3 days; it should preferably not be swallowed (unlicensed indication).

FLURBIPROFEN
Indications relief of sore throat
Cautions see section 10.1.1
Contra-indications see section 10.1.1
Side-effects taste disturbance, mouth ulcers (move lozenge around mouth); see also section 10.1.1

Strelen® (Crookes)
Lozenges, flurbiprofen 8.75 mg, net price 16 = £2.24

Dose ADULT and CHILD over 12 years, allow 1 lozenge to dissolve slowly in the mouth every 3–4 hours, max. 5 lozenges in 24 hours, for max. 3 days

LOCAL ANAESTHETICS
Indications relief of pain in oral lesions
Cautions avoid prolonged use; hypersensitivity; pregnancy (Appendix 4); avoid anaesthesia of the pharynx before meals—risk of choking
12.3.2 Oropharyngeal anti-infective drugs

**Lidocaine** (Non-proprietary)

**Ointment**, lidocaine 5% in a water-miscible basis, net price 15 g = 80p

**Dose** rub sparingly and gently on affected areas

*Dental prescribing on NHS* Lidocaine 5% Ointment may be prescribed

**Xylocaine** (AstraZeneca)

**Spray** (= pump spray), lidocaine 10% (100 mg/g) supplying 10 mg lidocaine/spray; 500 spray doses per container. Net price 50-mL bottle = £3.13

**Dose** apply thinly to the ulcer [unlicensed indication] using a cotton bud

*Dental prescribing on NHS* May be prescribed as Lidocaine Spray 10%

### Preparations on sale to the public

Many mouth ulcer preparations, throat lozenges, and throat sprays on sale to the public contain a **local anaesthetic**. To identify the active ingredients in such preparations, consult the product literature of the manufacturer.

**Note** The correct proprietary name should be ascertained—many products have very similar names but different active ingredients

#### SALICYLATES

**Indications** mild oral and perioral lesions

**Cautions** not to be applied to dentures—leave at least 30 minutes before re-insertion of dentures; frequent application, especially in children, may give rise to salicylate poisoning

**Note** CSM warning on aspirin and Reye's syndrome does not apply to salicylates in topical preparations such as teething gels and oral paints

**Choline salicylate**

**Choline Salicylate Dental Gel, BP**

**Oral gel**, choline salicylate 8.7% in a flavoured gel basis, net price 15 g = £1.89

**Brands** include Bonpepa (sugar-free)

**Dose** apply ½-inch of gel with gentle massage not more often than every 3 hours; **CHILD** over 4 months ¼-inch of gel not more often than every 3 hours; max. 6 applications daily

*Dental prescribing on NHS* Choline Salicylate Dental Gel may be prescribed

**Salicylic acid**

**Pyralvex** (Norgine)

**Oral paint**, brown, rhubarb extract (anthraquinone glycosides 0.5%), salicylic acid 1%. Net price 10 mL with brush = £3.38

**Dose** **ADULT** and **CHILD** over 12 years, apply 3–4 times daily

### 12.3.2 Oropharyngeal anti-infective drugs

The most common cause of a sore throat is a viral infection which does not benefit from anti-infective treatment. Streptococcal sore throats require systemic *penicillin* therapy (Table 1, section 5.1). Acute ulcerative gingivitis (Vincent's infection) responds to systemic *metronidazole* (section 5.1.11).

Preparations administered in the dental surgery for the local treatment of periodontal disease include gels of *metronidazole* (**Elyzol***, Colgate-Palmolive) and of minocycline (**Dentomycin***, Blackwell).

#### Oropharyngeal fungal infections

Fungal infections of the mouth are usually caused by *Candida* spp. (candidiasis or candidosis). Different types of oropharyngeal candidiasis are managed as follows:

**Thrush** Acute pseudomembranous candidiasis (thrust), is usually an acute infection but it may persist for months in patients receiving inhaled corticosteroids, cytotoxics or broad-spectrum antibacterials. Thrush also occurs in patients with serious systemic disease associated with reduced immunity such as leukaemia, other malignancies, and HIV infection. Any predisposing condition should be managed appropriately. When thrush is associated with corticosteroid inhalers, rinsing the mouth with water (or cleaning a child's teeth) immediately after using the inhaler may avoid the problem. **Treatment with** **nystatin**, **amphotericin**, or **miconazole** may be needed. Fluconazole (section 5.2) is effective for unresponsive infections or if a topical antifungal drug cannot be used or if the patient has dry mouth. Topical therapy may not be adequate in immunocompromised patients and an oral triazole antifungal is preferred (section 5.2).

**Acute erythematous candidiasis** Acute erythematous (atrophic candidiasis) is a relatively uncommon condition associated with corticosteroid and broad-spectrum antibacterial use and with HIV disease. It is usually treated with fluconazole (section 5.2).

**Denture stomatitis** Patients with denture stomatitis (chronic atrophic candidiasis), should cleanse their dentures thoroughly and leave them out as often as possible during the treatment period. To prevent recurrence of the problem, dentures should not normally be worn at night. New dentures may be required if these measures fail despite good compliance.

**Miconazole** oral gel can be applied to the fitting surface of the denture before insertion (for short periods only). Alternatively, **amphotericin** lozenges can be allowed to dissolve slowly in the mouth but they are less effective at resolving the stomatitis. Denture stomatitis is not always associated with candidiasis and other factors such as mechanical or chemical irritation, bacterial infection, or rarely allergy to the dental base material, may be the cause.

**Chronic hyperplastic candidiasis** Chronic hyperplastic candidiasis (candidal leucoplaclia) carries an increased risk of malignancy; biopsy is essential—this type of candidiasis may be associated with varying degrees of dysplasia, with oral cancer present in a high proportion of cases. Chronic hyperplastic candidiasis is treated with a systemic antifungal such as fluconazole (section 5.2) to eliminate candidal overgrowth. Patients should avoid the use of tobacco.

**Angular cheilitis** Angular cheilitis (angular stomatitis) is characterised by soreness, erythema and fissuring at the angles of the mouth. It is commonly associated with denture stomatitis but may represent a nutritional deficiency or it may be related to orofacial granulomatosis. While the underlying cause is being identified and
treated, it is often helpful to apply miconazole and hydrocortisone cream or ointment (see p. 622), miconazole cream (see p. 650), or sodium fusidate ointment (see p. 649).

**Immunocompromised patients** For advice on prevention of fungal infections in immunocompromised patients see p. 328.

**Drugs used in oropharyngeal candidiasis**

**Amphotericin** and nystatin are not absorbed from the gastro-intestinal tract and are applied locally (as lozenges or suspension) to the mouth for treating local fungal infections. Miconazole is applied locally (as an oral gel) in the mouth but it is absorbed to the extent that potential interactions need to be considered. Miconazole also has some activity against Gram-positive bacteria including streptococci and staphylococci.

**Fluconazole** (section 5.2) is given by mouth for infections that do not respond to topical therapy. It is reliably absorbed and effective. Itraconazole (section 5.2) can be used for fluconazole-resistant infections.

If candidal infection fails to respond to 1 to 2 weeks of treatment with antifungal drugs the patient should be sent for investigation to eliminate the possibility of underlying disease. Persistent infection may also be caused by reinfection from the genito-urinary or gastro-intestinal tract. Infection can be eliminated from these sources by appropriate anticandidal therapy; the patient’s partner may also require treatment to prevent reinfection.

For the role of antiseptic mouthwashes in the prevention of oral candidiasis in immunocompromised patients and treatment of denture stomatitis, see section 12.3.4.

### AMPHOTERICIN

**Indications** oral and peroral fungal infections

**Side-effects** mild gastro-intestinal disturbances reported

**Fungilin** (Squibb)


**Dose** allow 1 lozenge to dissolve slowly in the mouth 4 times daily for 10–15 days (continued for 48 hours after lesions have resolved); increase to 8 daily if infection severe

**Dental prescribing on NHS** May be prescribed as Amphotericin Lozenges

### MICONAZOLE

**Indications** see preparations

**Cautions** pregnancy (Appendix 4); breast-feeding; avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (antifungals, imidazole)

**Contra-indications** hepatic impairment; with oral gel, impaired swallowing reflex in infants, first 5–6 months of life of an infant born preterm

**Side-effects** nausea, vomiting, rash; with **buccal tablets**, abdominal pain, taste disturbance, burning sensation at application site, pruritus, and oedema; with **oral gel**, very rarely diarrhoea (usually on long-term treatment), hepatitis, toxic epidermal necrolysis, and Stevens-Johnson syndrome

**Dose** see preparations

### Nystatin

**Indications** oral and peroral fungal infections

**Side-effects** oral irritation and sensitisation, nausea reported; see also p. 332

**Dose**

- Treatment, ADULT and CHILD, 100 000 units 4 times daily after food, usually for 7 days (continued for 48 hours after lesions have resolved);
- **Note** Unlicensed for treating candidiasis in NEONATE

**Nystan** (Squibb)

**Oral suspension**, yellow, nystatin 100 000 units/mL. Net price 30 mL with pipette = £1.91. Label: 9, counselling, use of pipette, hold in mouth, after food

**Dental prescribing on NHS** Nystatin Oral Suspension may be prescribed

### Oropharyngeal viral infections

The management of primary herpetic gingivostomatitis is a soft diet, adequate fluid intake, and analgesics as required, including local use of **benzydamine** (section 12.3.1). The use of chlorhexidine mouthwash (section 12.3.4) will control plaque accumulation if toothbrushing is painful and will also help to control secondary infection in general.

In the case of severe herpetic stomatitis, a systemic antiviral such as aciclovir is required (section 5.3.2.1). Valaciclovir and famciclovir are suitable alternatives for oral lesions associated with herpes zoster. Aciclovir and valaciclovir are also used for the prevention of frequently recurring herpes simplex lesions of the mouth, particularly when implicated in the initiation of erythema multiforme. See section 13.10.3 for the treatment of labial herpes simplex infections.

Herpes infections of the mouth may also respond to rinsing the mouth with **doxycycline** (see p. 609).
12.3.3 Lozenges and sprays

There is no convincing evidence that antiseptic lozenges and sprays have a beneficial action and they sometimes irritate and cause sore tongue and sore lips. Some of these preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

12.3.4 Mouthwashes, gargles, and dentifrices

Superficial infections of the mouth are often helped by warm mouthwashes which have a mechanical cleansing effect and cause some local hyperaemia. However, to be effective, they must be used frequently and vigorously. A warm saline mouthwash is ideal and can be prepared either by dissolving half a teaspoonful of salt in a glassful of warm water or by diluting compound sodium chloride mouthwash with an equal volume of warm water. Mouthwash solution-tablets are used to remove unpleasant tastes.

Mouthwashes containing an oxidising agent, such as hydrogen peroxide, may be useful in the treatment of acute ulcerative gingivitis (Vincent’s infection) since the organisms involved are anaerobes. It also has a mechanical cleansing effect arising from frothing when in contact with oral debris.

Chlorhexidine is an effective antiseptic which has the advantage of inhibiting plaque formation on the teeth. It does not, however, completely control plaque deposition and is not a substitute for effective toothbrushing. Moreover, chlorhexidine preparations do not penetrate significantly into stagnation areas and are therefore of little value in the control of dental caries or of periodontal disease once pocketing has developed. Chlorhexidine mouthwash is used in the treatment of denture stomatitis. It is also used in the prevention of oral candidiasis in immunocompromised patients. Chlorhexidine mouthwash reduces the incidence of alveolar osteitis following tooth extraction. Chlorhexidine mouthwash should not be used for the prevention of endocarditis in patients undergoing dental procedures. Chlorhexidine can be used as a mouthwash, spray or gel for secondary infection in mucosal ulceration and for controlling gingivitis, as an adjunct to other oral hygiene measures. These preparations may also be used instead of toothbrushing where there is a painful periodontal condition (e.g. primary herpetic stomatitis) or if the patient has a haemorrhagic disorder, or is disabled. Chlorhexidine preparations are of little value in the control of acute necrotising ulcerative gingivitis.

There is no convincing evidence that gargles are effective.

CHLORHEXIDINE GLUCONATE

Indications  see under preparations below

Side-effects  mucosal irritation (if desquamation occurs, discontinue treatment or dilute mouthwash with an equal volume of water); taste disturbance; reversible brown staining of teeth, and of silicate or composite restorations; tongue discoloration; parotid gland swelling reported

Note  Chlorhexidine gluconate may be incompatible with some ingredients in toothpaste; leave an interval of at least 30 minutes between using mouthwash and toothpaste

Chlorhexidine (Non-proprietary)

Mouthwash, chlorhexidine gluconate 0.2%, net price 300 mL = £1.97
Dose  oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of aphthous ulcers, rinse mouth with 10 mL for about 1 minute twice daily
Denture stomatitis, cleanse and soak dentures in mouthwash solution for 15 minutes twice daily
Dental prescribing on NHS  Chlorhexidine Mouthwash may be prescribed

Chlorohex® (Colgate-Palmoive)

Chlorohex 1200® mouthwash, chlorhexidine gluconate 0.12% (mint-flavoured). Net price 300 mL = £2.00
Dose  oral hygiene and plaque inhibition, rinse mouth with 15 mL for about 30 seconds twice daily

Cordyol® (GSK Consumer Healthcare)

Dental gel, chlorhexidine gluconate 1%. Net price 50 g = £1.21
Dose  oral hygiene and plaque inhibition and gingivitis, brush on the teeth once or twice daily
Dental prescribing on NHS  May be prescribed as Chlorhexidine Gluconate Gel 1%

Mouthwash, chlorhexidine gluconate 0.2%. Net price 300 mL (original or mint) = £1.93, 600 mL (mint) = £3.85
Dose  oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of aphthous ulcers, rinse mouth with 10 mL for about 1 minute twice daily
Denture stomatitis, cleanse and soak dentures in mouthwash solution for 15 minutes twice daily

Oral spray, chlorhexidine gluconate 0.2% (mint-flavoured). Net price 60 mL = £4.10
Dose  oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of aphthous ulcers, apply as required to tooth, gingival, or ulcer surfaces using up to 12 actuations (approx. 0.14 mL/actuation) twice daily
Dental prescribing on NHS  May be prescribed as Chlorhexidine Oral Spray

With chlorobutanol

Eludril® (Fabre)

Mouthwash or gargle, chlorhexidine gluconate 0.1%, chlorobutanol 0.5% (mint-flavoured), net price 90 mL = £1.36, 250 mL = £2.83, 500 mL = £5.06
Dose  oral hygiene and plaque inhibition, use 10–15 mL (diluted with warm water in measuring cup provided) 2–3 times daily
Denture disinfection, soak previously cleansed dentures in mouthwash (diluted with 2 volumes of water) for 60 minutes

HEXETIDINE

Indications  oral hygiene

Side-effects  local irritation; very rarely taste disturbance and transient anaesthesia

Oraldene® (McNeil)

Mouthwash or gargle, red or blue-green (mint-flavoured), hexetidine 0.1%. Net price 100 mL = £1.31; 200 mL = £2.02
Dose  ADULT and CHILD over 6 years, use 15 mL undiluted 2–3 times daily

HYDROGEN PEROXIDE

Indications  oral hygiene, see notes above

Side-effects  hypertrophy of papillae of tongue on prolonged use
Hydrogen Peroxide Mouthwash, BP

Mouthwash, consists of Hydrogen Peroxide Solution 6% (= approx. 20 volume) BP

Dose  
- rinse the mouth for 2–3 minutes with 15 mL diluted in half a tumblerful of warm water 2–3 times daily

Dental prescribing on NHS  
Hydrogen Peroxide Mouthwash may be prescribed

Peroxyl® (Colgate-Palmolive)

Mouthwash, hydrogen peroxide 1.5%, net price 300 mL = £2.95

Dose  
- rinse the mouth with 10 mL for about 1 minute up to 4 times daily (after meals and at bedtime)

SOODIUM CHLORIDE

Indications  
oral hygiene, see notes above

Sodium Chloride Mouthwash, Compound, BP

Mouthwash, sodium bicarbonate 1%, sodium chloride 1.5% in a suitable vehicle with a peppermint flavour.

Dose  
- extemporaneous preparations should be prepared according to the following formula: sodium chloride 1.5 g, sodium bicarbonate 1 g, concentrated peppermint emulsion 2.5 mL, double-strength chloroform water 50 mL, water to 100 mL.

To be diluted with an equal volume of warm water

Dental prescribing on NHS  
Compound Sodium Chloride Mouthwash may be prescribed

THYMOL

Indications  
oral hygiene, see notes above

Mouthwash Solution-tablets

Consist of tablets which may contain antimicrobial, colouring, and flavouring agents in a suitable soluble effervescent basis to make a mouthwash suitable for dental purposes.

Dose  
- dissolve 1 tablet in a tumblerful of warm water

Note  
Mouthwash solution tablets may contain ingredients such as thymol.

Dental prescribing on NHS  
Mouthwash Solution-tablets may be prescribed

12.3.5 Treatment of dry mouth

Dry mouth (xerostomia) may be caused by drugs with antimuscarinic (anticholinergic) side-effects (e.g. antispasmodics, tricyclic antidepressants, and some antipsychotics), by diuretics, by irradiation of the head and neck region or by damage to or disease of the salivary glands. Patients with a persistently dry mouth may develop increased dental caries, periodontal disease, intolerance of dentures, and oral infections (particularly candidiasis). Dry mouth may be relieved in many patients by simple measures such as frequent sips of cool drinks or sucking pieces of ice or sugar-free fruit pastilles. Sugar-free chewing gum stimulates saliva in patients with residual salivary function.

Artificial saliva can provide useful relief of dry mouth. A properly balanced artificial saliva should be of a neutral pH and contain electrolytes (including fluoride) to correspond approximately to the composition of saliva. The acidic pH of some artificial saliva products may be inappropriate. Of the proprietary preparations, Luboran® is licensed for any condition giving rise to a dry mouth; Biotène Oralbalance®, BioXtra®, Glondosane®, Saliva Orthana®, and Saliveze®, have ACBS approval for dry mouth associated only with radiotherapy or sicca syndrome. Salivix® pastilles, which act locally as salivary stimulants, are also available and have similar ACBS approval. SST tablets may be prescribed for dry mouth in patients with salivary gland impairment (and patent salivary ducts). Salinum® may also be prescribed for relief of symptoms of dry mouth.

Pilocarpine tablets are licensed for the treatment of xerostomia following irradiation for head and neck cancer and for dry mouth and dry eyes (xerophthalmia) in Sjögren's syndrome. They are effective only in patients who have some residual salivary gland function, and therefore should be withdrawn if there is no response.

Local treatment

AS Saliva Orthana®  
(AS Pharma)

Oral spray, gastric mucin (porcine) 3.5%, xylitol 2%, sodium fluoride 4.2 mg/litre, with preservatives and flavouring agents, pH neutral. Net price 50-mL bottle = £4.92; 450-mL refill = £29.69

Dose  
- ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome, spray 2–3 times onto oral and pharyngeal mucosa, when required

Lozenges, mucin 65 mg, xylitol 59 mg, in a sorbitol basis, pH neutral. Net price 30-lozenge pack = £3.50

Dose  
- ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome

Note  
Avoid use with toothpastes containing detergents (including foaming agents)

Dental prescribing on NHS  
AS Saliva Orthana Oral Spray and Lozenges may be prescribed

Biotène Oralbalance®  
(Anglian)

Saliva replacement gel, lactoperoxidase, lactoferrin, lysozyme, glucose oxidase, xylitol in a gel basis, net price 50-g tube = £4.10, 24 × 12.4-mL tube = £30.40 (for hospital use)

Dose  
- ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome, apply to gums and tongue as required

Note  
Avoid use with toothpastes containing detergents (including foaming agents)

Dental prescribing on NHS  
Biotène Oralbalance Saliva Replacement Gel may be prescribed

BioXtra®  
(RIS Products)

Gel, lactoperoxidase, lactoferrin, lysozyme, whey collostrum, xylitol and other ingredients, net price 40-mL tube = £3.94, 50-mL spray = £3.94

Dose  
- ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome, apply to oral mucosa as required

Dental prescribing on NHS  
BioXtra Gel may be prescribed

Glandosane®  
(Fresenius Kabi)

Aerosol spray, carmellose sodium 500 mg, sorbitol 1.5 g, potassium chloride 60 mg, sodium chloride 42.2 mg, magnesium chloride 2.6 mg, calcium chloride 7.3 mg, and dipotassium hydrogen phosphate 17.1 mg/50-g, pH 5.75. Net price 50-mL unit (neutral, lemon or peppermint flavoured) = £4.48

Dose  
- ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome, spray onto oral and pharyngeal mucosa as required

Dental prescribing on NHS  
Glandosane Aerosol Spray may be prescribed

Luboran®  
(Goldshield)

Oral spray, pink, sorbitol 1.8 g, carmellose sodium (sodium carboxymethylcellulose) 390 mg, dibasic acid.
potassium phosphate 48.23 mg, potassium chloride 37.5 mg, monobasic potassium phosphate 21.97 mg, calcium chloride 9.972 mg, magnesium chloride 3.528 mg, sodium fluoride 258 micrograms/60 mL, with preservatives and colouring agents. Net price 60-mL unit = £3.96

Dose  saliva deficiency, 2–3 sprays onto oral mucosa up to 4 times daily; or as directed

Note  May be difficult to obtain

Dental prescribing on NHS  Luborant Oral Spray may be prescribed as Artificial Saliva

Salimun®  (Crawford)
Liquid, sugar-free, lined extract (containing polysaccharides) with dipotassium phosphate buffer and preservatives, pH 6–7, net price 300-mL bottle = £13.50

Dose  symptomatic treatment of dry mouth, approx. 2 mL rinsed around the mouth and then swallowed, when required

Saliveze®  (Wyvern)
Oral spray, carmellose sodium (sodium carboxymethylcellulose), calcium chloride, magnesium chloride, potassium chloride, sodium chloride, and dibasic sodium phosphate, pH neutral. Net price 50-mL bottle (mint-flavoured) = £3.50

Dose  ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome, 1 spray onto oral mucosa as required

Dental prescribing on NHS  Saliveze Oral Spray may be prescribed

Salivix®  (KoGEN)
Pastilles, sugar-free, reddish-amber, acacia, malic acid and other ingredients. Net price 50-pastille pack = £3.50

Dose  ACBS: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome, suck 1 pastille when required

Dental prescribing on NHS  Salivix Pastilles may be prescribed

SST  (Medac)
Tablets, sugar-free, citric acid, malic acid and other ingredients in a sorbitol base, net price 100-tab pack = £4.86

Dose  symptomatic treatment of dry mouth in patients with impaired salivary gland function and patent salivary ducts, allow 1 tablet to dissolve slowly in the mouth when required

Dental prescribing on NHS  May be prescribed as Saliva Stimulating Tablets

Systemic treatment

PILOCARPINE HYDROCHLORIDE

Indications  xerostomia following irradiation for head and neck cancer (see also notes above); dry mouth and dry eyes in Sjögren’s syndrome

Cautions  asthma and chronic obstructive pulmonary disease (avoid if uncontrolled, see Contra-indications), cardiovascular disease (avoid if uncontrolled); cholelithiasis or biliary-tract disease, peptic ulcer, hepatic impairment (Appendix 2), renal impairment; risk of increased urethral smooth muscle tone and renal colic; maintain adequate fluid intake to avoid dehydration associated with excessive sweating; cognitive or psychiatric disturbances; susceptibility to angle-closure glaucoma; interactions: Appendix 1 (parasympathomimetics)

Counselling  Blurred vision or dizziness may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting

Contra-indications  uncontrolled asthma and chronic obstructive pulmonary disease (increased bronchial secretions and increased airways resistance); uncontrolled cardiorenal disease; acute iritis; pregnancy (Appendix 4); breast-feeding (Appendix 5)

Side-effects  dyspepsia, diarrhoea, abdominal pain, nausea, vomiting, constipation; flushing, hypertension, palpitation, headache, dizziness, asthma, influenza-like symptoms, sweating; increased urinary frequency; visual disturbances, lacrimation, ocular pain, conjunctivitis; rhinitis, rash, pruritus; less commonly flatulence, urinary urgency

Dose  • Xerostomia following irradiation for head and neck cancer, 5 mg 3 times daily with or immediately after meals (last dose always with evening meal); if tolerated but response insufficient after 4 weeks, may be increased to max. 30 mg daily in divided doses; max. therapeutic effect normally within 4–8 weeks; discontinue if no improvement after 2–3 months; CHILD not recommended

• Dry mouth and dry eyes in Sjögren’s syndrome, 5 mg 4 times daily (with meals and at bedtime); if tolerated but response insufficient, may be increased to max. 30 mg daily in divided doses; discontinue if no improvement after 2–3 months; CHILD not recommended

Salagen®  (Novartis)  Tablets, f/c, pilocarpine hydrochloride 5 mg. Net price 84-tab pack = £51.43. Label: 21, 27, counselling, driving
13 Skin

13.1 Management of skin conditions

13.1.1 Vehicles

13.1.2 Suitable quantities for prescribing

13.1.3 Excipients and sensitisation

13.2 Emollient and barrier preparations

13.2.1 Emollients

13.2.2 Emollient bath additives

13.2.3 Barrier preparations

13.3 Topical local anaesthetics and antipruritics

13.4 Topical corticosteroids

13.5 Preparations for eczema and psoriasis

13.5.1 Preparations for eczema

13.5.2 Preparations for psoriasis

13.5.3 Drugs affecting the immune response

13.6 Acne and rosacea

13.6.1 Topical preparations for acne

13.6.2 Oral preparations for acne

13.7 Preparations for warts and calluses

13.8 Sunscreens and camouflage

13.8.1 Sunscreen preparations

13.8.2 Camouflage

13.9 Shampoos and other preparations for scalp and hair conditions

13.10 Anti-infective skin preparations

13.10.1 Antibacterial preparations

13.10.1.1 Antibacterial preparations only used topically

13.10.2 Antibacterial preparations also used systemically

13.10.3 Antifungal preparations

13.10.4 Antiviral preparations

13.10.5 Preparations for minor cuts and abrasions

13.11 Skin cleansers and antiseptics

13.11.1 Alcohols and saline

13.11.2 Chlorhexidine salts

13.11.3 Cationic surfactants and soaps

13.11.4 Iodine

13.11.5 Phenolics

13.11.6 Oxidisers and dyes

13.11.7 Preparations for promotion of wound healing

13.12 Antiperspirants

13.13 Topical circulatory preparations

This chapter also includes advice on the drug management of the following:
- candidiasis, p. 650
- crab lice, p. 654
- dermatophytoses, p. 649
- head lice, p. 653
- hirsutism, p. 646
- nappy rash, p. 620
- photodamage, p. 645
- pityriasis versicolor, p. 650
- scabies, p. 653

For further information on wound management products and elastic hosiery see Appendix 8, p. 883

The British Association of Dermatologists list of preferred unlicensed dermatological preparations (specials) is available at http://88.208.244.6/BAD/site/495/default.aspx

13.1 Management of skin conditions

13.11 Vehicles

Both vehicle and active ingredients are important in the treatment of skin conditions; the vehicle alone may have more than a mere placebo effect. The vehicle affects the degree of hydration of the skin, has a mild anti-inflammatory effect, and aids the penetration of active drug.

Applications are usually viscous solutions, emulsions, or suspensions for application to the skin (including the scalp) or nails.

Collodions are painted on the skin and allowed to dry to leave a flexible film over the site of application.

Creams are emulsions of oil and water and are generally well absorbed into the skin. They may contain an antimicrobial preservative unless the active ingredient or basis is intrinsically bactericidal and fungicidal. Generally, creams are cosmetically more acceptable than ointments because they are less greasy and easier to apply.
Gels consist of active ingredients in suitable hydrophilic or hydrophobic bases; they generally have a high water content. Gels are particularly suitable for application to the face and scalp.

Lotions have a cooling effect and may be preferred to ointments or creams for application over a hairy area. Lotions in alcoholic basis can sting if used on broken skin. Shake lotions (such as calamine lotion) contain insoluble powders which leave a deposit on the skin surface.

Ointments are greasy preparations which are normally anhydrous and insoluble in water, and are more occlusive than creams. They are particularly suitable for chronic, dry lesions. The most commonly used ointment bases consist of soft paraffin or a combination of soft, liquid and hard paraffin. Some ointment bases have both hydrophilic and lipophilic properties; they may have occlusive properties on the skin surface, encourage hydration, and also be miscible with water; they often have a mild anti-inflammatory effect. Water-soluble ointments contain macrogols which are freely soluble in water and are therefore readily washed off; they have a limited but useful role where ready removal is desirable.

Dusting powders are used only rarely. They reduce friction between opposing skin surfaces. Dusting powders should not be applied to moist areas because they can cake and abrade the skin. Talc is a lubricant but it does not absorb moisture; it can cause respiratory irritation. Starch is less lubricant but absorbs water.

Dilution The BP directs that creams and ointments should not normally be diluted but that should dilution be necessary care should be taken, in particular, to prevent microbial contamination. The appropriate diluent should be used and heating should be avoided during mixing; excessive dilution may affect the stability of some creams. Diluted creams should normally be used within 2 weeks of preparation.

13.1.2 Suitable quantities for prescribing

<table>
<thead>
<tr>
<th>Suitable quantities of dermatological preparations to be prescribed for specific areas of the body</th>
<th>Creams and Ointments</th>
<th>Lotions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>15–30 g</td>
<td>100 mL</td>
</tr>
<tr>
<td>Both hands</td>
<td>25–50 g</td>
<td>200 mL</td>
</tr>
<tr>
<td>Scalp</td>
<td>50–100 g</td>
<td>200 mL</td>
</tr>
<tr>
<td>Both arms or both legs</td>
<td>100–200 g</td>
<td>200 mL</td>
</tr>
<tr>
<td>Trunk</td>
<td>400 g</td>
<td>500 mL</td>
</tr>
<tr>
<td>Groins and genitalia</td>
<td>15–25 g</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for an adult for twice daily application for 1 week. The recommendations do not apply to corticosteroid preparations—for suitable quantities of corticosteroid preparations see section 13.4.

13.1.3 Excipients and sensitisation

Excipients in topical products rarely cause problems. If a patch test indicates allergy to an excipient, products containing the substance should be avoided (see also Anaphylaxis, p. 173). The following excipients in topical preparations are rarely associated with sensitisation; the presence of these excipients is indicated in the entries for topical products. See also Excipients under General Guidance, p. 2.

13.2 Emollient and barrier preparations

13.2.1 Emollients

Emollients soothe, smooth and hydrate the skin and are indicated for all dry or scaling disorders. Their effects are short-lived and they should be applied frequently even after improvement occurs. They are useful in dry and eczematous disorders, and to a lesser extent in psoriasis (section 13.5.2). Light emollients such as aqueous cream are suitable for many patients with dry skin but a wide range of more greasy preparations, including white soft paraffin, emulsifying ointment, and liquid and white soft paraffin ointment, are available; the severity of the condition, patient preference

1. Purified versions of wool fat have reduced the problem
Flammable

Preparations such as aqueous cream and emulsifying ointment can be used as soap substitutes for hand washing and in the bath; the preparation is rubbed on the skin before rinsing off completely. The addition of a bath oil (section 13.2.1) may also be helpful.

Preparations containing an antibacterial (section 13.10) should be avoided unless infection is present or is a frequent complication.

Urea is a hydrating agent used in the treatment of dry, scaling conditions (including ichthyosis) and may be useful in elderly patients. It is occasionally used with other topical agents such as corticosteroids to enhance penetration of the skin.

Non-proprietary emollient preparations

Aqueous Cream, BP
Cream, emulsifying ointment 30%, 1 phenoxyethanol 1% in freshly boiled and cooled purified water, net price 500 g = £1.68
Excipients include cetostearyl alcohol
1. The BP permits use of alternative antimicrobials provided their identity and concentration are stated on the label

Emulsifying Ointment, BP
Ointment, emulsifying wax 30%, white soft paraffin 50%, liquid paraffin 20%, net price 500 g = £2.10
Excipients include cetostearyl alcohol

Hydrous Ointment, BP
Ointment, (oily cream), dried magnesium sulphate 0.5%, phenoxyethanol 1%, wool alcohols ointment 50%, in freshly boiled and cooled purified water, net price 500 g = £2.12

Liquid and White Soft Paraffin Ointment, NPF
Ointment, liquid paraffin 50%, white soft paraffin 50%, net price 500 g = £3.94

Paraffin, White Soft, BP
White petroleum jelly, net price 100 g = 48p

Paraffin, Yellow Soft, BP
Yellow petroleum jelly, net price 100 g = 34p

Proprietary emollient preparations

Avene® (RJL)
Cream, colloidal oatmeal in emollient basis, net price 100 mL = £3.78; 300-mL pump pack = £6.80
Excipients include benzy! alcohol, cetyl alcohol, isopropyl palmitate
ACBS: For endogenous and exogenous eczema, xeroderma, ichthyosis, and senile pruritus (pruritus of the elderly) associated with dry skin

Cetabren® (Genus)
Emollient cream, white soft paraffin 13.2%, light liquid paraffin 10.5%, net price 50-g pump pack = £1.17; 150-g pump pack = £2.88; 500-g pump pack = £5.61, 1.05-kg pump pack = £11.11
Excipients include benzy! alcohol, cetyl alcohol, isopropyl palmitate
ACBS: as for Avene Cream

Dermamist® (Alliance)
Spray application, white soft paraffin 10% in a basis containing liquid paraffin, fractionated coconut oil, net price 250-mL pressurised aerosol unit = £9.22
Excipients none as listed in section 13.1.3
For dry skin conditions including eczema, ichthyosis, pruritus of the elderly
Note Flammable

Diprobase® (Schering-Plough)
Cream, cetomacrogol 2.25%, cetostearyl alcohol 7.2%, liquid paraffin 6%, white soft paraffin 15%, water-miscible basis used for Diprosone® cream, net price 50 g = £1.34; 500-g pump pack = £6.76
Excipients include cetostearyl alcohol, chlorocresol
For dry skin conditions

Ointment, liquid paraffin 5%, white soft paraffin 95%, basis used for Diprosone® ointment, net price 50 g = £1.34
Excipients none as listed in section 13.1.3
For dry skin conditions

Doublebase® (Dermal)
Gel, isopropyl myristate 15%, liquid paraffin 15%, net price 100 g = £2.77, 500 g = £6.09
Excipients none as listed in section 13.1.3
For dry chapped or itchy skin conditions

Emollient shower gel, isopropyl myristate 15%, liquid paraffin 15%, net price 200 g = £5.45
Excipients none as listed in section 13.1.3
For dry and chapped skin conditions

E45® (Crookes)
Cream, light liquid paraffin 12.6%, white soft paraffin 14.5%, hypoallergenic anhydrous wool fat (hypoallergenic lanolin) 1% in self-emulsifying monostearin, net price 50 g = £1.40, 125 g = £2.55, 350 g = £4.46, 500-g pump pack = £6.20
Excipients include cetyl alcohol, hydroxybenzenes (parabens)
For dry skin conditions

Emollient Wash Cream, soap substitute, zinc oxide 5% in an emollient basis, net price 250-mL pump pack = £3.19
Excipients none as listed in section 13.1.3
ACBS: For endogenous and exogenous eczema, xeroderma, ichthyosis and senile pruritus (pruritus of the elderly) associated with dry skin

Lotion, light liquid paraffin 4%, cetomacrogol, white soft paraffin 10%, hypoallergenic anhydrous wool fat
Emollients

Spray:
- QV Oilatum
- Linola
- Hydromol
- Hewletts
- Epaderm

For dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus, use as an emollient or soap substitute.

Epaderm® (Medlock): Ointment, emulsifying wax 30%, yellow soft paraffin 30%, liquid paraffin 40%, net price 125 g = £3.62, 500 g = £6.14, 1 kg = £11.44

For use as an emollient or soap substitute.

Hewletts® (Kestrel):
- Cream, hydrous wool fat 4%, zinc oxide 8%, arachis (peanut) oil, oleic acid, white soft paraffin, net price 35 g = £1.43, 400 g = £6.69

For use as an emollient or soap substitute.

Hydromol® (Alliance):
- Cream, sodium pidolate 2.5%, liquid paraffin 13.8%, net price 50 g = £2.04, 100 g = £3.80, 500 g = £12.60

For dry skin conditions.

Linola® Gamma (Lindera)
- Cream, evening primrose oil 20%, net price 50 g = £2.83, 250 g = £8.20

Cautions: epilepsy (but hazard unlikely with topical preparations).

For dry skin conditions.

Lipobase® (Astellas)
- Cream, fatty cream basis used for Locoid Lipocream®, net price 50 g = £2.08

Excipients include cetostearyl alcohol, alcohol, hydroxybenzoates (parabens).

For dry skin conditions, also for use during treatment with topical corticosteroids as a diluent for Locoid Lipocream.

Oilatum® (Stiefel)
- Cream, liquid paraffin 6%, white soft paraffin 15%, net price 40 g = £1.79, 150 g = £3.38, 500 mL pump pack = £6.35, 1.05-litre pump pack = £14.67

Excipients include cetostearyl alcohol, alcohol, hydroxybenzoates (parabens).

For dry skin conditions, for use during treatment with topical corticosteroids as a diluent for Locoid Lipocream.

QV® (Crawford)
- Cream, glycerol 10%, light liquid paraffin 10%, white soft paraffin 5%, net price 100 g = £1.95, 500 g = £5.60

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens).

For dry skin conditions including eczema, psoriasis, ichthyosis, pruritus.

Wash, glycerol 10%, net price 200 mL = £2.50

Excipients include hydroxybenzoates (parabens).

For dry skin conditions including eczema, psoriasis, ichthyosis, and pruritus, use as a soap substitute.

Ultrabase® (Valeant)
- Cream, water-miscible, containing liquid paraffin and white soft paraffin, net price 50 g = £8.90, 500-g pump pack = £6.44

Excipients include fragrance, alcohol, hydroxybenzoates (parabens), disodium edetate, alcohol.

For dry skin conditions.

Unguentum M® (Almirall)
- Cream, containing saturated neutral oil, liquid paraffin, white soft paraffin, net price 50 g = £1.41, 100 g = £2.78, 200-mL pump pack = £5.50, 500-g pump pack = £8.48

Excipients include cetostearyl alcohol, alcohol, propylene glycol, paraffin wax.

For dry skin conditions and nappy rash.

Zerobase® (Zeroderm)
- Cream, liquid paraffin 11%, net price 500-g pump pack = £5.89

Excipients include cetostearyl alcohol, cholesterol.

For dry skin conditions.

Preparations containing urea

Aquadrate® (Alliance)
- Cream, urea 10%, net price 30 g = £1.37, 100 g = £3.64

Excipients none as listed in section 13.1.3

Dose for dry, scaling and itching skin, apply thinly and rub into area when required.

Balneum® Plus (Almirall)
- Cream, urea 5%, laurmacrogols 3%, net price 100 g = £3.29, 175-g pump pack = £8.33, 500-g pump pack = £17.09

Excipients include benzy alcohol, polyols and polysorbates.

Dose for dry, scaling and itching skin, apply twice daily.

Calmurd® (Galderma)
- Cream, urea 10%, lactic acid 5%, net price 100 g = £7.36, 500-g pump pack = £28.37

Excipients none as listed in section 13.1.3

Dose for dry, scaling and itching skin, apply a thick layer for 3–5 minutes, massage into area, and remove excess, usually twice daily. Use half-strength cream for 1 week if stinging occurs.

Note: Can be diluted with aqueous cream (life of diluted cream 14 days).

E45® Itch Relief Cream (Crookes)
- Cream, urea 5%, macrogol lauryl ether 3%, net price 50 g = £2.55, 100 g = £3.47, 500-g pump pack = £17.09

Excipients include benzy alcohol, polyols and polysorbates.

Dose for dry, scaling and itching skin, apply twice a day.

Eucerin® Intensive (Beiersdorf)
- Cream, urea 10%, net price 100 mL = £7.59

Excipients include benzy alcohol, propyl palmitate, wool fat.

Dose for dry skin conditions including eczema, ichthyosis, xeroderma, hyperkeratosis, apply thinly and rub into area twice daily.

Lotion, urea 10%, net price 250 mL = £7.93

Excipients include benzy alcohol, propyl palmitate.

Dose for dry skin conditions including eczema, ichthyosis, xeroderma, hyperkeratosis, apply sparingly and rub into area twice daily.

Nutraplus® (Galderma)
- Cream, urea 10%, net price 100 g = £4.37

Excipients include hydroxybenzoates (parabens), alcohol.

Dose for dry, scaling and itching skin, apply 2–3 times daily.

With antimicrobials

Dermol® (Dermal)
- Cream, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, isopropyl myristate 10%, liquid.
paraffin 10%, net price 100-g tube = £3.22, 500-g pump pack = £7.45
Exipients include ceteareth alcohol
Dose for dry and pruritic skin conditions including eczema and dermatitis, apply to skin or use as soap substitute

Dermol® 500 Lotion, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, liquid paraffin 2.5%, isopropyl myristate 2.5%, net price 500-mL pump pack = £6.31
Exipients include ceteareth alcohol
Dose for dry and pruritic skin conditions including eczema and dermatitis, apply to skin or use as soap substitute

Dermol® 200 Shower Emollient, benzalkonium chloride 0.1%, chlorhexidine hydrochloride 0.1%, liquid paraffin 2.5%, isopropyl myristate 2.5%, net price 200 mL = £3.71
Exipients include ceteareth alcohol
Dose for dry and pruritic skin conditions including eczema and dermatitis, apply to skin or use as soap substitute

13.2.1 Emollient bath additives

Emollient bath additives should be added to bath water; hydration can be improved by soaking in the bath for 10–20 minutes. Some bath emollients can be applied to the skin or used as a soap substitute. The quantities of bath additives recommended for adults are suitable for an adult-size bath. Proportionately less should be used for a child-size bath (INFANT 10 mL), do not use undiluted

These preparations make skin and surfaces slippery—particular care is needed when bathing

Alpha Keri Bath® (Novartis Consumer Health)
Bath oil, liquid paraffin 91.7%, oil-soluble fraction of wool fat 3%, net price 240 mL = £3.45, 480 mL = £6.43
Exipients include fragrance
Dose for dry skin conditions including ichthyosis and pruritus of the elderly, add 10–20 mL/bath (INFANT 5 mL) or apply to wet skin and rinse

Aveeno® (J&J)
Aveeno® Bath oil, colloidal oatmeal, white oat fraction in emollient basis, net price 250 mL = £4.28
Exipients include beeswax, fragrance
Dose for dry skin conditions including ichthyosis and pruritus of the elderly, add 20–30 mL/bath or apply to wet skin and rinse

Aveeno Colloidal® Bath additive, oatmeal, white oat fraction in emollient basis, net price 10 × 50-g sachets = £7.33, Baby Bath Additive, 10 × 15-g sachets = £4.39
Exipients none as listed in section 13.1.3
Dose ACBS: as for Aveeno Bath oil, add 50 g/bath (INFANT and CHILD under 12 years, 15 g)

Balneum® (Almirall)
Balneum® bath oil, soya oil 84.75%, net price 200 mL = £2.48, 500 mL = £5.38, 1 litre = £10.39
Exipients include butylated hydroxytoluene, propylene glycol, fragrance
Dose for dry skin conditions including those associated with dermatitis and eczema, add 20–60 mL/bath (INFANT 5–15 mL), do not use undiluted

Balneum Plus® bath oil, soya oil 82.95%, mixed lauramidocrocols 15%, net price 500 mL = £6.66
Exipients include butylated hydroxytoluene, propylene glycol, fragrance
Dose for dry skin conditions including those associated with dermatitis and eczema where pruritus also experienced, add 20 mL/bath (INFANT 5 mL) or apply to wet skin and rinse

Cetran® (Genus)
Emollient bath additive, light liquid paraffin 82.8%, net price 500 mL = £5.25
Dose for dry skin conditions, including eczema, add 1–2 capfuls/bath (CHILD ½–1 capful) or apply to wet skin and rinse

Dermal® (Dermal)
Bath emollient, acetylated wool alcohols 5%, liquid paraffin 65%, net price 500 mL = £3.60
Exipients none as listed in section 13.1.3
Dose for dermatitis, dry skin conditions including ichthyosis and pruritus of the elderly, add 15–20 mL/bath (INFANT and CHILD 5–10 mL) or apply to wet skin and rinse

Diprobase® (Schering-Plough)
Bath additive, isopropyl myristate 39%, light liquid paraffin 46%, net price 500 mL = £6.97
Exipients none as listed in section 13.1.3
Dose for dry skin conditions including dermatitis and eczema; add 25–50 mL/bath (INFANT 10 mL), do not use undiluted

Doublebase® (Dermal)
Emollient bath additive, liquid paraffin 65%, net price 500 mL = £5.70
Exipients include ceteareth alcohol
Dose for dry skin conditions including dermatitis, ichthyosis, and pruritus of the elderly; add 15–20 mL/bath (INFANT and CHILD 5–10 mL)

E45® (Crookes)
Emollient bath oil, cetyl dimethicone 5%, light liquid paraffin 91%, net price 250 mL = £3.19, 500 mL = £5.11
Exipients none as listed in section 13.1.3
Dose ACBS: for endogenous and exogenous eczema, xeroderma, ichthyosis, and senile pruritus (pruritus of the elderly) associated with dry skin; add 15 mL/bath (CHILD 5–10 mL) or apply to wet skin and rinse

Hydromol® (Alliance)
Bath and Shower Emollient, isopropyl myristate 13%, light liquid paraffin 37.8%, net price 350 mL = £3.80, 500 mL = £5.14, 1 litre = £9.00
Exipients none as listed in section 13.1.3
Dose for dry skin conditions including eczema, ichthyosis and pruritus of the elderly; add 1–3 capfuls/bath (INFANT ½–2 capfuls) or apply to wet skin and rinse

Imuderm® (Goldshield)
Bath oil, almond oil 30%, light liquid paraffin 69.6%, net price 250 mL = £3.75
Exipients include butylated hydroxyanisole
Dose for dry skin conditions including dermatitis, eczema, pruritus of the elderly, and ichthyosis, add 15–30 mL/bath (INFANT and CHILD 7.5–15 mL) or rub into dry skin until absorbed

Oilatum® (Stiefel)
Emollient bath additive (emulsion), acetylated wool alcohols 5%, liquid paraffin 63.4%, net price 250 mL = £2.75, 500 mL = £4.57
Exipients include isopropyl palmitate, fragrance
Dose for dry skin conditions including dermatitis, pruritus of the elderly and ichthyosis; add 1–3 capfuls/bath (INFANT 0.5–2 capfuls) or apply to wet skin and rinse

Junior Emollient bath additive, light liquid paraffin 63.4%, net price 150 mL = £2.82, 250 mL = £3.25, 300 mL = £5.10, 500 mL = £5.75
Exipients include wool fat, isopropyl palmitate
Dose for dry skin conditions including dermatitis, pruritus of the elderly and ichthyosis; add 1–3 capfuls/bath (INFANT 0.5–2 capfuls) or apply to wet skin and rinse

QV® (Crawford)
Bath oil, light liquid paraffin 85.09%, net price 200 mL = £2.20, 500 mL = £4.50
Exipients include hydroxybenzenes (parabens)
Dose for dry skin conditions including eczema, ichthyosis, and pruritus of the elderly, add 10 mL/bath (CHILD 7 mL, INFANT 4 mL) or apply to wet skin and rinse
13.2.2 Barrier preparations

Barrier preparations often contain water-repellent substances such as dimeticone (dimethicone) or other silicones. They are used on the skin around stomas, bedsores, and pressure areas in the elderly where the skin is intact. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. They are not a substitute for adequate nursing care and it is doubtful if they are any more effective than barrier preparations, which are usually a topical treatment of eczema and ichthyosis.

Nappy rash
Barrier creams and ointments are used for protection against nappy rash which is usually a local dermatitis. The first line of treatment is to ensure that nappies are changed frequently and that tightly fitting nappies and waterproof pants are avoided. The rash may clear when left exposed to the air and a barrier preparation can be applied. If the rash is associated with a fungal infection, an antifungal cream such as clotrimazole (section 13.10) is useful. A mild corticosteroid such as hydrocortisone 1% is useful in moderate to severe inflammation.

Proprietary barrier preparations

**Conotrane** (Astellas)
Cream, benzalkonium chloride 0.1%, dimeticone ‘350’ 22%, net price 100 g = 74p, 200 g = £3.51 Excipients include cetostearyl alcohol, fragrance. For nappy and urinary rash and pressure sores

**Drapolene** (Chefarco UK)
Cream, benzalkonium chloride 0.01%, cetrimide 0.2% in a basis containing white soft paraffin, cetyl alcohol and wool fat, net price 100 g = £1.54, 200 g = £2.50, 350 g = £3.75 Excipients include cetyl alcohol, chlororessol, wool fat. For nappy and urinary rash; minor wounds

**Metanium** (Ransom)
Ointment, titanium dioxide 20%, titanium peroxide 5%, titanium salicylate 3% in a basis containing dimeticone, light liquid paraffin, white soft paraffin, and benzoin tincture, net price 30 g = £2.01 Excipients none as listed in section 13.1.3 For nappy rash

**Morhulin** (Actavis)
Ointment, cod-liver oil 11.4%, zinc oxide 38%, in a basis containing liquid paraffin and yellow soft paraffin, net price 50 g = £1.72 Excipients include wool fat derivative. For minor wounds, varicose ulcers, pressure sores, eczema and nappy rash

**Siope1** (Centrapharm)
Barrier cream, dimeticone ‘1000’ 10%, cetrimide 0.3%, arachis (peanut) oil, net price 50 g = £2.15 Excipients include butylated hydroxytoluene, cetostearyl alcohol, hydroxybenzoates (parabens). For protection against water-soluble irritants

**Sprilon** (Ayrton Saunders)
Spray application, dimeticone 1.04%, zinc oxide 12.5%, in a basis containing wool alcohols, cetostearyl alcohol, dextran, white soft paraffin, liquid paraffin, propellants, net price 115-g pressurised aerosol unit = £3.54 Excipients include cetostearyl alcohol, hydroxybenzoates (parabens), wool fat. For urinary rash, pressure sores, leg ulcers, moist eczema, fissures, fistulae and ileostomy care.

Note: Flammable
13.3 Topical local anaesthetics and antipruritics

Pruritus may be caused by systemic disease (such as drug hypersensitivity, obstructive jaundice, endocrine disease, and certain malignant diseases), skin disease (e.g. psoriasis, eczema, urticaria, and scabies) or as a side-effect of opioid analgesics. Where possible the underlying causes should be treated. An emollient (section 13.2.1) may be of value where the pruritus is associated with dry skin. Pruritus that occurs in otherwise healthy elderly people can also be treated with an emollient. For advice on the treatment of pruritus in palliative care, see p. 17.

Preparations containing crotamiton are sometimes used but are of uncertain value. Preparations containing calamine are often ineffective.

A topical preparation containing doxepin 5% is licensed for the relief of pruritus in eczema; it can cause drowsiness and there may be a risk of sensitisation.

Pruritus is common in biliary obstruction, especially in primary biliary cirrhosis and drug-induced cholestasis. Oral administration of colestyramine (cholestyramine) is the treatment of choice (section 1.9.2).

Topical antihistamines and local anaesthetics are only marginally effective and occasionally cause sensitisation. For insect stings and insect bites, a short course of a topical corticosteroid is appropriate. Short-term treatment with a sedating antihistamine (section 3.4.1) may help in insect stings and in intractable pruritus where sedation is desirable. Calamine preparations are of little value for the treatment of insect stings or bites.

For preparations used in pruritus ani, see section 1.7.1.

**CALAMINE**

**Indications** pruritus

Calamine (Non-proprietary)

Aqueous cream, calamine 4%, zinc oxide 3%, liquid paraffin 20%, self-emulsifying glyceryl monostearate 5%, cetomacrogol emulsifying wax 5%, phenoxethanol 0.5%, freshly boiled and cooled purified water 62.5%, net price 100 mL = 59p

Lotion (= cutaneous suspension), calamine 15%, zinc oxide 5%, glycerol 5%, bentonite 3%, sodium citrate 0.5%, liquefied petrolatum 0.5%, in freshly boiled and cooled purified water, net price 200 mL = 63p

**DOXEPIN HYDROCHLORIDE**

**Indications** pruritus in eczema; depressive illness (section 4.3.1)

**Cautions** susceptibility to angle-closure glaucoma, urinary retention, severe liver impairment, mania; avoid application to large areas; pregnancy and breast-feeding; **interactions**: Appendix 1 (antidepressants, tricyclic)

**Driving** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Side-effects** drowsiness; local burning, stinging, irritation, tingling and rash; systemic side-effects such as antimuscarinic effects, headache, fever, dizziness, gastro-intestinal disturbances also reported

**Dose**

- ADULT and CHILD over 12 years, apply thinly 3–4 times daily; usual max. 3 g per application; usual total max. 12 g daily; coverage should be less than 10% of body surface area

Xepin® (CHS) (FR)

**Cream**, doxepin hydrochloride 5%, net price 30 g = £11.70. Label: 2, 10, patient information leaflet

**Excipients** include benzyl alcohol

**TOPICAL LOCAL ANAESTHETICS**

**Indications** relief of local pain, see notes above. See section 15.2 for use in surface anaesthesia

**Cautions** occasionally cause hypersensitivity

**Note** Topical local anaesthetic preparations may be absorbed, especially through mucosal surfaces; therefore excessive application should be avoided and they should preferably not be used for more than about 3 days; not generally suitable for young children

**TOPICAL ANTIHISTAMINES**

**Indications** see notes above

**Cautions** may cause hypersensitivity; avoid in eczema; photosensitivity (diphenhydramine); not recommended for longer than 3 days
13.4 Topical corticosteroids

Topical corticosteroids are used for the treatment of inflammatory conditions of the skin (other than those arising from an infection), in particular eczema (section 13.5.1), contact dermatitis, insect stings (p. 36), and eczema of scabies (section 13.10.4). Corticosteroids suppress the inflammatory reaction during use; they are not curative and on discontinuation a rebound exacerbation of the condition may occur. They are generally used to relieve symptoms and suppress signs of the disorder when other measures such as emollients are ineffective.

Topical corticosteroids are of no value in the treatment of urticaria and they are contra-indicated in rosacea; they may worsen ulcerated or secondarily infected lesions. They should not be used indiscriminately in pruritus (where they will only benefit if inflammation is causing the itch) and are not recommended for acne vulgaris.

Systemic or potent topical corticosteroids should be avoided or given only under specialist supervision in psoriasis because, although they may suppress the psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal (sometimes precipitating severe pustular psoriasis). Topical use of potent corticosteroids on widespread psoriasis can lead to systemic as well as to local side-effects. It is reasonable, however, to prescribe a mild to moderate topical corticosteroid for a short period (2–4 weeks) for flexural and facial psoriasis and to use a more potent corticosteroid such as betamethasone or fluorocinonide for psoriasis of the scalp, palms, or soles (see below for cautions in psoriasis).

In general, the most potent topical corticosteroids should be reserved for recalcitrant dermatoses such as chronic discoid lupus erythematosus, lichen simplex chronicus, hypertrophic lichen planus, and palmoplantar pustulosis. Potent corticosteroids should generally be avoided on the face and skin flexures, but specialists occasionally prescribe them for use in these areas in certain circumstances.

When topical treatment has failed, intralesional corticosteroid injections (section 10.1.2.2) may be used. These are more effective than the very potent topical corticosteroid preparations and should be reserved for severe cases where there are localised lesions such as keloid scars, hypertrophic lichen planus, or localised alopecia areata.

Perioral lesions Hydrocortisone cream 1% can be used for up to 7 days to treat uninfected inflammatory lesions on the lips and on the skin surrounding the mouth. Hydrocortisone and miconazole cream or ointment is useful where infection by susceptible organisms and inflammation co-exist, particularly for initial treatment (up to 7 days) e.g. in angular cheilitis (see also p. 610). Organisms susceptible to miconazole include Candida spp. and many Gram-positive bacteria including streptococci and staphylococci.

Children Children, especially infants, are particularly susceptible to side-effects. However, concern about the safety of topical corticosteroids in children should not result in the child being undertreated. The aim is to control the condition as well as possible; inadequate treatment will perpetuate the condition. A mild corticosteroid such as hydrocortisone 1% ointment or cream is useful for treating nappy rash (section 13.2.2) and for atopic eczema in childhood (section 13.5.1). A moderately potent or potent corticosteroid may be appropriate for severe atopic eczema on the limbs, for 1–2 weeks only, switching to a less potent preparation as the condition improves. In an acute flare-up of atopic eczema, it may be appropriate to use more potent formulations of topical corticosteroids for a short period to regain control of the condition. A very potent corticosteroid should be initiated under the supervision of a specialist. Continuous daily application of a mild corticosteroid such as hydrocortisone 1% is equivalent to a potent corticosteroid such as betamethasone 0.1% applied intermittently. Carers of young children should be advised that treatment should not necessarily be reserved to ‘treat only the worst areas’ and they may need to be advised that patient information leaflets may contain inappropriate advice for the patient’s condition.

Choice of formulation Water-miscible corticosteroid creams are suitable for moist or weeping lesions whereas ointments are generally chosen for dry, lichenified or scaly lesions or where a more occlusive effect is required. Lotions may be useful when minimal application to a large or hair-bearing area is required or for the treatment of exudative lesions. Occlusive polyethylene or hydrocolloid dressings increase absorption, but also increase the risk of side-effects: they are therefore used only under supervision on a short-term basis for areas of very thick skin (such as the palms and soles). The inclusion of urea or salicylic acid also increases the penetration of the corticosteroid.

In the BNF topical corticosteroids for the skin are categorised as ‘mild’, ‘moderately potent’, ‘potent’ or ‘very potent’ (see p. 623); the least potent preparation which is effective should be chosen but dilution should be avoided whenever possible.

Cautions Avoid prolonged use of a topical corticosteroid on the face (and keep away from eyes). In children avoid prolonged use and use potent or very potent corticosteroids under specialist supervision; extreme caution is required in dermatoses of infancy including nappy rash—treatment should be limited to 5–7 days.

Psoriasis The use of potent or very potent corticosteroids in psoriasis can result in rebound relapse, development of generalised pustular psoriasis, and local and systemic toxicity.

Contra-indications Topical corticosteroids are contra-indicated in untreated bacterial, fungal, or viral skin lesions, in rosacea, and in perioral dermatitis; potent corticosteroids are contra-indicated in widespread plaque psoriasis (see notes above).

Side-effects Mild and moderately potent topical corticosteroids are associated with few side-effects but care is required in the use of potent and very potent corticosteroids. Absorption through the skin can rarely cause adrenal suppression and even Cushing’s syndrome (section 6.3.2), depending on the area of the body being treated and the duration of treatment. Absorption is greatest where the skin is thin or raw, and from inter-
triginous areas; it is increased by occlusion. Local side-effects include:

- spread and worsening of untreated infection;
- thinning of the skin which may be restored over a period after stopping treatment but the original structure may never return;
- irreversible striae atrophicae and telangiectasia;
- contact dermatitis;
- acne, or worsening of acne or rosacea;
- mild depigmentation which may be reversible;
- hypertrichosis also reported.

In order to minimise the side-effects of a topical corticosteroid, it is important to apply it thinly to affected areas only, no more frequently than twice daily, and to use the least potent formulation which is fully effective.

Application Topical corticosteroid preparations should be applied no more frequently than twice daily; once daily is often sufficient. Topical corticosteroids are spread thinly on the skin; the length of cream or ointment expelled from a tube may be used to specify the quantity to be applied to a given area of skin. This length can be measured in terms of a fingertip unit (the distance from the tip of the adult index finger to the first crease). One fingertip unit (approximately 500 mg) is sufficient to cover an area that is twice that of the flat adult palm.

Suitable quantities of corticosteroid preparations to be prescribed for specific areas of the body

<table>
<thead>
<tr>
<th>Creams and Ointments</th>
<th>Face and neck</th>
<th>15 to 30 g</th>
<th>Both hands</th>
<th>15 to 30 g</th>
<th>Scalp</th>
<th>15 to 30 g</th>
<th>Both arms</th>
<th>30 to 60 g</th>
<th>Both legs</th>
<th>100 g</th>
<th>Trunk</th>
<th>100 g</th>
<th>Groins and genitalia</th>
<th>15 to 30 g</th>
</tr>
</thead>
</table>

These amounts are usually suitable for an adult for a single daily application for 2 weeks

If a patient is using topical corticosteroids of different potencies, the patient should be told when to use each corticosteroid. The potency of each topical corticosteroid (see Topical Corticosteroid Preparation Potencies, below) should be included on the label with the directions for use. The label should be attached to the container (for example, the tube) rather than the outer packaging.

Mixing topical preparations on the skin should be avoided where possible; several minutes should elapse between application of different preparations. The practice of using an emollient immediately before a topical corticosteroid is inappropriate.

Compound preparations The advantages of including other substances (such as antibacterials or antifungals) with corticosteroids in topical preparations are uncertain, but such combinations may have a place where inflammatory skin conditions are associated with bacterial or fungal infection, such as infected eczema. In these cases the antimicrobial drug should be chosen according to the sensitivity of the infecting organism and used regularly for a short period (typically twice daily for 1 week). Longer use increases the likelihood of resistance and of sensitisation.

13.4 Topical corticosteroids

Topical corticosteroid preparation potencies

Potency of a topical corticosteroid preparation is a result of the formulation as well as the corticosteroid. Therefore, proprietary names are shown below.

Mild

- Hydrocortisone 0.1–2.5%, Dioderm, Mildison, Synalar 1 in 10 dilution
- Mild with antimicrobials: Canesten HC, Daktacort, Econacort, Econase, Nystaform-HC, Timodine, Vioform-Hydrocortisone
- Mild with crotamiton: Eurax-Hydrocortisone

Moderate

- Betnovate-RD, Eumovate, Haelan, Modrasone, Synalar 1 in 4 Dilution, Ultralanum Plain
- Moderate with antimicrobials: Trimovate
- Moderate with urea: Alphaderm, Calmurid HC

Potent

- Betamethasone valerate 0.1%, Betacap, Bettamousse, Betnovate, Cutivate, Diprosone, Elocon, Hydrocortisone butyrate, Locoid, Locoid Crelo, Metosyn, Nerison, Synalar
- Potent with antimicrobials: Aureocort, Betnovate-C, Betnovate-N, Fucibet, Lotriderm, Synalar C, Synalar N
- Potent with salicylic acid: Diproasalic

Very potent

- Clarelux, Dermovate, Etrivex, Nerison Forte

HYDROCORTISONE

Indications mild inflammatory skin disorders such as eczemas (but for over-the-counter preparations, see below); nappy rash, see notes above and section 13.2.2

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose

- Apply thinly 1–2 times daily

Hydrocortisone (Non-proprietary) 22

Cream, hydrocortisone 0.5%, net price, 15 g = £3.04, 30 g = £5.19, 1%, 15 g = £2.70, 30 g = £3.65, 50 g = £16.96, 2.5%, 15 g = £24.03. Label: 28, counselling, application, see above. Potency: mild

Dental prescribing on NHS Hydrocortisone Cream 1% 15 g may be prescribed

Ointment, hydrocortisone 0.5%, net price 15 g = £3.57, 30 g = £5.23; 1%, 15 g = £2.55, 30 g = £3.55, 50 g = £25.22; 2.5%, 15 g = £32.53. Label: 28, counselling, application, see above. Potency: mild

When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied.
Over-the-counter hydrocortisone preparations
Skin creams and ointments containing hydrocortisone (alone or with other ingredients) can be sold to the public for the treatment of allergic contact dermatitis, irritant dermatitis, insect bite reactions and mild to moderate eczema, to be applied sparingly over the affected area 1–2 times daily for max. 1 week. Over-the-counter hydrocortisone preparations should not be sold without medical advice for children under 10 years or for pregnant women; they should not be sold for application to the face, anogenital region, broken or infected skin (including cold sores, acne, and athlete’s foot).

Proprietary hydrocortisone preparations
Dioderm® (Dermal) 
Cream, hydrocortisone 0.1%, net price 30 g = £2.50. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include cetostearyl alcohol, propylene glycol
Note Although this contains only 0.1% hydrocortisone, the formulation is designed to provide a clinical activity comparable to that of Hydrocortisone Cream 1% BP

Midison® (Astellas)
Lipocream, hydrocortisone 1%, price 30 g = 87p. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Compound preparations
Compound preparations with coal tar see section 13.5.2

Alphaderm® (Alliance)
Cream, hydrocortisone 1%, urea 10%, net price 30 g = £1.98; 100 g = £5.86. Label: 28, counselling, application, see p. 623. Potency: moderate
Excipients none as listed in section 13.1.3

Calmurid HC® (Galderma)
Cream, hydrocortisone 1%, urea 10%, lactic acid 5%, net price 30 g = £2.80, 50 g = £4.67. Label: 28, counselling, application, see p. 623. Potency: moderate
Excipients none as listed in section 13.1.3
Note Manufacturer advises dilute to half-strength with aqueous cream for 1 week if stinging occurs then transfer to undiluted preparation (but see section 13.1.1 for advice to avoid dilution where possible)

Eurax-Hydrocortisone® (Novartis Consumer Health)
Cream, hydrocortisone 0.25%, crotamiton 10%, net price 30 g = £8.7p. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include fragrance, hydroxybenzoates (parabens), propylene glycol, stearyl alcohol
1. A 15-g tube is on sale to the public for the treatment of contact dermatitis and insect bites

With antimicrobials
See notes above for comment on compound preparations

Canesten HC® (Bayer Consumer Care)
Cream, hydrocortisone 1%, clotrimazole 1%, net price 30 g = £2.42. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include benzyl alcohol, cetostearyl alcohol
1. A 15-g tube is on sale to the public for the treatment of athlete’s foot and fungal infection of skin folds with associated inflammation

Daktacort® (Janssen-Cilag)
Cream, hydrocortisone 1%, miconazole nitrate 2%, net price 30 g = £2.08. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include butylated hydroxyanisole, disodium edetate
Note A 15-g tube is on sale to the public for the treatment of athlete’s foot and candidal intertrigo

Ointment, hydrocortisone 1%, miconazole nitrate 2%, net price 30 g = £2.09. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients none as listed in section 13.1.3

Econacort® (Squibb)
Cream, hydrocortisone 1%, econazole nitrate 1%, net price 30 g = £2.25. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include butylated hydroxyanisole

Fucidin H® (LEO)
Cream, hydrocortisone acetate 1%, fusidic acid 2%, net price 30 g = £5.30, 60 g = £10.60. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include butylated hydroxyanisole, hydrocortisone, cetyl alcohol, polysorbate 60, potassium sorbate

Ointment, hydrocortisone acetate 1%, sodium fusidate 2%, net price 30 g = £3.26, 60 g = £6.53. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include cetyl alcohol, wool fat

Nystaform-HC® (Typharm)
Cream, hydrocortisone 0.5%, nystatin 100 000 units/g, chlorhexidine hydrochloride 1%, net price 30 g = £2.66. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include benzyl alcohol, cetostearyl alcohol, polyoxyalkyle 60

Ointment, hydrocortisone 1%, nystatin 100 000 units/g, chlorhexidine acetate 1%, net price 30 g = £2.66. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients none as listed in section 13.1.3

Timodine® (R&C)
Cream, hydrocortisone 0.5%, nystatin 100 000 units/g, benzalkonium chloride solution 0.2%, dimeticone ‘350’ 10%, net price 30 g = £2.38. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include butylated hydroxyanisole, hydrocortisone aluminium, hydroxybenzoates (parabens), sodium metabisulphate, sorbic acid

Vioform-Hydrocortisone® (Novartis Consumer Health)
Cream, hydrocortisone 1%, clioquinol 3%, net price 30 g = £1.46. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients include cetostearyl alcohol

Ointment, hydrocortisone 1%, clioquinol 3%, net price 30 g = £1.46. Label: 28, counselling, application, see p. 623. Potency: mild
Excipients none as listed in section 13.1.3
Note Stains clothing

HYDROCORTISONE BUTYRATE
Indications severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above

HYDROCORTISONE BUTYRATE
Indications severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above
Cautions see notes above
Contra-indications see notes above
Side-effects see notes above
Dose

- Apply thinly 1–2 times daily

Locoid® (Astellas) (Non-proprietary)

Cream, hydrocortisone butyrate 0.1%, net price 30 g = £2.29, 100 g = £7.05. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Lipocream, hydrocortisone butyrate 0.1%, net price 30 g = £2.41, 100 g = £7.38. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, hydroxybenzoates (parabens)

Note For bland cream basis see Lipocide , section 13.2.1

Ointment, hydrocortisone butyrate 0.1%, net price 30 g = £2.29, 100 g = £7.05. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients none as listed in section 13.1.3

Scalp lotion, hydrocortisone butyrate 0.1%, in an aqueous isopropyl alcohol basis, net price 100 mL = £9.76. Label: 15, 28, counselling, application, see p. 623. Potency: potent

Excipients none as listed in section 13.1.3

Locoid Crelo® (Astellas) (Non-proprietary)

Lotion (topical emulsion), hydrocortisone butyrate 0.1% in a water-miscible basis, net price 100 g (with applicator nozzle) = £8.44. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include butylated hydroxytoluene, cetostearyl alcohol, hydroxybenzoates (parabens), propylene glycol

ALCLOMETASONE DIPROPIONATE

Indications inflammatory skin disorders such as eczemas

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Dose

- Apply thinly 1–2 times daily

Modrasone® (PLIVA) (Non-proprietary)

Cream, alclometasone dipropionate 0.05%, net price 50 g = £2.68. Label: 28, counselling, application, see p. 623. Potency: moderate

Excipients include cetostearyl alcohol, chlorocresol, propylene glycol

Ointment, alclometasone dipropionate 0.05%, net price 50 g = £2.68. Label: 28, counselling, application, see p. 623. Potency: moderate

Excipients include beeswax, propylene glycol

BETAMETHASONE ESTERS

Indications severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above

Cautions see notes above; use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression

Contra-indications see notes above

Side-effects see notes above

Dose

- Apply thinly 1–2 times daily

Betamethasone Valerate (Non-proprietary)

Cream, betamethasone (as valerate) 0.1%, net price 30 g = £1.63, 100 g = £4.36. Label: 28, counselling, application, see p. 623. Potency: potent

Ointment, betamethasone (as valerate) 0.1%, net price 30 g = £1.70, 100 g = £4.15. Label: 28, counselling, application, see p. 623. Potency: potent

Betacap® (Dermal) (Non-proprietary)

Scalp application, betamethasone (as valerate) 0.1% in a water-miscible basis containing coconut oil derivative, net price 100 mL = £3.92. Label: 15, 28, counselling, application, see p. 623. Potency: potent

Excipients none as listed in section 13.1.3

Betnovate® (GSK) (Non-proprietary)

Cream, betamethasone (as valerate) 0.1% in a water-miscible basis, net price 30 g = £1.43, 100 g = £4.05. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as valerate) 0.1% in an anhydrous paraffin basis, net price 30 g = £1.43, 100 g = £4.05. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Scalp application, betamethasone (as valerate) 0.1% in a water-miscible basis, net price 100 mL = £5.30. Label: 15, 28, counselling, application, see p. 623. Potency: potent

Excipients none as listed in section 13.1.3

Betnovate-RO® (GSK) (Non-proprietary)

Cream, betamethasone (as valerate) 0.025% in a water-miscible basis (1 in 4 dilution of Betnovate® cream), net price 100 g = £3.34. Label: 28, counselling, application, see p. 623. Potency: moderate

Excipients include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as valerate) 0.025% in an anhydrous paraffin basis (1 in 4 dilution of Betnovate® ointment), net price 100 g = £3.34. Label: 28, counselling, application, see p. 623. Potency: moderate

Excipients none as listed in section 13.1.3

Bettamousse® (UCB Pharma) (Non-proprietary)

Foam (= scalp application), betamethasone valerate 0.12% (= betamethasone 0.1%), net price 100 g = £9.75. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include cetyl alcohol, polysorbate 60, propylene glycol, stearyl alcohol

Note Flammable

Diprosone® (Scherling-Plough) (Non-proprietary)

Cream, betamethasone (as dipropionate) 0.05%, net price 30 g = £2.24, 100 g = £6.36. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as dipropionate) 0.05%, net price 30 g = £2.24, 100 g = £6.36. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients none as listed in section 13.1.3

Lotion, betamethasone (as dipropionate) 0.05%, net price 30 mL = £2.83, 100 mL = £8.10. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients none as listed in section 13.1.3
### With salicylic acid

See notes above for comment on compound preparations

**Diprosalic®** *(Scherling-Plough) (SM)*

**Ointment**, betamethasone (as dipropionate) 0.05%, salicylic acid 3%, net price 30 g = £3.30, 100 g = £9.50. Label: 28, counselling, application, see p. 623.

Potency: potent

**Excipients** none as listed in section 13.1.3

**Dose** apply thinly 1–2 times daily; max. 60 g per week

**Scalp application**, betamethasone (as dipropionate) 0.05%, salicylic acid 2%, in an alcoholic basis, net price 100 mL = £10.50. Label: 28, counselling, application, see p. 623.

Potency: potent

**Excipients** include disodium edetate

**Dose** apply a few drops 1–2 times daily

### With antimicrobials

See notes above for comment on compound preparations

**Betnovate-C®** *(Chemidex) (SM)*

**Cream**, betamethasone (as valerate) 0.1%, clioquinol 3%, net price 30 g = £1.76. Label: 28, counselling, application, see p. 623. Potency: potent

**Excipients** include cetoesteryl alcohol, chlororessol

**Note** Stains clothing

**Ointment**, betamethasone (as valerate) 0.1%, clioquinol 3%, net price 30 g = £1.76. Label: 28, counselling, application, see p. 623. Potency: potent

**Excipients** none as listed in section 13.1.3

**Note** Stains clothing

**Betnovate-N®** *(Chemidex) (SM)*

**Cream**, betamethasone (as valerate) 0.1%, neomycin sulphate 0.5%, net price 30 g = £1.76, 100 g = £4.88. Label: 28, counselling, application, see p. 623.

Potency: potent

**Excipients** include cetoesteryl alcohol, chlororessol

**Ointment**, betamethasone (as valerate) 0.1%, neomycin sulphate 0.5%, net price 30 g = £1.76, 100 g = £4.88. Label: 28, counselling, application, see p. 623. Potency: potent

**Excipients** none as listed in section 13.1.3

### CLOBETASONE BUTYRATE

**Indications** eczemas and dermatitis of all types; maintenance between courses of more potent corticosteroids

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- Apply thinly 1–2 times daily

**Eumovate®** *(GSK) (SM)*

**Cream**, clobetasone butyrate 0.05%, net price 30 g = £1.97, 100 g = £5.77. Label: 28, counselling, application, see p. 623. Potency: moderate

**Excipients** include beeswax substitute, cetoesteryl alcohol, chlororessol

**Ointment**, clobetasone butyrate 0.05%, net price 30 g = £1.97, 100 g = £5.77. Label: 28, counselling, application, see p. 623. Potency: moderate

**Excipients** none as listed in section 13.1.3

1. Cream can be sold to the public for short-term symptomatic treatment and control of patches of eczema and dermatitis (but not seborrhoeic dermatitis) in adults and children over 12 years provided pack does not contain more than 15 g

### CLOBETASOL PROPIONATE

**Indications** short-term treatment only of severe resistant inflammatory skin disorders such as recalcitrant eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**

- Apply thinly 1–2 times daily for up to 4 weeks; max. 50 g of 0.05% preparation per week

**Clarelux®** *(Fabre) (SM)*

**Foam** (= scalp application), clobetasol propionate 0.05%, net price 100 g = £11.06. Label: 15, 28, counselling, application, see p. 623. Potency: very potent

**Excipients** include cetly alcohol, polyisobutylate 60, propylene glycol, stearyl alcohol

**Caution** flammable

**Note** Apply directly to scalp lesions (foam begins to subside immediately on contact with skin)

**Dermovate®** *(GSK) (SM)*

**Cream**, clobetasol propionate 0.05%, net price 30 g = £2.86, 100 g = £8.39. Label: 28, counselling, application, see p. 623. Potency: very potent

**Excipients** include beeswax (or beeswax substitute), cetoesteryl alcohol, chlororessol, propylene glycol

**Ointment**, clobetasol propionate 0.05%, net price 30 g = £2.86, 100 g = £8.39. Label: 28, counselling, application, see p. 623. Potency: very potent

**Excipients** include propylene glycol

**Scalp application**, clobetasol propionate 0.05%, in a thickened alcoholic basis, net price 30 mL = £3.26, 100 mL = £11.06. Label: 15, 28, counselling, application, see p. 623. Potency: very potent

**Excipients** none as listed in section 13.1.3

**Etrivex®** *(Galdema) (SM)*

**Shampoo**, clobetasol propionate 0.05%, net price 125 mL = £11.94. Label: 28, counselling, application, see p. 623. Potency: very potent

**Excipients** none as listed in section 13.1.3

**Dose** moderate scalp psoriasis, ADULT over 18 years, apply thinly once daily, rinse off after 15 minutes; reduce frequency of application after clinical improvement; max. duration of treatment 4 weeks

**Clarex®** *(Schering-Plough) (SM)*

**Cream**, betamethasone (as valerate) 0.1%, fusidic acid 2%, net price 30 g = £5.62, 60 g = £11.23. Label: 28, counselling, application, see p. 623.

Potency: potent

**Excipients** include cetoesteryl alcohol, chlororessol

**Lipid cream**, betamethasone (as valerate) 0.1%, fusidic acid 2%, net price 30 g = £5.62. Label: 28, counselling, application, see p. 623.

Potency: potent

**Excipients** include cetoesteryl alcohol, chlororessol

**Lotiderm®** *(Pilva) (SM)*

**Cream**, betamethasone dipropionate 0.064% (= betamethasone 0.05%), clotrimazole 1%, net price 30 g = £6.34. Label: 28, counselling, application, see p. 623. Potency: potent

**Excipients** include benzyl alcohol, cetoesteryl alcohol, propylene glycol

**Trimovate®** *(GSK) (SM)*

**Cream**, clobetasone butyrate 0.05%, oxytetracycline 3% (as calcium salt), nystatin 100 000 units/g, net price 30 g = £3.49. Label: 28, counselling, application, see p. 623. Potency: moderate

**Excipients** include cetoesteryl alcohol, chlororessol, sodium metabisulphite

**Note** Stains clothing
**DIFLUCORTOLONE VALERATE**

**Indications** severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; high strength (0.3%), short-term treatment of severe exacerbations; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily for up to 4 weeks (0.1% preparations) or 2 weeks (0.3% preparations), reducing strength as condition responds; max. 60 g of 0.3% per week

**Nerisone** (Meadow) (Pf)

**Cream**
- fludrocortizone valerate 0.1%, net price 30 g = £1.59. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include disodium edetate, hydroxybenzoates (parabens), stearyl alcohol

**Oily cream**
- fludrocortizone valerate 0.1%, net price 30 g = £2.56. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include beeswax

**Ointment**
- fludrocortizone valerate 0.1%, net price 30 g = £1.59. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients none as listed in section 13.1.3

**Nerisone Forte** (Meadow) (Pf)

**Oily cream**
- fludrocortizone valerate 0.3%, net price 15 g = £2.09. Label: 28, counselling, application, see p. 623. Potency: very potent
- Excipients include beeswax

**Ointment**
- fludrocortizone valerate 0.3%, net price 15 g = £2.09. Label: 28, counselling, application, see p. 623. Potency: very potent
- Excipients none as listed in section 13.1.3

**FLUDROXYCORTIDE** (Flurandrenolone)

**Indications** inflammatory skin disorders such as eczemas

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily

**Haelan** (Typpharm) (Pf)

**Cream**
- fludrocortizone 0.0125%, net price 60 g = £3.26. Label: 28, counselling, application, see p. 623. Potency: moderate
- Excipients include cetyl alcohol, propylene glycol

**Ointment**
- fludrocortizone 0.0125%, net price 60 g = £3.26. Label: 28, counselling, application, see p. 623. Potency: moderate
- Excipients include beeswax, cetyl alcohol, polysorbate

**Tape**
- polythene adhesive film impregnated with fludrocortizone 4 micrograms/cm², net price 7.5 cm × 50 cm = £9.27. 7.5 cm × 200 cm = £24.95

**Dose** for chronic localised recalcitrant dermatoses (but not acute or weeping), cut tape to fit lesion, apply to clean, dry skin abom of hair, usually for 12 hours daily

---

**FLUCINOLONE ACETONIDE**

**Indications** inflammatory skin disorders such as eczemas; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily, reducing strength as condition responds

**Synalar** (GP Pharma) (Pf)

**Cream**
- fluocinolone acetonide 0.025%, net price 30 g = £3.76, 100 g = £10.68. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include benzyl alcohol, cetylstearyl alcohol, polysorbates, propylene glycol

**Gel**
- fluocinolone acetonide 0.025%, net price 30 g = £5.56, 60 g = £10.02. For use on scalp and other hairy areas. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include hydroxybenzoates (parabens), propylene glycol

**Ointment**
- fluocinolone acetonide 0.025%, net price 30 g = £3.76, 100 g = £10.68. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include propylene glycol, wool fat

**Synalar 1 in 4 Dilution** (GP Pharma) (Pf)

**Cream**
- fluocinolone acetonide 0.00625%, net price 50 g = £4.40. Label: 28, counselling, application, see p. 623. Potency: moderate
- Excipients include benzyl alcohol, cetylstearyl alcohol, polysorbates, propylene glycol

**Synalar 1 in 10 Dilution** (GP Pharma) (Pf)

**Cream**
- fluocinolone acetonide 0.0025%, net price 50 g = £4.16. Label: 28, counselling, application, see p. 623. Potency: mild
- Excipients include benzyl alcohol, cetylstearyl alcohol, polysorbates, propylene glycol

---

**With antibacterials**

See notes above for comment on compound preparations

**Synalar C** (GP Pharma) (Pf)

**Cream**
- fluocinolone acetonide 0.025%, clioquinol 3%, net price 15 g = £2.42. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include cetylstearyl alcohol, disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol

**Synalar N** (GP Pharma) (Pf)

**Cream**
- fluocinolone acetonide 0.025%, neomycin sulphate 0.5%, net price 30 g = £3.96. Label: 28, counselling, application, see p. 623. Potency: potent
- Excipients include propylene glycol, wool fat
FLUOCINONIDE

**Indications** severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily

**Metosyn** (GP Pharma)

FAPG cream, fluocinonide 0.05%, net price 25 g = £3.30, 100 g = £11.12. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include propylene glycol

Ointment, fluocinonide 0.05%, net price 25 g = £2.92, 100 g = £10.96. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include propylene glycol, wool fat

**FLUOCORTOLONE**

**Indications** severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily, reducing strength as condition responds

**Ultralanum Plain** (Meadow)

Cream, fluocortolone caproate 0.25%, fluocortolone pivalate 0.25%, net price 50 g = £2.95. Label: 28, counselling, application, see p. 623. Potency: moderate

Excipients include disodium edetate, fragrance, hydroxybenzoates (parabens), stearyl alcohol

Ointment, fluocortolone 0.25%, net price 50 g = £2.95. Label: 28, counselling, application, see p. 623. Potency: moderate

Excipients include wool fat, fragrance

**FLUTICASONE PROPIONATE**

**Indications** inflammatory skin disorders such as dermatitis and eczemas unresponsive to less potent corticosteroids

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily

**Cutivate** (GSK)

Cream, fluticasone propionate 0.05%, net price 15 g = £2.41, 50 g = £7.11. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include cetostearyl alcohol, imidurea, propylene glycol

Ointment, fluticasone propionate 0.005%, net price 15 g = £2.41, 50 g = £7.11. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include propylene glycol

**MOMETASONE FUROATE**

**Indications** severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly once daily (to scalp in case of lotion)

**Elocon** (Schering-Plough)

Cream, mometasone furoate 0.1%, net price 30 g = £4.54, 100 g = £13.07. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include propylene glycol, stearyl alcohol

Ointment, mometasone furoate 0.1%, net price 30 g = £4.54, 100 g = £13.07. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include propylene glycol

Scalp lotion, mometasone furoate 0.1% in an aqueous isopropyl alcohol basis, net price 30 mL = £4.54. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include propylene glycol

**TRIAMCINOLONE ACETONIDE**

**Indications** severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids; psoriasis, see notes above

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly 1–2 times daily

**Aureocort** (Goldshield)

Ointment, triamcinolone acetonide 0.1%, chlortetracycline hydrochloride 3%, in an anhydrous greasy basis containing wool fat and white soft paraffin, net price 15 g = £2.70. Label: 28, counselling, application, see p. 623. Potency: potent

Excipients include wool fat

Note: Stains clothing

---

13.5 Preparations for eczema and psoriasis

### 13.5.1 Preparations for eczema

Eczema (dermatitis) has several causes, which may influence treatment. The main types of eczema are irritant, allergic contact, atopic, venous and discoid; different types may co-exist. Lichenification, due to scratching and rubbing, may complicate any chronic
eczema. **Atopic eczema** is the most common type and it usually involves dry skin as well as infection and lichenification.

Management of eczema involves the removal or treatment of contributory factors including occupational and domestic irritants. Known or suspected contact allergens should be avoided. Rarely, ingredients in topical medicinal products may sensitise the skin; the BNF lists active ingredients together with excipients that have been associated with skin sensitisation.

Skin dryness and the consequent irritant eczema requires **emollients** (section 13.2.1) applied regularly and liberally to the affected area; this can be supplemented with bath or shower emollients. The use of emollients should continue even if the eczema improves or if other treatment is being used.

**Topical corticosteroids** (section 13.4) are also required in the management of eczema; the potency of the corticosteroid should be appropriate to the severity and site of the condition. Mild corticosteroids are generally used on the face and on flexures; potent corticosteroids are generally required for use on adults with discoid or lichenified eczema or with eczema on the scalp, limbs, and trunk. Treatment should be reviewed regularly, especially if a potent corticosteroid is required. Bandages (including those containing zinc and ichthammol) are sometimes applied over topical corticosteroids or emollients to treat eczema of the limbs.

For the role of topical pimecrolimus and tacrolimus in atopic eczema see section 13.5.3.

**Infection** Bacterial infection (commonly with *Staphylococcus aureus* and occasionally with *Streptococcus pyogenes*) can exacerbate eczema and requires treatment with topical or systemic **antibacterial drugs** (section 13.10.1 and section 5.1). Antibacterial drugs, particularly fusidic acid, should be used in short courses (typically 1 week) to reduce the risk of drug resistance or skin sensitisation. Associated eczema is treated simultaneously with a topical corticosteroid usually of moderate or high potency.

Eczema involving widespread or recurrent infection requires the use of a systemic antibacterial that is active against the infecting organism. Products that combine an antiseptic with an emollient application (section 13.2.1) and with a bath emollient (section 13.2.1.1) can also be used; antiseptic shampoos (section 13.9) and combinations of mild corticosteroids with suitable antimicrobials (section 13.4) are used.

**Severe refractory eczema** Severe refractory eczema is best managed under specialist supervision; it may require phototherapy or drugs that act on the immune system (section 13.5.3). **Alitretinoin** (see below) is licensed for the treatment of severe chronic hand eczema refractory to potent topical corticosteroids; patients with hyperkeratotic features are more likely to respond to alitretinoin than those with pompholyx.

**Seborrhoeic dermatitis** Seborrhoeic dermatitis (seborrhoeic eczema) is associated with species of the yeast *Malassezia* and affects the scalp, paranasal areas, and eyebrows. Shampoos active against the yeast (including those containing ketoconazole and coal tar, section 13.9) and combinations of mild corticosteroids with suitable antimicrobials (section 13.4) are used.

### Topical preparations for eczema

#### ICHTHAMMOL

- **Indications** chronic lichenified eczema
- **Side-effects** skin irritation
- **Dose**
  - Apply 1–3 times daily

**Ichthammol Ointment, BP 1980**

Ointment, ichthammol 10%, yellow soft paraffin 45%, wool fat 45%

**Zinc and Ichthammol Cream, BP**

Cream, ichthammol 3%, cetostearyl alcohol 3%, wool fat 10%, in zinc cream

**Zinc Paste and Ichthammol Bandage, BP 1993**

See Appendix 8 (section A8.2.9)

### Oral retinoid for eczema

The retinoid, alitretinoin, is licensed for the treatment of severe chronic hand eczema refractory to potent topical corticosteroids; patients with hyperkeratotic features are more likely to respond to alitretinoin than those with pompholyx.

Alitretinoin should be prescribed only by, or under the supervision of, a consultant dermatologist. Alitretinoin is *teratogenic* and must not be given to women of child-bearing potential unless they practise effective contraception and then only after detailed assessment and explanation by the physician. See also Pregnancy Prevention under Cautions, below.

#### ALITRETINOIN

- **Indications** severe chronic hand eczema refractory to potent topical corticosteroids
- **Cautions** avoid blood donation during treatment and for at least 1 month after stopping treatment; monitor
13.5.2 Preparations for psoriasis

Psoriasis is characterised by epidermal thickening and scaling. It commonly affects extensor surfaces and the scalp. For mild psoriasis, reassurance and treatment with an emollient may be all that is necessary.

Occasionally psoriasis is provoked or exacerbated by drugs such as lithium, chloroquine and hydroxychloroquine, beta-blockers, non-steroidal anti-inflammatory drugs, and ACE inhibitors. Psoriasis may not be seen until the drug has been taken for weeks or months.

Emollients (section 13.2.1), in addition to their effects on dryness, scaling and cracking, may have an anti-proliferative effect in psoriasis. They are particularly useful in inflammatory psoriasis and in plaque psoriasis of palms and soles, in which irritant factors can perpetuate the condition. Emollients are useful adjuncts to other more specific treatment.

More specific topical treatment for chronic stable plaque psoriasis on extensor surfaces of trunk and limbs involves the use of vitamin D analogues, coal tar, dithranol, and the retinoid tazarotene. However, they can irritate the skin and are not suitable for the more inflammatory forms of psoriasis; their use should be suspended during an inflammatory phase of psoriasis. The efficacy and the irritancy of each substance varies between patients. If a substance irritates significantly, it should be stopped or the concentration reduced, if it is tolerated, its effects should be assessed after 4 to 6 weeks and treatment continued if it is effective.

Widespread unstable psoriasis of erythematous or generalised pustular type requires urgent specialist assessment. Initial topical treatment should be limited to using emollients frequently and generously; emollients should be prescribed in quantities of 1 kg or more. More localised acute or subacute inflammatory psoriasis with hot, spreading or itchy lesions, should be treated topically with emollients or with a corticosteroid of moderate potency.

Calcipotriol and tacalcitol are analogues of vitamin D that affect cell division and differentiation. Calcitriol is an active form of vitamin D. Vitamin D and its analogues are used as first-line treatment for plaque psoriasis; they do not smell or stain and they may be more acceptable than tar or dithranol products. Of the vitamin D analogues, tacalcitol and calcitriol are less likely to irritate.

Coal tar has anti-inflammatory properties that are useful in chronic plaque psoriasis; it also has antiscaling properties. Crude coal tar (coal tar, BP) is the most effective form, typically in a concentration of 1 to 10% in a soft paraffin base, but few outpatient tolerate the smell and mess. Cleaner extracts of coal tar included in proprietary preparations, are more practicable for home use but they are less effective and improvement takes longer. Contact of coal tar products with normal skin is not normally harmful and they can be used for widespread small lesions; however, irritation, contact allergy, and sterile folliculitis can occur. The milder tar extracts can be used on the face and flexures. Tar baths and tar shampoos are also helpful.

Dithranol is effective for chronic plaque psoriasis. Its major disadvantages are irritation (for which individual susceptibility varies) and staining of skin and of clothing. It should be applied to chronic extensor plaques only, carefully avoiding normal skin. Dithranol is not generally suitable for widespread small lesions nor should it be used in the flexures or on the face. Treatment should be started with a low concentration such as dithranol 0.1%, and the strength increased gradually every few days up to 3%, according to tolerance. Proprietary preparations are more suitable for home use; they are usually washed off after 5 to 60 minutes (‘short contact’). Specialist nurses may apply intensive treatment with dithranol paste which is covered by stockinette dressings and usually retained overnight. Dithranol should be discontinued if even a low concentration causes acute inflammation; continued use can result
in the psoriasis becoming unstable. When applying dithranol, hands should be protected by gloves or they should be washed thoroughly afterwards.

**Tazarotene**, a retinoid, seems to be less effective than calcipotriol with a greater incidence of irritation. Although irritation is common, it is minimised by applying tazarotene sparingly to the plaques and avoiding normal skin. Tazarotene is clean and odourless.

A topical **corticosteroid** (section 13.4) is not generally suitable as the sole treatment of extensive chronic plaque psoriasis; any early improvement is not usually maintained and there is a risk of the condition deteriorating or of precipitating an unstable form of psoriasis (e.g. erythrodermic psoriasis or generalised pustular psoriasis). However, it may be appropriate to treat psoriasis in specific sites, such as the face and flexures, usually with a mild corticosteroid, and psoriasis of the scalp, palms, and soles with a potent corticosteroid.

Combining the use of a corticosteroid with another specific topical treatment may be beneficial in chronic plaque psoriasis; the drugs may be used separately at different times of the day or used together in a single formulation. **Eczema co-existing with psoriasis** may be treated with a corticosteroid, or coal tar, or both.

**Scalp psoriasis** is usually scaly, and the scale may be thick and adherent. This requires softening with an emollient ointment, cream, or oil and usually combined with **salicylic acid** as a keratolytic.

Some preparations prescribed for psoriasis affecting the scalp combine salicylic acid with coal tar or **sulphur**. Preparations containing salicylic acid, sulphur, and coal tar are available as proprietary products. The product should be applied generously and an adequate quantity should be prescribed. It should be left on for at least an hour, often more conveniently overnight, before washing it off. If a corticosteroid lotion or gel is required (e.g. erythrodermic psoriasis or generalised pustular psoriasis), it can be used in the morning.

**Tazarotene**, a retinoid, seems to be less effective than calcipotriol with a greater incidence of irritation. Although irritation is common, it is minimised by applying tazarotene sparingly to the plaques and avoiding normal skin. Tazarotene is clean and odourless.

A topical **corticosteroid** (section 13.4) is not generally suitable as the sole treatment of extensive chronic plaque psoriasis; any early improvement is not usually maintained and there is a risk of the condition deteriorating or of precipitating an unstable form of psoriasis (e.g. erythrodermic psoriasis or generalised pustular psoriasis). However, it may be appropriate to treat psoriasis in specific sites, such as the face and flexures, usually with a mild corticosteroid, and psoriasis of the scalp, palms, and soles with a potent corticosteroid.

Combining the use of a corticosteroid with another specific topical treatment may be beneficial in chronic plaque psoriasis; the drugs may be used separately at different times of the day or used together in a single formulation. **Eczema co-existing with psoriasis** may be treated with a corticosteroid, or coal tar, or both.

**Scalp psoriasis** is usually scaly, and the scale may be thick and adherent. This requires softening with an emollient ointment, cream, or oil and usually combined with **salicylic acid** as a keratolytic.

Some preparations prescribed for psoriasis affecting the scalp combine salicylic acid with coal tar or **sulphur**. Preparations containing salicylic acid, sulphur, and coal tar are available as proprietary products. The product should be applied generously and an adequate quantity should be prescribed. It should be left on for at least an hour, often more conveniently overnight, before washing it off. If a corticosteroid lotion or gel is required (e.g. for itch), it can be used in the morning.

**Phototherapy** **Phototherapy** is available in specialist centres under the supervision of a dermatologist. **Ultra-violet B** (UVB) radiation is usually effective for **chronic stable psoriasis** and for **guttate psoriasis**. It may be considered for patients with moderately severe psoriasis in whom topical treatment has failed, but it may irritate inflammatory psoriasis.

**Photochemotherapy** combining long-wave ultraviolet A radiation with a psoralen (PUVA) is available in specialist centres under the supervision of a dermatologist. The psoralen, which enhances the effect of irradiation, is administered either by mouth or topically. PUVA is effective in most forms of psoriasis, including **localised palmoplantar pustular psoriasis**. Early adverse effects include photocotoxicity and pruritus. Higher cumulative doses exaggerate skin ageing, increase the risk of dysplastic and neoplastic skin lesions, especially squamous cancer, and pose a theoretical risk of carcinogenesis. Photochemotherapy combined with coal tar, dithranol, tazarotene, topical vitamin D or vitamin D analogues, or oral acitretin, allows reduction of the cumulative dose of phototherapy required to treat psoriasis.

**Systemic treatment** **Systemic treatment** is required for severe, resistant, unstable or complicated forms of psoriasis, and it should be initiated only under specialist supervision. Systemic drugs for psoriasis include acitretin (see below) and drugs that affect the immune response (such as ciclosporin and methotrexate, section 13.5.3).

Systemic corticosteroids should be used only rarely in psoriasis because rebound deterioration may occur on reducing the dose.

**Acitretin**, a metabolite of etretinate, is a retinoid (vitamin A derivative); it is prescribed by specialists. The main indication for acitretin is psoriasis, but it is also used in disorders of keratinisation such as severe **Darier’s disease** (keratosis follicularis), and some forms of **ichthyosis**. Although a minority of cases of psoriasis respond well to acitretin alone, it is only moderately effective in many cases and it is combined with other treatments. A therapeutic effect occurs after 2 to 4 weeks and the maximum benefit after 4 to 6 weeks or longer. The manufacturers of acitretin do not recommend continuous treatment for longer than 6 months. However, some patients may benefit from longer treatment, provided that the lowest effective dose is used, patients are monitored carefully for adverse effects, and the need for treatment is reviewed regularly.

Apart from teratogenicity, which remains a risk for 3 years after stopping, acitretin is the least toxic systemic treatment for psoriasis; in women with a potential for child-bearing, the possibility of pregnancy must be excluded before treatment and effective contraception must be used during treatment and for at least 3 years afterwards (oral progestogen-only contraceptives not considered effective). Common side-effects derive from its widespread but reversible effects on epithelia, such as dry and cracking lips, dry skin and mucosal surfaces, hair thinning, paronychia, and soft and sticky palms and soles. Liver function and blood lipid concentration should be monitored.

---

**Topical preparations for psoriasis**

**Vitamin D and analogues**

Calcipotriol, calcitriol, and **tacalcitol** are used for the management of **plaque psoriasis**. They should be avoided by those with calcium metabolism disorders, and used with caution in **generalised pustular or erythrodermic exfoliative psoriasis** (enhanced risk of hypercalcaemia). Local skin reactions (itching, erythema, burning, paraesthesia, dermatitis) are common. Hands should be washed thoroughly after application to avoid inadvertent transfer to other body areas. Aggravation of psoriasis has also been reported.

**CALCIPOTRIOL**

**Indications** plaque psoriasis

**Cautions** see notes above; avoid use on face; avoid excessive exposure to sunlight and sunlamps; pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Contra-indications** see notes above

**Side-effects** see notes above; also photosensitivity; rarely facial or perioral dermatitis, skin atrophy

**Dose**

- *Cream or ointment* apply once or twice daily; max. 100 g weekly (less with scalp solution, see below).

- **CHILD** over 6 years, apply twice daily; 6–12 years max. 50 g weekly; over 12 years max. 75 g weekly

**Note** Patient information leaflet for Dovonex cream advises liberal application (but note max. recommended weekly dose, above)
Calcipotriol

**Ointment**, calcipotriol 50 micrograms/g, net price
120 g = £22.70, 120 g = £24.04

**Note** Not licensed for use in children under 18 years

**Dovonex** (LEO)

**Cream**, calcipotriol 50 micrograms/g, net price
60 g = £16.10, 120 g = £23.60

**Excipients** include cetostearyl alcohol, diosodium edetate

**Scalp solution**, calcipotriol 50 micrograms/mL, net price
60 mL = £13.04, 120 mL = £26.07

**Excipients** include propylene glycol

**Dose** scalp psoriasis, apply to scalp twice daily; max. 60 mL weekly (less with cream or ointment, see below); **CHILD** under 18 years, see **BNF for Children**

**Note** When preparations used together max. total calcipotriol 5 mg in any one week (e.g. scalp solution 60 mL with cream or ointment 30 g or cream or ointment 60 g with scalp solution 30 mL)

**With betamethasone**

For cautions, contra-indications, side-effects, and for comment on the limited role of corticosteroids in psoriasis, see section 13.4.

**Dovobet** (LEO)

**Ointment**, betamethasone 0.05% (as dipropionate), calcipotriol 50 micrograms/g, net price 60 g = £35.00, 120 g = £65.00. Label: 28

**Excipients** none as listed in section 13.1.3

**Dose** initial treatment of stable plaque psoriasis, apply once daily to max. 30% of body surface (max. 15 g daily, max. 100 g weekly) for 4 weeks; if necessary, subsequent courses repeated after an interval of at least 4 weeks; **CHILD** under 18 years see **BNF for Children**

**Note** When different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week

**Xamiol** (LEO)

**Scalp gel**, betamethasone 0.05% (as dipropionate), calcipotriol 50 micrograms/g, net price 60 g = £36.50. Label: 28

**Excipients** include butylated hydroxytoluene, disodium edetate, polysorbate 40

**Dose** scalp psoriasis, **ADULT** over 18 years, apply 1–4 g to scalp once daily; max. 30 g daily; **CHILD** over 12 years, apply twice daily; not more than 35% of body surface to be treated daily, max. 30 g daily

**Note** When different preparations containing calcipotriol used together, max. total calcipotriol 5 mg in any one week

**Calcitriol (Non-proprietary)**

**Ointment**, calcitriol 5 micrograms/g, net price
120 g = £25.88

**Note** Not licensed for use in children under 18 years

**Dovonex** (LEO)

**Cream**, calcipotriol 50 micrograms/g, net price 60 g = £12.02, 120 g = £24.04

**Excipients** include cetostearyl alcohol, diosodium edetate

**Scalp solution**, calcipotriol 50 micrograms/mL, net price
60 mL = £13.04, 120 mL = £26.07

**Excipients** include propylene glycol

**Dose** scalp psoriasis, apply to scalp twice daily; max. 60 mL weekly (less with cream or ointment, see below); **CHILD** under 18 years, see **BNF for Children**

**Note** When preparations used together max. total calcipotriol 5 mg in any one week (e.g. scalp solution 60 mL with cream or ointment 30 g or cream or ointment 60 g with scalp solution 30 mL)

**With betamethasone**

For cautions, contra-indications, side-effects, and for comment on the limited role of corticosteroids in psoriasis, see section 13.4.

**Dovonex** (LEO)

**Ointment**, betamethasone 0.05% (as dipropionate), calcipotriol 50 micrograms/g, net price 60 g = £35.00, 120 g = £65.00. Label: 28

**Excipients** none as listed in section 13.1.3

**Dose** ADULT and **CHILD** over 12 years, apply once daily preferably at bedtime; max. 10 g **ointment** or 10 mL **lotion** daily

**Note** When lotion and ointment used together, max. total tacalcitrol 280 micrograms in any one week (e.g. lotion 30 mL with ointment 40 g)

**Curatoderm** (Almirall)

**Lotion**, tacalcitol (as monohydrate) 4 micrograms/g, net price 30 mL = £12.73

**Excipients** include diosodium edetate, propylene glycol

**Ointment**, tacalcitol (as monohydrate) 4 micrograms/g, net price 30 g = £13.40, 60 g = £23.14, 100 g = £30.86

**Excipients** none as listed in section 13.1.3

**Tazarotene**

**TAZAROTENE**

**Indications** mild to moderate plaque psoriasis affecting up to 10% of skin area

**Cautions** wash hands immediately after use, avoid contact with eyes, face, intertriginous areas, hair-covered scalp, eczematous or inflamed skin; avoid excessive exposure to UV light (including sunlight, sunlamps, PUVA or UVB treatment); do not apply emollients or cosmetics within 1 hour of application

**Contra-indications** pregnancy—women of child-bearing potential must use effective contraception (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** local irritation (more common with higher concentration and may require discontinuation), pruritus, burning, erythema, desquamation, non-specific rash, contact dermatitis, and worsening of psoriasis; rarely stinging and inflamed, dry or painful skin

**Dose**

- **ADULT** and **CHILD** over 12 years, apply once daily in the evening usually for up to 12 weeks; **CHILD** under 18 years not recommended

**Zorac** (Allergan)

**Gel**, tazarotene 0.05%, net price 30 g = £14.09; 0.1%, 30 g = £14.80

**Excipients** include benzyl alcohol, butylated hydroxyanisole, butylated hydroxytoluene, diosodium edetate, polysorbate 40

**Tars**

**Indications** psoriasis and occasionally chronic atopic eczema

**Cautions** avoid eyes, mucosa, genital or rectal areas, and broken or inflamed skin; use suitable chemical protection gloves for extemporaneous preparation

**Contra-indications** not for use in sore, acute, or purpuric psoriasis or in presence of infection

**Side-effects** skin irritation and acne-like eruptions, photosensitivity, stains skin, hair, and fabric
**BNF 57**

### 13.5.2 Preparations for psoriasis 633

**Dose**
- Apply 1–3 times daily starting with low-strength preparations

**Note**
For shampoo preparations see section 13.9; impregnated dressings see Appendix 8 (section A8.2.9)

#### Non-proprietary preparations
May be difficult to obtain. Patients may find newer proprietary preparations more acceptable

- **Calamine and Coal Tar Ointment, BP**
  - **Ointment**, calamine 12.5 g, strong coal tar solution 2.5 g, zinc oxide 12.5 g, hydrous wool fat 25 g, white soft paraffin 47.5 g
  - **Excipients** include wool fat
  - **Dose** apply 1–2 times daily

- **Coal Tar and Salicylic Acid Ointment, BP**
  - **Ointment**, coal tar 2 g, salicylic acid 2 g, emulsifying wax 11.4 g, white soft paraffin 19 g, coconut oil 54 g, polysorbate ‘80’ 4 g, liquid paraffin 7.6 g
  - **Excipients** include cetostearyl alcohol
  - **Dose** apply 1–2 times daily

- **Coal Tar Paste, BP**
  - **Paste**, strong coal tar solution 7.5%, in compound zinc paste
  - **Dose** apply 1–2 times daily

- **Zinc and Coal Tar Paste, BP**
  - **Paste**, zinc oxide 6%, coal tar 6%, emulsifying wax 5%, starch 38%, yellow soft paraffin 45%
  - **Excipients** include cetostearyl alcohol
  - **Dose** apply 1–2 times daily

#### Proprietary preparations

- **Carbo-Dome** (Sandoz)
  - **Cream**, coal tar solution 10%, in a water-miscible basis, net price 30 g = £4.77, 100 g = £16.38
  - **Excipients** include beeswax, hydroxybenzoates (parabens)
  - **Dose** psoriasis, apply to skin 2–3 times daily

- **Clinitar** (CHS)
  - **Cream**, coal tar extract 1%, net price 100 g = £10.99
  - **Excipients** include cetostearyl alcohol, isopropyl palmitate, propylene glycol
  - **Dose** psoriasis and eczema, apply to skin 1–2 times daily

- **Cocos®** (UCB Pharma)
  - **Scalp ointment**, coal tar solution 12%, salicylic acid 2%, precipitated sulphur 4%, in a coconut oil emollient basis, net price 40 g (with applicator nozzle) = £6.22, 100 g = £11.69
  - **Excipients** include cetostearyl alcohol
  - **Dose** scalable scalp disorders including psoriasis, eczema, seborrheic dermatitis and dandruff, apply to scalp once weekly as necessary (if severe use daily for first 3–7 days), shampoo off after 1 hour, CHILD 6–12 years, medical supervision required (not recommended under 6 years)

- **Exorex®** (Forest)
  - **Lotion**, prepared coal tar 1% in an emollient basis, net price 100 mL = £8.11, 250 mL = £16.24
  - **Excipients** include hydroxybenzoates (parabens), polysorbate 80
  - **Dose** psoriasis, apply to skin or scalp 2–3 times daily, CHILD under 12 years and ELDERLY, lotion can be diluted with a few drops of water before applying

- **Psoriderm®** (Dermal)
  - **Cream**, coal tar 6%, lecithin 0.4%, net price 225 mL = £9.85
  - **Excipients** include isopropyl palmitate, propylene glycol
  - **Dose** psoriasis, apply to skin or scalp 1–2 times daily
  - **Scalp lotion**—section 13.9

### Sebco® (Centrapharm)

- **Scalp ointment**, coal tar solution 12%, salicylic acid 2%, precipitated sulphur 4%, in a coconut oil emollient basis, net price 40 g = £4.54, 100 g = £8.52
  - **Excipients** include cetostearyl alcohol
  - **Dose** scalable scalp disorders including psoriasis, eczema, seborrheic dermatitis and dandruff, apply to scalp as necessary (if severe use daily for first 3–7 days), shampoo off after 1 hour, CHILD 6–12 years, medical supervision required (not recommended under 6 years)

#### Bath preparations

- **Coal Tar Solution, BP**
  - **Solution**, coal tar 20%, polysorbate ‘80’ 5%, in alcohol (96%), net price 500 mL = £7.22
  - **Excipients** include polysorbates
  - **Dose** use 100 mL in a bath
  - **Note** Strong Coal Tar Solution BP contains coal tar 40%

- **Pinetarsol®** (Crawford)
  - **Bath oil**, tar 2.3% in a light liquid paraffin basis, net price 200 mL = £4.75, 500 mL = £7.95
  - **Excipients** include fragrance
  - **Dose** eczema and psoriasis, use 15–30 mL in a bath or apply directly to wet skin and rinse after a few minutes; can be used as soap substitute
  - **Gel**, tar 1.6%, net price 100 g = £4.95
  - **Dose** eczema and psoriasis, apply directly to wet skin and rinse after a few minutes; can be used as soap substitute
  - **Solution**, tar 2.3%, net price 200 mL = £4.45, 500 mL = £7.45
  - **Dose** eczema and psoriasis, use 15–30 mL in a bath or dilute 15 mL with 3 litres of water and apply to affected areas or apply solution directly to wet skin and rinse after a few minutes; can be used as soap substitute

- **Polytar Emollient®** (Stiefel)
  - **Bath additive**, coal tar solution 2.5%, arachis (peanut) oil extract of coal tar 7.5%, tar 7.5%, cadel oil 7.5%, liquid paraffin 35%, net price 500 mL = £5.78
  - **Excipients** include isopropl palmitate
  - **Dose** psoriasis, eczema, atopic and pruritic dermatoses, use 2–4 capfuls (15–30 mL) in bath and soak for 20 minutes

- **Psoriderm®** (Dermal)
  - **Bath emulsion**, coal tar 40%, net price 200 mL = £2.87
  - **Excipients** include polysorbate 20
  - **Dose** psoriasis, use 30 mL in a bath and soak for 5 minutes

#### With corticosteroids

- **Alphosyl HC®** (GSK Consumer Healthcare)
  - **Cream**, coal tar extract 5%, hydrocortisone 0.5%, allantoin 2%, net price 100 g = £3.54. Label: 28.
  - **Potency:** mild
  - **Excipients** include beeswax, cetyl alcohol, hydroxybenzoates (parabens), isopropl palmitate, wool fat
  - **Dose** ADULT and CHILD over 5 years, psoriasis, apply thinly twice daily

### Dithranol

#### DITHRANOL (Anthratin)

**Indications** subacute and chronic psoriasis, see notes above

**Cautions** avoid use near eyes and sensitive areas of skin; see also notes above

**Contra-indications** hypersensitivity; acute and pustular psoriasis

**Side-effects** local burning sensation and irritation; stains skin, hair, and fabrics
**Dose**

- See notes above and under preparations

**Note** Some of these dithranol preparations also contain coal tar or salicylic acid—for cautions, contra-indications, and side-effects see under Tars (above) or under Salicylic Acid

### Non-proprietary preparations

**1. Dithranol Ointment, BP**

**Ointment**
- dithranol, in yellow soft paraffin; usual strengths 0.1–2%. Part of basis may be replaced by hard paraffin if a stiffer preparation is required.
- Label: 28

**2. Dithranol Paste, BP**

**Paste**
- dithranol in zinc and salicylic acid (Lassar’s) paste. Usual strengths 0.1–1% of dithranol. Label: 28

### Proprietary preparations

**Dithrocream® (Derma)**

**Cream**
- dithranol 0.1%, net price 50 g = £3.94; 0.25%, 50 g = £4.23; 0.5%, 50 g = £4.87; 1%, 50 g = £5.67. **(Pf) 2%, 50 g = £7.10. Label: 28

**Excipients**
- cetostearyl alcohol, chlorocresol

**Dose**
- for application to skin or scalp: 0.1–0.5% cream suitable for overnight treatment; 1–2% cream for max. 1 hour

**Micanol® (GP Pharma)**

**Cream**
- dithranol 1% in a lipid-stabilised basis, net price 50 g = £13.48; 0.25%, 50 g = £16.79. **(Lab) 0.1%, 50 g = £3.94; 0.25%, 50 g = £4.23; 0.5%, 50 g = £4.87; 1%, 50 g = £5.67; 2%, 50 g = £7.10. Label: 28

**Excipients**
- cetostearyl alcohol, chlorocresol

**Dose**
- for application to skin or scalp, apply 1% cream for up to 30 minutes once daily, if necessary; 3% cream can be used under medical supervision

**Note** At the end of contact time, use plenty of lukewarm (not hot) water to rinse off cream; soap may be used after cream has been rinsed off, use shampoo before applying cream to scalp and if necessary after cream has been rinsed off

**Psorin® (LPC)**

**Ointment**
- dithranol 0.11%, coal tar 1%, salicylic acid 1.6%, net price 50 g = £9.22, 100 g = £18.44. **(Lab) 0.1%, 50 g = £3.94; 0.25%, 50 g = £4.23; 0.5%, 50 g = £4.87; 1%, 50 g = £5.67; 2%, 50 g = £7.10. Label: 28

**Excipients**
- beeswax, wool fat

**Dose**
- for application to skin up to twice daily

**Scalp gel**, dithranol 0.25%, salicylic acid 1.6% in gel basis containing methyl salicylate, net price 50 g = £7.03. **Label: 28**

**Scalp gel**
- none as listed in section 13.1.3

**Dose**
- for application to scalp, initially apply on alternate days for 10–20 minutes; may be increased to daily application for max. 1 hour and then wash off

### Salicylic acid

**SALICYLIC ACID**

For coal tar preparations containing salicylic acid, see under Tars, p. 632; for dithranol preparations containing salicylic acid see under Dithranol, p. 633

**Indications** hyperkeratotic skin disorders; acne (section 13.6.1); warts and calluses (section 13.7); scalp conditions (section 13.9); fungal nail infections (section 13.10.2)

**Cautions** see notes above; avoid broken or inflamed skin

**Salicylate toxicity** If large areas of skin are treated, salicylate toxicity may occur

**Side-effects** sensitivity, excessive drying, irritation, systemic effects after widespread use (see under Cautions)

**Dose**

- See preparations

### Oral retinoids for psoriasis

**ACITRETIN**

**Note** Acitretin is a metabolite of etretinate

**Indications** severe extensive psoriasis resistant to other forms of therapy; palmoplantar pustular psoriasis; severe congenital ichthyosis; severe Darier’s disease (keratosis follicularis)

**Cautions** exclude pregnancy before starting (test for pregnancy within 2 weeks before treatment and monthly thereafter; start treatment on day 2 or 3 of menstrual cycle)—women (including those with history of infertility) should avoid pregnancy for at least 1 month before, during, and for at least 3 years after treatment; patients should avoid concomitant tetracycline or methotrexate, high doses of vitamin A (more than 4000–5000 units daily) and use of keratolytics, and should not donate blood during or for at least 1 year after stopping therapy (teratogenic risk); check liver function at start, then every 1–2 weeks for 2 months, then every 3 months; monitor plasma lipids; diabetes (can alter glucose tolerance—initial frequent blood glucose checks); radiographic assessment on long-term treatment; investigate atypical musculoskeletal symptoms; in children use only in exceptional circumstances (premature epiphyseal closure reported); avoid excessive exposure to sunlight and unsupervised use of sunlamps; **interactions**: Appendix 1 (retinoids)

**Contra-indications** hepatic impairment (Appendix 2); renal impairment (Appendix 3); hyperlipidaemia, pregnancy (important teratogenic risk): see Cautions and Appendix 4); breast-feeding

**Side-effects** dryness of mucous membranes (sometimes erosion), of skin (sometimes scaling, thinning, erythema especially of face, and pruritus), and of conjunctiva (sometimes conjunctivitis and decreased tolerance of contact lenses); sticky skin, dermatitis; other side-effects reported include palmoplantar exfoliation, epistaxis, epidermal and nail fragility, oedema, paronychia, granulomatous lesions, bullous eruptions, reversible hair thinning and alopecia, myalgia and arthralgia, occasional nausea, headache, malaise, drowsiness, rhinitis, sweating, taste disturbance, gingivitis; benign intracranial hypertension (discontinue if severe headache, vomiting, diarrhoea, abdominal pain, and visual disturbance occur; avoid concomitant tetracyclines); photosensitivity, corneal opacity, ringing in ears, hearing loss, abdominal pain, and visual disturbance occur; **avoid** concomitant tetracyclines; photosensitivity, concomitant methotrexate; raised liver enzymes, rarely jaundice and hepatitis (**avoid** concomitant methotrexate); raised serum triglycerides or cholesterol; decreased night vision reported; skeletal hyperostosis and extra-ossseous calcification reported following long-term administration of etretinate and premature epiphyseal closure in children, see Cautions

**Dose**

- Under expert supervision, initially 25–30 mg daily (Darier’s disease 10 mg daily) for 2–4 weeks, then adjusted according to response, usual range 25–50 mg daily; up to 75 mg daily for short periods in psoriasis and ichthyosis; **CHILD** (important) exception
cumstances only, see Cautions), 500 micrograms/kg daily (occasionally up to 1 mg/kg daily to max. 35 mg daily) with careful monitoring of musculoskeletal development (see p. 631)

**Neotigason** (Actavis) [FR]

Capsules, acitretin 10 mg (brown/white), net price 60-cap pack = £25.25; 25 mg (brown/yellow), 60-cap pack = £58.59. Label: 10, patient information leaflet, 21

### 13.5.3 Drugs affecting the immune response

Drugs affecting the immune response are used for eczema or psoriasis. Systemic drugs acting on the immune system are used under specialist supervision.

**Pimecrolimus** by topical application is licensed for **mild to moderate atopic eczema**. **Tacrolimus** is licensed for topical use in **moderate to severe atopic eczema**. Both are drugs whose long-term safety and place in therapy is still being evaluated and they should not usually be considered first-line treatments unless there is a specific reason to avoid or reduce the use of topical corticosteroids. Short-term treatment with topical pimecrolimus or topical tacrolimus should be initiated only by prescribers experienced in treating atopic eczema; continuous long-term treatment should be avoided.

**NICE guidance**

**Tacrolimus and pimecrolimus for atopic eczema (August 2004)**

Topical pimecrolimus and tacrolimus are options for atopic eczema not controlled by maximal topical corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy).

Topical pimecrolimus is recommended for moderate atopic eczema on the face and neck of children aged 2–16 years and topical tacrolimus is recommended for moderate to severe atopic eczema in adults and children over 2 years. Pimecrolimus and tacrolimus should be used within their licensed indications.

For the role of topical corticosteroids in eczema, see section 13.5.1, and for comment on their limited role in psoriasis, see section 13.4. A short course of a systemic corticosteroid (section 6.3.2) can be given for eczema flares that have not improved despite appropriate corticosteroid treatment or if there is a risk of important corticosteroid side-effects (particularly skin atrophy).

**Ciclosporin** (cyclosporin) by mouth can be used for **severe psoriasis** and for **severe eczema**. **Azathioprine** (section 8.2.1) or **mycophenolate mofetil** (section 8.2.1) are used for severe refractory eczema [unlicensed indication]. **Hydroxyurea** (hydroxyurea) (section 8.1.5) is used by mouth for severe psoriasis [unlicensed indication].

**Methotrexate** can be used for **severe psoriasis**, the dose being adjusted according to severity of the condition and haematological and biochemical measurements; the usual dose is methotrexate 10 to 25 mg **once weekly**, by mouth. Folic acid 5 mg (section 9.1.2) can be given once weekly to reduce the possibility of side-effects associated with methotrexate; alternative regimens of folic acid may be used in some settings.

**Etanercept**, a cytokine modulator, is used for **severe plaque psoriasis** either refractory to at least 2 systemic treatments and photochemotherapy, or in patients intolerant of these treatments. **Efalizumab** (which inhibits T-cell activation) or another cytokine modulator, **adalimumab** or **infliximab**, are alternatives. Adalimumab, etanercept, and infliximab are also licensed for psoriatic arthritis (section 10.1.3).

**NICE guidance**

**Etanercept and efalizumab for plaque psoriasis in adults** (July 2006)

Etanercept is recommended for severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Etanercept should be withdrawn if the response is not adequate after 12 weeks.

Efalizumab is recommended for severe plaque psoriasis which has failed to respond to etanercept or when etanercept cannot be used because of intolerance or contra-indications. Efalizumab should be withdrawn if the response is not adequate after 12 weeks.

**NICE guidance**

**Infliximab for plaque psoriasis in adults** (January 2008)

Infliximab is recommended for the treatment of very severe plaque psoriasis which has failed to respond to standard systemic treatments (including ciclosporin and methotrexate) and to photochemotherapy, or when standard treatments cannot be used because of intolerance or contra-indications. Infliximab should be withdrawn if the response is not adequate after 10 weeks.

### Ciclosporin

**Ciclosporin** (Cyclosporin)

**Indications** see under Dose; severe acute ulcerative colitis (section 1.5.3); transplantation and graft-versus-host disease (section 8.2.2)

**Cautions** see section 8.2.2

**Additional cautions in atopic dermatitis and psoriasis Contra-indicated** in abnormal renal function, uncontrolled hypertension (see also below), infections not under control, and malignancy (see also below). Dermatological and physical examination, including blood pressure and renal function measurements required at least twice before starting. During treatment, monitor serum creatinine every 2 weeks

13 Skin hypersensitivity reactions, asthenia, immunodeficiency, severe infection.

Cautions moderate to severe chronic plaque psoriasis.

Dose moderate to severe chronic plaque psoriasis.

Side-effects see section 8.2.2

Dose Short-term treatment (usually for max. 8 weeks but can be longer under specialists) of severe atopic dermatitis where conventional therapy ineffective or inappropriate, administered in accordance with expert advice, by mouth, ADULT and CHILD over 16 years, initially 2.5 mg/kg daily in 2 divided doses, if good initial response not achieved within 2 weeks, increase rapidly to max. 5 mg/kg daily; initial dose of 5 mg/kg daily in 2 divided doses if very severe; CHILD under 16 years, see BNF for Children.

Severe psoriasis where conventional therapy ineffective or inappropriate, administered in accordance with expert advice, by mouth, ADULT and CHILD over 16 years, initially 2.5 mg/kg daily in 2 divided doses, increased gradually to max. 5 mg/kg daily if no improvement within 1 month (discontinue if response still insufficient after 6 weeks); initial dose of 5 mg/kg daily; CHILD under 16 years, see BNF for Children.

Important For preparations and counselling and for advice on conversion between the preparations, see section 8.2.2

EFALIZUMAB

Indications moderate to severe chronic plaque psoriasis for those whose disease is unresponsive to, or who are intolerant of other systemic therapy or photochemotherapy.

Cautions low platelet count (monitor platelet count before treatment, monthly during initial therapy then every 3 months); monitor for neurological deficits—if progressive multifocal leuкоencephalopathy suspected, suspend treatment until exclude; hepatic impairment; renal impairment; interactions: Appendix 1 (efalizumab).

Contra-indications immunodeficiency, severe infection, active tuberculosis; history of malignancy; pregnancy and breast-feeding (Appendix 5).

Side-effects hypersensitivity reactions, asthenia, influenza-like symptoms, leucocytosis, arthralgia, exacerbation of psoriasis or development of variant forms including psoriatic arthritis (discontinue treatment); less commonly thrombocytopenia and injection-site reactions; also reported progressive multifocal leuкоencephalopathy (see also under Contraindations) and inflammatory polyradiculoneuropathy.

Dose by subcutaneous injection, initially 700 micrograms/kg then 1 mg/kg weekly; discontinue if inadequate response after 12 weeks; CHILD and ADOLESCENT not recommended.

RAPTIVA (Serono) injection, powder for reconstitution, efalizumab, net price 125-mg vial = £169.20 (with 1.3 mL water for injections in prefilled syringe)

METHOTREXATE

Indications severe psoriasis unresponsive to conventional therapy (specialist use only); Crohn’s disease (section 1.5.3); malignant disease (section 8.1.3); rheumatoid arthritis (section 10.1.3).

Cautions section 10.1.3; also photosensitivity—psoriasis lesions aggravated by UV radiation (skin ulceration reported).

Contra-indications section 10.1.3

Side-effects section 10.1.3

Dose by mouth or by intramuscular or intravenous injection, 2.5–10 mg once weekly, increased according to response; max. weekly dose 30 mg; ELDERLY consider dose reduction (extreme caution); CHILD 12–18 years see BNF for Children.

Important Note that the above dose is a weekly dose. To avoid error with low dose methotrexate, it is recommended that:

- the patient is carefully advised of the dose and frequency and the reason for taking methotrexate and any other prescribed medicine (e.g. folic acid);
- only one strength of methotrexate tablet (usually 2.5 mg) is prescribed and dispensed;
- the prescription and the dispensing label clearly show the dose and frequency of methotrexate administration;
- the patient is warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine), and respiratory effects (e.g. shortness of breath).

Preparations Section 8.1.3 (parenteral) and section 10.1.3 (oral).

PIMECROLIMUS

Indications short-term treatment of mild to moderate atopic eczema (including flares) when topical corticosteroids cannot be used; see also notes above.

Cautions UV light (avoid excessive exposure to sunlight and sunlamps), avoid other topical treatments except emollients at treatment site; alcohol consumption (risk of facial flushing and skin irritation).

Contra-indications contact with eyes and mucous membranes, application under occlusion, injection at treatment site; congenital epidermal barrier defects; generalised erythroderma; immunodeficiency; concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists); application to malignant or potentially malignant skin lesions.

Side-effects burning sensation, pruritus, erythema, skin infections (including folliculitis and less commonly impetigo, herpes simplex and zoster, molluscum contagiosum); rarely papilloma, skin discoloration.
local reactions including pain, paraesthesia, peeling, dryness, oedema, and worsening of eczema; skin malignancy reported

**Dose**
- Apply twice daily until symptoms resolve (stop treatment if eczema worsens or no response after 6 weeks); **CHILD** under 2 years not recommended

**Elidel** (Novartis) **(NM)**

**Cream**, pimecrolimus 1%, net price 30 g = £19.69, 60 g = £37.41, 100 g = £59.07. Label: 4, 28

**Excipients** include benzyl alcohol, cetyl alcohol, propylene glycol, stearyl alcohol

**TACROLIMUS**

**Indications** short-term treatment of moderate to severe atopic eczema (including flares) either unresponsive to, or in patients intolerant of conventional therapy; see also notes above; other indications section 8.2.2

**Cautions** infection at treatment site, UV light (avoid excessive exposure to sunlight and sunlamps); alcohol consumption (risk of facial flushing and skin irritation); pregnancy

**Contra-indications** congenital epidermal barrier defects; generalised erythroderma; immunodeficiency; concomitant use with drugs that cause immunosuppression (may be prescribed in exceptional circumstances by specialists); application to malignant or potentially malignant skin lesions; avoid contact with eyes and mucous membranes; application under occlusion; breast-feeding (Appendix 5)

**Side-effects** application-site reactions including rash, irritation, pain and paraesthesia; herpes simplex infection, Kaposi’s varicelliform eruption; *less commonly* acne; rosacea and skin malignancy also reported

**Dose**
- **ADULT** and **CHILD** over 16 years initially apply 0.1% ointment thinly twice daily until lesion clears (consider other treatment if eczema worsens or no improvement after 2 weeks); reduce to once daily or switch to 0.03% ointment if condition allows; **CHILD** 2–16 years, initially apply 0.03% ointment twice daily for up to 3 weeks (consider other treatment if eczema worsens or if no improvement after 2 weeks) then reduce to once daily until lesion clears

**Protopic** (Astellas) **(NM)**

**Ointment**, tacrolimus (as monohydrate) 0.03%, net price 30 g = £19.44, 60 g = £36.94; 0.1%, 30 g = £21.60, 60 g = £41.04. Label: 4, 11, 28

**Excipients** include beeswax

**Cytokine modulators**

**ADALIMUMAB**

**Indications** see notes above; Crohn’s disease (section 1.5.3); ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis (section 10.1.3)

**Cautions** section 10.1.3

**Contra-indications** section 10.1.3

**Side-effects** section 10.1.3

**Dose**
- By subcutaneous injection, plaque psoriasis, **ADULT** over 18 years, initially 80 mg, then 40 mg on alternate weeks starting 1 week after initial dose; discontinue treatment if no response within 16 weeks

**Preparations** Section 10.1.3

**ETANERCEPT**

**Indications** see notes above; ankylosing spondylitis, psoriatic arthritis, polyarticular course juvenile idiopathic arthritis, rheumatoid arthritis (section 10.1.3)

**Cautions** section 10.1.3

**Contra-indications** section 10.1.3

**Side-effects** section 10.1.3

**Dose**
- By subcutaneous injection, plaque psoriasis, **ADULT** over 18 years, 25 mg twice weekly or 50 mg once weekly; max. treatment duration 24 weeks; discontinue if no response after 12 weeks

**Preparations** Section 10.1.3

**INFLIXIMAB**

**Indications** see notes above; inflammatory bowel disease (section 1.5.3); ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis (section 10.1.3)

**Cautions** section 10.1.3

**Contra-indications** section 10.1.3

**Side-effects** section 10.1.3

**Dose**
- By intravenous infusion, plaque psoriasis, **ADULT** over 18 years, 5 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks; discontinue if no response by 14 weeks of initial infusion

**Preparations** Section 10.1.3

**13.6 Acne and rosacea**

**13.6.1 Topical preparations for acne**

**13.6.2 Oral preparations for acne**

**Acne** Treatment of acne should be commenced early to prevent scarring. Patients should be counselled that an improvement may not be seen for at least a couple of months. The choice of treatment depends on whether the acne is predominantly inflammatory or comedonal and its severity.

*Mild to moderate acne* is generally treated with topical preparations (section 13.6.1). Systemic treatment (section 13.6.2) with oral antibacterials is generally used for moderate to severe acne or where topical preparations are not tolerated or are ineffective or where application to the site is difficult. Another oral preparation used for acne is the hormone treatment co-cyprindiol (cyproterone acetate with ethinylestradiol); it is for women only.

*Severe acne*, acne unresponsive to prolonged courses of oral antibacterials, scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist who may prescribe isotretinoin for administration by mouth.
13.6.1 Topical preparations for acne

In mild to moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide (see below) or to a topical retinoid (see p. 639). Alternatively, topical application of an antibacterial such as erythromycin or clindamycin may be effective for inflammatory acne. If topical preparations prove inadequate, oral preparations may be needed (section 13.6.2).

Benzoyl peroxide and azelaic acid

Benzoyl peroxide is effective in mild to moderate acne. Both comedones and inflamed lesions respond well to benzoyl peroxide. The lower concentrations seem to be as effective as higher concentrations in reducing inflammation. It is usual to start with a lower strength and to increase the concentration of benzoyl peroxide gradually. Adverse effects include local skin irritation, particularly when therapy is initiated, but the scaling and redness often subside with treatment continued at a reduced frequency of application. If the acne does not respond after 2 months then use of a topical antibiotic should be considered.

Azelaic acid has antimicrobial and anticomедoinal properties. It may be an alternative to benzoyl peroxide or to a topical retinoid for treating mild to moderate comedonal acne, particularly of the face. Some patients prefer azelaic acid because it is less likely to cause local irritation than benzoyl peroxide.

### BENZOYL PEROXIDE

#### Indications
acne vulgaris

#### Cautions
avoid contact with eyes, mouth, and mucous membranes; may bleach fabrics and hair; avoid excessive exposure to sunlight

#### Side-effects
skin irritation (reduce frequency or suspend use until irritation subsides and re-introduce at reduced frequency)

#### Dose
- Apply 1–2 times daily preferably after washing with soap and water, start treatment with lower-strength preparations
- Note: May bleach clothing

#### Acnecide® (Galderma)

- **Gel**: benzoyl peroxide 5% in an aqueous gel basis, net price 60 g = £5.69
  - Excipients include propylene glycol

### AZELAIC ACID

#### Indications
see preparations

#### Cautions
avoid contact with eyes, mouth, and mucous membranes

#### Side-effects
local irritation (reduce frequency or discontinue temporarily); less commonly skin discoloration; very rarely photosensitisation

#### Finacea® (Valeant)  

- **Gel**: azelaic acid 15%, net price 30 g = £7.48
  - Excipients include disodium edetate, propylene glycol, isopropyl palmitate
  - Dose: facial acne vulgaris; ADULT and CHILD over 14 years, apply twice daily; discontinue if no improvement after 1 month
  - Papulopustular rosacea, ADULT over 18 years, apply twice daily

#### Skinoren® (Valeant)  

- **Cream**: azelaic acid 20%, net price 30 g = £3.74
  - Excipients include propylene glycol
  - Dose: acne vulgaris, apply twice daily (sensitive skin, once daily for first week). Extended treatment may be required but manufacturer advises period of treatment should not exceed 5 months

### Topical antibacterials for acne

For many patients with mild to moderate inflammatory acne, topical antibacterials may be no more effective than topical benzoyl peroxide or tretinoin. Topical antibacterials are probably best reserved for patients who wish to avoid oral antibacterials or who cannot tolerate them. Topical preparations of erythromycin and clindamycin are effective for inflammatory acne. Topical antibacterials can produce mild irritation of the skin, and on rare occasions cause sensitisation. Antibacterial resistance of Propionibacterium acnes is increasing; there is cross-resistance between erythromycin and clindamycin.
**mycanyl and clindamycin. To avoid development of resistance:**
- when possible use non-antibiotic antimicrobials (such as benzoyl peroxide or azelaic acid);
- avoid concomitant treatment with different oral and topical antibacterials;
- if a particular antibacterial is effective, use it for repeat courses if needed (short intervening courses of benzoyl peroxide or azelaic acid may eliminate any resistant propionibacteria);
- do not continue treatment for longer than necessary (however, treatment with a topical preparation should be continued for at least 6 months).

**ANTIBACTERIALS**

**Indications** acne vulgaris

**Cautions** some manufacturers advise preparations containing alcohol are not suitable for use with benzoyl peroxide

**Dalacin T** (Pharmacia) (£)

- **Topical solution**, clindamycin 1% (as phosphate), in an aqueous alcoholic basis, net price (both with applicator) 30 mL = £4.34, 50 mL = £7.23
- **Excipients** include propylene glycol
- **Dose** apply twice daily

**Lotion**, clindamycin 1% (as phosphate) in an aqueous basis, net price 30 mL = £5.08, 50 mL = £8.47
- **Excipients** include cetostearyl alcohol, hydroxybenzoates (parabens)
- **Dose** apply twice daily

**Stiemycin** (Stiefel) (£)

- **Solution**, erythromycin 2% in an alcoholic basis, net price 50 mL = £8.00
- **Excipients** include propylene glycol
- **Dose** apply twice daily

**Zindacin** (Crawford) (£)

- **Gel**, clindamycin 1% (as phosphate), net price 30 g = £8.66
- **Excipients** include propylene glycol
- **Dose** apply once daily

**Zineryt** (Astellas) (£)

- **Topical solution**, powder for reconstitution, erythromycin 40 mg, zinc acetate 12 mg/mL when reconstituted with solvent containing ethanol, net price per pack of powder and solvent to provide 30 mL = £7.71, 90 mL = £22.24
- **Excipients** none as listed in section 13.1.3
- **Dose** apply twice daily

**Topical retinoids and related preparations for acne**

Topical **tretinoin** and its isomer **isotretinoin** are useful for treating comedones and inflammatory lesions in mild to moderate acne. Patients should be warned that some redness and skin peeling may occur initially but settles with time. Several months of treatment may be needed to achieve an optimal response and the treatment should be continued until no new lesions develop. Isotretinoin is given by mouth in severe acne; see section 13.6.2 for warnings relating to use by mouth.

Adapalene, a retinoid-like drug, is licensed for mild to moderate acne. It is less irritating than topical retinoids.

**Cautions** Topical retinoids should be avoided in severe acne involving large areas. Contact with eyes, nostrils, mouth and mucous membranes, eczematous, broken or sunburned skin should be avoided. These drugs should be used with caution in sensitive areas such as the neck, and accumulation in angles of the nose should be avoided. Exposure to UV light (including sunlight, solariums) should be avoided; if sun exposure is unavoidable, an appropriate sunscreen or protective clothing should be used. Use of retinoids with abrasive cleaners, comedogenic or astringent cosmetics should be avoided. Allow peeling (e.g. resulting from use of benzoyl peroxide) to subside before using a topical retinoid; alternating a preparation that causes peeling with a topical retinoid may give rise to contact dermatitis (reduce frequency of retinoid application).

**Contra-indications** Topical retinoids are contra-indicated in pregnancy (Appendix 4); women of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective). Tretinoin is contra-indicated in personal or familial history of cutaneous epithelioma.

**Side-effects** Local reactions include burning, erythema, stinging, pruritus, dry or peeling skin (discontinue if severe). Increased sensitivity to UVB light or sunlight occurs. Temporary changes of skin pigmentation have been reported. Eye irritation and oedema, and blistering or crumbling of skin have been reported rarely.

**ADAPALENE**

**Indications** mild to moderate acne

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- Apply thinly once daily before retiring

**Differin** (Galderma) (£)

- **Cream**, adapalene 0.1%, net price 45 g = £11.40
- **Excipients** include disodium edetate, hydroxybenzoates (parabens)
- **Dose** apply once daily

**TRETINOIN**

**Note** Tretinoin is the acid form of vitamin A

**Indications** see preparations; malignant disease (section 8.1.5)

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Dose**
- See preparations

**Retin-A** (Janssen-Cilag) (£)

- **Gel**, tretinoin 0.01%, net price 60 g = £3.61; 0.025%, 60 g = £5.61
- **Excipients** include butylated hydroxytoluene
- **Dose** acne vulgaris, apply thinly 1–2 times daily

**With antibacterial**

**Aknemycin® Plus** (Almirall) (£)

- **Solution**, tretinoin 0.025%, erythromycin 4% in an alcoholic basis, net price 25 mL = £7.05
- **Excipients** none as listed in section 13.1.3
- **Dose** acne, apply thinly 1–2 times daily
ISOTRETINOIN

Note
Isotretinoin is an isomer of tretinoin

Important
For indications, cautions, contra-indications and side-effects of isotretinoin when given by mouth, see p. 641

Indications
see notes above; oral treatment (see section 13.6.2)

Cautions
(topical application only) see notes above

Contra-indications
(topical application only) see notes above

Dose
- Apply thinly 1–2 times daily

Isotrexin\(^\text{c}\) (Stiefel) \(\text{PH}\)
Gel, isotretinoin 0.05%, net price 30 g = £6.18
Excipients include butylated hydroxytoluene

With antibacterial

Isotrexin\(^\text{c}\) (Stiefel) \(\text{PH}\)
Gel, isotretinoin 0.05%, net price 30 g = £7.78
Excipients include butylated hydroxytoluene

Other topical preparations for acne

Salicylic acid is available in various preparations for sale direct to the public for the treatment of mild acne. Other products are more suitable for acne; salicylic acid is used mainly for its keratolytic effect.

Preparations containing sulphur and abrasive agents are not considered beneficial in acne.

Topical corticosteroids should not be used in acne.

A topical preparation of nicotinamide is available for inflammatory acne.

ABRASIVE AGENTS

Indications
acne vulgaris (but see notes above)

Cautions
avoid contact with eyes; discontinue use temporarily if skin becomes irritated

Contra-indications
superficial venules, telangiectasia

Brasivol\(^\text{c}\) (Stiefel) \(\text{PH}\)
Paste No. 1, aluminium oxide 38.09% in fine particles, in a soap-detergent basis, net price 75 g = £2.21
Excipients include fragrance, \(N\)-(3-Chloroallyl)hexaminium chloride (quaternium 15)
Dose
use instead of soap 1–3 times daily

CORTICOSTEROIDS

Indications
use in acne not recommended (see notes above)

Cautions
see section 13.4 and notes above

Contra-indications
see section 13.4 and notes above

Side-effects
see section 13.4 and notes above

Actinac\(^\text{c}\) (Peckforton) \(\text{PH}\)
Lotion (powder for reconstitution with solvent), chloramphenicol 40 mg, hydrocortisone acetate 40 mg, allantoin 24 mg, butoxyethyl nicotinate 24 mg, precipitated sulphur 320 mg/g. Discard 21 days after reconstitution, net price 2 × 6.25-g bottles powder with 2 × 20-mL bottles solvent = £16.28. Label: 28. Potency: mild
Excipients none as listed in section 13.1.3

NICOTINAMIDE

Indications
see under preparation

Cautions
avoid contact with eyes and mucous membranes (including nose and mouth); reduce frequency of application if excessive dryness, irritation or peeling

Side-effects
dryness of skin; also pruritus, erythema, burning and irritation

Nicam\(^\text{c}\) (Dermal) \(\text{PH}\)
Gel, nicotinamide 4%, net price 60 g = £7.42
Excipients none as listed in section 13.1.3
Dose
inflammatory acne vulgaris, apply twice daily; reduce to once daily or on alternate days if irritation occurs

SALICYLIC ACID

Indications
acne; psoriasis (section 13.5.2), warts and calluses (section 13.7); fungal nail infections (section 13.10.2)

Cautions
avoid contact with mouth, eyes, mucous membranes; systemic effects after excessive use (see section 4.7.1)

Side-effects
local irritation

Acnisal\(^\text{c}\) (Alliance) \(\text{PH}\)
Topical solution, salicylic acid 2% in a detergent and emollient basis, net price 177 mL = £4.03.
Excipients include benzyl alcohol
Dose
use up to 3 times daily

13.6.2 Oral preparations for acne

Oral antibacterials for acne

Systemic antibacterial treatment is useful for inflammatory acne if topical treatment is not adequately effective or if it is inappropriate. Anticomendal treatment (e.g. with topical benzoyl peroxide) may also be required.

Either oxytetracycline or tetracycline (section 5.1.3) is usually given for acne in a dose of 500 mg twice daily. If there is no improvement after the first 3 months another oral antibacterial should be used. Maximum improvement usually occurs after 4 to 6 months but in more severe cases treatment may need to be continued for 2 years or longer.

Doxycycline and lymecycline (section 5.1.3) are alternatives to tetracycline. Doxycycline can be used in a dose of 100 mg daily. Lymecycline is given in a dose of 408 mg daily.

Although minocycline is as effective as other tetracyclines for acne, it is associated with a greater risk of lupus erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation; it is given in a dose of 100 mg once daily or 50 mg twice daily.

Erythromycin (section 5.1.5) in a dose of 500 mg twice daily is an alternative for the management of acne but propionibacteria strains resistant to erythromycin are becoming widespread and this may explain poor response.

Trimethoprim (section 5.1.8) in a dose of 300 mg twice daily may be used for acne resistant to other antibacterials [unlicensed indication]. Prolonged treatment with
trimethoprim may depress haematopoiesis; it should generally be initiated by specialists. Concomitant use of different topical and systemic antibacterials is undesirable owing to the increased likelihood of the development of bacterial resistance.

### Hormone treatment for acne

**Co-cyprindiol** (cyproterone acetate with ethinylestradiol) contains an anti-androgen. It is no more effective than an oral broad-spectrum antibacterial but is useful in women who also wish to receive oral contraception. Improvement of acne with co-cyprindiol probably occurs because of decreased sebum secretion which is under androgen control. Some women with moderately severe hirsutism may also benefit because hair growth is also androgen-dependent. Contra-indications of co-cyprindiol include pregnancy and a predisposition to thrombosis.

**Side-effects** see under Combined Hormonal Contraceptives, section 7.3.1

**Contra-indications** see under Combined Hormonal Contraceptives, section 7.3.1

**Dose**

- 1 tablet daily for 21 days starting on day 1 of menstrual cycle and repeated after a 7-day interval, usually for several months; withdraw 3–4 months after acne or hirsutism completely resolved (repeat courses may be given if recurrence); long-term treatment may be necessary for severe symptoms

**Co-cyprindiol** (Non-proprietary) *(Schering Health)*

- **Tablets**, co-cyprindiol 2000/35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms), net price 21-tab pack = £3.74
- **Brands** include Acnecin, Cicafem, Clairette, Diva

**Dianette** *(Schering Health)*

- **Tablets**, beige, s/c, co-cyprindiol 2000/35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms), net price 21-tab pack = £3.70

### Oral retinoid for acne

The retinoid **isotretinoin** reduces sebum secretion. It is used for the systemic treatment of nodulo-cystic and conglobate acne, severe acne, scarring, acne which has not responded to an adequate course of a systemic antibacterial, or acne which is associated with psychological problems. It is also useful in women who develop acne in the third or fourth decades of life, since late onset acne is frequently unresponsive to antibacterials. Isotretinoin is a toxic drug that should be prescribed only by, or under the supervision of, a consultant dermatologist. It is given for at least 16 weeks; repeat courses are not normally required.

**Side-effects of isotretinoin** include severe dryness of the skin and mucous membranes, nose bleeds, and joint pains. The drug is **teratogenic** and must not be given to women of child-bearing age unless they practise effective contraception (oral progestogen-only contraceptives not considered effective) and then only after detailed assessment and explanation by the physician. Women must also be registered with a pregnancy prevention programme (see under Cautions below).

Although a causal link between isotretinoin use and psychiatric changes (including suicidal ideation) has not been established, the possibility should be considered before initiating treatment; if psychiatric changes occur during treatment, isotretinoin should be stopped, the prescriber informed, and specialist psychiatric advice should be sought.

### ISOTRETINOIN

**Note** Isotretinoin is an isomer of tretinoin

**Indications** see notes above

**Cautions** exclude pregnancy before starting (perform pregnancy test 2–3 days before expected menstruation, start treatment on day 2 or 3 of menstrual cycle)—women must practice effective contraception at least 1 month before, during, and for at least 1 month after treatment (see also notes above); avoid blood donation during treatment and for at least 1 month after treatment; history of depression; measure hepatic function and serum lipids before treatment, 1 month after starting and then every 3 months (reduce dose or discontinue if transaminase or serum lipids persistently raised); discontinue if uncontrolled hypertriglyceridaemia or pancreatitis; diabetes; dry eye syndrome (associated with risk of keratitis); avoid keratolytics; renal impairment (Appendix 3); interactions: Appendix 1 (retinoids)

**Counselling** Warn patient to avoid wax epilation (risk of epidermal stripping), dermabrasion, and laser skin treatments (risk of scarring) during treatment and for at least 6 months after stopping; patient should avoid exposure to UV light (including sunlight) and use sunscreen and emollient (including lip balm) preparations from the start of treatment.

**Contra-indications** pregnancy (important teratogenic risk: see Cautions above and Appendix 4); breast-feeding; hepatic impairment (Appendix 2); hypervitaminosis A, hyperlipidaemia

**Side-effects** dryness of skin (with dermatitis, scaling, thinning, erythema, puritus), epidermal fragility (trauma may cause blistering), dryness of lips (sometimes cheilitis), dryness of eyes (with blepharitis and conjunctivitis), dryness of pharyngeal mucosa (with hoarseness), dryness of nasal mucosa (with epistaxis), headache, myalgia and arthralgia, raised plasma concentration of triglycerides, of glucose, of serum
transaminases, and of cholesterol (risk of pancreatitis if triglycerides above 9 mmol/litre), haematuria and proteinuria, thrombocytopenia, thrombocytosis, neutropenia and anaemia; rarely mood changes (depression, suicidal ideation, aggressive behaviour, anxiety)—expert referral required, exacerbation of acne, acne fulminans, allergic skin reactions, and hypersensitivity, alopecia; very rarely nausea, inflammatory bowel disease, diarrhoea (discontinue if severe), benign intracranial hypertension (avoid concomitant tetracyclines), convulsions, malaise, drowsiness, dizziness, lymphadenopathy, increased sweating, hyperuricaemia, raised serum creatinine concentration and glomerulonephritis, hepatitis, tendinitis, bone changes (including reduced bone density, early epiphyseal closure, and skeletal hyperostosis following long-term administration), visual disturbances (papilloedema, corneal opacities, cataracts, decreased night vision, photophobia, blurred vision, colour blindness)—expert referral required and consider withdrawal, decreased tolerance to contact lenses and keratitis, impaired hearing, Gram-positive infections of skin and mucous membranes, allergic vasculitis and granulomatous lesions, paronychia, hirsutism, nail dystrophy, skin hyperpigmentation, photosensitivity

**Dose**

- ADULT and CHILD over 12 years, 500 micrograms/kg daily increased if necessary to 1 mg/kg (1–2 divided doses) for 16–24 weeks (repeat treatment course after a period of at least 8 weeks if failure or relapse after first course); max. cumulative dose 150 mg/kg per course

**Isotretinoin (Non-proprietary)** [FR]

- **Capsules**; isotretinoin 5 mg, net price 56-cap pack = £14.99; 20 mg, 56-cap pack = £39.99. Label: 10, patient information leaflet, 11, 21

**Roaccutane® (Roche)** [FR]

- **Capsules**; isotretinoin 5 mg (red-violet/white), net price 30-cap pack = £9.08; 20 mg (red-violet/white), 30-cap pack = £25.02. Label: 10, patient information leaflet, 11, 21

- Excipients include arachis (peanut) oil

**13.7 Preparations for warts and calluses**

Warts (verrucas) are caused by a human papillomavirus, which most frequently affects the hands, feet (plantar warts), and the anogenital region (see below); treatment usually relies on local tissue destruction. Warts may regress on their own and treatment is required only if the warts are painful, unsightly, persistent, or cause distress.

Preparations of salicylic acid, formaldehyde, gluconolactone or silver nitrate are available for purchase by the public; they are suitable for the removal of warts on hands and feet. Salicylic acid is a useful keratolytic which may be considered first; it is also suitable for the removal of corns and calluses. Preparations of salicylic acid in a collodion basis are available but some patients may develop an allergy to colophony in the formulation.

An ointment combining salicylic acid with podophyllin resin (Posaflin®) is available for treating plantar warts. Cryotherapy causes pain, swelling, and blistering and may be no more effective than topical salicylic acid in the treatment of warts.

### SALICYLIC ACID

**Indications** see under preparations; psoriasis (section 13.5.2); acne (section 13.6.1); fungal nail infections (section 13.10.2)

**Cautions** significant peripheral neuropathy, patients with diabetes at risk of neuropathic ulcers; protect surrounding skin and avoid broken skin; not suitable for application to face, anogenital region, or large areas

**Side-effects** skin irritation, see notes above

**Dose**

- See under preparations; advise patient to apply carefully to wart and to protect surrounding skin (e.g. with soft paraffin or specially designed plaster); rub wart surface gently with file or pumice stone once weekly; treatment may need to be continued for up to 3 months

**Cuplex® (Crawford)**

- Gel, salicylic acid 11%, lactic acid 4%, in a collodion basis, net price 5 g = £2.23. Label: 15

**Duofilm® (Stiefel)**

- Paint, salicylic acid 16.7%, lactic acid 16.7%, in flexible collodion, net price 15 mL (with applicator) = £2.25. Label: 15

**Occusal® (Alliance)**

- Cutaneous solution, salicylic acid 26% in polyacrylic solution, net price 10 mL (with applicator) = £3.39. Label: 15

**Salactol® (Dermal)**

- Paint, salicylic acid 16.7%, lactic acid 16.7%, in flexible collodion, net price 10 mL (with applicator) = £1.79. Label: 15

**Salatac® (Dermal)**

- Gel, salicylic acid 12%, lactic acid 4% in a collodion basis, net price 8 g (with applicator) = £3.12. Label: 15

**Verrugon® (Ransom)**

- Ointment, salicylic acid 50% in a paraffin basis, net price 6 g = £2.83

### With podophyllum

**Posaflin® (Norgine)**

- Ointment, podophyllin resin 20%, salicylic acid 25%, net price 10 g = £3.51

**Note** Owing to the salicylic acid content, not suitable for genital warts; owing to the podophyllin content also contra-indicated in pregnancy and breast-feeding
### FORMALDEHYDE

**Indications** see under preparations

**Cautions** see under Salicylic Acid

**Side-effects** see under Salicylic Acid

**Veracur®** (Typharm)

* Gel, formaldehyde 0.75% in a water-miscible gel basis, net price 15 g = £2.41.

**Dose** for warts, particularly planter warts, apply twice daily

### GLUTARALDEHYDE

**Indications** warts, particularly planter warts

**Cautions** protect surrounding skin; not for application to face, mucosa, or anogenital areas

**Side-effects** rashes, skin irritation (discontinue if severe); stains skin brown

**Dose**
- Apply twice daily (see also under Salicylic acid)

**Glutarol®** (Dermal)

* Solution (= application), glutaraldehyde 10%, net price 10 mL (with applicator) = £2.17

### SILVER NITRATE

**Indications** warts, verrucas, umbilical granulomas, over-granulating tissue, cauterisation

**Cautions** protect surrounding skin and avoid broken skin; not suitable for application to face, ano-genital region, or large areas

**Side-effects** chemical burns on surrounding skin; stains skin and fabric

**Dose**
- Common warts and verrucas, apply moistened caustic pencil tip for 1–2 minutes; repeat after 24 hours up to max. 3 applications for warts or max. 6 applications for verrucas
- Instructions in proprietary packs generally incorporate advice to remove dead skin before use by gentle filing and to cover with adhesive dressing after application
- Umbilical granulomas, apply moistened caustic pencil tip (usually containing silver nitrate 40%) for 1–2 minutes while protecting surrounding skin with soft paraffin

**Silver nitrate** (Non-proprietary)

* Caustic pencil, tip containing silver nitrate 40%, potassium nitrate 60%, net price = 93p

**AVOCA®** (Bray)

* Caustic pencil, tip containing silver nitrate 95%, potassium nitrate 5%, net price, treatment pack (including emery file, 6 adhesive dressings and protector pads) = £1.94.

### IMIQUIMOD

**Indications** see under Dose

**Cautions** avoid normal or broken skin, and open wounds; not suitable for internal genital warts; uncircumcised males (risk of phimosis or stricture of foreskin); autoimmune disease; immunosuppressed patients; pregnancy (Appendix 4)

**Side-effects** local reactions (including itching, burning sensation, erythema, erosion, oedema, excoriation, and scabbing); headache; influenza-like symptoms; myalgia; less commonly local ulceration and alopecia; rarely Stevens-Johnson syndrome and cutaneous lupus erythematosus-like effect; very rarely dysuria in women; permanent hypopigmentation or hyperpigmentation reported

**Dose**
- Warts (external genital and perianal), apply thinly 3 times a week at night until lesions resolve (max. 16 weeks)
- Superficial basal cell carcinoma, apply to lesion (and 1 cm beyond it) on 5 days each week for 6 weeks; assess response 12 weeks after completing treatment
- Actinic keratosis, apply to lesion 3 times a week for 4 weeks; assess response after a 4 week treatment-free interval; repeat 4-week course if lesions persist; max. 2 courses
- **CHILD** under 18 years, see BNF for Children

**Important** Should be rubbed in and allowed to stay on the treated area for 6–10 hours for warts or for 8 hours for basal cell carcinoma and actinic keratosis, then washed off with mild soap and water (uncircumcised males treating warts under foreskin should wash the area daily). The cream should be washed off before sexual contact

**Aldara®** (3M)

* Cream, imiquimod 5%, net price 12-sachet pack = £61.32. Label: 10, patient information leaflet

**Excipients** include benzyl alcohol, cetyl alcohol, hydroxybenzamides (parabens), polysorbate 60, stearyl alcohol

**Condoms** may damage latex condoms and diaphragms

### PODOPHYLLOTOXIN

**Indications** see under preparations

**Cautions** avoid normal skin and open wounds; keep away from face; very irritant to eyes

**Contra-indications** pregnancy and breast-feeding; children

**Side-effects** see notes above

**Condyline®** (Ardern)

* Solution, podophyllotoxin 0.5% in alcohol basis, net price 3.5 mL (with applicators) = £14.49. Label: 15

**Dose** condylomata acuminata affecting the penis or the female external genitalia, apply twice daily for 3 consecutive days.

**Condyline®** (Ardern) may be used for soft, non-keratinised external anogenital warts; it may cause considerable irritation of the treated area. It can also cause severe systemic toxicity on excessive application including gastro-intestinal, renal, haematological, and CNS effects. Patients with a limited number of external warts or keratinised lesions may be better treated with cryotherapy or other forms of physical ablation.

### Anogenital warts

The treatment of anogenital warts (condylomata acuminata) should be accompanied by screening for other sexually transmitted diseases. Podophyllotoxin (the major active ingredient of podophyllum) may be used for soft, non-keratinised external anogenital warts; it can cause considerable irritation of the treated area. It can also cause severe systemic toxicity on excessive application including gastro-intestinal, renal, haematological, and CNS effects. Patients with a limited number of external warts or keratinised lesions may be better treated with cryotherapy or other forms of physical ablation.

Imiquimod cream is licensed for the treatment of external anogenital warts; it may be used for both keratinised and non-keratinised lesions. It is also licensed for the treatment of superficial basal cell carcinoma and actinic keratosis (section 13.8.1).

Inosine pranobex (section 5.3.2.1) is licensed for adjunctive treatment of genital warts but it has been superseded by more effective drugs.
Skin
the changes responsible for
UVB contribute to long-term
(320–400 nm, known as UVA) are responsible for many
is lower than that found in experimental studies.
apply sufficient sunscreen product and the protection
without burning. However, in practice, users do not
apply protections provided against burning, compared
protection offered against UVB; it indicates the multi-
preparations title) provides guidance on the degree of
protection against UVA and UVB radiation, but they are no
protection against UVB. It indicates the multiples of
protection provided against burning, compared with unprotected skin; for example, an SPF of 8 should
eable a person to remain 8 times longer in the sun
without burning. However, in practice, users do not
apply sufficient sunscreen product and the protection
is lower than that found in experimental studies.

solution, blue, photoprotectin 0.5% in alcoholic
basis, net price 3 mL (with applicators—Warticon®
[for men]; with applicators and mirror—Warticon Fem®
[for women]) = £12.88. Label: 15
Dose
condylo mata acuminata affecting the penis or the female
external genitalia, apply twice daily for 3 consecutive days.
treatment may be repeated at weekly intervals if necessary for a
total of four 3-day treatment courses; direct medical supervision
for lesions greater than 4 cm.

Solution, blue, photoprotectin 0.5% in alcoholic
basis, net price 3 mL (with applicators—Warticon®
[for men]; with applicators and mirror—Warticon Fem®
[for women]) = £12.88. Label: 15
Dose
condylo mata acuminata affecting the penis or the female
external genitalia, apply twice daily for 3 consecutive days.
treatment may be repeated at weekly intervals if necessary for a
total of four 3-day treatment courses; direct medical supervision
for lesions greater than 4 cm.

13.8 Sunscreens and camouflage

13.8.1 Sunscreen preparations

Solar ultraviolet irradiation can be harmful to the skin. It
is responsible for disorders such as polymorphic light
eruption, solar urticaria, and it provokes the various
cutaneous porphyrias. It also provokes (or at least aggra-
vates) skin lesions of lupus erythematosus and may
aggravate rosacea and some other dermatoses. Certain
drugs, such as demeclocycline, phenothiazines, or ami-
darone, can cause photosensitivity. All these conditions
(as well as sunburn) may occur after relatively short
periods of exposure to the sun. Solar ultraviolet irradia-
tion may provoke attacks of recurrent herpes labialis
(but it is not known whether the effect of sunlight
exposure is local or systemic).
The effects of exposure over longer periods include
ageing changes and more importantly the initiation of
skin cancer.
Solar ultraviolet radiation is approximately 200–400 nm
in wavelength. The medium wavelengths (290–320 nm, known as UVA) cause sunburn. The long wavelengths
(320–400 nm, known as UVA) are responsible for many
photosensitivity reactions and photodermatoses. Both UVA
and UVB contribute to long-term photodamage and to
the changes responsible for skin cancer and ageing.
Sunscreen preparations contain substances that protect
the skin against UVA and UVB radiation, but they are no
substitute for covering the skin and avoiding sunlight.
The sun protection factor (SPF, usually indicated in the
preparation title) provides guidance on the degree of
protection offered against UVB; it indicates the multiply-
ies of protection provided against burning, compared with unprotected skin; for example, an SPF of 8 should enable a person to remain 8 times longer in the sun without burning. However, in practice, users do not apply sufficient sunscreen product and the protection is lower than that found in experimental studies.

Some manufacturers use a star rating system to indicate
the protection against UVA relative to protection against
UVB for sunscreen products. However, the usefulness of
the star rating system remains controversial. The EU
Commission (September 2006) has recommended that
the UVA protection factor for a sunscreen should be at
least one-third of the sun protection factor (SPF); pro-
ducts that achieve this requirement will be labelled with a
UVA logo alongside the SPF classification. Prepara-
tions that also contain reflective substances, such as
titanium dioxide, provide the most effective protection
against UVA.
Sunscreen preparations may rarely cause allergic reac-
tions.

Borderline substances
The preparations marked ‘ACBS’ are regarded as drugs when prescribed for skin protection against ultraviolet radiation in abnormal cutaneous photosensitivity resulting from genetic dis-
orders or photodermatoses, including vitiligo and those
resulting from radiotherapy; chronic or recurrent herpes
simplex labialis. Preparations with SPF less than 30
should not normally be prescribed. See also Appendix 7.

Delph (Fenton)
Lotion, (UVA and UVB protection; UVB-SPF 30), avoben-
zone 4%, octinoxate 4.8%, oxybenzone 1.5%, titanium
dioxide 2.5%, net price 200 mL = £3.53. ACBS
Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens), imidurea
E45 Sun (Crookes)
Reflective Sunscreen (UVA and UVB protection; UVB-SPF 50), water resistant, avobenzone 2%, oxybenzone 3%, padimate-O 8%,
titanium dioxide 2%, net price 150 mL = £7.09. ACBS
Excipients include hydroxybenzoates (parabens), isopropyl palmitate
Spectran (Stiefel)
Ultra lotion (UVA and UVB protection; UVB-SPF 28), water resistant, avobenzone 2%, oxybenzone 3%, padimate-O 8%,
titanium dioxide 2%, net price 150 mL = £6.54. ACBS
Excipients include benzyl alcohol, disodium edetate, sorbic acid, fragrance
Sunsense Ultra (Crawford)
Lotion (UVA and UVB protection; UVB-SPF 60), octinoxate
7.5% oxybenzone 3%, titanium dioxide 3.5%, net price 50-
Ml bottle with roll-on applicator = £3.11, 125 mL = £5.10.
ACBS
Excipients include butylated hydroxytoluene, cetyl alcohol, fragrance, hydroxybenzoates (parabens), propylene glycol
Uvistat (LPC)
Cream (UVA and UVB protection; UVB-SPF 30), avoben-
zone 5%, bisoctoctrizole 1.5%, octinoxate 7.5%, octocorraine 4%, titanium dioxide 5.2%, net price 125 mL = £7.45. ACBS
Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol
Cream (UVA and UVB protection; UVB-SPF 50), amiloxole 2%, avobenzone 5%, bisoctoctrizole 6%, octinoxate 10%,
ococtorraine 4%, titanium dioxide 4.8%, net price 125 mL = £8.45. ACBS
Excipients include disodium edetate, polyborate 60, propylene glycol
Lipscreen (UVA and UVB protection; UVB-SPF 50), avoben-
zone 5%, bemozatinol 3%, octinoxate 10%, octocorraine 4%, titanium dioxide 3%, net price 5 g = £2.99. ACBS
Excipients include butylated hydroxytoluene, hydroxybenzoates (parabens)
Photodamage

Patients should be advised to use a high-SPF sunscreen and to minimise exposure of the skin to direct sunlight or sun lamps.

Topical treatments are used for non-hypertrophic actinic keratosis. An emollient may be sufficient for mild lesions. Diclofenac gel is suitable for the treatment of superficial lesions in mild disease. Fluorouracil cream is effective against most types of non-hypertrophic actinic keratosis. Imiquimod (section 13.7) is used for lesions on the face and scalp when cryotherapy or other topical treatments cannot be used. Fluorouracil and imiquimod produce a more marked inflammatory reaction than diclofenac but lesions resolve faster. Photodynamic therapy in combination with methyl-5-aminolevulinate cream (Metvix®, available from Galderma) is used in specialist centres for treating superficial and confluent, non-hypertrophic actinic keratosis when other treatments are inadequate or unsuitable; it is particularly suitable for multiple lesions, for periorbital lesions, or for lesions located at sites of poor healing.

Imiquimod or topical fluorouracil is used for treating superficial basal cell carcinomas. Photodynamic therapy in combination with methyl-5-aminolevulinate cream is used in specialist centres for treating superficial, nodular basal cell carcinomas when other treatments are unsuitable.

**DICLOFENAC SODIUM**

**Indications** actinic keratosis

**Cautions** as for topical NSAIDs, see section 10.3.2

**Contra-indications** as for topical NSAIDs, see section 10.3.2

**Side-effects** as for topical NSAIDs, see section 10.3.2; also paraesthesia; application of large amounts may result in systemic effects, see section 10.1

**Dose**

- Apply thinly twice daily for 60–90 days; max. 8 g daily

Solaraze® (Almirall) **Gel**, diclofenac sodium 3% in a sodium hyaluronate basis, net price 50 g = £33.30

Excipients include benzyl alcohol

**FLUOROURACIL**

**Indications** superficial malignant and pre-malignant skin lesions; other malignant disease (section 8.1.3)

**Caution** avoid contact with mucous membranes; caution in handling—irritant to tissues

**Contra-indications** pregnancy (Appendix 4); breastfeeding

**Side-effects** local irritation (use a topical cortico-steroid for severe discomfort associated with inflammatory reactions), photosensitivity; rarely erythema multiforme

**Dose**

- Apply thinly to the affected area once or twice daily; if possible, cover malignant lesions with occlusive dressing; max. area of skin treated at one time, 500 cm²; usual duration of initial therapy, 3–4 weeks

**Note** Alternative regimens may be in use in some settings

Efudix® (Valeant) **Cream**, fluorouracil 5%, net price 20 g = £17.72, 40 g = £35.44

Excipients include hydroxybenzoates (parabens), polysorbate 60, propylene glycol, stearyl alcohol

**13.9 Shampoos and other preparations for scalp and hair conditions**

**Dandruff** is considered to be a mild form of seborrhoeic dermatitis (see also section 13.5.1). Shampoos containing antimicrobial agents such as pyrithione zinc (which are widely available) and selenium sulphide may have beneficial effects. Shampoos containing tar extracts may be useful and they are also used in psoriasis. Ketoconazole shampoo should be considered for more persistent or severe dandruff or for seborrhoeic dermatitis of the scalp.

**Corticosteroid** gels and lotions (section 13.4) can also be used.

Shampoos containing coal tar and salicylic acid may also be useful. A cream or an ointment containing coal tar and salicylic acid is very helpful in psoriasis that affects the scalp (section 13.5.2). Patients who do not respond to these treatments may need to be referred to exclude the possibility of other skin conditions.

**Cradle cap** in infants may be treated with coconut oil or olive oil applications followed by shampooing.
See below for male-pattern baldness and also section 13.5 (psoriasis and eczema), section 13.10.4 (lice), and section 13.10.2 (ringworm).

### Shampoos

1. **Ketoconazole** (Non-proprietary) *(NH)*
   - **Cream**—section 13.10.2
   - **Shampoo**, ketoconazole 2%, net price 120 mL = £2.26
     - **Excipients** include imidurea
     - **Brands** include **Dandraxol**
     - **2% Shampoo, Nizoral**
     - **Dose**—treatment of seborrhoeic dermatitis and dandruff apply twice weekly for 2–4 weeks (prophylaxis apply every 1–2 weeks); treatment of pityriasis versicolor apply once daily for max. 5 days (prophylaxis apply once daily for up to 3 days before sun exposure); leave preparation on at least 3–5 minutes before rinsing

2. **Can be sold to the public for the prevention and treatment of**
   - **Ketoconazole** section 13.10.2 (ringworm).
   - **Ketoconazole** section 13.5 (psoriasis and eczema), section 13.10.4 (lice), and
   - **See below for male-pattern baldness and also section 646**

### Other preparations for scalp and hair conditions

#### Shampoos and other preparations for scalp and hair conditions BNF 57

- **Section 13.9**

**Psoriderm** *(Dermal)*
- **Scalp lotion** *(= shampoo)*, coal tar 2.5%, lecinthin 0.3%, net price 250 mL = £4.96
  - **Excipients** include disodium edetate
  - **Dose**—scalp psoriasis, seborrhoeic dermatitis, and dandruff, use as necessary

**Selsun** *(Chattem UK)*
- **Shampoo**, selenium sulphide 2.5%, net price 50 mL = £1.44, 100 mL = £1.96, 150 mL = £2.75
  - **Excipients** include fragrance
  - **Cautions** avoid using 48 hours before or after applying hair colouring, straightening or waving preparations
  - **Dose**—seborrhoeic dermatitis and dandruff, apply twice weekly for 2 weeks then once weekly for 2 weeks and then as necessary; **CHILD** under 5 years not recommended, pityriasis versicolor, section 13.10.2 [unlicensed indication]

#### T/Gel (® & ™)
- **Shampoo**, coal tar extract 2%, net price 125 mL = £3.18, 250 mL = £4.78
  - **Excipients** include fragrance, hydroxybenzoates (parabens), imidurea, tetradecimid edetate
  - **Dose**—scalp psoriasis, seborrhoeic dermatitis, dandruff, apply as necessary

### Other scalp preparations

#### Cocos®
- **Section 13.5.2**

#### Etrivex®
- **Section 13.4**

#### Polytar® (® & ™)
- **Dermal**
  - **Liquid**, arachis (peanut) oil extract of coal tar 0.3%, cade oil 0.3%, coal tar solution 0.1%, oleyl alcohol 1%, tar 0.3%, net price 250 mL = £2.23
    - **Excipients** include fragrance, hydroxybenzoates (parabens), imidurea, polsorbate 80
    - **Dose**—scalp disorders including psoriasis, seborrhoea, eczema, pruritus, and dandruff, apply 1–2 times weekly

#### Polytar Plus® (® & ™)
- **Liquid**, ingredients as **Polytar®** liquid with hydrolysed animal protein 3%, net price 500 mL = £3.91
  - **Excipients** include fragrance, hydroxybenzoates (parabens), polsorbate 80
  - **Dose**—scalp disorders including psoriasis, seborrhoea, eczema, pruritus, and dandruff, apply 1–2 times weekly

### Hirustim

Hirustim may result from hormonal disorders or as a side-effect of drugs such as minoxidil, corticosteroids, anabolic steroids, androgens, danazol, and progestogens.

Weight loss can reduce hirustim in obese women. Women should be advised about local methods of hair removal, and in the mildest cases this may be all that is required.

Eflornithine, an antiprotozoal drug, inhibits the enzyme ornithine decarboxylase in hair follicles. Topical eflornithine can be used as an adjunct to laser therapy for facial hirustim in women. Eflornithine should be discontinued in the absence of improvement after treatment for 4 months.

**Co-cyprindiol** *(section 13.6.2)* may be effective for moderately severe hirustim. **Metformin** *(section 6.1.2.2)* is an alternative in women with polycystic ovary syndrome [unlicensed indication]. Systemic treatment is required for 6–12 months before benefit is seen.
**EFLORNITHINE**

**Indications**
- see notes above

**Contra-indications**
- pregnancy (Appendix 4); breastfeeding (Appendix 5)

**Side-effects**
- acne, application site reactions including burning and stinging sensation, rash; less commonly abnormal hair texture and growth

**Dose**
- Apply thinly twice daily; CHILD under 12 years not recommended
  - Note Preparation must be rubbed in thoroughly; cosmetics may be applied over treated area 5 minutes after eflornithine; do not wash treated area for 4 hours after application

**Vaniqa® (Almirall) ▼ (OH)**
- Cream, eflornithine (as hydrochloride) 11.5%, net price 30 g = £26.04
- Excipients include cetostearyl alcohol, hydroxybenzoates, stearyl alcohol
  - Note The Scottish Medicines Consortium has advised (September 2005) that eflornithine for facial hirsutism be restricted for use in women in whom alternative drug treatment cannot be used

**Androgenetic alopecia**

Finasteride is licensed for the treatment of androgenetic alopecia in men. Continuous use for 3–6 months is required before benefit is seen, and effects are reversed 6–12 months after treatment is discontinued.

Topical application of minoxidil may stimulate limited hair growth in a small proportion of adults but only for as long as it is used.

**FINASTERIDE**

**Indications**
- androgenetic alopecia in men

**Cautions**
- see section 6.4.2

**Side-effects**
- see section 6.4.2

**Dose**
- By mouth 1 mg daily

**Propecia® (MSD) ▼ (MS)**
- Tablets, 1/c, beige, finasteride 1 mg, net price 28-tab pack = £26.99, 84-tab pack = £81.55

**MINOXIDIL**

**Indications**
- androgenetic alopecia (men and women)

**Cautions**
- section 2.5.1 (only about 1.4–1.7% absorbed); avoid contact with eyes, mouth and mucous membranes, broken, infected, shaved, or inflamed skin; avoid inhalation of spray mist; avoid occlusive dressings and topical drugs which enhance absorption

**Contra-indications**
- section 2.5.1

**Side-effects**
- section 2.5.1; irritant dermatitis, allergic contact dermatitis, changes in hair colour or texture, discontinue if increased hair loss persists for more than 2 weeks

**Dose**
- Apply 1 mL twice daily to dry hair and scalp (discontinue if no improvement after 1 year); 5% strength licensed for use in men only

**Regaine® (McNeil) ▼ (MS)**
- **Regaine® Regular Strength topical solution**, minoxidil 2% in an aqueous alcohol basis, net price 60-mL bottle with applicators = £14.16
- Excipients include propylene glycol
  - Cautions flammable; wash hands after application

**13.10 Anti-infective skin preparations**

**13.10.1 Antibacterial preparations only used topically**

**13.10.1.1 Antibacterial preparations only used topically**

**13.10.1.2 Antibacterial preparations also used systemically**

Cellulitis, a rapidly spreading deeply seated inflammation of the skin and subcutaneous tissue, requires systemic antibacterial treatment (see Table 1, section 5.1); it often involves staphylococcal infection. Lower leg infections or infections spreading around wounds are almost always cellulitis. Erysipelas, a superficial infection with clearly defined edges (and often affecting the face), is also treated with a systemic antibacterial (see Table 1, section 5.1); it usually involves streptococcal infection.

In the community acute impetigo on small areas of the skin may be treated by short-term topical application of fusidic acid; mupirocin should be used only to treat methicillin-resistant *Staphylococcus aureus*. If the impetigo is extensive or longstanding, an oral antibacterial such as *fluoxacillin* (or *erythromycin* in penicillin-allergy) (Table 1, section 5.1) should be used. Mild antiseptics such as *povidone–iodine* (section 13.11.4) should be used to soften crusts and exudate.

Although many antibacterial drugs are available in topical preparations, some are potentially hazardous and frequently their use is not necessary if adequate hygiene measures can be taken. Moreover, not all skin conditions that are oozing, crusted, or characterised by pustules are actually infected. Topical antibacterials should be avoided on leg ulcers unless used in short courses for defined infections; treatment of bacterial colonisation is generally inappropriate.

To minimise the development of resistant organisms it is advisable to limit the choice of antibacterials applied topically to those not used systemically. Unfortunately some of these, for example neomycin, may cause sensitisation, and there is cross-sensitivity with other aminoglycoside antibiotics, such as gentamicin. If *large areas of skin* are being treated, ototoxicity may also be a hazard with aminoglycoside antibiotics (and also with polymyxins), particularly in children, in the elderly, and in those
with renal impairment. *Resistant organisms* are more common in hospitals, and whenever possible swabs should be taken for bacteriological examination before beginning treatment.

**Mupirocin** is not related to any other antibacterial in use; it is effective for skin infections, particularly those due to Gram-positive organisms but it is not indicated for pseudomonal infection. Although *Staphylococcus aureus* strains with low-level resistance to mupirocin are emerging, it is generally useful in infections resistant to other antibiotics. To avoid the development of resistance, mupirocin or fusidic acid should not be used for longer than 10 days and local microbiology advice should be sought before using it in hospital. In the presence of mupirocin-resistant MRSA infection, a topical antisepptic such as povidone–iodine, chlorhexidine, or alcohol can be used; their use should be discussed with the local microbiologist.

**Retapamulin** can be used for impetigo and other superficial bacterial skin infections caused by *Staphylococcus aureus* and *Streptococcus pyogenes* that are resistant to first-line topical antibacterials. However, it is not effective against MRSA. The Scottish Medicines Consortium (p. 3) has advised (March 2008) that retapamulin (*Altargo*®) is not recommended for use within NHS Scotland for the treatment of superficial skin infections.

**Silver sulfadiazine** (silver sulphadiazine) is used in the treatment of infected burns.

---

**13.10.1 Antibacterial preparations only used topically**

**MUPIROCIN**

**Indications** bacterial skin infections (see also notes above)

**Side-effects** local reactions including urticaria, pruritus, burning sensation, rash

**Dose**

- **ADULT** and **CHILD** over 1 year, apply up to 3 times daily for up to 10 days; **CHILD** under 1 year see **BNF for Children**

**Bactroban®** (GSK)

---

**NEOMYCIN SULPHATE**

**Indications** bacterial skin infections

**Cautions** large areas, see below

**Large areas** If large areas of skin are being treated ototoxicity may be a hazard, particularly in children, in the elderly, and in those with renal impairment

**Contra-indications** neonates

**Side-effects** sensitisation (see also notes above)

**Neomycin Cream BPC**

Cream, neomycin sulphate 0.5%, cetomacrogol emulsifying ointment 30%, chlorocresol 0.1%, disodium edetate 0.01%, in freshly boiled and cooled purified water, net price 15 g = £2.17

**Excipients** include cetostearyl alcohol, edetic acid (EDTA)

**Dose** apply up to 3 times daily (short-term use)

---

**POLYMIXINS**

**Indications** bacterial skin infections

**Cautions** large areas, see below

**Large areas** If large areas of skin are being treated nephrotoxicity and neurotoxicity may be a hazard, particularly in children, in the elderly, and in those with renal impairment

**Side-effects** sensitisation (see also notes above)

**Polyfax**® (**PLIVA**) Ointment, polymyxin B sulphate 10 000 units, bacitracin zinc 500 units/g, net price 4 g = £3.26, 20 g = £4.62

**Excipients** none as listed in section 13.1.3

**Dose** apply twice daily or more frequently if required

---

**RETPAMULIN**

**Indications** superficial bacterial skin infections (see also notes above)

**Contra-indications** contact with eyes and mucous membranes

**Side-effects** local reactions including irritation, erythema, pain, and pruritus

**Dose**

- **ADULT** and **CHILD** over 9 months, apply thinly twice daily for 5 days; review treatment if no response within 2–3 days

**Altargo**® (GSK) Ointment, retapamulin 1%, net price 5 g = £7.89.

Label: 28

**Excipients** include butylated hydroxytoluene

---

**SILVER SULFADIAZINE**

(Silver sulphadiazine)

**Indications** prophylaxis and treatment of infection in burn wounds; as an adjunct to short-term treatment of infection in leg ulcers and pressure sores; as an adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions; for conservative management of finger-tip injuries

**Cautions** hepatic impairment; renal impairment; G6PD deficiency; pregnancy and breast-feeding (avoid in late pregnancy and in neonate—see also Appendix 4); may inactivate enzymatic debriding agents—concomitant use may be inappropriate; for large amounts see also **interactions**—Appendix 1 (sulphonamides)

**Large areas** Plasma-sulfadiazine concentrations may approach therapeutic levels with *side-effects* and **interactions** as for sulphonamides (see section 5.1.8) if large areas of skin are treated. Owing to the association of sulphonamides with severe blood and skin disorders treatment should be stopped immediately if blood disorders or rashes develop—but leucopenia developing 2–3 days after starting treatment of burns patients is reported usually to be self-limiting and silver sulfadiazine need not usually be discontinued provided blood counts are monitored carefully to ensure return to normality within a few days. Argyria may also occur if large areas of skin are treated (or if application is prolonged).

**Contra-indications** pregnancy (Appendix 4) and breast-feeding (Appendix 5); sensitivity to sulphonamides; not recommended for neonates (see also Appendix 4)
13.10.2 Antifungal preparations

Most localised fungal infections are treated with topical preparations. To prevent relapse, local antifungal treatment should be continued for 1–2 weeks after the disappearance of all signs of infection. Systemic therapy (section 5.2) is necessary for nail or scalp infection or if the skin infection is widespread, disseminated, or intractable. Skin scrapings should be examined if systemic therapy is being considered or where there is doubt about the diagnosis.

**Dermatophyotoses** Ringworm infection can affect the scalp (tinea capitis), body (tinea corporis), groin (tinea cruris), hand (tinea manuum), foot (tinea pedis, athlete’s foot), or nail (tinea unguium). Scalp infection requires systemic treatment (section 5.2); additional application of a topical antifungal, during the early stages of treatment, may reduce the risk of transmission. A topical antifungal can also be used to treat asymptomatic carriers of ringworm. Most other local ringworm infections can be treated adequately with topical antifungal preparations including chloretamizole, econazole,
Skin

If topical therapy fails, or if the infection is widespread, contra-indications to systemic therapy. Limited to mild distal disease in up to 2 nails, or for treating early onychomycosis when involvement is more effective than topical therapy. However, topical antifungals are on sale to the public. This may cause skin irritation; they may have some role in preventing re-infection.

Antifungal treatment may not be necessary in asymptomatic patients with tinea infection of the nails. If treatment is necessary, a systemic antifungal (section 5.2) is more effective than topical therapy. However, topical application of amorolfine or tioconazole may be useful for treating early onychomycosis when involvement is limited to mild distal disease in up to 2 nails, or for superficial white onychomycosis, or where there are contra-indications to systemic therapy.

**Pityriasis versicolor**

Pityriasis (tinea) versicolor can be treated with ketoconazole shampoo (section 13.9). Alternatively, selenium sulphide shampoo [unlicensed indication] (section 13.9) can be used as a lotion (diluted with water to reduce irritation) and left on for at least 30 minutes or overnight; it is applied 2–7 times over a fortnight and the course repeated if necessary.

Topical imidazole antifungals clotrimazole, econazole, ketocanazole, and miconazole and topical terbinafine are alternatives but large quantities may be required.

If topical therapy fails, or if the infection is widespread, pityriasis versicolor is treated systemically with a triazole antifungal (section 5.2). Relapse is common, especially in the immunocompromised.

**Candidiasis**

Candidal skin infections can be treated with a topical imidazole antifungal, such as clotrimazole, econazole, ketoconazole, miconazole, or sulconazole; topical terbinafine is an alternative. Topical application of nystatin is also effective for candidiasis but it is ineffective against dermatophytons. Refractory candidiasis requires systemic treatment (section 5.2) generally with a triazole such as fluconazole; systemic treatment with terbinafine is not appropriate for refractory candidiasis.

**Angular cheilitis**

Miconazole cream is used in the fissures of angular cheilitis when associated with Candida. For further information on angular cheilitis, see p. 610.

**Compound topical preparations**

Combination of an imidazole and a mild corticosteroid (such as hydrocortisone 1%) (section 13.4) may be of value in the treatment of eczematous intertrigo and, in the first few days only, of a severely inflamed patch of ringworm. Combination of a mild corticosteroid with either an imidazole or nystatin may be of use in the treatment of intertrigo associated with candida.

**Side-effects**

Occasional local irritation and hypersensitivity reactions include mild burning sensation, erythema, and itching. Treatment should be discontinued if these are severe.

**AMOROLFINE**

**Indications** see under preparations

**Cautions** see notes above; also avoid contact with ears; pregnancy and breast-feeding

**Side-effects** see notes above

**Loceryl** (Guilderma) (BNF)

Cream, amorolfine (as hydrochloride) 0.25%, net price 20 g = £4.83. Label: 10, patient information leaflet

Exipients include cetostearyl alcohol, disodium edetate

Dose fungal skin infections, apply once daily after cleansing in the evening for at least 2–3 weeks (up to 6 weeks for foot infection) continuing for 3–5 days after lesions have healed

Nail lacquer, amorolfine (as hydrochloride) 5%, net price 5-mL pack (with nail files, spatulas and cleansing swabs) = £18.71. Label: 10, patient information leaflet

Exipients none as listed in section 13.1.3

Dose fungal nail infections, apply to infected nails 1–2 times weekly after filing and cleansing; allow to dry (approx. 3 minutes); treat finger nails for 6 months, toe nails for 9–12 months (review at intervals of 3 months); avoid nail varnish or artificial nails during treatment

**Note** Amorolfine nail lacquer can be sold to the public if supplied for the treatment of mild cases of distal and lateral subungual onychomycoses caused by dermatophytons, yeasts and moulds; subject to treatment of max. 2 nails, max. strength of nail lacquer amorolfine 5% and a pack size of 3 mL

**BENZOIC ACID**

**Indications** ringworm (tinea), but see notes above

**BENZOIC ACID OINTMENT, COMPOUND, BP** (Whitfield’s ointment)

Ointment, benzoic acid 6%, salicylic acid 3%, in emulsifying ointment

Exipients include cetostearyl alcohol

Dose apply twice daily

**CLOTRIMAZOLE**

**Indications** fungal skin infections; vaginal candidiasis (section 7.2.2); otitis externa (section 12.1.1)

**Cautions** see notes above

**Side-effects** see notes above

**Dose**

- Apply 2–3 times daily

**Clotrimazole** (Non-proprietary)

Cream, clotrimazole 1%, net price 20 g = £1.92

**Canesten** (Bayer Consumer Care)

Cream, clotrimazole 1%, net price 20 g = £2.14, 50 g = £3.80

Exipients include benzyl alcohol, cetearyl alcohol, polysorbate 60

Powder, clotrimazole 1%, net price 30 g = £1.52

Exipients none as listed in section 13.1.3

Solution, clotrimazole 1% in macrogol 400 (polyethylene glycol 400), net price 20 mL = £2.43. For hairy areas

Exipients none as listed in section 13.1.3

Spray, clotrimazole 1%, in 30% isopropyl alcohol, net price 40-mL atomiser = £4.99. Label: 15. For large or hairy areas

Exipients include propylene glycol
ECONAZOLE NITRATE

**Indications**  fungal skin infections; vaginal candidiasis (section 7.2.2)

**Cautions**  see notes above

**Side-effects**  see notes above

**Dose**
- Skin infections: apply twice daily; nail infections, apply once daily under occlusive dressing

**Ecocystatin**  (Squibb)

**Cream**, econazole nitrate 1%, net price 15 g = £1.49; 30 g = £2.75

**Exipients**  include butylated hydroxyanisole, fragrance

**Pevaryl**  (Janssen-Cilag)

**Cream**, econazole nitrate 1%, net price 30 g = £2.65

**Exipients**  include butylated hydroxyanisole, fragrance

GRISEOFULVIN

**Indications**  tinea pedis; resistant fungal infections (section 5.2)

**Cautions**  see notes above

**Side-effects**  see notes above

**Dose**
- Apply 400 micrograms (1 spray) to an area approx. 13 cm once daily, increased to 1.2 mg (3 sprays, allowing each spray to dry between applications) once daily if necessary; max. treatment duration 4 weeks

**Grisol AF**  (Transdermal)

**Spray**, griseofulvin 400 micrograms/metered spray, net price 20 mL (400-dose) spray = £4.00. Label: 15

**Exipients**  include benzyl alcohol

KETOCONAZOLE

**Indications**  fungal skin infections; systemic or resistant fungal infections (section 5.2); vulval candidiasis (section 7.2.2)

**Cautions**  see notes above; do not use within 2 weeks of a topical corticosteroid for seborrhoeic dermatitis—risk of skin sensitisation

**Side-effects**  see notes above

**Dose**
- Tinea pedis, apply twice daily; other fungal infections, apply 1–2 times daily

**Nizoral**  (Janssen-Cilag)

**Cream**, ketoconazole 2%, net price 30 g = £3.54

**Exipients**  include cetyl alcohol, polysorbates, propylene glycol, stearyl alcohol

**Note**  A 15-g tube is available for sale to the public

**Shampoo**—section 13.9

1. **SLS** except for seborrhoeic dermatitis and pityriasis versicolor and endorsed ‘SLS’

MICONAZOLE NITRATE

**Indications**  fungal skin infections; oral and intestinal fungal infections (section 12.3.2); vaginal candidiasis (section 7.2.2)

**Cautions**  see notes above

**Side-effects**  see notes above

**Dose**
- Apply twice daily continuing for 10 days after lesions have healed; nail infections, apply 1–2 times daily

Miconazole  (Non-proprietary)

**Cream**, miconazole nitrate 2%, net price 20 g = £2.05, 45 g = £1.97

**Dental prescribing on NHS**  Miconazole cream may be prescribed

Daktarin  (Janssen-Cilag)

**Cream**, miconazole nitrate 2%, net price 30 g = £1.93

**Exipients**  include butylated hydroxyanisole

**Note**  A 15-g tube is on sale to the public

**Powder**, miconazole nitrate 2%, net price 20 g = £1.81

**Exipients**  none as listed in section 13.13

**Dual Action Spray powder**, miconazole nitrate 0.16%, in an aerosol basis, net price 100 g = £2.27

**Exipients**  none as listed in section 13.13

NYSTATIN

**Indications**  skin infections due to *Candida* spp.; intestinal candidiasis (section 5.2); oral fungal infections (section 12.3.2)

**Cautions**  see notes above

**Side-effects**  see notes above

**Nystaform**  (Typharm)

**Cream**, nystatin 100 000 units/g, chlorhexidine hydrochloride 1%, net price 30 g = £2.62

**Exipients**  include benzyl alcohol, cetostearyl alcohol, polysorbate 60

**Dose**  apply 2–3 times daily continuing for 7 days after lesions have healed.

**Tinaderm-M**  (Schering-Plough)

**Cream**, nystatin 100 000 units/g, tolnaftate 1%, net price 20 g = £1.83

**Exipients**  include butylated hydroxytoluene, cetostearyl alcohol, hydroxybenzoates (parabens), fragrance

**Dose**  apply 2–3 times daily

SALICYLIC ACID

**Indications**  fungal nail infections, particularly tinea; hyperkeratotic skin disorders (section 13.5.2); acne vulgaris (section 13.6.1); warts and calluses (section 13.7)

**Cautions**  avoid broken or inflamed skin

**Salicylate toxicity**  Salicylate toxicity can occur particularly if applied on large areas of skin

**Contra-indications**  pregnancy

**Side-effects**  see notes above

**Dose**
- **ADULT** and **CHILD** over 5 years, apply twice daily and after washing

**Phytex**  (Wynlit)

**Paint**, salicylic acid 1.46% (total combined), tannic acid 4.89% and boric acid 3.12% (as borotannic complex), in a vehicle containing alcohol and ethyl acetate, net price 25 mL (with brush) = £1.56

**Exipients**  none as listed in section 13.13

**Note**  Flammable

SULCONAZOLE NITRATE

**Indications**  fungal skin infections

**Cautions**  see notes above

**Side-effects**  see notes above; also blistering

**Dose**
- Apply 1–2 times daily continuing for 2–3 weeks after lesions have healed
13 Skin

TERBINAFINE

**Indications** fungal skin infections

**Side-effects** see notes above

**Dose**

- Apply thinly 1–2 times daily usually for up to 1 week in tinea pedis, 1–2 weeks in tinea corporis and tinea cruris, 2 weeks in cutaneous candidiasis and pityriasis versicolor; review after 2 weeks; CHILD see BNF for Children

1 Terbinafine (Non-proprietary) THM.

**Cream**, terbinafine hydrochloride 1%, net price 15 g = £4.86, 30 g = £8.76

1. Preparations of terbinafine hydrochloride (max. 1%) can be prescribed to the public for external use for the treatment of tinea pedis as a cutaneous solution in a pack containing max. 15 g, or for the treatment of tinea pedis and cruris as a cream in a pack containing max. 15 g, or for the treatment of tinea pedis, cruris, and corporis as a spray in a pack containing max. 30 mL spray or as a gel in a pack containing max. 20 g gel

Lamisil® (Novartis Consumer Health) THM.

**Cream**, terbinafine hydrochloride 1%, net price 15 g = £4.86, 30 g = £8.76

**Excipients** include benzyl alcohol, cetyl alcohol, polysorbate 60, stearyl alcohol

**Tablets**—section 5.2

TOCONAZOLE

**Indications** fungal nail infections

**Contra-indications** pregnancy

**Side-effects** see notes above

**Dose**

- Apply to nails and surrounding skin twice daily usually for up to 6 months (may be extended to 12 months)

Trosyl® (Pfizer) THM.

**Cutaneous solution**, tioconazole 28%, net price 12 mL (with applicator brush) = £27.38

**Excipients** none as listed in section 13.1.3

UNDECENOATES

**Indications** see under preparations below

**Side-effects** see notes above

**Dose**

- See under preparations below

Mycotha® (Thornton & Ross)

**Cream**, zinc undecenoate 20%, undecenoic acid 5%, net price 25 g = £1.37

**Excipients** include fragrance

**Dose** treatment of athlete’s foot, apply twice daily continuing for 7 days after lesions have healed

Prevention of athlete’s foot, apply once daily

Prevention of athlete’s foot, apply once daily

**Spray application**, undecenoic acid 3.9%, dichlorophen 0.4% (pressurised aerosol pack), net price 100 mL = £2.28

**Excipients** include fragrance

**Dose** treatment of athlete’s foot, apply twice daily continuing for 7 days after lesions have healed

Prevention of athlete’s foot, apply once daily

13.10.3 Antiviral preparations

Aciclovir cream is licensed for the treatment of initial and recurrent labial and genital herpes simplex infections; treatment should begin as early as possible. Systemic treatment is necessary for buccal or vaginal infections and for herpes zoster (shingles) (for details of systemic use see section 5.3.2.1).

Idoxuridine solution (5% in dimethyl sulfoxide) is of little value.

**Herpes labialis** Aciclovir cream can be used for the treatment of initial and recurrent labial herpes simplex infections (cold sores). It is best applied at the earliest possible stage, usually when prodromal changes of sensation are felt in the lip and before vesicles appear.

Penciclovir cream is also licensed for the treatment of herpes labialis; it needs to be applied more frequently than aciclovir cream. These creams should not be used in the mouth.

Systemic treatment is necessary if cold sores recur frequently or for infections in the mouth (see p. 343).

ACICLOVIR (Acyclovir)

**Indications** see notes above; herpes simplex and varicella–zoster infections (section 5.3.2.1); eye infections (section 11.3.3)

**Contra-indications** avoid contact with eyes and mucous membranes

**Side-effects** transient stinging or burning; occasionally erythema, itching or drying of the skin

**Dose**

- Apply to lesions every 4 hours (5 times daily) for 5–10 days, starting at first sign of attack

1 Aciclovir (Non-proprietary) THM.

**Cream**, aciclovir 5%, net price 2 g = £1.10, 10 g = £2.16

**Excipients** include propylene glycol

**Brands include** Zarcon (excipients also include cetyl alcohol, propylene glycol)

**Dental prescribing on NHS** Aciclovir Cream may be prescribed

1. A 2-g tube and a pump pack are on sale to the public for the treatment of cold sores

Zovirax® (GSK) THM.

**Cream**, aciclovir 5%, net price 2 g = £3.98, 10 g = £14.82

**Excipients** include cetostearyl alcohol, propylene glycol

**Eye ointment**—section 11.3.3

**Tablets**—section 5.3.2.1
**13.10.4 Parasiticidal preparations**

### Indications

- **PENCICLOVIR**
  - Notes above
- **Cautions**
  - Avoid contact with the eyes and mucous membranes.
- **Side-effects**
  - Transient stinging, burning, numbness; hypersensitivity reactions also reported.
- **Vectavir®** (Novartis Consumer Health) (TMR)
  - **Cream**
    - Penciclovir 1%
    - Net price 2 g = £4.20
  - **Excipients**
    - Include cetostearyl alcohol, propylene glycol.
  - **Dose**
    - Herpes labialis, apply to lesions every 2 hours during waking hours for 4 days, starting at first sign of attack; **CHILD** under 12 years, not recommended.
  - **Dental prescribing** on NHS May be prescribed as Penciclovir Cream.

### Indications

- **IDOXURIDINE IN DIMETHYL SULFOXIDE**
  - **Indications**
    - Herpes simplex and herpes zoster infection but of little value.
  - **Cautions**
    - Avoid contact with the eyes, mucous membranes, and textiles; breast-feeding (Appendix 5); interactions: Appendix 1 (dimethyl sulfoxide).
  - **Contra-indications**
    - Pregnancy (Appendix 4); not to be used in mouth.
  - **Side-effects**
    - Stinging on application, changes in taste; overuse may cause maceration.
  - **Herpid®** (Astellas) (TMR)
    - **Application**
      - Idoxuridine 5% in dimethyl sulfoxide, net price 5 mL (with applicator) = £6.33
    - **Dose**
      - Apply to lesions 4 times daily for 4 days, starting at first sign of attack; **CHILD** under 12 years, not recommended.

### Scabies

- **Permethrin** is used for the treatment of scabies (*Sarcoptes scabiei*); *malathion* can be used if permethrin is inappropriate.
- Aqueous preparations are preferable to alcoholic lotions, which are not recommended owing to irritation of excoriated skin and the genitalia.
- **Benzybenzoate** is an irritant and should be avoided in children; it is less effective than malathion and permethrin.
- **Ivermectin** (available on a named patient basis from ‘special-order’ manufacturers or specialist importing companies, see p. 939) in a single dose of 200 micrograms/kg by mouth has been used, in combination with topical drugs, for the treatment of hyperkeratotic (crusted or ‘Norwegian’) scabies that does not respond to topical treatment alone.

### Application

- Although acaricides have traditionally been applied after a hot bath, this is not necessary and there is even evidence that a hot bath may increase absorption into the blood, removing them from their site of action on the skin.
- All members of the affected household should be treated simultaneously. Treatment should be applied to the whole body including the scalp, neck, face, and ears. Particular attention should be paid to the webs of the fingers and toes and lotion brushed under the ends of nails. It is now recommended that malathion and permethrin should be applied twice, one week apart; in the case of benzybenzoate up to 3 applications on consecutive days may be needed. It is important to warn users to reapply treatment to the hands if they are washed.
- Patients with hyperkeratotic scabies may require 2 or 3 applications of acaricide on consecutive days to ensure that enough penetrates the skin crusts to kill all the mites.

### Itching

- **The itch** and **eczema** of scabies persists for some weeks after the infestation has been eliminated and treatment for pruritus and eczema (section 13.5.1) may be required. Application of crotamiton can be used to control itching after treatment with more effective acaricides. A topical corticosteroid may help to reduce itch and inflammation after scabies has been treated successfully; however, persistent symptoms suggest that scabies eradication was not successful. Oral administration of a sedating antihistamine (section 3.4.1) at night may also be useful.

### Head lice

- **Malathion** and the pyrethroid (phenothrin) can be used against head lice (*Pediculus humanus capitis*) but lice in some districts have developed resistance; resistance to two or more parasiticidal preparations has also been reported. Careful application of **dimeticone**, which acts on the surface of head lice, is also effective. Benzyl benzoate is licensed for the treatment of head lice but it is less effective than other drugs.
- **Application**
  - Head lice infestation (pediculosis) should be treated using lotion or liquid formulations. Shampoos are diluted too much in use to be effective. Alcoholic formulations are effective but aqueous formulations are preferred in severe eczema, for patients with asthma, and small children. A contact time of 12 hours or overnight treatment is recommended for lotions and liquids; a 2-hour treatment is not sufficient to kill eggs.
  - In general, a course of treatment for head lice should be 2 applications of product 7 days apart to prevent lice emerging from any eggs that survive the first application.
  - The policy of rotating insecticides on a district-wide basis is now considered outmoded. To overcome the development of resistance, a mosaic strategy is required whereby, if a course of treatment fails to cure, a different insecticide is used for the next course. If a course of treatment with either permethrin or phenothrin fails, then a non-pyrethroid parasiticidal product should be used for the next course.
**Wet combing methods**  Head lice can be mechanically removed by combing wet hair meticulously with a plastic detection comb (probably for at least 30 minutes each time) over the whole scalp at 4-day intervals for a minimum of 2 weeks; hair conditioner or vegetable oil can be used to facilitate the process. Several products are available and some are prescribable on the NHS.

---

**Crab lice**

Permethrin, phenothrin, and malathion are used to eliminate crab lice (*Pthirus pubis*). An aqueous preparation should be applied, allowed to dry naturally and washed off after 12 hours; a second treatment is needed after 7 days to kill lice emerging from surviving eggs. All surfaces of the body should be treated, including the scalp, neck, and face (paying particular attention to the eyebrows and other facial hair). A different insecticide should be used if a course of treatment fails. Alcoholic lotions are not recommended (owing to irritation of excoriated skin and the genitalia).

---

**Benzyl benzoate**

Benzyl benzoate is effective for scabies but is not a first-choice for scabies (see notes above).

---

**DIMETICONE**

**Indications** head lice

**Cautions** avoid contact with eyes; children under 6 months, medical supervision required

**Side-effects** skin irritation

**Dose**

- Rub into dry hair and scalp, allow to dry naturally, shampoo after minimum 8 hours (or overnight); repeat application after 7 days

**Hedrin** (Thornton & Ross)

Lotion, dimeticone 4%, net price 50 mL = £2.98, 120 mL spray pack = £7.14, 150 mL = £6.83

**Note** Patients should be told to keep hair away from fire and flames during treatment

---

**MALATHION**

**Indications** see notes above and under preparations

**Cautions** avoid contact with eyes; do not use on broken or secondarily infected skin; do not use lotion more than once a week for 3 consecutive weeks; children under 6 months, medical supervision required; alcoholic lotions not recommended for head lice in severe eczema or in small children, or for scabies or crab lice

**Side-effects** skin irritation

**Dose**

- Head lice, rub 0.5% preparation into dry hair and scalp, allow to dry naturally, remove by washing after 12 hours (see also notes above); repeat application after 7 days
- Crab lice, apply 0.5% aqueous preparation over whole body, allow to dry naturally, wash off after 12 hours or overnight; repeat application after 7 days
- Scabies, apply 0.5% preparation over whole body, and wash off after 24 hours; if hands are washed with soap within 24 hours, they should be retreated; see also notes above; repeat application after 7 days

**Note** For scabies, manufacturer recommends application to the body but not necessarily to the head and neck. However, application should be extended to the scalp, neck, face, and ears

**Derbac-M** (SSL)

Liquid, malathion 0.5% in an aqueous basis, net price 50 mL = £2.27, 200 mL = £5.70

**Excipients** include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens)

For crab lice, head lice, and scabies

**Prioderm** (SSL)

Lotion, malathion 0.5%, in an alcoholic basis, net price 50 mL = £2.22, 200 mL = £5.70. Label: 15

**Excipients** include fragrance

For head lice (alcoholic formulation, see notes above)

Cream shampoo prioderm malathion 1%, net price 40 g = £2.77

**Excipients** include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens), sodium edetate, wool fat

**Dose** head and crab lice, not recommended, therefore no dose stated (product too diluted in use and insufficient contact time)


**Phenothrin**

Indications

- see notes above and under preparations

Cautions

- avoid contact with eyes; do not use on broken or secondarily infected skin; do not use more than once a week for 3 weeks at a time; children under 6 months, medical supervision required; alcoholic preparations not recommended for head lice in severe eczema, in asthma, in small children, or for crab lice (see notes above)

Side-effects

- skin irritation

Dose

- See under preparations

Full Marks® (SSL)

- Liquid, phenothrin 0.5% in an aqueous basis, net price 50 mL = £2.22, 200 mL = £5.70
- Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens)
- Dose head lice, apply to dry hair; allow to dry naturally; shampoo after 12 hours or next day, comb wet hair; repeat application after 7 days [unlicensed use]

- Lotion, phenothrin 0.2% in basis containing isopropyl alcohol 69.3%, net price 50 mL = £2.22, 200 mL = £5.70. Label: 15
- Excipients include fragrance
- Dose crab lice and head lice (alcoholic formulation, see notes above), apply to dry hair, allow to dry naturally; shampoo after 12 hours [unlicensed contact duration], comb wet hair; repeat application after 7 days [unlicensed use]

- Mousse (= foam application) phenothrin 0.5% in an alcoholic basis, net price 50 g = £2.53, 150 g = £6.11. Label: 15
- Excipients include cetostearyl alcohol
- Dose head lice (alcoholic formulation, see notes above), apply to dry hair, shampoo after 30 minutes, comb wet hair—but product not recommended because contact time insufficient (longer contact time not recommended because of risk of irritation)

---

**Permethrin**

Permethrin is effective for scabies and crab lice (for details see notes above). Permethrin is active against head lice but the formulation and licensed methods of application of the current products make them unsuitable for the treatment of head lice.

**PERMETHRIN**

**Indications**

- see notes above and under Dose

**Cautions**

- avoid contact with eyes; do not use on broken or secondarily infected skin; children under 6 months, medical supervision required for cream rinse (head lice); children aged 2 months–2 years, medical supervision required for dermal cream (scabies)

**Side-effects**

- pruritus, erythema, and stinging; rarely rashes and oedema

**Dose**

- Scabies, apply 5% preparation over whole body and wash off after 8–12 hours; CHILD (see also Cautions, above) apply over whole body including face, neck, scalp and ears; if hands washed with soap within 8 hours of application, they should be treated again with cream (see notes above); repeat application after 7 days

**Note**

- Manufacturer recommends application to the body but to exclude head and neck. However, application should be extended to the scalp, neck, face, and ears
- Larger patients may require up to two 30-g packs for adequate treatment
- Crab lice, ADULT over 18 years, apply 5% cream over whole body, allow to dry naturally and wash off after 12 hours or after leaving on overnight; repeat application after 7 days

**Permethrin** (Non-proprietary)

- Cream, permethrin 5%, net price 30 g = £5.55

**Lyclear® Creme Rinse** (Chefaro UK)

- Cream rinse, permethrin 1% in basis containing isopropyl alcohol 20%, net price 59 mL = £2.38, 2 x 59 mL pack = £4.32
- Excipients include cetyl alcohol
- Dose head lice, not recommended, therefore no dose stated (insufficient contact time)

**Lyclear® Dermal Cream** (Chefaro UK)

- Dermal cream, permethrin 5%, net price 30 g = £5.71
- Label: 10, patient information leaflet
- Excipients include butylated hydroxytoluene, wool fat derivative

**Phenothrin**

Phenothrin is recommended for head lice and crab lice (for details see notes above).
Preparations for boils

Magnesium Sulphate Paste, BP

Paste, dried magnesium sulphate 45 g, glycerol 55 g, phenol 500 mg, net price 25 g = 69p, 50 g = 81p

Note Should be stirred before use

Dose apply under dressing

Collodion

Flexible collodion may be used to seal minor cuts and wounds that have partially healed.

Collodion, Flexible, BP

Collodion, castor oil 2.5%, colophony 2.5% in a collodion basis, prepared by dissolving pyroxylin (10%) in a mixture of 3 volumes of ether and 1 volume of alcohol (90%), net price 10 mL = 25p. Label: 15

Contra indications allergy to colophony in elastic adhesive

Skin tissue adhesive

Tissue adhesives are used for closure of minor skin wounds and for additional suture support. They should be applied by an appropriately trained healthcare professional. Skin tissue adhesives may cause skin sensitisation.

Dermabond ProPen (Ethicon)

Topical Skin Adhesive, sterile, octyl 2-cyanoacrylate, net price 0.5 mL = £18.38

Epiglu (Schuco)

Tissue adhesive, sterile, ethyl-2-cyanoacrylate 954.5 mg/g, polymethylmethacrylate, net price 4 × 3-g vials = £49.50 (with dispensing pipettes and pallete)

Histacryl (Braun)

Tissue adhesive, sterile, enbucrilate, net price 500-mg unit (clear or blue) = £34.65, 10 × 500-mg unit (blue) = £69.30

LiquiBand (MedLogic)

Tissue adhesive, sterile, enbucrilate, net price 0.5-g amp = £5.50

13.11 Skin cleansers and antiseptics

13.11.1 Alcohols and saline

ALCOHOL

Indications skin preparation before injection

Cautions flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants

Industrial Methylated Spirit, BP

Solution, 19 volumes of ethanol and 1 volume approved wood naphtha, net price ‘65 OP’ (containing 95% by volume alcohol) 100 mL = 39p; ‘74 OP’ (containing 99% by volume alcohol) 100 mL = 39p. Label: 15

Surgical Spirit, BP

Spirit, methyl salicylate 0.5 mL, diethyl phthalate 2%, castor oil 2.5%, in industrial methylated spirit, net price 100 mL = 20p. Label: 15

SODIUM CHLORIDE

Indications see notes above; nebuliser diluent (section 3.1.5); sodium depletion (section 9.2.1.2); electrolyte imbalance (section 9.2.2.1); eye (section 11.8.1); oral hygiene (section 12.3.4)

Sodium Chloride (Non-proprietary)

Solution (sterile), sodium chloride 0.9%, net price 25 × 20-ml unit = £5.50, 200-ml can = £2.65, 1 litre = 97p

Flowfusor® (Fresenius Kabi)

Solution (sterile), sodium chloride 0.9%, net price 120-ml Bellows Pack = £1.53

Irriclens® (Convatec)

Solution in aerosol can (sterile), sodium chloride 0.9%, net price 240-ml can = £3.24

Irripod® (C D Medical)

Solution (sterile), sodium chloride 0.9%, net price 25 × 20-ml sachet = £5.50

Miniversol® (Aguettant)

Solution (sterile), sodium chloride 0.9%, net price 30 × 45-ml unit = £13.20; 30 × 100-ml unit = £19.50

Normasol® (Medlock)

Solution (sterile), sodium chloride 0.9%, net price 25 × 25-ml sachet = £5.98; 10 × 100-ml sachet = £7.27

Soap or detergent is used with water to cleanse intact skin; emollient preparations such as aqueous cream or emulsifying ointment (section 13.2.1) that do not irritate the skin are best used in place of soap or detergent for cleansing dry skin.

An antiseptic is used for skin that is infected or that is susceptible to recurrent infection. Detergent preparations containing chlorhexidine, triclosan, or povidone–iodine, which should be thoroughly rinsed off, are used. Emollients may also contain antiseptics (section 13.2.1).

Antiseptics such as chlorhexidine or povidone–iodine are used on intact skin before surgical procedures; their antiseptic effect is enhanced by an alcoholic solvent. Antiseptic solutions containing cetrimide can be used if a detergent effect is also required.

For irrigating ulcers or wounds, lukewarm sterile sodium chloride 0.9% solution is used, but tap water is often appropriate.

Potassium permanganate solution 1 in 10,000, a mild antiseptic with astringent properties, can be used for exudative eczematous areas; treatment should be stopped when the skin becomes dry. It can stain skin and nails especially with prolonged use.
Stericlen® (C D Medical)  
**Solution** in aerosol can (sterile), sodium chloride 0.9%, net price 100-mL can = £1.94, 240-mL can = £2.95  

Steripod® Sodium Chloride (Medlock)  
**Solution** (sterile), sodium chloride 0.9%, net price 25 x 20-mL sachet = £7.36

### 13.11.2 Chlorhexidine salts

#### CHLORHEXIDINE

**Indications** see under preparations; bladder irrigation and catheter patency solutions (see section 7.4.4)  
**Cautions** avoid contact with eyes, brain, meninges and middle ear; not for use in body cavities; alcoholic solutions not suitable before diathermy  
**Side-effects** occasional sensitivity

Chlorhexidine 0.05% (Baxter)  
**2000 Solution** (sterile), pink, chlorhexidine acetate 0.05%, net price 500 mL = 72p, 1000 mL = 77p  
For cleansing and disinfecting wounds and burns

Cepton® (LPC)  
**Skin wash** (= solution), red, chlorhexidine gluconate 1%, net price 150 mL = £2.48  
For use as skin wash in acne  
**Lotion**, blue, chlorhexidine gluconate 0.1%, net price 150 mL = £2.48  
For skin disinfection in acne

Chloraprep® (Enturia)  
**Cutaneous solution**, sterile, chlorhexidine gluconate 2% in isopropyl alcohol 70%, net price (single applicator) 0.67 mL = 30p, 1.5 mL = 55p, 3 mL = 85p, 10.5 mL = £2.92, 26 mL = £6.50  
For skin disinfection before invasive procedures; **CHILD** under 2 months, not recommended  
**Note** Flammable

CX Antiseptic Dusting Powder® (Ecolab)  
**Dusting powder**, sterile, chlorhexidine acetate 1%, net price 15 g = £2.68  
For skin disinfection

Hibiscrub® (Regent Medical)  
**Cleansing solution**, red, chlorhexidine gluconate 4%, perfumed, in a surfactant solution, net price 250 mL = £4.25, 500 mL = £5.25, 5 litres = £16.20  
**Excipients** include fragrance  
Use instead of soap for pre-operative hand and skin preparation and for general hand and skin disinfection

Hibisol® (Regent Medical)  
**Solution**, chlorhexidine gluconate 0.5%, in isopropyl alcohol 70% with emollients, net price 500 mL = £5.25  
To be used undiluted for hand and skin disinfection

Hibitane Obstetric® (Centrapharm)  
**Cream**, chlorhexidine gluconate solution 5% (= 1% chlorhexidine gluconate), in a pourable water-miscible basis, net price 250 mL = £4.44  
For use in obstetrics and gynaecology as an antiseptic and lubricant (for application to skin around vulva and perineum and to hands of midwife or doctor)

Hydrex® (Ecolab)  
**Solution**, chlorhexidine gluconate solution 2.5% (= chlorhexidine gluconate 0.5%), in an alcoholic solution, net price 600 mL (clear) = £2.06; 600 mL (pink) = £2.06, 200-mL spray = £1.77, 500-mL spray = £3.01; 600 mL (blue) = £2.26  
For pre-operative skin disinfection  
**Note** Flammable

**Surgical scrub**, chlorhexidine gluconate 4% in a surfactant solution, net price 250 mL = £1.93, 500 mL = £2.05  
For pre-operative hand and skin preparation and for general hand disinfection

Unisept® (Medlock)  
**Solution** (sterile), pink, chlorhexidine gluconate 0.05%, net price 25 x 25-mL sachet = £5.40; 10 x 100-mL sachet = £6.67  
For cleansing and disinfecting wounds and burns and swabbing in obstetrics  

- **With cetrimide**

  Tisept® (Medlock)  
  **Solution** (sterile), yellow, chlorhexidine gluconate 0.015%, cetrimide 0.15%, net price 25 x 25-mL sachet = £5.20; 10 x 100-mL sachet = £6.68  
  To be used undiluted for general skin disinfection and wound cleansing

  **Travasept 100**® (Baxter)  
  **Solution** (sterile), yellow, chlorhexidine acetate 0.015%, cetrimide 0.15%, net price 500 mL = 72p, 1 litre = 77p  
  To be used undiluted in skin disinfection such as wound cleansing and obstetrics

- **Concentrates**

  Hibitane 5% Concentrate® (Regent Medical)  
  **Solution**, red, chlorhexidine gluconate 5%, in a perfumed aqueous solution, net price 5 litres = £14.50  
  **Dose** to be used diluted 1 in 10 (0.5%) with alcohol 70% for pre-operative skin preparation, or 1 in 100 (0.05%) with water for general skin disinfection  
  **Note** Alcoholic solutions not suitable before diathermy (see Alcohol, p. 656)

### 13.11.3 Cationic surfactants and soaps

#### CETRIMIDE

**Indications** skin disinfection  
**Cautions** avoid contact with eyes; avoid use in body cavities  
**Side-effects** skin irritation and occasionally sensitization

**Preparations** Ingredient of Tisept® and Travasept® 100, see above

### 13.11.4 Iodine

#### Povidone–Iodine

**Indications** skin disinfection  
**Cautions** pregnancy (Appendix 4), breast-feeding (Appendix 5); broken skin (see below); renal impairment (Appendix 3)  
**Large open wounds** the application of povidone–iodine to large wounds or severe burns may produce systemic adverse
effects such as metabolic acidosis, hypernatraemia and impairment of renal function.

**Contra-indications** preterm neonate gestational age under 32 weeks; avoid regular use in patients with thyroid disorders or those receiving lithium therapy

**Side-effects** rarely sensitivity; may interfere with thyroid function tests

**Betadine** (Mölnlycke)

Dry powder spray, povidone–iodine 2.5% in a pressurised aerosol unit, net price 150-g unit = £2.63
For skin disinfection, particularly minor wounds and infections; CHILD under 2 years not recommended
Note Not for use in serous cavities

Ointment, povidone–iodine 10%, in a water-miscible basis, net price 20 g = £1.33, 80 g = £2.66
Excipients none as listed in section 13.1.3
For skin disinfection, particularly minor wounds and infections; CHILD under 2 years not recommended

**Savlon** Dry (Novartis Consumer Health)

Powder spray, povidone–iodine 1.14% in a pressurised aerosol unit, net price 50-mL unit = £2.39
For minor wounds

**Videne** (Ecolab)

Alcoholic tincture, povidone–iodine 10%, net price 500 mL = £2.50
To be applied undiluted in pre-operative skin disinfection

Antiseptic solution, povidone–iodine 10% in aqueous solution, net price 500 mL = £2.50
To be applied undiluted in pre-operative skin disinfection and general antisepsis

Surgical scrub, povidone–iodine 7.5% in aqueous solution, net price 500 mL = £2.50
To be used as a pre-operative scrub for hand and skin disinfection

**Solution 3%** (10 vols), net price 200 mL = 41p
For skin disinfection, particularly cleansing and deodorising wounds and ulcers
Note The BP directs that when hydrogen peroxide is prescribed, hydrogen peroxide solution 6% (20 vols) should be dispensed.

**Important** Strong solutions of hydrogen peroxide which contain 27% (90 vols) and 30% (100 vols) are only for the preparation of weaker solutions

**Crystacide** (GP Pharma)

Cream, hydrogen peroxide 1%, net price 10 g = £4.82, 25 g = £8.07, 40 g = £11.62
Dose superficial bacterial skin infection, apply 2–3 times daily for up to 3 weeks
Excipients include edetic acid (EDTA), propylene glycol

**POTASSIUM PERMANGANATE**

**Indications** cleansing and deodorising suppurating eczematous reactions and wounds

**Cautions** irritant to mucous membranes

**Dose**
- Wet dressings or baths, approx. 0.01% solution
Note Stains skin and clothing

**Potassium Permanganate Solution**

**Solution**, potassium permanganate 0.1% (1 in 1000) in water
Dose to be diluted 1 in 10 to provide a 0.01% (1 in 10 000) solution

**Permitabs** (Alliance)

**Solution tablets**, for preparation of topical solution, potassium permanganate 400 mg, net price 30-tab pack = £6.22
Note 1 tablet dissolved in 4 litres of water provides a 0.01% (1 in 10 000) solution

**13.11.5 Phenolics**

**TRICLOSAN**

**Indications** skin disinfection

**Cautions** avoid contact with eyes

**Aquasept** (Medlock)

Skin cleanser, blue, triclosan 2%, net price 250 mL = £1.08, 500 mL = £1.67
Excipients include chlorocresol, propylene glycol, fragrance, trisodium edetate
For disinfection and pre-operative hand preparation

**Ster-Zac Bath Concentrate** (Medlock)

**Solution**, triclosan 2%, net price 28.5 mL = 40p, 500 mL = £2.24
Dose for prevention of cross-infection use 28.5 mL/bath
Excipients include trisodium edetate

**13.11.6 Oxidisers and dyes**

**HYDROGEN PEROXIDE**

**Indications** see under preparations below

**Cautions** large or deep wounds; avoid on healthy skin and eyes; bleaches fabric; incompatible with products containing iodine or potassium permanganate

**Hydrogen Peroxide Solution, BP**

**Solution 6%** (20 vols), net price 200 mL = 42p

**Desloughing agents**

Alginate, hydrogel and hydrocolloid dressings (Appendix 8) are effective at wound debrideinent. Sterile larvae (maggots) (LarvE, Zoobiotic) are also used for manageing sloughing wounds and are prescribable on the NHS.

Desloughing solutions and creams are of little clinical value. Substances applied to an open area are easily absorbed and perilesional skin is easily sensitised; gravitational dermatitis may be complicated by superimposed contact sensitivity to substances such as neomycin or lanolin.

For further information on wound management products see Appendix 8, p. 883.

**13.11.7 Preparations for promotion of wound healing**

**Growth factor**

A topical preparation of becaplermin (recombinant human platelet-derived growth factor) is licensed as an adjunct treatment of full-thickness, neuropathic, diabetic ulcers. It enhances the formation of granulation tissue, thereby promoting wound healing.
BECAPLERMIN
(Recombinant human platelet-derived growth factor)

**Indications** see notes above

**Cautions** malignant disease; avoid on sites with infection, malignancy, or peripheral arteriopathy

**Side-effects** pain; infections including cellulitis and osteomyelitis; local reactions including erythema; rarely bullous eruption, oedema, and hypertrophic granulation

**Dose**
- Full-thickness, neuropathic, diabetic ulcers (no larger than 5 cm), apply thin layer daily and cover with gauze dressing moistened with physiological saline; max. duration of treatment 20 weeks (reassess if no healing after first 10 weeks);
- CHILD under 18 years, see BNF for Children

Regranex® (Janssen-Cilag)
Gel, becaplermin (recombinant human platelet-derived growth factor) 0.01%, net price 15 g = £255.75

**Excipients** include hydroxybenzoates (parabens)

13.12 Antiperspirants

Aluminium chloride is a potent antiperspirant used in the treatment of hyperhidrosis. Aluminium salts are also incorporated in preparations used for minor fungal skin infections associated with hyperhidrosis.

In more severe cases specialists use glycopyrronium bromide as a 0.05% solution in the iontophoretic treatment of hyperhidrosis of plantar and palmar areas.

Botulinum A toxin-haemagglutinin complex (section 4.9.3) is licensed for use intradermally for severe hyperhidrosis of the axillae unresponsive to topical antiperspirant or other anticholinergic treatment.

**ALUMINIUM SALTS**

**Indications** see under Dose below

**Cautions** avoid contact with eyes or mucous membranes; avoid use on broken or irritated skin; do not shave axillae or use depilatories within 12 hours of application; avoid contact with clothing

**Side-effects** skin irritation

**Dose**
- Hyperhidrosis affecting axillae, hands or feet, apply liquid formulation at night to dry skin, wash off the following morning, initially daily then reduce frequency as condition improves—do not bathe immediately before use
- Hyperhidrosis, bromhidrosis, intertrigo, and prevention of tinea pedis and related conditions, apply powder to dry skin

Anhydrol® Forte (Dermal)
**Solution (= application), aluminium chloride hexahydrate 20% in an alcoholic basis, net price 60-mL bottle with roll-on applicator = £2.62. Label: 15**

**Excipients** none as listed in section 13.1.3

GLYCOPYRRONIUM BROMIDE

**Indications** iontophoretic treatment of hyperhidrosis; other indications section 15.1.3

**Cautions** see section 15.1.3 (but poorly absorbed and systemic effects unlikely)

**Contra-indications** see section 15.1.3 (but poorly absorbed and systemic effects unlikely), infections affecting the treatment site

**Side-effects** see section 15.1.3 (but poorly absorbed and systemic effects unlikely), tingling at administration site

**Dose**
- Consult product literature; only 1 site to be treated at a time, max. 2 sites treated in any 24 hours, treatment not to be repeated within 7 days

Robinul® (Antigen)
**Powder, glycopyrronium bromide, net price 3 g = £110.00**

13.13 Topical circulatory preparations

These preparations are used to improve circulation in conditions such as bruising, superficial thrombophlebitis, chilblains and varicose veins but are of little value. Chilblains are best managed by avoidance of exposure to cold; neither systemic nor topical vasodilator therapy is established as being effective. Sclerotherapy of varicose veins is described in section 2.13.

Rubefacients are described in section 10.3.2.

Hirudoid® (Genus)
**Cream, heparinoid 0.3% in a vanishing-cream basis, net price 50 g = £3.99**

**Excipients** include cetostearyl alcohol, hydroxybenzoates (parabens)

**Gel, heparinoid 0.3%, net price 50 g = £3.99**

**Excipients** include propylene glycol, fragrance

**Dose** apply up to 4 times daily on superficial soft-tissue injuries and superficial thrombophlebitis
14 Immunological products and vaccines

14.1 Active immunity

Active immunity can be acquired by natural disease or by vaccination. Vaccines stimulate production of antibodies and other components of the immune mechanism; they consist of either:
1. a live attenuated form of a virus (e.g. measles, mumps and rubella vaccine) or bacteria (e.g. BCG vaccine), or
2. inactivated preparations of the virus (e.g. influenza vaccine) or bacteria, or
3. extracts of or detoxified exotoxins produced by a micro-organism (e.g. tetanus vaccine).

Live attenuated vaccines usually produce a durable immunity, but not always as long-lasting as that resulting from natural infection.

Inactivated vaccines may require a primary series of injections of vaccine to produce adequate antibody response and in most cases booster (reinforcing) injections are required; the duration of immunity varies from months to many years. Some inactivated vaccines are adsorbed onto an adjuvant (such as aluminium hydroxide) to enhance the antibody response.

Advice in this chapter reflects that in the handbook *Immunisation against Infectious Disease* (2006), which in turn reflects the guidance of the Joint Committee on Vaccination and Immunisation (JCVI). Chapters from the handbook are available at www.dh.gov.uk

The advice in this chapter also incorporates changes announced by the Chief Medical Officer and Health Department Updates.

Cautions Most individuals can safely receive the majority of vaccines. Vaccination may be postponed if the individual is suffering from an acute illness, however, it is not necessary to postpone immunisation in patients with minor illnesses without fever or systemic upset. See also Predisposition to Neurological Problems, below. For individuals with bleeding disorders, see Route of administration, below. If alcohol or disinfectant is used for cleansing the skin it should be allowed to evaporate before vaccination to prevent possible inactivation of live vaccines.

When two live virus vaccines are required (and are not available as a combined preparation) they should be given either simultaneously at different sites or separated by an interval of at least 4 weeks. For interactions see Appendix 1 (vaccines).

See also Cautions under individual vaccines

Contra-indications Vaccines are contra-indicated in those who have a confirmed anaphylactic reaction to a preceding dose of a vaccine containing the same antigens or vaccine component (such as bacteria in viral vaccines). The presence of the following excipients in vaccines and immunological products has been noted under the relevant entries:

- Hypersensitivity to egg: with evidence of previous anaphylactic reaction, contra-indicates influenza vaccine, tick-borne encephalitis vaccine, and yellow fever vaccine.
- See also Contra-indications under individual vaccines.

**Contra-indications under individual vaccines.**

**Immunised response** Immune response to vaccines may be reduced in immunosuppressed patients and there is also a risk of generalised infection with live vaccines. Severely immunosuppressed patients should not be given live vaccines (including those with severe primary immunodeficiency). Specialist advice should be sought for those being treated with high doses of corticosteroids (dose equivalents of prednisolone: adults, at least 40 mg daily for more than 1 week; children, 2 mg/kg daily for at least 1 week or 1 mg/kg daily for 1 month), or other immunosuppressive drugs, and those being treated for malignant conditions with chemotherapy or generalised radiotherapy. For special reference to HIV infection, see below.


Pregnancy and breast-feeding Live vaccines should not be administered routinely to pregnant women.

---

1. Live vaccines should be postponed until at least 3 months after stopping high-dose systemic corticosteroids and at least 6 months after stopping other immunosuppressive drugs or generalised radiotherapy (at least 12 months after discontinuing immunosuppressants following bone-marrow transplantation).
2. Use of normal immunoglobulin should be considered after exposure to measles (see p. 681) and varicella–zoster immunoglobulin considered after exposure to chickenpox or herpes zoster (see p. 682).
Side-effects

Injection of a vaccine may be followed by local reactions such as pain, inflammation, redness, and lymphangitis. An induration or sterile abscess may develop at the injection site. Gastro-intestinal disturbances, fever, headache, irritability, loss of appetite, fatigue, myalgia, and malaise are among the most commonly reported side-effects. Other side-effects include influenza-like symptoms, dizziness, paraesthesia, asthena, drowsiness, arthralgia, rash, and lymphadenopathy. Hypersensitivity reactions, such as bronchospasm, angioedema, urticaria, and anaphylaxis, are very rare but can be fatal (see section 3.4.3 for management of allergic emergencies).

Oral vaccines such as cholera, live poliomyelitis, rotavirus, and live typhoid can also cause gastro-intestinal disturbances such as nausea, vomiting, abdominal pain and cramps, and diarrhoea.

See also Predisposition to neurological problems, below.

Some vaccines (e.g. poliomyelitis) produce very few reactions, while others (e.g. measles, mumps and rubella) may cause a very mild form of the disease. Occasionally more serious adverse reactions can occur—these should always be reported to the CHM (see Adverse Reactions to Drugs, p. 11).

There is no evidence that premature babies are at increased risk of adverse reactions from vaccines, see also Prematurity, below.

Predisposition to neurological problems

When there is a personal or family history of febrile convulsions, there is an increased risk of these occurring during fever from any cause including immunisation, but this is not a contra-indication to immunisation. In children who have had a seizure associated with fever without neurological deterioration, immunisation is recommended; advice on the prevention of fever (see Post-immunisation pyrexia in infants, above) should be given before immunisation. When a child has had a convulsion not associated with fever, and the neurological condition is not deteriorating, immunisation is recommended.

Children with stable neurological disorders (e.g. spina bifida, congenital brain abnormality, and perinatal hypoxic-ischaemic encephalopathy) should be immunised according to the recommended schedule. Where there is a still evolving neurological problem, including poorly controlled epilepsy, immunisation should be deferred and the child referred to a specialist. Immunisation is recommended if a cause for the neurological disorder is identified. If a cause is not identified, immunisation should be deferred until the condition is stable.

Further information on adverse effects associated with specific vaccines can be found under individual vaccines.

Vaccines and HIV infection

HIV-positive individuals with or without symptoms can receive the following live vaccines:

- MMR (but avoid if immunity significantly impaired), varicella-zoster (but avoid if immunity significantly impaired—consult product literature); 1, 2

and the following inactivated vaccines:

- anthrax, cholera (oral), diphtheria, haemophilus influenzae type b, hepatitis A, hepatitis B, human papilloma virus, influenza, meningococcal, pertussis, pneumococcal, polio-vaccine, rabies, tetanus, tick-borne encephalitis, typhoid (injection).

HIV-positive individuals should not receive:

- BCG, typhoid (oral), yellow fever

Note The above advice differs from that for other immunocompromised patients: Immunisation Guidelines for HIV-infected Adults issued by British HIV Association (BHIVA) are available at www.bhiva.org and, Immunisation of HIV-infected Children issued by Children’s HIV Association (CHIVA) are available at www.chiva.org.uk

Vaccines and asplenia

The following vaccines are recommended for asplenic patients or those with splenic dysfunction:

- haemophilus influenzae type b, influenza, meningococcal group C, pneumococcal.

For antibiotic prophylaxis in asplenia see p. 288.

Route of administration

Vaccines should not be given intravenously. Most vaccines are given by the intramuscular route; some vaccines are given by others routes—the intradermal route for BCG vaccine, deep subcutaneous route for Japanese encephalitis, and varicella vaccine, and the oral route for cholera, live poliomyelitis, rotavirus, and live typhoid vaccines. The intramuscular route should not be used in patients with bleeding disorders such as haemophilia or thrombocytopenia. Vaccines usually given by the intramuscular route should be given by deep subcutaneous injection instead.

Note The Department of Health has advised against the use of jet guns for vaccination owing to the risk of transmitting bloodborne infections, such as HIV.

1. Use of normal immunoglobulin should be considered after exposure to measles (see p. 681) and varicella—zoster immunoglobulin considered after exposure to chickenpox or herpes zoster (see p. 682).

2. The Royal College of Paediatrics and Child Health recommends that MMR is not given to a child with HIV infection whilst severely immunosuppressed.

3. If yellow fever risk is unavoidable, specialist advice should be sought.
## Immunisation schedule

Vaccines for the childhood immunisation schedule should be obtained from local health organisations or direct from Movianto—not to be prescribed on FP10 (HS21 in Northern Ireland; GP10 in Scotland; WP10 in Wales).

### Prematurity

Children born prematurely should receive all routine immunisations based on the actual date of birth. There is no evidence that premature infants are at increased risk of adverse reactions from vaccines. Seroconversion may be unreliable in babies born earlier than 28 weeks’ gestation or in babies treated with corticosteroids for chronic lung disease; consideration should be given to testing for antibodies against *Haemophilus influenzae* (type b), meningococcal C, and hepatitis B after primary immunisation.

### When to immunise (for premature infants—see note above)

<table>
<thead>
<tr>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonates at risk only</strong></td>
</tr>
<tr>
<td>● BCG Vaccine</td>
</tr>
<tr>
<td>● See section 14.4, BCG Vaccines</td>
</tr>
<tr>
<td>● Hepatitis B Vaccine</td>
</tr>
<tr>
<td>● See section 14.4, Hepatitis B Vaccine</td>
</tr>
<tr>
<td><strong>2 months</strong></td>
</tr>
<tr>
<td>● Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and <em>Haemophilus Type b</em> Conjugate Vaccine (Adsorbed)</td>
</tr>
<tr>
<td>● First dose</td>
</tr>
<tr>
<td>● Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)</td>
</tr>
<tr>
<td>● First dose</td>
</tr>
<tr>
<td><strong>3 months</strong></td>
</tr>
<tr>
<td>● Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and <em>Haemophilus Type b</em> Conjugate Vaccine (Adsorbed)</td>
</tr>
<tr>
<td>● Second dose</td>
</tr>
<tr>
<td>● Meningococcal Group C Conjugate Vaccine</td>
</tr>
<tr>
<td>● First dose</td>
</tr>
<tr>
<td><strong>4 months</strong></td>
</tr>
<tr>
<td>● Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and <em>Haemophilus Type b</em> Conjugate Vaccine (Adsorbed)</td>
</tr>
<tr>
<td>● Third dose</td>
</tr>
<tr>
<td>● Meningococcal Group C Conjugate Vaccine</td>
</tr>
<tr>
<td>● Second dose</td>
</tr>
<tr>
<td>● Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)</td>
</tr>
<tr>
<td>● Second dose</td>
</tr>
<tr>
<td><strong>12 months</strong></td>
</tr>
<tr>
<td>● <em>Haemophilus Type b</em> Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine</td>
</tr>
<tr>
<td>● Single booster dose</td>
</tr>
<tr>
<td><strong>13 months</strong></td>
</tr>
<tr>
<td>● Measles, Mumps and Rubella Vaccine, Live (MMR)</td>
</tr>
<tr>
<td>● First dose</td>
</tr>
<tr>
<td>● Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)</td>
</tr>
<tr>
<td>● Single booster dose</td>
</tr>
</tbody>
</table>

### Between 3 years and 4 months, and 5 years

<table>
<thead>
<tr>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
</tr>
</thead>
</table>
| ● *Adsorbed Diphtheria* [low dose], Tetanus, Pertussis (Acellular, Component) and Inactivated Poliomyelitis Vaccine  
 | or  
 | ● *Adsorbed Diphtheria*, Tetanus, Pertussis (Acellular, Component) and Inactivated Poliomyelitis Vaccine  
 | or  
 | ● *Diphtheria*, Tetanus, Pertussis (Acellular, Component) Poliomyelitis (Inactivated) and *Haemophilus Type b* Conjugate Vaccine (Adsorbed) |
| ● Single booster dose |
| **Note:** Preferably allow interval of at least 3 years after completing primary course; can be given at same session as MMR Vaccine but use separate syringe and needle, and give in different limb |
| ● Measles, Mumps and Rubella Vaccine, Live (MMR) |
| ● Single booster dose |

### 12–13 years (females only)

<table>
<thead>
<tr>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
</tr>
</thead>
</table>
| ● Human Papilloma Virus Vaccine  
 | 3 doses; second dose 1–2 months, and third dose 6 months after first dose |

### 13–18 years

<table>
<thead>
<tr>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
</tr>
</thead>
</table>
| ● *Adsorbed Diphtheria* [low dose], Tetanus, and Inactivated Poliomyelitis Vaccine  
 | or  
 | ● *Measles, Mumps and Rubella Vaccine, Live (MMR)*  
 | or  
 | ● *Diphtheria*, Tetanus, Pertussis (Acellular, Component) Poliomyelitis (Inactivated) and *Haemophilus Type b* Conjugate Vaccine (Adsorbed) |
| ● Single booster dose |

### During adult life

**Women of child-bearing age susceptible to rubella**

- **Measles, Mumps and Rubella Vaccine, Live (MMR)**
- Women of child-bearing age who have not received 2 doses of a rubella-containing vaccine or who do not have a positive antibody test for rubella should be offered rubella immunisation (using the MMR vaccine)—exclude pregnancy before immunisation, but see also section 14.4, Measles, Mumps and Rubella Vaccine

### During adult life

**If not previously immunised**

- **Measles, Mumps and Rubella Vaccine, Live (MMR)**
- 3 doses at intervals of 1 month
- Booster dose at least 1 year after primary course and again 5–10 years later

---

1. For children born between 13 March 2003 and 3 September 2005 who have not received a booster dose of *Haemophilus Type b Conjugate Vaccine* at 12 months of age, see also p. 677.

2. The two human papilloma virus vaccines are not interchangeable and one vaccine product should be used for the entire course; however for individuals with previous incomplete vaccination with *Gardasil* who are eligible for HPV vaccination under the national programme, *Cervarix* can be used to complete the vaccination course if necessary; the individual must be informed that *Cervarix* does not protect against genital warts.

3. For females aged 14 to under 18 years, see ‘Catch-Up’ Programme, p. 671.
High-risk groups
For information on high-risk groups, see section 14.4 under individual vaccines

BCG Vaccines
Hepatitis A Vaccine
Hepatitis B Vaccine
Influenza Vaccine
Pneumococcal Vaccines
Tetanus Vaccines

14.2 Passive immunity

Immunity with immediate protection against certain infective organisms can be obtained by injecting preparations made from the plasma of immune individuals with adequate levels of antibody to the disease for which protection is sought (see under Immunoglobulins, section 14.5). The duration of this passive immunity varies according to the dose and the type of immunoglobulin. Passive immunity may last only a few weeks; where necessary, passive immunisation can be repeated.

Antibodies of human origin are usually termed immunoglobulins. The term antiserum is applied to material prepared in animals. Because of serum sickness and other allergic-type reactions that may follow injections of antiserum, this therapy has been replaced wherever possible by the use of immunoglobulins. Reactions are theoretically possible after injection of human immunoglobulins but reports of such reactions are very rare.

14.3 Storage and use

Care must be taken to store all vaccines and other immunological products under the conditions recommended in the product literature, otherwise the preparation may become ineffective. Refrigerated storage is usually necessary; many vaccines and immunoglobulins need to be stored at 2–8°C and not allowed to freeze. Vaccines and immunoglobulins should be protected from light. Reconstituted vaccines and opened multidose vials must be used within the period recommended in the product literature. Unused vaccines should be disposed of by incineration at a registered disposal contractor.

Particular attention must be paid to instructions on the use of diluents. Vaccines which are liquid suspensions or are reconstituted before use should be adequately mixed to ensure uniformity of the material to be injected.

14.4 Vaccines and antisera

Availability Anthrax and yellow fever vaccines, botulism antitoxin, diphtheria antitoxin, and snake and spider venom antitoxins are available from local designated holding centres.

For antivenom, see Emergency Treatment of Poisoning, p. 36.

Enquiries for vaccines not available commercially can also be made to:

Immunisation Policy, Monitoring and Surveillance Department of Health
Wellington House
133–155 Waterloo Road
London, SE1 8UG
Tel: (020) 7972 4047

In Scotland information about availability of vaccines can be obtained from a Specialist in Pharmaceutical Public Health. In Wales enquiries for vaccines not available commercially should be directed to:

Welsh Medicines Information Centre
University Hospital of Wales
Cardiff, CF14 4XW
Tel: (029) 2074 2979

and in Northern Ireland:
Regional Pharmacist (procurement co-ordination) United Hospitals Trust Pharmacy Dept
Whiteabbey Hospital
Doagh Road
Newtownabbey, BT37 9RH
Tel: (028) 9086 5181 ext 2386

For further details of availability, see under individual vaccines.

Anthrax vaccine

Anthrax vaccine is made from antigens from *B. anthracis*. Anthrax immunisation is indicated for individuals who handle infected animals, for those exposed to imported infected animal products, and for laboratory staff who work with *Bacillus anthracis*. A 4-dose regimen is used for primary immunisation; booster doses should be given annually to workers at continued risk of exposure to anthrax.

In the event of possible contact with *B. anthracis*, post-exposure immunisation may be indicated, in addition to antimicrobial prophylaxis (section 5.1.12). Advice on the use of anthrax vaccine for post-exposure prophylaxis must be obtained from the Centre for Infections, Health Protection Agency (tel. 020 8200 4400).

**ANTHRAX VACCINE**

**Indications** pre-exposure immunisation against anthrax; post-exposure immunisation (see notes above)

**Cautions** see section 14.1

**Contra-indications** see section 14.1

**Side-effects** see section 14.1

**Dose**

- By intramuscular injection in deltoid region, initial course 3 doses of 0.5 mL at intervals of 3 weeks followed by a fourth dose after an interval of 6 months; booster, 0.5 mL every 12 months

**Anthrax Vaccine (parenteral)**

**Injection**, suspension of anthrax antigens (not less than 0.125 mL/0.5 mL dose), sterile filtrate, adsorbed on to aluminium potassium sulphate

Excipients include thiomersal

Available from the Health Protection Agency’s Centre for Emergency Preparedness and Response (Porton Down)
BCG vaccines

BCG (Bacillus Calmette-Guérin) is a live attenuated strain derived from Mycobacterium bovis which stimulates the development of hypersensitivity to M. tuberculosis. BCG vaccine should be given intradermally by operators skilled in the technique (see below).

The expected reaction to successful BCG vaccination is induration at the site of injection followed by a local lesion which starts as a papule 2 or more weeks after vaccination; the lesion may ulcerate then subside over several weeks or months, leaving a small, flat scar. A dry dressing may be used if the ulcer discharges, but air should not be excluded.

Apart from children under 6 years, any person being considered for BCG immunisation must first be given a skin test for hypersensitivity to tuberculoprotein (see under Diagnostic Agents, below). A skin test is not necessary for a child under 6 years provided that the child has not stayed for longer than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000, the child has not had contact with a person with tuberculosis, and there is no family history of tuberculosis within the last 5 years.

BCG is recommended for the following groups if BCG immunisation has not previously been carried out:

- all neonates and infants (0–12 months) born in areas where the incidence of tuberculosis is greater than 40 per 100 000;
- neonates, infants, and children under 16 years with a parent or grandparent born in a country with an incidence of tuberculosis greater than 40 per 100 000;
- new immigrants aged under 16 years who were born in, or lived for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000;
- new immigrants aged 16–35 years from Sub-Saharan Africa or a country with an incidence of tuberculosis greater than 500 per 100 000;
- contacts aged under 36 years of those with active tuberculosis (for healthcare or laboratory workers who have had contact with clinical materials or patients with tuberculosis, age limit does not apply);
- healthcare workers and laboratory staff (irrespective of age) who are likely to have contact with patients, clinical materials, or derived isolates; other individuals under 35 years of age with occupational risk including veterinary and other staff who handle animal species susceptible to tuberculosis, and staff working directly with prisoners, in care homes for the elderly, or in hostels or facilities for the homeless or refugees;
- individuals under 16 years intending to live with local people for more than 3 months in a country with an incidence of tuberculosis greater than 40 per 100 000 (section 14.6).

BCG vaccine can be given simultaneously with another live vaccine (see also section 14.1), but if they are not given at the same time an interval of 4 weeks should normally be allowed. When BCG is given to infants, there is no need to delay routine primary immunisations. No further vaccination should be given in the arm used for BCG vaccination for at least 3 months because of the risk of regional lymphadenitis.

Bladder instillations of BCG are licensed for the management of bladder carcinoma (section 8.2.4).

For advice on chemoprophylaxis against tuberculosis, see section 5.1.9; for the treatment of infection following vaccination, seek expert advice.

**BACILLUS CALMETTE-GUÉRIN VACCINE**

**BCG Vaccine**

**Indications** immunisation against tuberculosis

**Cautions** see section 14.1; **Interactions**: Appendix 1 (vaccines)

**Contra-indications** see section 14.1; also neonate in household contact with known or suspected case of active tuberculosis; generalised septic skin conditions (for patients with eczema, lesion-free site should be used)

**Side-effects** see section 14.1 and notes above; also at the injection site, subcutaneous abscess, prolonged ulceration; rarely disseminated complications such as osteitis or osteomyelitis

**Dose**

- By intradermal injection **ADULT** and **CHILD** over 1 year, 0.1 mL; **NEONATE** and **CHILD** under 1 year, 0.05 mL

**Intradermal injection technique** Skin is stretched between thumb and forefinger and needle (size 25G or 26G) inserted (bevel upwards) for about 3 mm into superficial layers of dermis (almost parallel with surface). Needle should be short with short bevel (can usually be seen through epidermis during insertion). Tense raised blanched bleb showing tips of hair follicles is sign of correct injection; 7 mm bleb = 0.1 mL injection, 3.5 mm bleb = 0.05 mL injection; if considerable resistance not felt, needle too deep and should be removed and reinserted before giving more vaccine.

To be injected at insertion of deltoid muscle onto humerus (keloid formation more likely with sites higher on arm); tip of shoulder should be avoided.

**Intradermal Bacillus Calmette-Guérin Vaccine (PoP)**

BCG Vaccine, Dried/Tub/BCG

Injection (powder for suspension), freeze-dried preparation of live bacteria of a strain derived from the bacillus of Calmette and Guérin.

Available from health organisations or direct from Movianto (SSI brand, multidose vial with diluent)

**Diagnostic agents**

The Mantoux test is recommended for tuberculin skin testing, but no licensed preparation is currently available. Guidance for healthcare professionals is available at [www.immunisation.nhs.uk](http://www.immunisation.nhs.uk).

In the Mantoux test, the diagnostic dose is administered by intradermal injection of Tuberculin Purified Protein Derivative (PPD).
The Heaf test (involving the use of multiple-puncture apparatus) is no longer available. **Note** Response to tuberculin may be suppressed by live viral vaccines, viral infection, sarcoidosis, corticosteroid therapy, or immunosuppression due to disease or treatment. Tuberculin testing should not be carried out within 4 weeks of receiving a live viral vaccine.

**Tuberculin Purified Protein Derivative** (Tuberculin PPD)

**Injection**, heat-treated products of growth and lysis of appropriate Mycobacterium spp. 20 units/mL (2 units/0.1 mL dose) (for routine use), 1.5-mL vial; 100 units/mL (10 units/0.1 mL dose), 1.5-mL vial

**Dose** by intradermal injection, for Mantoux test, 2 units (0.1 mL of 20 units/mL strength) for routine Mantoux test; if first test is negative and a further test is considered appropriate 10 units (0.1 mL of 100 units/mL strength)

**Available from** Movianto (SSI brand)

**Note** The strength of tuberculin PPD in this product may be different to the strengths of products used previously for the Mantoux test; care is required to select the correct strength

**Botulism antitoxin**

A polyvalent botulism antitoxin is available for the post-exposure prophylaxis of botulism and for the treatment of persons thought to be suffering from botulism. It specifically neutralises the toxins produced by *Clostridium botulinum* types A, B, and E. It is not effective against infantile botulism as the toxin (type A) is seldom, if ever, found in the blood in this type of infection.

Hypersensitivity reactions are a problem. It is essential to read the contra-indications, warnings, and details of sensitivity tests on the package insert. Prior to treatment checks should be made regarding previous administration of any antitoxin and history of any allergic condition, e.g. asthma, hay fever, etc. All patients should be tested for sensitivity (diluting the antitoxin if history of allergy).

**Botulism Antitoxin**

A preparation containing the specific antitoxic globulins that have the power of neutralising the toxins formed by types A, B, and E of *Clostridium botulinum*. **Note** The BP title Botulinum Antitoxin is not used because the preparation currently in use may have a different specification.

**Dose** prophylaxis, consult product literature

**Available from** local designated centres, for details see TOXBASE (requires registration) www.toxbase.org. For supplies outside working hours apply to other designated centres or to the duty doctor at the Health Protection Agency (Tel (020) 8200 6868). For major incidents, obtain supplies from the local blood bank

**Cholera vaccine**

**Cholera vaccine** (oral) contains inactivated Inaba (including El-Tor biotype) and Ogawa strains of *Vibrio cholerae*, serotype O1 together with recombinant B-subunit of the cholera toxin produced in Inaba strains of *V.cholerae*, serotype O1.

Oral cholera vaccine is licensed for travellers to endemic or epidemic areas on the basis of current recommendations (see also section 14.6). Immunisation should be completed at least 1 week before potential exposure. However, there is no requirement for cholera vaccination for international travel.

Immunisation with cholera vaccine does not provide complete protection and all travellers to a country where cholera exists should be warned that scrupulous attention to food, water, and personal hygiene is essential. **Injectable cholera vaccine** provides unreliable protection and is no longer available in the UK.

**CHOLERA VACCINE**

**Indications** see notes above

**Cautions** see section 14.1 and notes above

**Contra-indications** see section 14.1

**Side-effects** see section 14.1; also rarely respiratory symptoms such as rhinitis and cough; very rarely sore throat, insomnia

**Dose**

- **ADULT and CHILD** over 6 years 2 doses separated by an interval of 1–6 weeks; **CHILD** 2–6 years 3 doses each separated by an interval of 1–6 weeks

**Note** If more than 6 weeks have elapsed between doses, the primary course should be restarted

- A single booster dose can be given 2 years after primary course for adults and children over 6 years, and 6 months after primary course for children 2–6 years. If more than 2 years have elapsed since the last vaccination, the primary course should be repeated

**Counselling** Dissolve effervescent sodium bicarbonate granules in a glassful of water (approximately 150 mL). For adults and children over 6 years, add vaccine suspension to make one dose. For child 2–6 years, discard half (approximately 75 mL) of the solution, then add vaccine suspension to make one dose. Drink within 2 hours. Food, drink, and other oral medicines should be avoided for 1 hour before and after vaccination

**Dukoral®** (Novartis Vaccines)

**Oral suspension**, for dilution with solution of effervescent sodium bicarbonate granules, heat- and formaldehyde-inactivated Inaba (including El-Tor biotype) and Ogawa strains of *Vibrio cholerae* bacteria and recombinant cholera toxin B-subunit produced in *V. cholerae*, net price 2-dose pack = £23.42. Counselling, administration

**Diphtheria vaccines**

Diphtheria vaccines are prepared from the toxin of *Corynebacterium diphtheriae* and adsorption on aluminium hydroxide or aluminium phosphate improves antigenicity. The vaccine stimulates the production of the protective antitoxin. The quantity of diphtheria toxoid in a preparation determines whether the vaccine is defined as ‘high dose’ or ‘low dose’. Vaccines containing the higher dose of diphtheria toxoid are used for primary immunisation of children under 10 years of age. Vaccines containing the lower dose of diphtheria toxoid are used for primary immunisation in adults and children over 10 years. Single-antigen diphtheria vaccine is not available and adsorbed diphtheria vaccine is given as a combination product containing other vaccines.

For primary immunisation of children aged between 2 months and 10 years vaccination is recommended usually in the form of 3 doses (separated by 1-month intervals) of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) (see Immunisation schedule, section 14.1). In unimmunised individuals aged over 10 years the primary course comprises of 3 doses of adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine.
A booster dose should be given 3 years after the primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed). Children under 10 years should receive either adsorbed diphtheria, tetanus, pertussis (acellular, component) and inactivated poliomyelitis vaccine or adsorbed diphtheria [low dose], tetanus, pertussis (acellular, component) and inactivated poliomyelitis vaccine; for children requiring a booster dose of haemophilus influenzae type b vaccine as part of a ‘catch-up’ programme see p. 687. Individuals aged over 10 years should receive adsorbed diphtheria [low dose], tetanus, and inactivated poliomyelitis vaccine.

A second booster dose, of adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine, should be given 10 years after the previous booster dose (this interval can be reduced to a minimum of 5 years if previous doses were delayed).

**Travel**

Those intending to travel to areas with a risk of diphtheria infection should be fully immunised according to the UK schedule (see also section 14.6). If more than 10 years have lapsed since completion of the UK schedule, a dose of adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine should be administered.

**Contacts**

Staff in contact with diphtheria patients or with potentially pathogenic clinical specimens or working directly with C. diphtheriae or C. ulcerans should receive a booster dose if fully immunised (with 5 doses of diphtheria-containing vaccine given at appropriate intervals); further doses should be given at 10-year intervals if risk persists. Individuals at risk who are not fully immunised should complete the primary course; a booster dose should be given after 5 years and then at 10-year intervals. Adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine is used for this purpose; immunity should be checked by antibody testing at least 3 months after completion of immunisation.

Advice on the management of cases, carriers, contacts and outbreaks must be sought from health protection units. The immunisation history of infected individuals and their contacts should be determined; those who have been incompletely immunised should complete their immunisation and fully immunised individuals should receive a reinforcing dose. For advice on antibacterial treatment to prevent a secondary case of diphtheria in a non-immune individual, see Table 2, section 5.1.

### Diphtheria-containing vaccines for children under 10 years

**Important**

Not recommended for persons aged 10 years or over (see Diphtheria-containing Vaccines for Children over 10 years and Adults, below)

**Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed)**

- **Injection**, suspension of diphtheria toxoid, tetanus toxoid, acellular pertussis and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £17.56
- **Excipients** may include neomycin, polymyxin B and streptomycin
- **Dose** by intramuscular injection, CHILD 2 months–10 years, primary immunisation, 3 doses each of 0.5 mL separated by intervals of 1 month; see also notes on booster doses, above
- **Brands include** Infanrix-IPV+Hib, Pedvax ; available as part of childhood immunisation schedule, from health organisations or Movianto

**Adsorbed Diphtheria, Tetanus, Pertussis (Acellular, Component) and Inactivated Poliomyelitis Vaccine**

- **Injection**, suspension of diphtheria toxoid, tetanus toxoid, acellular pertussis and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £11.98
- **Excipients** may include neomycin, polymyxin B and streptomycin
- **Dose** by intramuscular injection, CHILD 3–10 years, first booster dose 3 years after primary immunisation, 0.5 mL; see also notes on booster doses, above
- **Brands include** Infanrix-IPV ; available as part of childhood immunisation schedule, from health organisations or Movianto

### Diphtheria-containing vaccines for children over 10 years and adults

A low dose of diphtheria toxoid is sufficient to recall immunity in individuals previously immunised against diphtheria but whose immunity may have diminished with time; it is insufficient to cause serious reactions in an individual who is already immune. Preparations containing low dose diphtheria should be used for adults and children over 10 years, for both primary immunisation and booster doses.

**Adsorbed Diphtheria [low dose], Tetanus and Inactivated Poliomyelitis Vaccine**

- **Injection**, suspension of diphtheria toxoid [low dose], tetanus toxoid, acellular pertussis and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £14.00
- **Excipients** may include neomycin, polymyxin B and streptomycin
- **Dose** by intramuscular injection, ADULT over 10 years, primary immunisation, 3 doses each of 0.5 mL separated by intervals of 1 month, second booster dose, 0.5 mL given 10 years after first booster dose (may be also used as first booster dose in those over 10 years who have received only 3 previous doses of a diphtheria-containing vaccine); see also notes on booster doses and contact above
- **Brands include** Revanex ; available as part of immunisation schedule, from health organisations or Movianto
Diphtheria antitoxin

Diphtheria antitoxin is used for passive immunisation in suspected cases of diphtheria only (without waiting for bacteriological confirmation); tests for hypersensitivity should be first carried out. It is derived from horse serum, and reactions are common after administration; resuscitation facilities should be available immediately.

It is no longer used for prophylaxis because of the risk of hypersensitivity; unimmunised contacts should be promptly investigated and given antibacterial prophylaxis (section 5.1, table 2) and vaccine (see Contacts above).

Diphtheria Antitoxin

Dose prophylaxis, not recommended therefore no dose stated (see notes above)

Treatment, consult product literature

Available from Centre for Infections (Tel (020) 8200 6868) or in Northern Ireland from Public Health Laboratory, Belfast City Hospital (Tel (028) 9032 9241)

Haemophilus type B conjugate vaccine

Haemophilus influenzae type b (Hib) vaccine is made from capsular polysaccharide; it is conjugated with a protein such as tetanus toxoid to increase immunogenicity, especially in young children. Haemophilus influenzae type b vaccine immunisation is given in combination with diphtheria, tetanus, pertussis (acellular, component) and inactivated poliomyelitis vaccine, as a component of the primary course of childhood immunisation (see Immunisation schedule, section 14.1) (see under Diphtheria-containing Vaccines). For infants under 1 year, the course consists of 3 doses of a vaccine containing haemophilus influenzae type b component with an interval of 1 month between doses. A booster dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) should be given at around 12 months of age.

‘Catch-up’ programme

Children born between 13 March 2003 and 3 September 2005 who have not received a booster dose of haemophilus influenzae type b vaccine at 12 months of age will be offered combined diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed) as part of a 'catch-up' programme before school entry; children who have already received their pre-school immunisation without the Hib component will be offered haemophilus influenzae type b vaccine combined with meningococcal group C conjugate vaccine. The ‘catch-up’ dose should be given 3 years after the primary course (this interval can be reduced to a minimum of 1 year if the primary course was delayed).

Children 1–10 years who have not been immunised against Haemophilus influenzae type b need to receive only 1 dose of Haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine). However, if a primary course of immunisation has not been completed, these children should be given 3 doses of diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed). The risk of infection falls sharply in older children and the vaccine is not normally required for children over 10 years.

Haemophilus influenzae type b vaccine may be given to those over 10 years who are considered to be at increased risk of invasive H. influenzae type b disease (such as those with sickle-cell disease and those receiving treatment for malignancy).

For use of Rifampicin in the prevention of secondary cases of Haemophilus influenzae type b disease, see Table 2, section 5.1.

Asplenia or splenic dysfunction

Haemophilus influenzae type b vaccine is recommended for patients with asplenia or splenic dysfunction. Immunised adults and children over 1 year, who develop splenic dysfunction, should be given 1 additional dose of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine). For elective splenectomy, the vaccine should ideally be given at least 2 weeks before surgery. Adults and children over 1 year, who are not immunised against haemophilus influenzae type b, should be given 2 doses of haemophilus influenzae type b vaccine (combined with meningococcal group C conjugate vaccine) with an interval of 2 months between doses. However, children under 10 years, who are not immunised against diphtheria, tetanus, pertussis, poliomyelitis, and haemophilus influenzae type b should be given 3 doses (with an interval of 1 month between doses) of combined diphtheria, tetanus, pertussis (acellular component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine.

HAEMOPHILUS TYPE B CONJUGATE VACCINE

Indications see notes above

Cautions see section 14.1

Contra-indications see section 14.1

Side-effects see section 14.1; also atopic dermatitis and hypotonia

Dose

- Primary immunisation, see under Diphtheria
- Booster dose, see notes above and under preparation below

Menitorix® (GSK)

Injection, powder for reconstitution, capsular polysaccharide of Haemophilus influenzae type b and capsular polysaccharide of Neisseria meningitidis group C (both conjugated to tetanus protein), net price single-dose vial (with syringe containing 0.5 mL diluent) = £39.87

Dose by intramuscular injection, CHILD 1–10 years, 0.5 mL

ADULT and CHILD over 1 year, with asplenia or splenic dysfunction (see notes above), 0.5 mL

Available as part of the childhood immunisation schedule from Movianto

Combined vaccines

See also under Diphtheria-containing Vaccines
Hepatitis A vaccine

Hepatitis A vaccine is prepared from formaldehyde-inactivated hepatitis A virus grown in human diploid cells.

Immunisation is recommended for:
- laboratory staff who work directly with the virus;
- staff and residents of homes for those with severe learning difficulties;
- workers at risk of exposure to untreated sewage;
- individuals who work with primates;
- patients with haemophilia treated with plasma-derived clotting factors;
- patients with severe liver disease;
- travellers to high-risk areas (see p. 684);
- individuals who are at risk due to their sexual behaviour;
- parenteral drug abusers.

Immunisation should be considered for:
- patients with chronic liver disease including chronic hepatitis B or chronic hepatitis C;
- prevention of secondary cases in close contacts of confirmed cases of hepatitis A, within 7 days of onset of disease in the primary case.

A booster dose is usually given 6–12 months after the initial dose. A second booster dose can be given 20 years after the previous booster dose to those who continue to be at risk. Specialist advice should be sought on re-immunisation of immunocompromised individuals.

HEPATITIS A VACCINE

Indications immunisation against hepatitis A infection
Cautions see section 14.1
contra-indications see section 14.1
Side-effects see section 14.1; for combination vaccines, see also Typhoid vaccine, p. 679

Dose
- See under preparations

Single component

Avaxim® (Sanofi Pasteur) (UK)
Injection, suspension of formaldehyde-inactivated hepatitis A virus (GBM grown in human diploid cells) 320 antigen units/mL adsorbed onto aluminium hydroxide, net price 0.5-mL prefilled syringe = £19.19
Exipients include neomycin
Dose by intramuscular injection (see note below), ADULT and CHILD over 16 years, 0.5 mL as a single dose; booster dose 0.5 mL 6–12 months after initial dose
Note Booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose with Avaxim. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders; not to be injected into the buttock (vaccine efficacy reduced)

Epalax® (MASTA) (UK)
Injection, suspension of formaldehyde-inactivated hepatitis A virus (RG-SB grown in human diploid cells) at least 48 units/mL, net price 0.5-mL prefilled syringe = £23.81
Dose by intramuscular injection (see note below), ADULT and CHILD over 1 year, 0.5 mL as a single dose; booster dose 0.5 mL 6–12 months after initial dose (1–6 months if splenectomised)
Note Booster dose may be delayed by up to 4 years in adults if not given after recommended interval following primary dose. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

Important Epalax contains influenza virus haemagglutinin grown in the allantoic cavity of chick embryos, therefore contra-indicated in those hypersensitive to eggs or chicken protein.

Havrix Monodose® (GSK) (UK)
Injection, suspension of formaldehyde-inactivated hepatitis A virus (HM 175 grown in human diploid cells) 1440 ELISA units/mL adsorbed onto aluminium hydroxide, net price 1-mL prefilled syringe = £22.14, 0.5-mL (720 ELISA units) prefilled syringe (Havrix Junior Monodose®) = £16.77
Exipients include neomycin
Dose by intramuscular injection (see note below), ADULT and CHILD over 16 years, 1 mL as a single dose; booster dose, 1 mL 6–12 months after initial dose; CHILD 1–15 years 0.5 mL, booster dose 0.5 mL 6–12 months after initial dose
Note Booster dose may be delayed by up to 3 years if not given after recommended interval following primary dose with Havrix Monodose®. The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders

Vaqta® Paediatric (Sanofi Pasteur) (UK)
Injection, suspension of formaldehyde-inactivated hepatitis A virus (grown in human diploid cells) 50 antigen units/mL adsorbed onto aluminium hydroxyphosphate sulphate, net price 0.5-mL prefilled syringe = £15.65
Exipients include neomycin
Dose by intramuscular injection (see note below) CHILD 1–17 years, 0.5 mL as a single dose; booster dose 0.5 mL 6–18 months after initial dose; under 1 year, not recommended
Note The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders (but immune response may be reduced)

With hepatitis B vaccine

Ambrix® (GSK) (UK)
Injection, suspension of inactivated hepatitis A virus (grown in human diploid cells) 720 ELISA units/mL adsorbed onto aluminium hydroxide, and recombinant (DNA) hepatitis B surface antigen (grown in yeast cells) 20 micrograms/mL adsorbed onto aluminium phosphate, net price 1-mL prefilled syringe = £31.18
Exipients include neomycin and traces of thiomersal
Dose CHILD 1–15 years, by intramuscular injection (see note below) primary course, 2 doses of 1 mL, the second 6–12 months after initial dose
Note Primary course should be completed with Ambrix (single component vaccines given at appropriate intervals may be used for booster dose); the deltoid region is the preferred site of injection in older children; anterolateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for patients with bleeding disorders (but immune response may be reduced)

Important Ambrix is not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular, or mucous membrane exposure to hepatitis B virus

Twinrix® (GSK) (UK)
Injection, inactivated hepatitis A virus (grown in human diploid cells) 720 ELISA units/mL adsorbed onto aluminium hydroxide and recombinant (DNA) hepatitis B surface antigen (grown in yeast cells) 20 micrograms/mL adsorbed onto aluminium phosphate, net price 1-mL prefilled syringe (Twinrix® Adult) = £27.76, 0.5-mL prefilled syringe (Twinrix® Paediatric) = £20.79
Exipients include neomycin and traces of thiomersal
Dose by intramuscular injection (see note below), ADULT and CHILD over 16 years, primary course of 3 doses of 1 mL, the second 1 month and the third 6 months after the first dose; CHILD 1–15 years, 3 doses of 0.5 mL.
Accelerated schedule (e.g. for travellers departing within 1 month), ADULT, second dose 7 days after first dose, third dose after further 14 days and a fourth dose 12 months after the first dose
Note Primary course should be completed with Twinrix (single component vaccines given at appropriate intervals may be
used for booster dose); the deltoid region is the preferred site of injection in adults and older children; anterolateral thigh is preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for patients with bleeding disorders (but immune response may be reduced).

**Important**

Twinrix® not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular or mucous membrane exposure to hepatitis B virus.

**With typhoid vaccine**

**Hepatix®** (GSK) \( \text{REM} \)

**Injection**, suspension of inactivated hepatitis A virus (grown in human diploid cells) 1440 ELISA units/mL adsorbed onto aluminium hydroxide, combined with typhoid vaccine containing 25 micrograms/mL virulence polysaccharide antigen of *Salmonella typhi*, net price 1-mL prefilled syringe = £32.08

**Excipients** include neomycin

**Dose** by intramuscular injection (see note below), ADULT and CHILD over 15 years, 1 mL as a single dose; booster doses, see under single component hepatitis A vaccine (above) and under polysaccharide typhoid vaccine, p. 679

**Note** The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders; not to be injected into the buttock (vaccine efficacy reduced)

**VIATIM** (Sanofi Pasteur) \( \text{REM} \)

**Injection**, suspension of inactivated hepatitis A virus (grown in human diploid cells) 160 antigen units/mL adsorbed onto aluminium hydroxide, combined with typhoid vaccine containing 25 micrograms/mL virulence polysaccharide antigen of *Salmonella typhi*, net price 1-mL prefilled syringe = £30.22

**Excipients** include neomycin

**Dose** by intramuscular injection (see note below), ADULT and CHILD over 15 years, 1 mL as a single dose; booster doses, see under single component hepatitis A vaccine (above) and under polysaccharide typhoid vaccine, p. 679

**Note** The deltoid region is the preferred site of injection. The subcutaneous route may be used for patients with bleeding disorders; not to be injected into the buttock (vaccine efficacy reduced)

### Hepatitis B vaccine

**Hepatitis B vaccine** contains inactivated hepatitis B virus surface antigen (HBsAg) adsorbed on aluminium hydroxide adjuvant. It is made biosynthetically using recombinant DNA technology. The vaccine is used in individuals at high risk of contracting hepatitis B.

In the UK, groups at high-risk of hepatitis B include:

- parents of drug misusers, their sexual partners, and household contacts; other drug misusers who are likely to ‘progress’ to injecting;
- individuals who change sexual partners frequently;
- close family contacts of a case or carrier;
- babies whose mothers have had acute hepatitis B during pregnancy or are positive for hepatitis B surface antigen (regardless of e-antigen markers); hepatitis B vaccination is started immediately on delivery and hepatitis B immunoglobulin (see p. 682) given at the same time (but preferably at a different site). Babies whose mothers are positive for hepatitis B surface antigen and for e-antigen antibody should receive the vaccine only (but babies weighing 1.5 kg or less should also receive the immunoglobulin regardless of the mother’s e-antigen antibody status);
- individuals with haemophilia, those receiving regular blood transfusions or blood products, and carers responsible for the administration of such products;
- patients with chronic renal failure including those on haemodialysis. Haemodialysis patients should be monitored for antibodies annually and re-immunised if necessary. Home carers (of dialysis patients) should be vaccinated;
- individuals with chronic liver disease;
- healthcare personnel (including trainees) who have direct contact with blood or blood-stained body fluids or with patients’ tissues;
- laboratory staff who handle material that may contain the virus;
- other occupational risk groups such as morticians and embalmers;
- staff and patients of day-care or residential accommodation for those with severe learning difficulties;
- staff and inmates of custodial institutions;
- those travelling to areas of high or intermediate prevalence who are at increased risk or who plan to remain there for lengthy periods (see p. 684);
- families adopting children from countries with a high or intermediate prevalence of hepatitis B;
- foster carers and their families.

Different immunisation schedules for hepatitis B vaccine are recommended for specific circumstances (see under individual preparations). Generally, three or four doses are required for primary immunisation; an ‘accelerated schedule’ is recommended for pre-exposure prophylaxis in high-risk groups where rapid protection is required, and for post-exposure prophylaxis (see below).

Immunisation may take up to 6 months to confer adequate protection; the duration of immunity is not known precisely, but a single booster 5 years after the primary course may be sufficient to maintain immunity for those who continue to be at risk.

Immunisation does not eliminate the need for commonsense precautions for avoiding the risk of infection from known carriers by the routes of infection which have been clearly established, consult Guidance for Clinical Health Care Workers Protection against Infection with Blood-borne Viruses (available at www.dh.gov.uk). Accidental inoculation of hepatitis B virus-infected blood into a wound, incision, needle-prick, or abrasion may lead to infection, whereas it is unlikely that indirect exposure to a carrier will do so.

Following significant exposure to hepatitis B, an accelerated schedule, with the second dose given 1 month, and the third dose 2 months after the first dose, is recommended. For those at continued risk, a fourth dose should be given 12 months after the first dose. More detailed guidance is given in the memorandum Immunisation against Infectious Disease. Specific hepatitis B immunoglobulin (‘HBIG’) is available for use with the vaccine in those accidentally inoculated and in neonates at special risk of infection (section 14.5).

A combined hepatitis A and hepatitis B vaccine is also available.
HEPATITIS B VACCINE

**Indications** Immunisation against hepatitis B infection

**Cautions** see section 14.1

**Contra-indications** see section 14.1

**Side-effects** see section 14.1

**Dose**

- See under preparations

### Single component

**Engerix B** (GSK) (Sanofi Pasteur)

**Injection**, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 20 micrograms/mL adsorbed onto aluminium hydroxide, net price 0.5-mL (paediatric) vial = £9.16, 0.5-mL (paediatric) prefilled syringe = £9.67, 1-mL vial = £12.34, 1-mL prefilled syringe = £12.99

**Excipients** include traces of thiomersal

**Dose** by intramuscular injection (see note below), ADULT and CHILD over 16 years, 3 doses of 20 micrograms, the second 1 month and the third 6 months after the first dose, NEONATE (except if born to hepatitis B surface antigen positive mother, see below) and CHILD 1 month–16 years, 3 doses of 10 micrograms Accelerated schedule (all ages), second dose 1 month after first dose, third dose 2 months after first dose and fourth dose 12 months after first dose; exceptionally (e.g. for travellers departing within 1 month), ADULT over 18 years, second dose 7 days after first dose, third dose 21 days after first dose, and fourth dose 12 months after first dose

**Alternative schedule for CHILD 11–15 years, 2 doses of 20 micrograms, the second dose 6 months after the first dose (this schedule not suitable if high risk of infection between doses or if compliance with second dose uncertain)**

**NEONATE** born to hepatitis B surface antigen positive mother (see also notes above), 4 doses of 10 micrograms, first dose at birth, hepatitis B immunoglobulin injection (separate site) the second 1 month, the third 2 months and the fourth 12 months after the first dose

Renal insufficiency (including haemodialysis patients), by intramuscular injection (see note below), ADULT and CHILD over 16 years, 4 doses of 40 micrograms, the second 1 month, the third 2 months and the fourth 6 months after the first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration; **NEONATE** (except if born to hepatitis B surface antigen positive mother, see above) and CHILD 1 month–16 years 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose or accelerated schedule, 4 doses of 10 micrograms, second dose 1 month, third dose 2 months and fourth dose 12 months after first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration

**Note** Deltoid muscle is preferred site of injection in adults and older children; anterolateral thigh is preferred site in neonates and infants; not to be injected into the buttoc (vaccine efficacy reduced)

**Fendrix** (GSK) (Sanofi Pasteur)

**Injection**, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 40 micrograms/mL adsorbed onto aluminium phosphate, net price 0.5-mL prefilled syringe = £38.10

**Excipients** include traces of thiomersal

**Dose** ADULT and CHILD over 15 years with renal insufficiency (including pre-haemodialysis and haemodialysis patients), by intramuscular injection (see note below) 4 doses of 20 micrograms, the second 1 month, the third 2 months and the fourth 6 months after the first dose; immunisation schedule and booster doses may need to be adjusted in those with low antibody concentration

**Note** Deltoid muscle is preferred site of injection; not to be injected into the buttoc (vaccine efficacy reduced)

**HBVaxPRO** (Sanofi Pasteur)

**Injection**, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 10 micrograms/mL adsorbed onto aluminium hydroxyphosphosphate sulphate, net price 0.5-mL (5-microgram) prefilled syringe = £9.50, 1-mL (10-microgram) prefilled syringe = £12.95; 40 micrograms/mL, 1-mL (40-microgram) vial = £29.30

**Dose** by intramuscular injection (see note below), ADULT and CHILD over 16 years, 3 doses of 10 micrograms, the second 1 month and the third 6 months after the first dose, CHILD under 16 years, 3 doses of 5 micrograms

**Accelerated schedule (all ages)**, second dose 1 month after first dose, third dose 2 months after first dose with fourth dose at 12 months

Booster doses may be required in immunocompromised patients with low antibody concentration

**NEONATE** born to hepatitis B surface antigen-positive mother (see also notes above), 5 micrograms, first dose at birth with hepatitis B immunoglobulin injection (separate site), the second 1 month, the third 2 months and the fourth 12 months after the first dose

**Cervarix** (GSK) is licensed for use in females for the prevention of cervical cancer, genital warts and pre-cancerous lesions caused by human papilloma virus types 16 and 18. **Gardasil** is licensed for use in females for the prevention of cervical cancer, genital warts and pre-cancerous lesions caused by human papilloma virus types 6, 11, 16, and 18. The two vaccines are not interchangeable and one vaccine product should be used for an entire course. However, the Department of Health (November 2008) states that for individuals with previous incomplete vaccination with Gardasil®, who are eligible for HPV vaccination under the national programme, Cervarix® can be used to complete the vaccination course if necessary; the individual must be informed that Cervarix® does not protect against genital warts.

Human papilloma virus vaccine will be most effective if given before sexual activity starts. The first dose is given to females aged 12 to 13 years, the second and third doses are given 1–2 and 6 months after the first dose (see Immunisation schedule, section 14.1); all 3 doses should be given within a 12-month period. If the course is interrupted, it should be resumed but not repeated, allowing the appropriate interval between the remaining doses. Where there are significant challenges in scheduling vaccinations, or a high likelihood that the third dose will not be given, the third dose of Cervarix® can be given 3 months after the second dose. Where appropriate, immunisation with human papilloma virus vaccine should be offered to females coming into the UK as they may not have been offered protection in their country of origin. The duration of protection has not been established, but current studies suggest that protection is maintained for at least 6 years after completion of the primary course.

As the vaccines do not protect against all strains of human papilloma virus, routine cervical screening should continue.
**Human papilloma virus vaccine ‘Catch-up’ programme for England, Wales, and Northern Ireland**

A ‘catch-up’ programme will be offered as follows:
- from September 2008 to all females born between 1 September 1990 and 31 August 1991 (aged 17–18 years)
- from September 2009 to all females born between 1 September 1991 and 31 August 1995 (aged 14–18 years) [under review in Wales]

**Human papilloma virus vaccine ‘Catch-up’ programme for Scotland**

The ‘catch-up’ programme in Scotland will be offered as follows:
- from 1 September 2008 to all females aged 16–17 years
- from September 2009 to all females aged 14–16 years

**HUMAN PAPILLOMA VIRUS VACCINES**

**Indications** see notes above and under preparations

**Cautions** see section 14.1

**Contra-indications** see section 14.1

**Side-effects** see section 14.1

**Dose**
- see notes above and under preparations

**Note** To avoid confusion, prescribers should specify the brand to be dispensed

**Cervarix® (GSK)** ▼ ▼

*Injection*, suspension of virus-like particles of human papilloma virus type 16 (40 micrograms/mL), type 18 (40 micrograms/mL) capsid protein (prepared by recombinant DNA technique using a Baculovirus expression system) in monophosphoryl lipid A adjuvant adsorbed onto aluminium hydroxide, net price 0.5-mL prefilled syringe = £80.50

**Dose** prevention of premalignant genital lesions and cervical cancer, by intramuscular injection into deltoid region, ADULT and CHILD 9–25 years, 3 doses of 0.5 mL, the second 1 month and the third 6 months after the first dose

**Gardasil® (Sanofi Pasteur)** ▼ ▼

*Injection*, suspension of Virus-like particles of human papilloma virus type 6 (40 micrograms/mL), type 11 (80 micrograms/mL), type 16 (80 micrograms/mL), type 18 (40 micrograms/mL) capsid protein (prepared from yeast cells by recombinant DNA technique) adsorbed onto aluminium hydroxyphosphate sulphate, net price 0.5-mL prefilled syringe = £80.50

**Dose** prevention of premalignant genital lesions, cervical cancer and genital warts, by intramuscular injection preferably into deltoid region or higher anterolateral thigh, ADULT and CHILD 9–26 years, 3 doses of 0.5 mL, the second 2 months and the third 6 months after the first dose

Alternative schedule for ADULT and CHILD 9–26 years, 3 doses of 0.5 mL, the second at least 1 month, and the third at least 4 months after the first dose; schedule should be completed within 12 months

**Influenza vaccines**

While most viruses are antigenically stable, the influenza viruses A and B (especially A) are constantly altering their antigenic structure as indicated by changes in the haemagglutinins (H) and neuraminidases (N) on the surface of the viruses. It is essential that influenza vaccines in use contain the H and N components of the prevalent strain or strains as recommended each year by the World Health Organization.

**Influenza vaccines** will not control epidemics—immunisation is recommended only for persons at high risk. Annual immunisation is strongly recommended for individuals aged over 6 months with the following conditions:
- chronic respiratory disease (includes asthma treated with continuous or repeated use of inhaled or systemic corticosteroids or asthma with previous exacerbations requiring hospital admission);
- chronic heart disease;
- chronic liver disease;
- chronic renal disease;
- chronic neurological disease
- diabetes mellitus
- immunosuppression because of disease (including asplenia or splenic dysfunction) or treatment (including prolonged corticosteroid treatment);
- HIV infection (regardless of immune status).

Influenza immunisation is also recommended for all persons aged over 65 years, for residents of nursing or residential homes for the elderly and other long-stay facilities, and for carers of persons whose welfare may be at risk if the carer falls ill. Influenza immunisation should also be considered for household contacts of immunocompromised individuals.

As part of winter planning, NHS employers should offer vaccination to healthcare workers who are directly involved in patient care. Employers of social care workers should consider similar action.

Where possible, pregnant women and children should receive a thiomersal-free influenza vaccine; if this is not available, a thiomersal-containing influenza vaccine should be given.

For people who work in close contact with poultry on a regular basis, influenza immunisation is recommended as a precautionary public health measure. Seasonal human influenza vaccine does not protect against avian influenza, but it reduces the risk of poultry workers contracting both human and avian influenza simultaneously, and therefore also reduces the risk of a new influenza virus emerging.

Information on pandemic influenza and avian influenza may be found at [www.dh.gov.uk/pandemicflu](http://www.dh.gov.uk/pandemicflu) and at [www.hpa.org.uk](http://www.hpa.org.uk).

**INFLUENZA VACCINE**

**Indications** annual immunisation against influenza

**Cautions** see section 14.1 interactions: Appendix 1 (vaccines)

**Contra-indications** see section 14.1

**Side-effects** see section 14.1; also reported febrile convulsions and transient thrombocytopenia

**Dose**
- By intramuscular injection ADULT and CHILD over 13 years, 0.5 mL as a single dose; CHILD 6 months–3 years, 0.25–0.5 mL; 3–13 years 0.5 mL; for children 6 months to 13 years who have not been previously vaccinated repeat after 4–6 weeks
Inactivated Influenza Vaccine (Split Virion) *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (split virion, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £6.59

Excipients may include neomycin and polymyxin B

Available from Novartis Vaccines

**Note** Not licensed for children under 4 years

Agrippal® *(Novartis Vaccines)* *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £5.85

Excipients include kanamycin and neomycin

Begrivac® *(Novartis Vaccines)* *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (split virion, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £5.55

Excipients include polymyxin B

Enzira® *(Wyeth)* *(Flu)

Injection, suspension of inactivated influenza virus (split virion, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £4.49

Excipients include gentamicin

Fluvirin® *(Novartis Vaccines)* *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £5.55

Excipients may include neomycin and polymyxin B

**Note** Not licensed for use in children under 4 years

Imuvac® *(Solvay)* *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £6.59

Excipients include gentamicin

Influvac Sub-unit® *(Solvay)* *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £5.22

Excipients include gentamicin

Mastalu® *(MASTA)* *(Flu)*

Injection, suspension of formaldehyde-inactivated influenza virus (surface antigen, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £6.50

Excipients include gentamicin

Viroflu® *(Sanofi Pasteur)* *(Flu)*

Injection, suspension of inactivated influenza virus (surface antigen, virosoome, grown in fertilised hens’ eggs), net price 0.5-mL prefilled syringe = £6.59

Excipients include neomycin and polymyxin B

**Measles vaccine**

Measles vaccine has been replaced by a combined live measles, mumps and rubella vaccine (MMR vaccine). MMR vaccine may be used in the control of outbreaks of measles (see under MMR Vaccine).

- **Single antigen vaccine**
  - No longer available in the UK

- **Combined vaccines**
  - See MMR vaccine

**Measles, Mumps and Rubella (MMR) vaccine**

A combined live measles, mumps, and rubella vaccine (MMR vaccine) aims to eliminate measles, mumps, and rubella (and congenital rubella syndrome).

Every child should receive two doses of MMR vaccine by entry to primary school, unless there is a valid contra-indication (see section 14.1). MMR vaccine should be given irrespective of previous measles, mumps, or rubella infection or vaccination.

The first dose of MMR vaccine is given to children aged 13 months. A second dose is given before starting school at 3–5 years of age (see Immunisation Schedule, section 14.1).

When protection against measles is required urgently (e.g. during a measles outbreak), the second dose of MMR vaccine can be given 1 month after the first dose; if the second dose is given before 18 months of age, then children should still receive the routine dose before starting school at 3–5 years of age.

Children presenting for pre-school booster who have not received the first dose of MMR vaccine should be given a dose of MMR vaccine followed 3 months later by a second dose. At school-leaving age or at entry into further education, MMR immunisation should be offered to individuals of both sexes who have not received 2 doses during childhood. In a young adult who has received only a single dose of MMR in childhood, a second dose is recommended to achieve full protection. If 2 doses of MMR vaccine are required, the second dose should be given one month after initial dose.

MMR vaccine should be used to protect against rubella in seronegative women of child-bearing age (see Immunisation Schedule, section 14.1); unimmunised healthcare workers who might put pregnant women and other vulnerable groups at risk of rubella (or measles) should be vaccinated. MMR vaccine may also be offered to previously unimmunised and seronegative post-partum women—vaccination a few days after delivery is important because about 60% of congenital abnormalities from rubella infection occur in babies of women who have borne more than one child. Immigrants arriving after the age of school immunisation are particularly likely to require immunisation.

**Contacts** MMR vaccine may also be used in the control of outbreaks of measles and should be offered to susceptible children aged over 6 months who are contacts of a case, within 3 days of exposure to infection; these children should still receive routine MMR vaccinations at the recommended ages. Children aged under 9 months for whom avoidance of measles infection is particularly important (such as those with history of recent severe illness) can be given normal immunoglobulin (section 14.5) after exposure to measles; rou-
tine MMR immunisation should then be given after at least 3 months at the appropriate age.

MMR vaccine is not suitable for prophylaxis following exposure to mumps or rubella since the antibody response to the mumps and rubella components is too slow for effective prophylaxis.

Children and adults with impaired immune response should not receive live vaccines (for advice on HIV see section 14.1). If they have been exposed to measles infection they should be given normal immunoglobulin (section 14.5).

Travel Unimmunised travellers, including children over 6 months, to areas where measles is endemic or epidemic should receive MMR vaccine. Children immunised before 12 months of age should still receive two doses of MMR at the recommended ages. If one dose of MMR has already been given to a child, then the second dose should be brought forward to at least one month after the first, to ensure complete protection. If the child is under 18 months of age and the second dose is given within 3 months of the first, then the routine dose before starting school at 3–5 years should still be given.

Side-effects See section 14.1; also malaise, fever, or a rash may occur after the first dose of MMR vaccine, most commonly about a week after vaccination and lasting about 2 to 3 days. Leaflets are available for parents on advice for reducing fever (including the use of paracetamol). Febrile seizures occur less commonly 6 to 11 days after MMR vaccination; the incidence of febrile seizures is lower than that following measles infection. Parotid swelling occurs occasionally, usually in the third week, and rarely, arthopathy 2 to 3 weeks after immunisation. Adverse reactions are considerably less frequent after the second dose of MMR vaccine than after the first dose.

Hypersensitivity to egg— there is increasing evidence that MMR vaccine can be given safely even when the child has had an anaphylactic reaction to food containing egg (dislike of egg or refusal to eat eggs is not a contra-indication). For children with a confirmed anaphylactic reaction to egg-containing food, MMR vaccine should be administered in a hospital setting.

Contra-indications see section 14.1; also pregnancy

Side-effects see section 14.1; also less commonly sleep disturbances, unusual crying in infants; also reported peripheral and optic neuritis

Dose

- By intramuscular or deep subcutaneous injection, ADULT and CHILD over 9 months (but see also notes above), primary immunisation, 2 doses each of 0.5 mL, see Immunisation Schedule , section 14.1, p. 662; see also notes above for use in outbreaks, for contacts of cases, and for travel

Combined vaccines

MMRvaxPro® (Sanofi Pasteur) Injection, powder for reconstitution, live attenuated, measles virus (Edners’ Edmonston strain) and mumps virus (Jeryl Lynn strain) prepared in chick embryo cells, and rubella virus (Wistar RA 27/3 strain); single-dose vial (with syringe containing solvent). Excipients include gelatin and neomycin. Only available as part of childhood immunisation schedule from health organisations or Movianto

Priorix (GSK) Injection, powder for reconstitution, live attenuated, measles virus (Schwarz strain) and mumps virus (RIT 4385 strain) prepared in chick embryo cells, and rubella virus (Wistar RA 27/3 strain); net price single-dose vial (with syringe containing solvent) = £6.37 Excipients include neomycin. Also available as part of childhood immunisation schedule from health organisations or Movianto

Meningococcal vaccines

Almost all childhood meningococcal disease in the UK is caused by Neisseria meningitidis serogroups B and C. Meningococcal group C conjugate vaccine protects only against infection by serogroup C. The risk of
mucococcal disease declines with age—immunisation is not generally recommended after the age of 25 years.

**Childhood immunisation** Meningococcal group C conjugate vaccine provides long-term protection against infection by serogroup C of *Neisseria meningitidis*. Immunisation consists of 2 doses given at 3 months and 4 months of age; a booster should be given at 12 months of age, usually combined with haemophilus influenzae type b vaccine. This routine booster dose should be given one month before the booster dose of pneumococcal conjugate vaccine (see Immunisation schedule, section 14.1, p. 662). It is recommended that meningococcal group C conjugate vaccine be given to anyone aged under 25 years who has not been vaccinated previously with this vaccine; those over 1 year receive a single dose.

A single dose of meningococcal group C conjugate vaccine is also recommended for unimmunised individuals attending university, irrespective of age.

**Meningococcal group C conjugate vaccine in patients with asplenia or splenic dysfunction** Meningococcal group C conjugate vaccine is recommended for patients with asplenia or splenic dysfunction. Children under 1 year should be vaccinated according to the Immunisation Schedule (section 14.1). Unimmunised adults and children over 1 year should be given 2 doses of meningococcal group C conjugate vaccine (usually combined with haemophilus influenzae type b vaccine) with an interval of 2 months between doses. Immunised adults and children who develop splenic dysfunction should be given 1 additional dose of meningococcal group C conjugate vaccine (usually combined with haemophilus influenzae type b vaccine).

**Travel** Individuals travelling to countries of risk (see below) should be immunised with a meningococcal polysaccharide vaccine that covers serotypes A, C, W135, and Y, even if they have previously received meningitis C conjugate vaccine. If an individual has recently received meningococcal group C conjugate vaccine, an interval of at least 2 weeks should be allowed before administration of the tetravalent (A, C, W135, and Y) vaccine. The antibody response to serotype C in unconjugated meningococcal polysaccharide vaccines in children under 18 months may be suboptimal.

**Immunisation recommendations and requirements for visa entry for individual countries should be checked before travelling, particularly to countries in Sub-Saharan Africa, Asia, and the Indian sub-continent where epidemics of meningococcal outbreaks and infection are reported. Country-by-country information is available from the National Travel Health Network and Centre (www.nathnac.org).

Proof of vaccination with the tetravalent (A, C, W135, and Y) meningococcal vaccine is required for those travelling to Saudi Arabia during the Hajj and Umrah pilgrimages (where outbreaks of the W135 strain have occurred).

**Contacts** For advice on the immunisation of laboratory workers and close contacts of cases of meningococcal disease in the UK and on the role of the vaccine in the control of local outbreaks, consult Guidance for Public Health Management of Meningococcal Disease in the UK at www.hpa.org.uk. See Table 2, section 5.1 for antibacterial prophylaxis for prevention of secondary cases of meningococcal meningitis.

The need for immunisation of laboratory staff who work directly with *Neisseria meningitidis* should be considered.

### Meningococcal Vaccines

#### Indications

Immunisation against *Neisseria meningitidis*

**Cautions** see section 14.1

**Contra-indications** see section 14.1

**Side-effects** see section 14.1; also rarely symptoms of meningitis reported (but no evidence that the vaccine causes meningococcal C meningitis)

**Dose**

- See under preparations

#### Meningococcal group C conjugate vaccine

**Menigitec®** (Wyeth)  
Injection, suspension of capsular polysaccharide antigen of *Neisseria meningitidis* group C (conjugated to *Corynebacterium diphtheriae* protein), adsorbed onto aluminium phosphate, net price 0.5-mL prefilled syringe = £7.50

**Dose** by intramuscular injection, ADULT and CHILD over 1 year 0.5 mL as a single dose, for routine immunisation in CHILD 2 months–1 year, 0.5 mL, see notes above and Immunisation schedule, section 14.1

Available as part of childhood immunisation schedule from Movianto

**Menjugate Kit®** (Sanofi Pasteur)  
Injection, powder for reconstitution, capsular polysaccharide antigen of *Neisseria meningitidis* group C (conjugated to *Corynebacterium diphtheriae* protein), adsorbed onto aluminium hydroxide, single-dose vial with diluent

**Dose** by intramuscular injection, ADULT and CHILD over 1 year 0.5 mL as a single dose, for routine immunisation in CHILD 2 months–1 year, 0.5 mL, see notes above and Immunisation schedule, section 14.1

**NeisVac-C®** (Baxter)  
Injection, suspension of polysaccharide antigen of *Neisseria meningitidis* group C (conjugated to tetanus toxoid protein), adsorbed onto aluminium hydroxide, 0.5-mL prefilled syringe

**Dose** by intramuscular injection, ADULT and CHILD over 1 year 0.5 mL as a single dose, for routine immunisation in CHILD 3 months–1 year, 0.5 mL, see notes above and Immunisation schedule, section 14.1

**Meningococcal Group C conjugate vaccine with Haemophilus Influenzae type B vaccine**

See Haemophilus Influenzae type B vaccine

**Meningococcal polysaccharide A, C, W135 and Y vaccine**

**ACWY Vax®** (GSK)  
Injection, powder for reconstitution, capsular polysaccharide antigens of *Neisseria meningitidis* groups A, C, W135, and Y, net price single-dose vial (with syringe containing diluent) = £16.73

**Dose** by deep subcutaneous injection, ADULT and CHILD over 2 years 0.5 mL as a single dose; booster dose for those at
Pneumococcal vaccines

Pneumococcal vaccines protect against infection with *Streptococcus pneumoniae* (pneumococcus); the vaccines contain polysaccharide from capsular pneumococci. 

**Pneumococcal polysaccharide vaccine** contains purified polysaccharide from 23 capsular types of pneumococcus whereas** pneumococcal polysaccharide conjugate vaccine** (adsorbed) contains polysaccharide from 7 capsular types, the polysaccharide being conjugated to protein. The conjugate vaccine is used for childhood immunisation schedule. The recommended schedule consists of 3 doses, the first at 2 months of age, the second at 4 months, and the third at 13 months (see Immunisation Schedule, section 14.1).

Pneumococcal vaccination is recommended for individuals at increased risk of pneumococcal infection as follows:

- age over 65 years;
- asplenia or splenic dysfunction (including homozygous sickle cell disease and coeliac disease which could lead to splenic dysfunction);
- chronic respiratory disease (includes asthma treated with continuous or frequent use of a systemic corticosteroid);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- diabetes mellitus requiring insulin or oral hypoglycaemic drugs;
- immune deficiency because of disease (e.g. HIV infection) or treatment (including prolonged systemic corticosteroid treatment);
- presence of cochlear implant;
- conditions where leakage of cerebrospinal fluid may occur;
- child under 5 years with a history of invasive pneumococcal disease.

Where possible, the vaccine should be given at least 2 weeks before splenectomy, cochlear implant surgery, and chemotherapy; patients should be given advice about increased risk of pneumococcal infection. Prophylactic antibacterial therapy against pneumococcal infection (Table 2, section 5.1) should not be stopped after immunisation. A patient card and information leaflet for patients with asplenia are available from the Department of Health or in Scotland from the Scottish Executive, Public Health Division 1 (Tel (0131) 244 2501).

**Choice of vaccine** Children under 2 years at increased risk of pneumococcal infection (see list above) should receive pneumococcal polysaccharide conjugate vaccine (adsorbed) at the recommended ages, followed by a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday (see below). Children at increased risk of pneumococcal infection presenting late for vaccination should receive 2 doses (separated by at least 1 month) of pneumococcal polysaccharide conjugate vaccine (adsorbed) before the age of 12 months, and a third dose at 13 months. Children over 12 months and under 5 years (who have not been vaccinated or not completed the primary course) should receive a single dose of pneumococcal polysaccharide conjugate vaccine (adsorbed) (2 doses separated by an interval of 2 months

### Mumps vaccine

- **Single antigen vaccine**
  - No longer available in the UK

- **Combined vaccines**
  - See MMR Vaccine

### Pertussis vaccine

**Pertussis vaccine** is given as a combination preparation containing other vaccines (see Diphtheria-containing Vaccines). Acellular vaccines are derived from highly purified components of *Bordetella pertussis*. Primary immunisation against pertussis (whooping cough) requires 3 doses of an acellular pertussis-containing vaccine (see Immunisation schedule, section 14.1), given at intervals of 1 month from the age of 2 months.

A booster dose of an acellular pertussis-containing vaccine should be given 3 years after the primary course.

All children up to the age of 10 years should receive primary immunisation with diphtheria, tetanus, pertussis (acellular, component), poliomyelitis (inactivated) and haemophilus type b conjugate vaccine (adsorbed). Children aged 1–10 years who have not received a pertussis-containing vaccine as part of their primary immunisation should be offered 1 dose of a suitable pertussis-containing vaccine; after an interval of at least 1 year, a booster dose of a suitable pertussis-containing vaccine should be given. Immunisation against pertussis is not currently recommended in individuals over 10 years of age.

**Cautions** Section 14.1.

**Contra-indications** Section 14.1.

**Side-effects** See also section 14.1. The incidence of local and systemic effects is generally lower with vaccines containing acellular pertussis components than with the whole-cell pertussis vaccine used previously. However, compared with primary vaccination, booster doses with vaccines containing acellular pertussis are reported to increase the risk of injection-site reactions (some of which affect the entire limb); local reactions do not contra-indicate further doses (see below).

The vaccine should not be withheld from children with a history to a preceding dose of:

- fever, irrespective of severity;
- persistent crying or screaming for more than 3 hours;
- severe local reaction, irrespective of extent.

These side-effects were associated with whole-cell pertussis vaccine.

### Combined vaccines

Combined vaccines, see under Diphtheria-containing vaccines

---

**Note** Two doses of 0.5 mL separated by an interval of 3 months can be given to children under 5 years of age when first vaccinated, should be given a booster dose after 2–3 years.

**Note** Two doses of 0.5 mL separated by an interval of 3 months can be given to CHILD 3 months–2 years [unlicensed] but antibody response may be suboptimal.
in the immunocompromised or those with asplenia or splenic dysfunction). All children under 5 years at increased risk of pneumococcal infection should receive a single dose of the 23-valent pneumococcal polysaccharide vaccine after their second birthday and at least 2 months after the final dose of the 7-valent pneumococcal polysaccharide conjugate vaccine (adsorbed).

Children over 5 years and adults who are at increased risk of pneumococcal disease should receive a single dose of the 23-valent unconjugated pneumococcal polysaccharide vaccine.

Revaccination In individuals with higher concentrations of antibodies to pneumococcal polysaccharides, revaccination with the 23-valent pneumococcal polysaccharide vaccine more commonly produces adverse reactions. Revaccination is therefore not recommended, except every 5 years in individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia, splenic dysfunction and nephrotic syndrome). If there is doubt, the need for revaccination should be discussed with a haematologist, immunologist, or microbiologist.

PNEUMOCOCCAL VACCINE

Indications immunisation against pneumococcal infection

Cautions see section 14.1

Contra-indications see section 14.1

Side-effects see section 14.1; also Revaccination, above

Dose

● See under preparations

Pneumococcal polysaccharide vaccine

Pneumovax® II (Sanofi Pasteur) [PM]

Injection, polysaccharide from each of 23 capsular types of pneumococcus, net price 0.5-mL vial = £8.83

Dose by intramuscular or subcutaneous injection, ADULT and CHILD over 2 years, 0.5 mL, revaccination, see notes above

Pneumococcal polysaccharide conjugate vaccine (adsorbed)

Prevenar® (Wyeth) [PM]

Injection, polysaccharide from each of 7 capsular types of pneumococcus (conjugated to diphtheria toxin) adsorbed onto aluminium phosphate, net price 0.5-mL prefilled syringe = £34.50

Dose by intramuscular injection, CHILD 2 months–5 years, 0.5 mL (see notes above and Immunisation schedule, section 14.1)

Note Deltoid muscle is preferred site of injection in young children; anterolateral thigh is preferred site in infants

The dose in the BNF may differ from that in product literature

Travel Unimmunised travellers to areas with a high incidence of poliomyelitis should receive a full 3-dose course of a preparation containing inactivated poliomyelitis vaccine. Those who have not been vaccinated in the last 10 years should receive a booster dose of adsorbed diphtheria (low dose), tetanus and inactivated poliomyelitis vaccine. Information about countries with a high incidence of poliomyelitis can be obtained from www.travax.nhs.uk or from the National Travel Health Network and Centre (www.nathnac.org).

POLIOMYELITIS VACCINES

Indications immunisation against poliomyelitis

Cautions see section 14.1; also for live vaccine, interactions: Appendix 1 (vaccines)

Contra-indications see notes above and section 14.1

Side-effects see notes above and section 14.1

Dose

● See under preparations

Combined vaccines

See under Diphtheria-containing Vaccines

Inactivated (Salk) vaccine

Inactivated Poliomyelitis Vaccine (Non-proprietary) [PN]

IPV

Injection, inactivated suspension of suitable strains of poliomyelitis virus, types 1, 2, and 3, net price 0.5-mL prefilled syringe = £10.35

Excipients may include neomycin, polymyxin B and streptomycin

Dose by intramuscular injection, ADULT and CHILD over 2 months, 0.5 mL (see notes above)

Note Only combination vaccines are recommended for routine immunisation and boosters (see Immunisation schedule, section 14.1) and travel (see notes above)
Post-exposure management

Pre-exposure prophylaxis

embryo cells; vaccines are used for pre- and post-vaccinated in either human diploid cells or purified chick embryo cells, net price single-dose vial = £24.40

Rabies vaccine

Rabies vaccine contains inactivated rabies virus cultivated in either human diploid cells or purified chick embryo cells; vaccines are used for pre- and post-exposure prophylaxis.

Pre-exposure prophylaxis

Immunisation should be offered to those at high risk of exposure to rabies—laboratory staff who handle the rabies virus, those working in quarantine stations, animal handlers, veterinary surgeons and field workers who are likely to be bitten by infected wild animals, certain port officials, and bat handlers. Transmission of rabies by humans has not been recorded but it is advised that those caring for patients with the disease should be vaccinated.

Immunisation against rabies is also recommended where there is limited access to prompt medical care for those living in areas where rabies is enzootic, for those travelling to such areas for longer than 1 month, and for those on shorter visits who may be exposed to unusual risk.

Immunisation against rabies is indicated during pregnancy if there is substantial risk of exposure to rabies and rapid access to post-exposure prophylaxis is likely to be limited.

Up-to-date country-by-country information on the incidence of rabies can be obtained from the National Travel Health Network and Centre (www.nathnac.org) and, in Scotland, from Health Protection Scotland (www.hps.scot.nhs.uk).

Immunisation against rabies requires 3 doses of rabies vaccine, with further booster doses for those who remain at continued risk. To ensure continued protection in persons at high risk (e.g. laboratory workers), the concentration of antirabies antibodies in plasma is used to determine the intervals between doses.

Post-exposure management

Following potential exposure to rabies, the wound or site of exposure (e.g. mucous membrane) should be cleansed under running water and washed for several minutes with soapy water as soon as possible after exposure. Disinfectant and a simple dressing can be applied, but suturing should be delayed because it may increase the risk of introducing rabies virus into the nerves.

Post-exposure prophylaxis against rabies depends on the level of risk in the country, the nature of exposure, and the individual’s immunity. In each case, expert risk assessment and advice on appropriate management should be obtained from the Health Protection Agency Virus Reference Department, Colindale, London (tel. (020) 8200 4400) or the Centre for Infections (tel. (020) 8200 6868), in Scotland from Health Protection Scotland (tel. (0141) 300 1100), in Northern Ireland from the Public Health Laboratory, Belfast City Hospital (tel. (028) 9032 9241).

There are no specific contra-indications to the use of rabies vaccine for post-exposure prophylaxis and its use should be considered whenever a patient has been attacked by an animal in a country where rabies is enzootic, even if there is no direct evidence of rabies in the attacking animal. Because of the potential consequences of untreated rabies exposure and because rabies vaccination has not been associated with fetal abnormalities, pregnancy is not considered a contra-indication to post-exposure prophylaxis.

For post-exposure prophylaxis of fully immunised individuals (who have previously received pre-exposure or post-exposure prophylaxis with cell-derived rabies vaccine), 2 doses of cell-derived vaccine, given on day 0 and day 3, are likely to be sufficient. Rabies immunoglobulin is not necessary in such cases.

Post-exposure treatment for unimmunised individuals (or those whose prophylaxis is possibly incomplete) comprises 5 doses of rabies vaccine given over 1 month (on days 0, 3, 7, 14, and 30); also, depending on the level of risk (determined by factors such as the nature of the bite and the country where it was sustained), rabies immunoglobulin (section 14.5) is given on day 0. The immunisation course can be discontinued if it is proved that the individual was not at risk.

Rabies Vaccine

Indications

immunisation against rabies

Cautions

see section 14.1

Contra-indications

see section 14.1; but see also Post-exposure Management in notes above

Side-effects

see section 14.1; also reported paresis

Dose

- Pre-exposure prophylaxis, by intramuscular injection in deltoid region or anterolateral thigh in infants, 1 mL on days 0, 7, and 21 or 28; for those at continued risk give a single reinforcing dose 1 year after the primary course is completed and booster doses every 3–5 years; for those at intermittent risk give booster doses every 2–5 years
- Post-exposure prophylaxis, by intramuscular injection in deltoid region or anterolateral thigh in infants, 1 mL (see notes above)

Rabipur® (Novartis Vaccines)

Injection, powder for reconstitution, freeze-dried inactivated Wister rabies virus strain PM/WI 38 1503-3M cultivated in human diploid cells, net price single-dose vial with syringe containing diluent = £24.40

Excipients include neomycin and polymyxin B

Rotavirus vaccine

Rotavirus vaccine a live, oral vaccine is licensed for immunisation of infants over 6 weeks of age for protection against gastro-enteritis caused by rotavirus infection. The rotavirus vaccine virus is excreted in the stool and may be transmitted to close contacts; the vaccine should be used with caution in those with immunosup-
pressed close contacts. Carers of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby’s nappies.

**ROTAVIRUS VACCINE**

**Indications** immunisation against gastro-enteritis caused by rotavirus

**Cautions** see section 14.1; also diarrhoea or vomiting (postpone vaccination); immunosuppressed close contacts (see notes above); interactions: Appendix 1 (vaccines)

**Contra-indications** see section 14.1; also predisposition to, or history of, intussusception

**Side-effects** see section 14.1

- By mouth, **CHILD** over 6 weeks, 2 doses of 1 mL separated by an interval of at least 4 weeks; course should be completed before 24 weeks of age (preferably before 16 weeks)

**Rotarix** (GSK) ▼ ▼ ➯

**Oral suspension**, powder for reconstitution, live attenuated rotavirus (RIX4414 strain), net price single-dose vial (with oral syringe containing diluent) = £41.38

**Rubella vaccine**

A combined measles, mumps and rubella vaccine (MMR vaccine) aims to eliminate rubella (German measles) and congenital rubella syndrome. MMR vaccine is used for childhood vaccination as well as for vaccinating adults (including women of child-bearing age) who do not have immunity against rubella (see MMR vaccine, p. 672)

**Single antigen vaccine** No longer available in the UK, the combined live measles, mumps and rubella vaccine is a suitable alternative

**Combined vaccines** see MMR vaccine

**Smallpox vaccine**

Limited supplies of smallpox vaccine are held at the Specialist and Reference Microbiology Division, Health Protection Agency (Tel. (020) 8200 4400) for the exclusive use of workers in laboratories where pox viruses (such as vaccinia) are handled.

If a wider use of the vaccine is being considered, Guidelines for smallpox response and management in the post-eradication era should be consulted at www.dh.gov.uk

**Tetanus Vaccines**

**Tetanus vaccine** contains a cell-free purified toxin of Clostridium tetani adsorbed on aluminium hydroxide or aluminium phosphate to improve antigenicity.

Primary immunisation for children under 10 years consists of 3 doses of a combined preparation containing adsorbed tetanus vaccine (see Diphtheria-containing Vaccines), with an interval of 1 month between doses. Following routine childhood vaccination, 2 booster doses of a preparation containing adsorbed tetanus vaccine are recommended, the first before school entry and the second before leaving school. (see Immunisation schedule, section 14.1).

The recommended schedule of tetanus vaccination not only gives protection against tetanus in childhood but also gives the basic immunity for subsequent booster doses. In most circumstances, a total of 5 doses of tetanus vaccine is considered sufficient for long term protection.

For primary immunisation of adults and children over 10 years previously unimmunised against tetanus, 3 doses of adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine are given with an interval of 1 month between doses (see Diphtheria-containing Vaccines).

**Cautions** See also section 14.1. When an individual presents for a booster dose but has been vaccinated following a tetanus-prone wound, the vaccine preparation administered at the time of injury should be determined. If this is not possible, the booster should still be given to ensure adequate protection against all antigens in the booster vaccine.

Very rarely, tetanus has developed after abdominal surgery; patients awaiting elective surgery should be asked about tetanus immunisation and immunised if necessary.

Parenteral drug abuse is also associated with tetanus; those abusing drugs by injection should be vaccinated if unimmunised—booster doses should be given if there is any doubt about their immunisation status.

All laboratory staff should be offered a primary course if unimmunised.

Travel recommendations see section 14.6.

**Contra-indications** See section 14.1.

**Side effects** See section 14.1.

**Wounds** Wounds are considered to be tetanus-prone if they are sustained more than 6 hours before surgical treatment or at any interval after injury and are puncture-type (particularly if contaminated with soil or masure) or show much devitalised tissue or are septic or have compound fractures or contain foreign bodies. All wounds should receive thorough cleansing.

- For clean wounds: fully immunised individuals (those who have received a total of 5 doses of a tetanus-containing vaccine at appropriate intervals) and those whose primary immunisation is complete (with boosters up to date), do not require tetanus vaccine; individuals whose primary immunisation is incomplete or whose boosters are not up to date require a reinforcing dose of a tetanus-containing vaccine (followed by further doses as required to complete the schedule); non-immunised individuals (or those whose immunisation status is not known or who have been fully immunised but are now immunocompromised) should be given a dose of the appropriate tetanus-containing vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).

- For tetanus-prone wounds: management is as for clean wounds with the addition of a dose of tetanus immunoglobulin (section 14.5) given at a different site; in fully immunised individuals and those whose primary immunisation is complete (with boosters up to date) the immunoglobulin is needed only if the...
risk of infection is especially high (e.g. contamination with manure). Antibacterial prophylaxis (with benzylpenicillin, co-amoxiclav, or metronidazole) may also be required for tetanus-prone wounds.

**Combined vaccines**
See Diphtheria-containing Vaccines

---

**Tick-borne encephalitis vaccine**

Tick-borne encephalitis vaccine contains inactivated tick-borne encephalitis virus cultivated in chick embryo cells. It is recommended for immunisation of those working in, or visiting, high-risk areas (see International Travel, section 14.6). Those working, walking or camping in warm forested areas of Central and Eastern Europe and Scandinavia, particularly from April to October when ticks are most prevalent, are at greatest risk of tick-borne encephalitis. For full protection, 3 doses of the vaccine are required; booster doses are required every 3–5 years for those still at risk. Ideally, immunisation should be completed at least one month before travel.

---

**TICK-BORNE ENCEPHALITIS VACCINE, INACTIVATED**

- **Indications** immunisation against tick-borne encephalitis
- **Cautions** see section 14.1
- **Side-effects** see section 14.1
- **Dose**
  - Initial immunisation, by intramuscular injection in deltoid region or anterolateral thigh in infants, ADULT and CHILD over 16 years, 3 doses each of 0.5 mL, second dose after 1–3 months and third dose after further 5–12 months; CHILD 1–16 years 3 doses of 0.25 mL, second dose after 1–3 months and third dose after further 5–12 months; ELDERLY over 60 years and immunocompromised (including those receiving immunosuppressants), antibody concentration may be measured 4 weeks after second dose and dose repeated if protective levels not achieved
- **Note** To achieve more rapid protection, second dose may be given 14 days after first dose
- **Booster doses** give first dose within 3 years after initial course completed, then every 3–5 years

**TicoVac® (MASTA)**
Injection, suspension, formaldehyde-inactivated Neudörfl tick-borne encephalitis virus strain (cultivated in chick embryo cells) adsorbed onto hydrated aluminium hydroxide, net price 0.25–mL prefilled syringe = £9.93, 0.5-mL prefilled syringe = £32.00

**Excipients** include gentamicin and neomycin

---

**Typhoid vaccines**

Typhoid vaccine is available as Vi capsular polysaccharide (from *Salmonella typhi*) vaccine for injection and as live attenuated *Salmonella typhi* for oral use.

Typhoid immunisation is advised for
- **travellers to areas where typhoid is endemic, especially if staying with or visiting local people**
- **travellers to endemic areas where frequent or prolonged exposure to poor sanitation and poor food hygiene is likely**
- **laboratory personnel who, in the course of their work, may be exposed to *Salmonella typhi***

Typhoid vaccination is not a substitute for scrupulous personal hygiene (see p. 685).

Capsular polysaccharide typhoid vaccine is usually given by intramuscular injection. Children under 2 years may respond suboptimally to the vaccine, but children aged between 1–2 years should be immunised if the risk of typhoid fever is considered high (immunisation is not recommended for infants under 12 months). Booster doses are needed every 3 years on continued exposure.

Oral typhoid vaccine is a live attenuated vaccine contained in an enteric-coated capsule. 3 doses of one capsule taken on alternate days, provides protection 7–10 days after the last dose. Protection may persist for up to 3 years in those constantly (or repeatedly) exposed to *Salmonella typhi*, but occasional travellers require further courses at intervals of 1 year.

**Interactions** Oral typhoid vaccine is inactivated by concomitant administration of antibacterials or antimalarials:
- **Antibacterials** should be avoided for 3 days before and after oral typhoid vaccination;
- **Mefloquine** should be avoided for at least 12 hours before or after oral typhoid; vaccination with oral typhoid should preferably be completed at least 3 days before the first dose of mefloquine;
- For other antimalarials vaccination with oral typhoid vaccine should be completed at least 3 days before the first dose of the antimalarial (except proguanil hydrochloride with atovaquone, which may be given concomitantly).

---

**TYPHOID VACCINE**

- **Indications** immunisation against typhoid fever
- **Cautions** see section 14.1; **interactions**: see above and Appendix 1 (vaccines)
- **Contra-indications** section 14.1; also for oral vaccine, acute gastro-intestinal illness
- **Side-effects** section 14.1
- **Dose**
  - **See under preparations**

**Typhoid polysaccharide vaccine for injection**

**Typherix® (GSK)**
Injection, Vi capsular polysaccharide typhoid vaccine, 50 micrograms/mL virulence polysaccharide antigen of *Salmonella typhi*, net price 0.5-mL prefilled syringe = £9.93

**Dose** by intramuscular injection, 0.5 mL at least 2 weeks before potential exposure to typhoid infection; CHILD under 2 years (see notes above)

**Typhim Vi® (Sanofi Pasteur)**
Injection, Vi capsular polysaccharide typhoid vaccine, 50 micrograms/mL virulence polysaccharide antigen of formaldehyde-inactivated *Salmonella typhi*, net price 0.5-mL prefilled syringe = £9.49

**Dose** by intramuscular injection, 0.5 mL, at least 2 weeks before potential exposure to typhoid infection CHILD under 2 years (see notes above)

**Polysaccharide vaccine with hepatitis A vaccine**
See Hepatitis A Vaccine
Typhoid vaccine, live (oral)

**Vivotif® (MASTA)**
Capsules, e/c, live attenuated Salmonella typhi (Ty21a), net price 3-cap pack = £14.77. Label: 23, 25, counselling, administration

**Dose**
- **ADULT** and **CHILD** over 6 years, 1 capsule on days 1, 3, and 5

**Counselling**
Swallow as soon as possible after placing in mouth with a cold or lukewarm drink; it is important to store capsules in a refrigerator

Varicella–zoster vaccine

Varicella–zoster vaccine (live) is licensed for immunisation against varicella in seronegative individuals. It is not recommended for routine use in children but can be given to seronegative healthy children over 1 year who come into close contact with individuals at high risk of severe varicella infections. The Department of Health recommends varicella–zoster vaccine for seronegative healthcare workers who come into direct contact with patients. Those with a history of chickenpox or shingles can be considered immune, but healthcare workers with a negative or uncertain history should be tested.

Rarely, the varicella–zoster vaccine virus has been transmitted from the vaccinated individual to close contacts. Therefore, contact with the following should be avoided if a vaccine-related cutaneous rash develops within 4–6 weeks of the first or second dose:
- varicella-susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy.

Healthcare workers who develop a generalised papular or vesicular rash on vaccination should avoid contact with susceptible individuals (see notes above);

- varicella-susceptible pregnant women;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy.

Yellow fever vaccine

Live yellow fever vaccine is indicated for those travelling or living in areas where infection is endemic (see p. 684) and for laboratory staff who handle the virus or who handle clinical material from suspected cases. Infants under 6 months of age should not be vaccinated because there is a small risk of encephalitis; infants aged 6–9 months should be vaccinated only if the risk of yellow fever is high and unavoidable (seek expert advice). The immunity which probably lasts for life is officially accepted for 10 years starting from 10 days after primary immunisation and for a further 10 years immediately after revaccination.

Very rare, vaccine-associated adverse effects have been reported, such as viscerotropic disease (yellow fever vaccine-associated viscerotropic disease, YEL-AVD), a syndrome which may include metabolic acidosis, muscle and liver cytolysis, and multi-organ failure. Neurological disorders (yellow fever vaccine-associated neurotropic disease, YEL-AND) such as encephalitis have also been reported. These very rare adverse effects usually have occurred after the first dose of yellow fever vaccine in those with no previous immunity.

Pregnancy and breast-feeding

Live yellow fever vaccine should not be given during pregnancy but if a significant risk of exposure cannot be avoided then vaccination should be delayed to the third trimester if possible (but the need for immunisation usually outweighs risk to the fetus). Vaccination should be considered in breast-feeding women when there is a real risk to the mother from yellow fever disease.

**VARICELLA-ZOSTER VACCINE**

**Indications**
immunisation against varicella infection

(see notes above)

**Cautions**
see section 14.1; also post-vaccination close-contact with susceptible individuals (see notes above);

**interactions:** Appendix 1 (vaccines)

**Contra-indications**
see section 14.1; also pregnancy (avoid pregnancy for 3 months after vaccination)

**Side-effects**
see section 14.1; also varicella-like rash; rarely thrombocytopenia

**Dose**
- See under preparations

**Varivax® (Sanofi Pasteur)**
Injection powder for reconstitution, live attenuated varicella-zoster virus (Oka/Merck strain) propagated in human diploid cells, net price 0.5-mL vial (with diluent) = £32.14

**Excipients**
include gelatin and neomycin

**Dose**
- by intramuscular or subcutaneous injection into deltoid region (or higher anterolateral thigh in children), ADULT and CHILD over 13 years (see notes above), 2 doses of 0.5 mL separated by 4–8 weeks; CHILD 1–13 years (but see notes above), 0.5 mL as a single dose (2 doses separated by 12 weeks in children with asymptomatic HIV infection)

**Yellow Fever Vaccine, Live**

**Yel(live)**
Injection, powder for reconstitution, live, attenuated 17D-204 strain of yellow fever virus, cultivated in chick embryos; single dose vial with syringe containing 0.5 mL diluent

Available (only to designated Yellow Fever Vaccination centres) as Stamari

in human diploid cells, net price 0.5-mL vial (with diluent) = £32.14

**Excipients**
include gelatin and neomycin

**Dose**
- by intramuscular or subcutaneous injection into deltoid region (or higher anterolateral thigh in children), ADULT and CHILD over 13 years (see notes above), 2 doses of 0.5 mL separated by 4–8 weeks; CHILD 1–13 years (but see notes above), 0.5 mL as a single dose (2 doses separated by 12 weeks in children with asymptomatic HIV infection)
**14.5 Immunoglobulins**

Human immunoglobulins have replaced immunoglobulins of animal origin (antiserum) which were frequently associated with hypersensitivity. Injection of immunoglobulins produces immediate protection lasting for several weeks.

Immunoglobulins are produced from pooled human plasma or serum, and are tested and found non-reactive for hepatitis B surface antigen and for antibodies against hepatitis C virus and human immunodeficiency virus (types 1 and 2)

The two types of human immunoglobulin preparation are **Normal immunoglobulin** and **Specific immunoglobulins**.

Further information about immunoglobulins is included in *Immunisation against Infectious Disease* (see section 14.1), in the Health Protection Agency’s Immunoglobulin Handbook [www.hpa.org.uk](http://www.hpa.org.uk), and in the Department of Health’s *Clinical Guidelines for Immunoglobulin use* [www.dh.gov.uk](http://www.dh.gov.uk).

**Availability** Normal immunoglobulin is available from Health Protection and microbiology laboratories only for contacts and the control of outbreaks. It is available commercially for other purposes.

**Specific immunoglobulins** are available from Health Protection and microbiology laboratories with the exception of **tetanus immunoglobulin** which is distributed through BPL to hospital pharmacies or blood transfusion departments and is also available to general medical practitioners. **Rabies immunoglobulin** is available from the Specialist and Reference Microbiology Division, Health Protection Agency. The large amounts of **hepatitis B immunoglobulin** required by transplant centres should be obtained commercially.

In Scotland all immunoglobulins are available from the Blood Transfusion Service. **Tetanus immunoglobulin** is distributed by the Blood Transfusion Service to hospitals and general medical practitioners on demand.

**Normal immunoglobulin**

Human **normal immunoglobulin** (‘HNIG’) is prepared from pools of at least 1000 donations of human plasma; it contains antibody to measles, mumps, varicella, hepatitis A, and other viruses that are currently prevalent in the general population.

**Cautions and side-effects** Normal immunoglobulin is **contra-indicated** in patients with known class-specific antibody to immunoglobulin A (IgA). **CHM advice**

Intravenous normal immunoglobulin may very rarely induce thromboembolic events and should be used with caution in those with risk factors for arterial or venous thrombotic events and in obese individuals.

Normal immunoglobulin may interfere with the immune response to live virus vaccines which should therefore only be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).

Side-effects of immunoglobulins include malaise, chills, fever, and rarely anaphylaxis.

**Uses** Normal immunoglobulin is administered by intramuscular injection for the protection of susceptible contacts against **hepatitis A** virus (infectious hepatitis), **measles** and, to a lesser extent, **rubella**.

Special formulations of immunoglobulins for intravenous administration are available for **replacement therapy** for patients with congenital agammaglobulinaemia and hypogammaglobulinaemia, for the treatment of idiopathic thrombocytopenic purpura and Kawasaki syndrome, and for the prophylaxis of infection following bone-marrow transplantation and in children with symptomatic HIV infection who have recurrent bacterial infections. Normal immunoglobulin may also be given intramuscularly or subcutaneously for replacement therapy, but intravenous formulations are normally preferred.

Intravenous immunoglobulin is also used in the treatment of Guillain-Barré syndrome in preference to plasma exchange.

**Hepatitis A** Hepatitis A vaccine is preferred for individuals at risk of infection (see p. 668) including those visiting areas where the disease is highly endemic (all countries excluding Northern and Western Europe, North America, Japan, Australia, and New Zealand). In unimmunised individuals, transmission of hepatitis A is reduced by good hygiene. Intramuscular normal immunoglobulin is no longer recommended for routine prophylaxis in travellers but it may be indicated for immunocompromised patients if their antibody response to vaccine is unlikely to be adequate.

Intramuscular normal immunoglobulin is of value in the prevention of infection in close contacts of confirmed cases of hepatitis A where there has been a delay of more than 7 days in identifying contacts, or for close contacts at high risk of severe disease.

**Measles** Intramuscular normal immunoglobulin may be given to prevent or attenuate an attack of measles in individuals who do not have adequate immunity. Children and adults with compromised immunity who have come into contact with measles should receive intramuscular normal immunoglobulin as soon as possible after exposure. It is most effective if given within 72 hours but can be effective if given within 6 days. For individuals receiving intravenous immunoglobulin, 100 mg/kg given within 3 weeks before measles exposure should prevent measles. Intramuscular normal immunoglobulin should also be considered for the following individuals if they have been in contact with a confirmed case of measles or with a person associated with a local outbreak:

- non-immune pregnant women;
- infants under 9 months.

Further advice should be sought from the Centre for Infections, Health Protection Agency (tel. (020) 8200 6868).

Individuals with normal immunity who are not in the above categories and who have not been fully immunised against measles, can be given MMR vaccine (section 14.4) for prophylaxis following exposure to measles.

**Rubella** Intramuscular immunoglobulin after exposure to rubella does not prevent infection in non-immune
contacts and is not recommended for protection of pregnant women exposed to rubella. It may, however, reduce the likelihood of a clinical attack which may possibly reduce the risk to the fetus. It should be used only if termination of pregnancy would be unacceptable to the pregnant woman, when it should be given as soon as possible after exposure. Serological follow-up of recipients is essential to determine if the woman has become infected despite receiving immunoglobulin. For routine prophylaxis, see MMR vaccine (p. 672).

**For intramuscular use**

**Normal Immunoglobulin**

Normal immunoglobulin injection. 250-mg vial; 750-mg vial

Dose by deep intramuscular injection, to control outbreaks of hepatitis A (see notes above), 500 mg; CHILD under 10 years 250 mg

Measles prophylaxis, CHILD under 1 year 250 mg, 1–2 years 500 mg, 3 years and over 750 mg

Rubella in pregnancy, prevention of clinical attack, 750 mg

Available from the Centre for Infections and other regional Health Protection Agency offices (for contacts and control of outbreaks only, see above)

**For subcutaneous use**

Subcuvia® (Baxter) (NB)

Normal immunoglobulin injection, net price 5-mL vial = £22.56; 10-mL vial = £28.50

Dose by subcutaneous injection, antibody deficiency syndromes, consult product literature

Note May be administered by intramuscular injection (if subcutaneous route not possible) but not for patients with thrombocytopenia or other bleeding disorders

Subgam® (BPL) (NB)

Normal immunoglobulin injection, net price 250-mg vial = £11.20, 750-mg vial = £28.50, 1.5-g vial = £57.00

Dose by subcutaneous injection, antibody deficiency syndromes, consult product literature

Note May be administered by intramuscular injection (if subcutaneous route not possible) but not for patients with thrombocytopenia or other bleeding disorders

Subcuvia® (BPL) (NB)

Normal immunoglobulin injection, net price 3-mL vial = £17.76, 10-mL vial = £28.50, 20-mL vial = £11.8.40

Dose by subcutaneous injection, antibody deficiency syndromes, consult product literature

**For intravenous use**

**Normal Immunoglobulin for Intravenous Use**

Brands include Flabogamma 5% (0.5 g, 2.5 g, 5 g, 10 g); Gammagard S/D (0.5 g, 2.5 g, 5 g, 10 g); Octagam (5%/—2.5 g, 5 g, 10 g, 10%—5 g, 10 g); Privigen (5 g, 10 g, 20 g); Sandoglobulin NF Liquid (6 g, 12 g); Vigam S (2.5 g, 5 g); Vigam Liquid (2.5 g, 5 g, 10 g)

Dose consult product literature

**Specific immunoglobulins**

Specific immunoglobulins are prepared by pooling the plasma of selected donors with high levels of the specific antibody required.

Although a hepatitis B vaccine is now available for those at high risk of infection, specific hepatitis B immunoglobulin (‘HBIG’) is available for use in association with hepatitis B vaccine for the prevention of infection in laboratory and other personnel who have been accidentally inoculated with hepatitis B virus, and in infants born to mothers who have become infected with this virus in pregnancy or who are high-risk carriers (see Hepatitis B Vaccine, p. 669).

Following exposure of an unimmunised individual to an animal in or from a high-risk country, the site of the bite should be washed with soapy water and specific rabies immunoglobulin of human origin administered; as much of the dose as possible should be injected in and around the cleansed wound. Rabies vaccine should also be given (for details see Rabies Vaccine, p. 677).

For the management of tetanus-prone wounds, tetanus immunoglobulin of human origin (‘HTIG’) should be used in addition to wound cleansing and, where appropriate, antibacterial prophylaxis and a tetanus-containing vaccine (section 14.4). Tetanus immunoglobulin, together with metronidazole (section 5.11) and wound cleansing, should also be used for the treatment of established cases of tetanus.

Varicella–zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella and who have no antibodies to varicella–zoster virus and who have significant exposure to chickenpox or herpes zoster. Those at increased risk include:

- neonates whose mothers develop chickenpox in the period 7 days before to 7 days after delivery;
- susceptible neonates exposed in the first 7 days of life;
- susceptible neonates or infants exposed whilst requiring intensive or prolonged special care nursing;
- susceptible women exposed at any stage of pregnancy (but when supplies of VZIG are short, may only be issued to those exposed in the first 20 weeks’ gestation or to those near term) providing VZIG is given within 10 days of contact;
- immunosuppressed individuals including those who have received corticosteroids in the previous 3 months at the following dose equivalents of prednisolone: children 2 mg/kg daily for at least 1 week or 1 mg/kg daily for 1 month; adults about 40 mg daily for more than 1 week.

Important: for full details consult Immunisation against Infectious Disease. Varicella–zoster vaccine is available—see section 14.4.

**Hepatitis B**

**Hepatitis B Immunoglobulin**

See notes above

Dose by intramuscular injection (as soon as possible after exposure; ideally within 12 hours, but no later than 7 days after exposure), ADULT and CHILD over 10 years 500 units; CHILD under 5 years 200 units, 5–9 years 300 units, NEONATE 200 units as soon as possible after birth; for full details consult Immunisation against Infectious Disease

Available from selected Health Protection Agency and NHS laboratories (except for Transplant Centres, see p. 681), also available from BPL

Note Hepatitis B immunoglobulin for intravenous use is available from BPL on a named-patient basis

**Rabies**

Rabies Immunoglobulin

(Antirabies Immunoglobulin Injection)

See notes above

Dose 20 units/kg by infiltration in and around the cleansed wound; if wound not visible or healed or if infiltration of whole volume not possible, give remainder by intramuscular injection into anterolateral thigh (remote from vaccination site)

Available from Specialist and Reference Microbiology Division, Health Protection Agency (also from BPL)
**Anti-D (Rh) immunoglobulin**

Anti-D (Rh) immunoglobulin is available to prevent a rhesus-negative mother from forming antibodies to fetal rhesus-positive cells which may pass into the maternal circulation. The objective is to protect any subsequent child from the hazard of haemolytic disease of the newborn.

Anti-D immunoglobulin should be administered following any sensitising event (e.g. abortion, miscarriage and birth); it should be injected within 72 hours of the episode but even if a longer period has elapsed it may still give protection and should be administered. The dose of anti-D immunoglobulin is determined according to the level of exposure to rhesus-positive blood.

For routine antenatal prophylaxis (see also NICE guidance below), two doses of at least 500 units of anti-D immunoglobulin should be given, the first at 28 weeks' gestation and the second at 34 weeks; alternatively a single dose of 1500 units given between 28 and 30 weeks gestation can be used.

**NICE guidance**

Routine antenatal anti-D prophylaxis for rhesus-negative women (August 2008)

Routine antenatal anti-D prophylaxis should be offered to all non-sensitised pregnant women who are rhesus negative.

Use of routine antenatal anti-D prophylaxis should not be affected by previous anti-D prophylaxis for a sensitising event early in the same pregnancy. Similarly, postpartum anti-D prophylaxis should not be affected by previous routine antenatal anti-D prophylaxis or by antenatal anti-D prophylaxis for a sensitising event.

**Note**

MMR vaccine may be given in the postpartum period with anti-D (Rh) immunoglobulin injection provided that separate syringes are used and the products are administered into different limbs. If blood is transfused, the antibody response to the vaccine may be inhibited—measure rubella antibodies after 6–8 weeks and revaccinate if necessary.
episode (after 12 weeks, 1500 units) immediately or within 72 hours
Antenatal prophylaxis, by intramuscular or intravenous injection, 1500 units given at week 28 of pregnancy, if infant rhesus positive; a further dose is still needed immediately or within 72 hours of delivery
Following Rh (D) incompatible blood transfusion, by intravenous injection, 50 units per mL transfused rhesus-positive blood (or 100 units per mL of erythrocyte concentrate), if intramuscular route used give in divided doses over several days
Following Rh (D) incompatible thrombocyte transfusion in rhesus-negative female child or woman of child-bearing age, by intravenous injection, 600 units
Autoimmune (idiopathic) thrombocytopenic purpura, consult product literature
Note Intravenous route used for patients with bleeding disorders

Interferons
Interferon gamma-1b is licensed to reduce the frequency of serious infection in chronic granulomatous disease and in severe malignant osteopetrosis.

INTERFERON GAMMA-1b
(Innate interferon)
Indications see notes above
Cautions severe hepatic impairment (Appendix 2), renal impairment (Appendix 3); seizure disorders (including seizures associated with fever); cardiac disease (including ischaemia, congestive heart failure, and arrhythmias); monitor before and during treatment; haematological tests (including full blood count, differential white cell count, and platelet count), blood chemistry tests (including renal and liver function tests) and urinalysis; avoid simultaneous administration of foreign proteins including immunological products (risk of exaggerated immune response); pregnancy (Appendix 4); breast-feeding (Appendix 5);
interactions: Appendix 1 (interferons)
Driving May impair ability to drive or operate machinery; effects may be enhanced by alcohol
Side-effects nausea, vomiting; headache, fatigue, fever; myalgia, arthralgia; rash, injection-site reactions; rarely confusion and systemic lupus erythematosus; also reported, neutropenia, thrombocytopenia, and raised liver enzymes
Dose
• See under Preparations

immunokin® (Boehringer Ingelheim) 
Injection recombinant human interferon gamma-1b 200 micrograms/mL, net price 0.5-mL vial = £88.00
Dose by subcutaneous injection, 50 micrograms/m 2 times a week; patients with body surface area of 0.5 m 2 or less, 1.5 micrograms/kg 3 times a week; not yet recommended for children under 6 months with chronic granulomatous disease

14.6 International travel

Note For advice on malaria chemoprophylaxis, see section 5.4.1.
No special immunisation is required for travellers to the United States, Europe, Australia, or New Zealand although all travellers should have immunity to tetanus and poliomyelitis (and childhood immunisations should be up to date). Certain special precautions are required in non-European areas surrounding the Mediterranean, in Africa, the Middle East, Asia, and South America.
Travellers to areas that have a high incidence of poliomyelitis or tuberculosis should be immunised with the appropriate vaccine; in the case of poliomyelitis previously immunised adults may be given a booster dose of a preparation containing inactivated poliomyelitis vaccine (see p. 676). BCG immunisation (see p. 664) is recommended for travellers aged under 35 years 1 proposing to stay for longer than 3 months (or in close contact with the local population) in countries with an incidence of tuberculosis greater than 40 per 100 000 2; it should preferably be given three months or more before departure.

Yellow fever immunisation (see p. 680) is recommended for travel to the endemic zones of Africa and South America. Many countries require an International Certificate of Vaccination from individuals arriving from, or who have been travelling through, endemic areas, whilst other countries require a certificate from all entering travellers (consult the Department of Health handbook, Health Information for Overseas Travel, www.dh.gov.uk).
Immunisation against meningococcal meningitis is recommended for a number of areas of the world (for details, see p. 673).
Protection against hepatitis A is recommended for travellers to high-risk areas outside Northern and Western Europe, North America, Japan, Australia and New Zealand. Hepatitis A vaccine (see p. 668) is preferred and it is likely to be effective even if given shortly before departure; normal immunoglobulin is no longer given routinely but may be indicated in the immunocompromised (see p. 681). Special care must also be taken with food hygiene (see below).
Hepatitis B vaccine (see p. 669) is recommended for those travelling to areas of high or intermediate prevalence who intend to seek employment as healthcare workers or who plan to remain there for lengthy periods and who may therefore be at increased risk of acquiring infection as the result of medical or dental procedures carried out in those countries. Short-term tourists or business travellers are not generally at increased risk of infection but may place themselves at risk by their sexual behaviour when abroad.
Prophylactic immunisation against rabies (see p. 677) is recommended for travellers to enzootic areas on long journeys or to areas out of reach of immediate medical attention.
Travellers who have not had a tetanus booster in the last 10 years and are visiting areas where medical attention may not be accessible should receive a booster dose of adsorbed diphtheria [low dose], tetanus and inactivated poliomyelitis vaccine (see p. 665), even if they have received 5 doses of a tetanus-containing vaccine previously.
Typhoid vaccine (see p. 679) is indicated for travellers to those countries where typhoid is endemic but the vaccine is no substitute for personal precautions (see below).

1 There is inadequate evidence of protection by BCG vaccine in adults aged over 35 years; however, vaccination is recommended for healthcare workers irrespective of age because of the increased risk to them or their patients
2 List of countries where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.hpa.org.uk
There is no requirement for cholera vaccination as a condition for entry into any country, but oral cholera vaccine (see p. 665) may be considered for backpackers and those travelling to situations where the risk is greatest (e.g., refugee camps). Regardless of vaccination, travellers to areas where cholera is endemic should take special care with food hygiene (see below).

Advice on diphtheria (see p. 666), on Japanese encephalitis (vaccine available on named-patient basis from Sanofi Pasteur and MASTA) and on tick-borne encephalitis (see p. 679) is included in Health Information for Overseas Travel, see below.

Food hygiene In areas where sanitation is poor, good food hygiene is important to help prevent hepatitis A, typhoid, cholera, and other diarrhoeal diseases (including travellers’ diarrhoea). Food should be freshly prepared and hot, and uncooked vegetables (including green salads) should be avoided; only fruits which can be peeled should be eaten. Only suitable bottled water, or tap water that has been boiled, or treated with sterilising tablets should be used for drinking.

Immunisation requirements change from time to time, and information on the current requirements for any particular country may be obtained from the embassy or legation of the appropriate country or from:

- National Travel Health Network and Centre
  - Hospital for Tropical Diseases
  - Mortimer Market Centre
  - Capper Street, off Tottenham Court Road
  - London, WC1E 6AU
  - Tel: 0845 602 6712
  - (9 a.m.–noon, 2–4.30 p.m. weekdays for healthcare professionals only)
  - www.nathnac.org

- Travel Medicine Team
  - Health Protection Scotland
  - Clifton House
  - Clifton Place
  - Glasgow, G3 7LN
  - Tel: (0141) 300 1100
  - (2 p.m.–4 p.m. weekdays)
  - www.travax.nhs.uk (registration required. Annual fee may be payable for users outside NHS Scotland)

- Welsh Medicines Information Centre
  - University Hospital of Wales
  - Cardiff, CF14 4XW
  - Tel: (029) 2074 2979 (8.30 a.m.–5 p.m. weekdays for health professionals in Wales only)

- Department of Health and Social Services
  - Castle Buildings
  - Stormont
  - Belfast, BT4 3PP
  - Tel: (028) 9052 0000

1. Japanese encephalitis vaccine not prescribable on the NHS; health authorities may investigate circumstances under which vaccine prescribed
15 Anaesthesia

15.1 General anaesthesia

15.1.1 Intravenous anaesthetics

15.1.2 Inhalational anaesthetics

15.1.3 Antimuscarinic drugs

15.1.4 Sedative and analgesic peri-operative drugs

15.1.4.1 Anxiolytics and neuroleptics

15.1.4.2 Non-opioid analgesics

15.1.4.3 Opioid analgesics

15.1.5 Neuromuscular blocking drugs

15.1.6 Drugs for reversal of neuromuscular blockade

15.1.7 Antagonists for central and respiratory depression

15.1.8 Drugs for malignant hyperthermia

Note: The drugs in section 15.1 should be used only by experienced personnel and where adequate resuscitation equipment is available.

Several different types of drug are given together during general anaesthesia. Anaesthesia is induced with either a volatile drug given by inhalation (section 15.1.2) or with an intravenously administered drug (section 15.1.1); anaesthesia is maintained with an intravenous or inhalational anaesthetic. Analgesics (section 15.1.4), usually short-acting opioids, are also used. The use of neuromuscular blocking drugs (section 15.1.5) necessitates intermittent positive-pressure ventilation. Following surgery, anticholinesterases (section 15.1.6) can be given to reverse the effects of neuromuscular blocking drugs; specific antagonists (section 15.1.7) can be used to reverse central and respiratory depression caused by some drugs used in surgery. A local anaesthetic (section 15.2) can be used to reduce pain at the injection site. Individual requirements vary considerably and the recommended doses are only a guide. Smaller doses are indicated in ill, shocked, or debilitated patients and in significant hepatic impairment, while robust individuals may require larger doses. The required dose of induction agent may be less if the patient has been premedicated with a sedative agent or if an opioid analgesic has been used.

Surgery and long-term medication The risk of losing disease control on stopping long-term medication before surgery is often greater than the risk posed by continuing it during surgery. It is vital that the anaesthetist knows about all drugs that a patient is (or has been) taking.

Patients with adrenal atrophy resulting from long-term corticosteroid use (section 6.3.2) may suffer a precipitous fall in blood pressure unless corticosteroid cover is provided during anaesthesia and in the immediate post-operative period. Anaesthetists must therefore know whether a patient is, or has been, receiving corticosteroids (including high-dose inhaled corticosteroids).

Other drugs that should normally not be stopped before surgery include antiepileptics, antiparkinsonian drugs, antipsychotics, anxiolytics, bronchodilators, cardiovas-
cular drugs (but see potassium-sparing diuretics, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor antagonists below), glaucoma drugs, immunosuppressants, drugs of dependence, and thyroid or antithyroid drugs. Expert advice is required for patients receiving antivirals for HIV infection. For general advice on surgery in diabetic patients see section 6.1.1.

Patients taking aspirin or an oral anticoagulant present an increased risk for surgery. In these circumstances, the anaesthetist and surgeon should assess the relative risks and decide jointly whether aspirin or the anticoagulant should be stopped or replaced with heparin therapy.

Drugs that should be stopped before surgery include combined oral contraceptives (see Surgery, section 7.3.1 for details); for advice on hormone replacement therapy, see section 6.4.1.1. If antidepresants need to be stopped, they should be withdrawn gradually to avoid withdrawal symptoms. In view of their hazardous interactions MAOIs should normally be stopped 2 weeks before surgery. Tricyclic antidepressants need not be stopped, but there may be an increased risk of arrhythmias and hypotension (and dangerous interactions with vasopressor drugs); therefore, the anaesthetist should be informed if they are not stopped. Lithium should be stopped 24 hours before major surgery but the normal dose can be continued for minor surgery (with careful monitoring of fluids and electrolytes). Potassium-sparing diuretics may need to be withheld on the morning of surgery because hyperkalaemia may develop if renal perfusion is impaired or if there is tissue damage. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin-II receptor antagonists can be associated with severe hypotension after induction of anaesthesia; these drugs may need to be discontinued 24 hours before surgery.

**Anaesthesia and driving**

Patients given sedatives and analgesics during minor outpatient procedures should be very carefully warned about the risk of driving afterwards. For intravenous benzodiazepines and for a short general anaesthetic the risk extends to the morning after administration. Responsible persons should be available to take patients home. The dangers of taking alcohol should also be emphasised.

**Prophylaxis of acid aspiration**

Regurgitation and aspiration of gastric contents (Mendelson’s syndrome) is an important complication of general anaesthesia, particularly in obstetrics and during emergency surgery, and requires prophylaxis against acid aspiration. Prophylaxis is also needed in those with gastro-oesophageal reflux disease and in circumstances where gastric emptying may be delayed.

An H-receptor antagonist (section 1.3.1) or a proton pump inhibitor (section 1.3.5) such as omeprazole may be used before surgery to increase the pH and reduce the volume of gastric fluid. They do not affect the pH of fluid already in the stomach and this limits their value in emergency procedures; oral H-receptor antagonists can be given 1–2 hours before the procedure but omeprazole must be given at least 12 hours earlier. Antacids are frequently used to neutralise the acidity of the fluid already in the stomach; ‘clear’ (non-particulate) antacids such as sodium citrate are preferred. Sodium citrate 300 mmol/litre (88.2 mg/mL) oral solution is licensed for use before general anaesthesia for caesarean section (available from Viridian).

**Gas cylinders**

Each gas cylinder bears a label with the name of the gas contained in the cylinder. The name or chemical symbol of the gas appears on the shoulder of the cylinder and is also clearly and indelibly stamped on the cylinder valve.

The colours on the valve end of the cylinder extend down to the shoulder; in the case of mixed gases the colours for the individual gases are applied in four segments, two for each colour.

Gas cylinders should be stored in a cool well-ventilated room, free from flammable materials.

**No lubricant of any description should be used on the cylinder valves.**

**Anaesthesia, sedation, and resuscitation in dental practice**

For details see A Conscious Decision: A review of the use of general anaesthesia and conscious sedation in primary dental care; report by a group chaired by the Chief Medical Officer and Chief Dental Officer, July 2000 and associated documents. Further details can also be found in Conscious Sedation in the Provision of Dental Care; report of an Expert Group on Sedation for Dentistry (commissioned by the Department of Health), 2003. Both documents are available at www.dh.gov.uk.

Guidance is also included in Standards for Dental Professionals, London, General Dental Council, May 2005 (and as amended subsequently), and Conscious Sedation in Dentistry: Dental Clinical Guidance, Scottish Dental Effectiveness Programme, May 2006.

**15.1.1 Intravenous anaesthetics**

Intravenous anaesthetics may be used either to induce anaesthesia or for maintenance of anaesthesia throughout surgery. Intravenous anaesthetics nearly all produce their effect in one arm-brain circulation time and can cause apnoea and hypotension, and so adequate resuscitative facilities must be available. They are contra-indicated if the anaesthetist is not confident of being able to maintain the airway (e.g. in the presence of a tumour in the pharynx or larynx). Extreme care is required in surgery of the mouth, pharynx, or larynx and in patients with acute circulatory failure (shock) or fixed cardiac output.

To facilitate tracheal intubation, induction is usually followed by a neuromuscular blocking drug (section 15.1.3) or short-acting opioid (section 15.1.4.3).

**Total intravenous anaesthesia**

This is a technique in which major surgery is carried out with all drugs given intravenously. Respiration can be spontaneous, or controlled with oxygen-enriched air. Neuromuscular blocking drugs can be used to provide relaxation and prevent reflex muscle movements. The main problem to be overcome is the assessment of depth of anaesthesia. Target Controlled Infusion (TCI) systems can be used to titrate intravenous anaesthetic infusions to predicted plasma-drug concentrations in ventilated adult patients.

**Anaesthesia and driving**

See section 15.1.
Barbiturates

Thiopental sodium (thiopentone sodium) is used widely for induction of anaesthesia, but it has no analgesic properties. Induction is generally smooth and rapid, but dose-related cardiorespiratory depression can occur.

Awakening from a moderate dose of thiopental is rapid because the drug redistributes into other tissues, particularly fat. However, metabolism is slow and sedative effects can persist for 24 hours. Repeated doses have a cumulative effect and recovery is much slower.

**THIOPENTAL SODIUM**
(Thiopentone sodium)

**Indications** induction of general anaesthesia; anaesthesia of short duration; reduction of raised intracranial pressure if ventilation controlled; status epilepticus (see also section 4.8.2)

**Cautions** see notes above; cardiovascular disease; reconstituted solution is highly alkaline—extravasation causes tissue necrosis and severe pain; avoid intra-arterial injection; hepatic impairment (Appendix 2); pregnancy (Appendix 4); interactions: Appendix 1 (anaesthetics, general)

**Contra-indications** see notes above; acute porphyria (section 9.8.2); myotonic dystrophy; breast-feeding (Appendix 5)

**Side-effects** hypotension, arrhythmias, myocardial depression, laryngeal spasm, cough, sneezing, hypersensitivity reactions, rash, injection-site reactions; excessive doses associated with hypothermia and profound cerebral impairment

**Dose**
- Induction of general anaesthesia, by slow intravenous injection usually as a 2.5% (25 mg/mL) solution, ADULT over 18 years, fit and premedicated, initially 100–150 mg (reduced in elderly or debilitated) over 10–15 seconds (longer in elderly or debilitated), followed by further quantity if necessary according to response after 30–60 seconds; or up to 4 mg/kg (max. 500 mg); CHILD 1 month–18 years, initially up to 4 mg/kg, then 1 mg/kg repeated as necessary (max. total dose 7 mg/kg)
- Raised intracranial pressure, by slow intravenous injection, 1.5–3 mg/kg, repeated as required
- Status epilepticus (only if other measures fail, see section 4.8.2), by slow intravenous injection as a 2.5% (25 mg/mL) solution, ADULT over 18 years, 75–125 mg as a single dose; CHILD 1 month–18 years, initially up to 4 mg/kg by slow intravenous injection, then up to 8 mg/kg/hour by continuous intravenous infusion, adjusted according to response

**Injection**, powder for reconstitution, thiopental sodium, net price 500-mg vial = £3.06

Other intravenous anaesthetics

Propofol is associated with rapid recovery without a hangover effect and is widely used. There is sometimes pain on intravenous injection, which can be reduced by intravenous lidocaine. Significant extraneous muscle movements may occur. Convulsions, anaphylaxis, and delayed recovery from anaesthesia can occur after propofol administration; since the onset of convulsions can be delayed the CSM has advised special caution after day surgery. Propofol is associated with bradycardia, occasionally profound; intravenous administration of an antimuscarinic drug may prevent this.

**Etomidate** is an induction agent associated with rapid recovery without a hangover effect. It causes less hypotension than thiopental and propofol during induction. It produces a high incidence of extraneous muscle movement, which can be minimised by an opioid analgesic or a short-acting benzodiazepine given just before induction. Pain on injection can be reduced by injecting into a larger vein or by giving an opioid analgesic just before induction. Etomidate can suppress adrenocortical function, particularly during continuous administration, and it should not be used for maintenance of anaesthesia.

**Ketamine** is used rarely. It has good analgesic properties at sub-anaesthetic dosage and is used under specialist supervision in palliative care for pain that is unresponsive to standard treatment. Ketamine causes less hypotension than thiopental and propofol during induction. It is used mainly for paediatric anaesthesia, particularly when repeated administration is required (such as for serial burns dressings); recovery is relatively slow and there is a high incidence of extraneous muscle movements. The main disadvantage of ketamine is the high incidence of hallucinations, nightmares, and other transient psychotonic effects; these can be reduced by a benzodiazepine such as diazepam or midazolam. Ketamine also has abuse potential and can itself cause dependence.

**ETOMIDATE**

**Indications** induction of anaesthesia

**Cautions** see under Intravenous Anaesthetics and notes above; hepatic impairment (Appendix 2); avoid in acute porphyria (section 9.8.2); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (anaesthetics, general)

**Contra-indications** see under Intravenous Anaesthetics and notes above

**Side-effects** see notes above; also coughing, hiccups, shivering, allergic reaction (including bronchospasm and anaphylaxis); respiratory depression, arrhythmia, and convulsions also reported

**Dose**
- See under preparations

**Etomidate-Lipuro®** (Braun) (†)

**Injection** (emulsion), etomidate 2 mg/mL, net price 10-mL amp = £1.53

**Dose** ADULT and CHILD over 6 months, by slow intravenous injection, 150–300 micrograms/kg; CHILD under 10 years may need up to 400 micrograms/kg; ELDERLY 150–200 micrograms/kg

**Hypnomidate®** (Janssen-Cilag) (†)

**Injection**, etomidate 2 mg/mL, net price 10-mL amp = £1.47

**Excipients** include propylene glycol (see Excipients, p. 2)

**Dose** ADULT and CHILD, by slow intravenous injection, 300 micrograms/kg max. total dose 60 mg; ELDERLY 150–200 micrograms/kg; max. total dose 60 mg

**KETAMINE**

**Indications** induction and maintenance of anaesthesia (but rarely used)
Cautions see under Intravenous Anaesthetics and notes above; increased cerebrospinal fluid pressure; predisposition to hallucinations or nightmares; pregnancy (Appendix 4); interactions: Appendix 1 (anaesthetics, general)

Contra-indications see under Intravenous Anaesthetics; hypertension, pre-eclampsia or eclampsia, severe cardiac disease, stroke; raised intracranial pressure; head trauma; acute porphyria (section 9.8.2)

Side-effects see notes above; also tachycardia, hypertension, arrhythmias, hypotension, bradycardia; increased salivation, laryngospasm; anxiety, insomnia; diaphoria, nystagmus, raised intra-ocular pressure; rashes, injection-site reactions; anaphylaxis also reported

Dose

- By intramuscular injection, short procedures, initially 6.5–13 mg/kg, adjusted according to response (10 mg/kg usually produces 12–25 minutes of surgical anaesthesia)
- By intravenous injection over at least 60 seconds, short procedures, initially 1–4.5 mg/kg, adjusted according to response (2 mg/kg usually produces 5–10 minutes of surgical anaesthesia)
- By intravenous infusion of a solution containing 1 mg/mL, longer procedures, induction, total dose of 0.5–2 mg/kg; maintenance, 10–45 micrograms/kg/minute, rate adjusted according to response

Ketalar® (Pfizer) ℜ

Injection, ketamine (as hydrochloride) 10 mg/mL, net price 20-mL vial = £4.22, 50 mg/mL, 10-mL vial = £8.77, 100 mg/mL, 10-mL vial = £16.10

Note For intravenous injection, dilute 100 mg/mL strength to a concentration of not more than 50 mg/mL with Glucose 5% or Sodium Chloride 0.9% or Water for Injections

PROPOFOL

Indications see under dose

Cautions see under Intravenous Anaesthetics and notes above; cardiac impairment; respiratory impairment; elderly; hypovolaemia; epilepsy; hypotension; raised intracranial pressure; monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days; hepatic impairment; renal impairment; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (anaesthetics, general)

Contra-indications see notes above; sedation of ventilated children under 17 years in intensive care (risk of potentially fatal effects including metabolic acidosis, cardiac failure, rhabdomyolysis, hyperlipidaemia, and hepatomegaly)

Side-effects see notes above; also hypotension, tachycardia, flushing; transient apnoea, hyperventilation, coughing, and hiccup during induction; headache; less commonly thrombosis, phlebitis; rarely arrhythmia, headache, vertigo, shivering, euphoria; very rarely pancreatitis, pulmonary oedema, sexual disinhibition, and discoloration of urine; serious and sometimes fatal side-effects reported with prolonged infusion of doses exceeding 5 mg/kg/hour, including metabolic acidosis, rhabdomyolysis, hyperkalaemia, and cardiac failure, dystonia and dyskinesia also reported

Dose

- 1% injection
- Induction of anaesthesia, by intravenous injection or infusion, 1.5–2.5 mg/kg (1–1.5 mg in those over 55 years) at a rate of 20–40 mg every 10 seconds until response; CHILD over 1 month, administer slowly until response (usual dose in child over 8 years 2.5 mg/kg, may need more in younger child e.g. 2.5–4 mg/kg)
- Maintenance of anaesthesia, by intravenous infusion, 4–12 mg/kg/hour or by intravenous injection, 25–50 mg repeated according to response; CHILD over 1 month, by intravenous infusion, 9–15 mg/kg/hour
- Sedation of ventilated patients in intensive care, by intravenous infusion, ADULT and CHILD over 17 years, 0.3–4 mg/kg/hour
- Sedation for surgical and diagnostic procedures, ADULT and CHILD over 17 years, initially by intravenous injection over 1–5 minutes, 0.5–1 mg/kg; maintenance, by intravenous infusion, 1.5–4.5 mg/kg/hour (additionally, if rapid increase in sedation required, by intravenous injection, 10–20 mg); patients over 55 years may require lower dose

- 2% injection
- Induction of anaesthesia, by intravenous infusion, 1.5–2.5 mg/kg (1–1.5 mg in those over 55 years) at a rate of 20–40 mg every 10 seconds; CHILD over 3 years, administer slowly until response (usual dose in child over 8 years 2.5 mg/kg, may need more in younger child e.g. 2.5–4 mg/kg)
- Maintenance of anaesthesia, by intravenous infusion, 4–12 mg/kg/hour; CHILD over 3 years, by intravenous infusion, 9–15 mg/kg/hour
- Sedation in intensive care, by Intravenous infusion, ADULT and CHILD over 17 years, 0.3–4 mg/kg/hour

Propofol (Non-proprietary) ℜ

1% injection (emulsion), propofol 10 mg/mL, net price 20-mL amp = £2.33, 50-mL bottle = £5.82, 100-mL bottle = £11.64
2% injection (emulsion), propofol 20 mg/mL, net price 50-mL vial = £11.64
Brands include Propofol-Lipuro®, Propoven

Diprivan® (AstraZeneca) ℜ

1% injection (emulsion), propofol 10 mg/mL, net price 20-mL amp = £3.88, 50-mL prefilled syringe (for use with Diprifusor® TCI system) = £10.67
2% injection (emulsion), propofol 20 mg/mL, net price 50-mL prefilled syringe (for use with Diprifusor® TCI system) = £20.37

Note Diprifusor® TCI (target controlled infusion) system is licensed only for induction and maintenance of general anaesthesia in adults

15.1.2 Inhalational anaesthetics

Inhalational anaesthetics may be gases or volatile liquids. They can be used both for induction and maintenance of anaesthesia and can also be used following induction with an intravenous anaesthetic (section 15.1.1).

Gaseous anaesthetics require suitable equipment for storage and administration. They may be supplied via hospital pipelines or from metal cylinders. Volatile liquid...
Anaesthesics are administered using calibrated vapourisers, using air, oxygen, or nitrous oxide–oxygen mixtures as the carrier gas; all can trigger malignant hyperthermia (section 15.1.8) and are contra-indicated in those susceptible to malignant hyperthermia. Volatile liquid anaesthetics can increase cerebrospinal pressure and should be used with caution in those with raised intracranial pressure.

In children with neuromuscular disease, inhalational anaesthetics are associated with very rare cases of hyperkalaemia resulting in cardiac arrhythmias and death. To prevent hypoxia, the inspired gas mixture should contain a minimum of 25% oxygen at all times. Higher concentrations of oxygen (greater than 30%) are usually required during inhalational anaesthesia when nitrous oxide is being administered.

**Anaesthesia and driving**  See section 15.1.

**Volatile liquid anaesthetics**

**Isoflurane** is a volatile liquid anaesthetic. Heart rhythm is generally stable during isoflurane anaesthesia, but heart-rate can rise, particularly in younger patients. Systemic arterial pressure can fall and cardiac output can decrease, owing to a decrease in systemic vascular resistance. Respiration is depressed. Muscle relaxation occurs and the effects of muscle relaxant drugs are potentiated. Isoflurane may also cause hepatotoxicity in those sensitised to halogenated anaesthetics.

**Desflurane** is a rapid acting volatile liquid anaesthetic; it is reported to have about one-fifth the potency of isoflurane. Emergence and recovery from anaesthesia are particularly rapid because of its low solubility. Desflurane is not recommended for induction of anaesthesia as it is irritant to the upper respiratory tract; cough, breath-holding, apnoea, laryngospasm, and increased secretions can occur. The risk of hepatotoxicity with desflurane in those sensitised to halogenated anaesthetics appears to be remote.

**Sevoflurane** is a rapid acting volatile liquid anaesthetic and is more potent than desflurane. Emergence and recovery are particularly rapid, but slower than desflurane. Sevoflurane is non-irritant and is therefore often used for inhalational induction of anaesthesia. Sevoflurane can interact with carbon dioxide absorbents to form compound A, a potentially nephrotoxic vinyl ether. However, in spite of extensive use, no cases of sevo-flurane-induced permanent renal injury have been reported and the carbon dioxide absorbents used in the UK produce very low concentrations of compound A, even in low-flow anaesthetic systems.

**Halothane** is a volatile liquid anaesthetic. It has largely been superseded by newer agents but is useful for inhalation induction of anaesthesia. Its advantages are that it is potent, induction is smooth, and the vapour is non-irritant and seldom induces coughing or breath holding. Despite these advantages, halothane is not widely used because of its association with severe hepatotoxicity (important: see CSM advice, below).

Halothane causes cardiorespiratory depression. Respiratory depression results in raised arterial carbon dioxide tension and sometimes ventricular arrhythmias. Halothane also depresses the cardiac muscle fibres and can cause bradycardia, resulting in diminished cardiac output and fall of arterial pressure. Adrenaline (epinephrine) infiltrations should be avoided in patients anaesthetised with halothane because ventricular arrhythmias can result.

Halothane produces moderate muscle relaxation, but this may be inadequate for major abdominal surgery for which specific muscle relaxants should be used.

---

**CSM advice (halothane hepatotoxicity)**

Severe hepatotoxicity can follow halothane anaesthesia. The CSM has reported that this occurs more frequently after repeated exposure to halothane and has a high mortality. The risk of severe hepatotoxicity appears to be increased by repeated exposures within a short time interval, but even after a long interval (sometimes of several years), susceptible patients have been reported to develop jaundice. Since there is no reliable way of identifying susceptible patients, the CSM recommends the following precautions before the use of halothane:

- a careful anaesthetic history should be taken to determine previous exposure and previous reactions to halothane;
- repeated exposure to halothane within a period of at least 3 months should be avoided unless there are overriding clinical circumstances;
- a history of unexplained jaundice or pyrexia in a patient following exposure to halothane is an absolute contra-indication to its future use in that patient.

---

**DESFLURANE**

**Indications**  see notes above

**Cautions**  see notes above; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (anaesthetics, general)

**Contra-indications**  see notes above; susceptibility to malignant hyperthermia

**Side-effects**  see notes above

**Dose**

- Induction of anaesthesia, by inhalation through specifically calibrated vaporiser, ADULT over 18 years, 4–11%; CHILD see BNF for Children
- Maintenance of anaesthesia, by inhalation through specifically calibrated vaporiser, ADULT over 18 years, 2–6% in nitrous oxide; 2.5–8.5% in oxygen or oxygen-enriched air; CHILD see BNF for Children

**Suprane® (Baxter)** (FL)

Desflurane, net price 240 mL = £58.62

---

**HALOTHANE**

**Indications**  see notes above

**Cautions**  see notes above (important: CSM advice above); avoid for dental procedures in those under 18 years, 2–6% in nitrous oxide; 2.5–8.5% in oxygen or oxygen-enriched air; CHILD see BNF for Children

**Contra-indications**  see notes above; susceptibility to malignant hyperthermia

**Side-effects**  see notes above
Nitrous oxide is used for maintenance of anaesthesia and, in sub-anaesthetic concentrations, for analgesia. For anaesthesia it is commonly used in a concentration of 50 to 66% in oxygen as part of a balanced technique in association with other inhalational or intravenous agents. Nitrous oxide is unsatisfactory as a sole anaesthetic owing to lack of potency, but is useful as part of a combination of drugs since it allows a significant reduction in dosage. For analgesia (without loss of consciousness) a mixture of nitrous oxide and oxygen containing 50% of each gas (Entonox®, Equanox®) is used. Self-administration using a demand valve is popular in obstetric practice, for changing painful dressings, as an aid to postoperative physiotherapy, and in emergency ambulances. Nitrous oxide may have a deleterious effect if used in patients with an air-containing closed space since nitrous oxide diffuses into such a space with a resulting increase in pressure. This effect may be dangerous in the presence of a pneumothorax, which may enlarge to compromise respiration, or in the presence of intracranial air after head injury. Following administration of nitrous oxide, hypoxia can occur; additional oxygen should always be administered for several minutes to prevent hypoxaemia. Special care is needed to avoid hypoxia if an anaesthetic machine is being used; machines should incorporate an anti-hypoxia device. Exposure of patients to nitrous oxide for prolonged periods, either by continuous or by intermittent administration, may result in megaloblastic anaemia owing to interference with the action of vitamin B12; neurological toxic effects can occur without preceding overt haematological changes. For the same reason, exposure of theatre staff to nitrous oxide should be minimised. Depression of white cell formation may also occur. Assessment of plasma-vitamin B concentration should be considered in those at risk of deficiency, including the elderly, those who have a poor or vegetarian diet, and those with a history of anaemia. Nitrous oxide should not be given continuously for longer than 24 hours or more frequently than every 4 days without close supervision and haematological monitoring.
Hyoscine hydrobromide reduces secretions and also provides a degree of amnesia, sedation and anti-emesis. Unlike atropine it may produce bradycardia rather than tachycardia. In some patients, especially the elderly, hyoscine may cause the central anticholinergic syndrome (excitement, ataxia, hallucinations, behavioural abnormalities, and drowsiness).

Glycopyrronium bromide reduces salivary secretions. When given intravenously it produces less tachycardia than atropine. It is widely used with neostigmine for reversal of non-depolarising neuromuscular blocking drugs (section 15.1.5).

Phenothiazines do not effectively reduce secretions when used alone.

### ATROPINE SULPHATE

**Indications** drying secretions; reversal of excessive bradycardia; with anticholinesterases for reversal of non-depolarising neuromuscular block; antidote to organophosphorous poisoning (see Emergency Treatment of Poisoning p. 36), antispsychotic (section 1.2); bradycardia (section 2.3.1); cardiopulmonary resuscitation (section 2.7.3); eye (section 11.5)

**Cautions** section 1.2; also paralytic ileus; pyloric stenosis; cardiovascular disease; myasthenia gravis; prostatic enlargement; pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (antimuscarinics)

**Duration of action** Since atropine has a shorter duration of action than neostigmine, late unopposed bradycardia may result; close monitoring of the patient is necessary

**Side-effects** section 1.2

**Dose**

- Premedication, by intravenous injection, 300–600 micrograms immediately before induction of anaesthesia; CHILD 20 micrograms/kg (max. 600 micrograms)

By subcutaneous or intramuscular injection, 300–600 micrograms 30–60 minutes before induction; CHILD 20 micrograms/kg (max. 600 micrograms)

- Intra-operative bradycardia, by intravenous injection, 300–600 micrograms (larger doses in emergencies); CHILD [unlicensed indication] 1–12 years 10–20 micrograms/kg

- Control of muscarinic side-effects of neostigmine or edrophonium in reversal of competitive neuromuscular block, by intravenous injection, 0.6–1.2 mg; CHILD under 12 years 20 micrograms/kg (max. 600 micrograms)

- Arrhythmias after myocardial infarction, see section 2.3.1 and 2.7.3; see also cardiopulmonary resuscitation algorithm, inside back cover

**Special strengths**

- **Atropine (Non-proprietary)**
  - Injection, atropine sulphate 100 micrograms/mL, net price 5 mL = £4.58, 10 mL = £5.39, 30 mL = £8.95
  - 1. **Minijet® Atropine** (UCB Pharma) Injection, atropine sulphate 100 micrograms/mL, net price 5 mL = £4.58, 10 mL = £5.39, 30 mL = £8.95
  - 2. **Robinul® (Anpharm)** Injection, glycopyrronium bromide 200 micrograms/mL, net price 1-mL amp = 70p; 3-mL amp = £1.50
    - **Note** May be difficult to obtain

**With neostigmine metilsulphate** Section 15.1.6

### GLYCOPHYRONIUM BROMIDE

**(Glycopyrrolate)**

**Indications** drying secretions (see Prescribing in Palliative Care, p. 16); reversal of excessive bradycardia; with neostigmine for reversal of non-depolarising neuromuscular block; hyperhidrosis (section 13.12)

**Cautions** section 1.2; also paralytic ileus, pyloric stenosis; cardiovascular disease; myasthenia gravis; prostatic enlargement; interactions: Appendix 1 (antimuscarinics)

**Side-effects** see section 1.2

**Dose**

- Premedication, by intramuscular or intravenous injection, 200–400 micrograms or 4–5 micrograms/kg (max. 400 micrograms); CHILD by intramuscular or by intravenous injection, 4–8 micrograms/kg (max. 200 micrograms)

- Intra-operative use, by intravenous injection, 200–400 micrograms or 4–5 micrograms/kg (max. 400 micrograms), repeated if necessary; CHILD under 18 years 4–8 micrograms/kg (max. 200 micrograms), repeated if necessary

- Control of muscarinic side-effects of neostigmine in reversal of non-depolarising neuromuscular block, by intravenous injection, 200 micrograms per 1 mg of neostigmine, or 10–15 micrograms/kg; CHILD 10 micrograms/kg

**With neostigmine metilsulphate** Section 15.1.6

### HYOSCINE HYDROBROMIDE

**(Scopolamine hydrobromide)**

**Indications** drying secretions (see Prescribing in Palliative Care, p. 16), amnesia; other indications (section 4.6)

**Cautions** see under Hyoscine Butylbromide (section 1.2); also paralytic ileus, myasthenia gravis, epilepsy, prostatic enlargement; avoid in the elderly (see notes above)

**Side-effects** see under Atropine Sulphate; also bradycardia

**Dose**

- Premedication, by subcutaneous or intramuscular injection, 200–600 micrograms 30–60 minutes before induction of anaesthesia; CHILD 15 micrograms/kg

**Hyoscine** (Non-proprietary) Injection, hyoscine hydrobromide 400 micrograms/mL, net price 1-mL amp = £2.67; 600 micrograms/mL, 1-mL amp = £2.67

**With papaveretum**

See under papaveretum (section 4.7.2)
### 15.1.4 Sedative and analgesic peri-operative drugs

#### 15.1.4.1 Anxiolytics and neuroleptics

Anxiolytic benzodiazepines are widely used for premedication; neuroleptics such as chlorpromazine are rarely used.

#### 15.1.4.2 Non-opioid analgesics

Benzodiazepines possess useful properties for premedication including relief of anxiety, sedation, and amnesia; short-acting benzodiazepines taken by mouth are the most common premedicants. They have no analgesic effect so an opioid analgesic may sometimes be required for pain.

Benzodiazepines can alleviate anxiety at doses that do not necessarily cause excessive sedation and they are of particular value during short procedures or during operations under local anaesthesia (including dentistry).

Amnesia reduces the likelihood of any unpleasant memories of the procedure (although benzodiazepines, particularly when used for more profound sedation, can sometimes induce sexual fantasies). Benzodiazepines are also used in intensive care units for sedation, particularly in those receiving assisted ventilation.

Benzodiazepines may occasionally cause marked respiratory depression and facilities for its treatment are essential; flumazenil (section 15.1.7) is used to antagonise the effects of benzodiazepines. They are best avoided in myasthenia gravis, especially peri-operatively.

**Diazepam** is used to produce mild sedation with amnesia. It is a long-acting drug with active metabolites and a second period of drowsiness can occur several hours after its administration. Peri-operative use of diazepam in children is not generally recommended; its effect and timing of response are unreliable and paradoxical effects may occur.

Diazepam is relatively insoluble in water and preparations formulated in organic solvents are painful on intravenous injection and give rise to a high incidence of venous thrombosis (which may not be noticed for several days after the injection). Intramuscular injection of diazepam is painful and absorption is erratic. An emulsion formulated for intravenous injection is less irritant and reduces the risk of venous thrombosis; it is not suitable for intramuscular injection. Diazepam is also available as a rectal solution but this preparation is not used for premedication or sedation.

**Temazepam** is given by mouth and has a shorter duration of action and a more rapid onset than diazepam given by mouth. It has been used as a premedicant in inpatient and day-case surgery; anxiolytic and sedative effects last about 90 minutes although there may be residual drowsiness.

**Lorazepam** produces more prolonged sedation than temazepam and it has marked amnesic effects. It is used as a premedicant the night before major surgery; a further, smaller dose may be required the following morning if any delay in starting surgery is anticipated. Alternatively the first dose may be given early in the morning on the day of operation.

**Midazolam** is a water-soluble benzodiazepine which is often used in preference to intravenous diazepam; recovery is faster than from diazepam. Midazolam is associated with profound sedation when high doses are given intravenously or when used with certain other drugs.

There have been reports of overdosage when high strength midazolam has been used for conscious sedation. The use of high strength midazolam (5 mg/mL in 2 mL and 10 mL ampoules, or 2 mg/mL in 5 mL ampoules) should be restricted to general anaesthesia, intensive care, palliative care, or other situations where the risk has been assessed. It is advised that flumazenil (section 15.1.7) is available where midazolam is used, to reverse the effects if necessary.

**DIAZEPAM**

**Indications** premedication; sedation with amnesia, and in conjunction with local anaesthesia; other indi-
cations (section 4.1.2, section 4.8.2, and section 10.2.2).

**Contraindications** see notes above, section 4.1.2, and section 4.8.2.

**Side-effects** see notes above and section 4.1.2.

**Dose**
- **By mouth,** 5 mg on night before minor or dental surgery then 5 mg 2 hours before procedure; **Elderly** (or debilitated), half adult dose
- **By intravenous injection** into a large vein, sedative cover for minor surgical and medical procedures, **Adult** over 18 years, 10–20 mg over 2–4 minutes, immediately before procedure; premedication 100–200 micrograms/kg, **Child** under 18 years see **BNF for Children**
- **By rectum, Child** 1–18 years, see **BNF for Children**

**LORAZEPAM**

**Indications** sedation with amnesia; premedication; other indications (section 4.1.2 and section 4.8.2).

**Cautions** see notes above and section 4.1.2; **Interactions:** Appendix I (anxiolytics and hypnotics).

**Contra-indications** see notes above and section 4.1.2.

**Side-effects** see notes above and under Diazepam (section 4.1.2).

**Dose**
- **By mouth,** 2–3 mg the night before operation; 2–4 mg 1–2 hours before operation
- **By slow intravenous injection,** preferably diluted with an equal volume of sodium chloride intravenous infusion 0.9% or water for injections, 50 micrograms/kg 30–45 minutes before operation
- **By intramuscular injection,** diluted as above, 50 micrograms/kg 60–90 minutes before operation

**Preparations**

Section 4.1.2

**MIDAZOLAM**

**Indications** sedation with amnesia; sedation in intensive care; premedication, induction of anaesthesia; status epilepticus [unlicensed use], section 4.8.2.

**Cautions** see notes above; cardiac disease; respiratory disease; myasthenia gravis; neonates; children (particularly if cardiovascular impairment); risk of airways obstruction and hypventilation in children under 6 months (monitor respiratory rate and oxygen saturation); history of drug or alcohol abuse; reduce dose in elderly and debilitated; avoid prolonged use (and abrupt withdrawal thereafter); concentration of midazolam in children under 15 kg not to exceed 25 mg/mL; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4) and breast-feeding (Appendix 5); **Interactions:** Appendix I (anxiolytics and hypnotics).

**Contra-indications** marked neuromuscular respiratory weakness including unstable myasthenia gravis; severe respiratory depression; acute pulmonary insufficiency

**Side-effects** see notes above; gastro-intestinal disturbances, increased appetite, jaundice; hypotension, cardiac arrest, heart rate changes, anaphylaxis, thrombosis; laryngospasm, bronchospasm, respiratory depression and respiratory arrest (particularly with high doses or on rapid injection); drowsiness, confusion, ataxia, amnesia, headache; euphoria, hallucinations, convulsions (more common in neonates); dizziness, vertigo, involuntary movements, paradoxical excitement and aggression (especially in children and elderly), dysarthria; urinary retention, incontinence, changes in libido; blood disorders; muscle weakness; visual disturbances; salivation changes; skin reactions; injection-site reactions.

**Dose**
- **Conscious sedation,** by slow intravenous injection (approx. 2 mg/minute) 5–10 minutes before procedure, initially 2–2.5 mg (Elderly 0.5–1 mg), increased if necessary in steps of 1 mg (Elderly 0.5–1 mg); usual total dose 3.5–5 mg (max. 7.5 mg).
- **Elderly** max. 3.5 mg; **Child** by intravenous injection over 2–3 minutes, 6 months–5 years initially 50–100 micrograms/kg, dose increased if necessary in small steps (max. total dose 6 mg), 6–12 years initially 25–50 micrograms/kg, dose increased if necessary in small steps (max. total dose 10 mg)
- **By intramuscular injection,** **Child** 1–15 years 50–150 micrograms/kg; max. 10 mg
- **By rectum, Child** 6 months–18 years, see **BNF for Children**

**Sedative in combined anaesthesia,** by intravenous injection, 30–100 micrograms/kg repeated as required or by continuous intravenous infusion, 30–100 micrograms/kg/hour **(Elderly** lower doses needed); **Child** not recommended.

- **Premedication,** by deep intramuscular injection, 70–100 micrograms/kg **(Elderly** and debilitated) 25–50 micrograms/kg 20–60 minutes before induction; **Child** 1–15 years 80–200 micrograms/kg
- **By intravenous injection,** 1–2 mg repeated as required **(Elderly** and debilitated 0.5 mg, repeat dose slowly as required)
- **By rectum, Child** 6 months–12 years, see **BNF for Children**

**Induction** (but rarely used), by slow intravenous injection, 150–200 micrograms/kg **(Elderly** and debilitated 50–150 micrograms/kg) given in divided doses (max. 5 mg) at intervals of 2 minutes; max. total dose 600 micrograms/kg; **Child** 7–18 years initially 150 micrograms/kg (max. 7.5 mg) given in steps of 50 micrograms/kg (max. 2.5 mg) over 2–5 minutes; wait for 2–5 minutes then give additional doses of 50 micrograms/kg (max. 2.5 mg) every 2 minutes if necessary; max. total dose 500 micrograms/kg (not exceeding 25 mg).

- **Sedation of patients receiving intensive care,** by slow intravenous injection, initially 30–300 micrograms/kg given in steps of 1–2.5 mg every 2 minutes, then by slow intravenous injection or by continuous intravenous infusion, 30–200 micrograms/kg/hour; reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia; lower doses may be adequate if opioid analgesic also used; **Neonate** under 32 weeks gestational age by continuous intravenous infusion, 30 micrograms/kg/hour, **Neonate** over 32 weeks gestational age and **Child** under 6 months 60 micro-
Acemetacin is inadequate for the relief of severe pain. For the relief of postoperative pain, NSAIDs may be useful alternatives (or adjuncts) to the use of opioids. Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastrointestinal motility, and do not cause dependence, they may be preferred to opioid analgesics.

By mouth

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diclofenac</td>
<td>75 mg/5 mL, 2-mL amp = 90p</td>
<td>Hypersensitivity; inflammatory bowel disease; allergic drug reactions including sulphonamide reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, anaphylaxis</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>10 mg/mL, 2-mL amp = £2.50</td>
<td>Vascular bleeding; hypovolaemia or dehydration</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>1 g/kg, then 120 micrograms/kg/hour, adjusted according to response</td>
<td>Dehydration; following coronary artery bypass graft surgery; interactions: Appendix 1 (NSAIDs)</td>
</tr>
</tbody>
</table>

Hypnovel (Roche)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Injection</th>
<th>Dose and side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam</td>
<td>1 mg/mL, net price £12.75</td>
<td>Side-effects: see notes above and under Diazepam (section 4.1.2)</td>
</tr>
</tbody>
</table>

TEMAZEPAM

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temezepam</td>
<td>3 mg/kg/hour, 10 mg/kg/hour</td>
<td>Hypersensitivity; inflammatory bowel disease; allergic drug reactions including sulphonamide reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis, anaphylaxis</td>
</tr>
</tbody>
</table>

Preparations

Section 4.1.1

15.1.4.2 Non-opioid analgesics

Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastrointestinal motility, and do not cause dependence, they may be useful alternatives (or adjuncts) to the use of opioids for the relief of postoperative pain. NSAIDs may be inadequate for the relief of severe pain.

Acemetacin, diclofenac, flurbiprofen, ibuprofen, ketoprofen, (section 10.1.1), paracetamol (section 4.7.1), parecoxib, and ketorolac are licensed for postoperative use. Diclofenac, ketoprofen, ketorolac, and paracetamol can be given by injection as well as by mouth. Intramuscular injections of diclofenac and ketoprofen are given deep into the gluteal muscle to minimise pain and tissue damage; diclofenac can also be given by intravenous infusion for the treatment or prevention of postoperative pain. Ketorolac is less irritant on intramuscular injection but pain has been reported; it can also be given by intravenous injection.

Parecoxib (a selective inhibitor of cyclo-oxygenase-2) can be given by intramuscular or intravenous injection (but see also NSAIDs and Cardiovascular Events, section 10.1.1). The Scottish Medicines Consortium has advised (January 2003) that parecoxib should not be used because there is no evidence of a reduction in postoperative haemorrhagic or gastrointestinal complications compared with non-selective NSAIDs.

KETOROLAC TROMETAMOL

Indications short-term management of moderate to severe acute postoperative pain only

Cautions section 10.1.1; avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (NSAIDs)

Contra-indications section 10.1.1; also complete or partial syndrome of nasal polyps; haemorrhagic diatheses (including coagulation disorders) and following operations with high risk of haemorrhage or incomplete haemostasis; confirmed or suspected cerebral-vascular bleeding; hypovolaemia or dehydration

Side-effects section 10.1.1; also gastro-intestinal disturbances; flushing, bradycardia, palpitation, chest pain; dyspnoea, asthma; malaise, euphoria, psychosis, paraesthesia, convulsions, abnormal dreams, hyperkinesia; urinary frequency, thirst; hypoponataemia, hyperkalaemia, myalgia; visual disturbances (including optic neuritis); pallor, purpura, pain at injection site

Dose

- **ADULT** and **CHILD** over 16 years, by mouth, 10 mg every 4–6 hours **ELDERLY** every 6–8 hours as required; max. 40 mg daily; max. duration of treatment 7 days
- **ADULT** and **CHILD** over 16 years, by intramuscular injection or by intravenous injection over at least 15 seconds, initially 10 mg, then 10–30 mg every 4–6 hours as required (up to every 2 hours during initial postoperative period); max. 90 mg daily **ELDERLY** and patients weighing less than 50 kg max. 60 mg daily; max. duration of treatment 2 days

**Note** When converting from parenteral to oral administration, total combined dose on the day of converting should not exceed 40 mg (60 mg in the elderly and patients weighing less than 50 kg) of which the oral component should not exceed 40 mg

Toradol (Roche)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Tablets</th>
<th>Injection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketorolac</td>
<td>17, 21 tablets, 10 mg, net price £5.79</td>
<td>Ketorolac trometamol 10 mg/mL, net price £1.14</td>
</tr>
</tbody>
</table>

PARECOXIB

Indications short-term management of acute postoperative pain

Cautions section 10.1.1; dehydration; following coronary artery bypass graft surgery; interactions: Appendix 1 (NSAIDs)

Contra-indications section 10.1.1; also history of allergic drug reactions including sulphonamide hypersensitivity; inflammatory bowel disease

Side-effects section 10.1.1; also flatulence; hyper-tension, hypotension, peripheral oedema; pharyngitis, respiratory insufficiency; hypoaesthesia; alveolar ostitis; oliguria; postoperative anaemia, hypokalaemia; respiratory pain; pruritus; less commonly bradycardia, cardiovascular events, increased blood urea nitrogen, ecchymosis, thrombocytopenia, rarely vomiting, tachycardia, rash (discontinue—risk of serious reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis), anaphylaxis
**Dose**
- By deep intramuscular injection or by intravenous injection, initially 40 mg, then 20–40 mg every 6–12 hours when required; max. 80 mg daily; EDERLY weighing less than 50 kg, initially 20 mg, then max. 40 mg daily; CHILD and ADOLESCENT under 18 years, not recommended.

**Dynastat** (Pharmacia) ▪ Pharmacodynamic
Injection, powder for reconstitution, parecoxib (as sodium salt), net price 40-mg vial = £4.96, 40-mg vial (with solvent) = £5.67.

**15.1.4.3 Opioid analgesics**

Opioid analgesics are now rarely used as premedicants; they are more likely to be administered at induction. Pre-operative use of opioid analgesics is generally limited to those patients who require control of existing pain. The main side-effects of opioid analgesics are respiratory depression, cardiovascular depression, nausea, and vomiting; for general notes on opioid analgesics and their use in postoperative pain, see section 4.7.2.

For the management of opioid-induced respiratory depression, see section 15.1.7.

**Intra-operative analgesia** Opioid analgesics given in small doses before or with induction reduce the dose requirement of some drugs used during anaesthesia.

**Alfentanil, fentanyl, and remifentanil** are particularly useful because they act within 1–2 minutes and have short durations of action. The initial doses of alfentanil or fentanyl are followed either by successive intravenous injections or by an intravenous infusion; prolonged infusions increase the duration of effect. Repeated intra-operative doses of alfentanil or fentanyl should be given with care since the resulting respiratory depression can persist postoperatively and occasionally it may become apparent for the first time postoperatively in patients receiving intensive care, with assisted ventilation, for up to 4 days when required. By intravenous injection, initially 40 mg, then 20–40 mg every 6–12 hours when required; max. 80 mg daily; EDERLY weighing less than 50 kg, initially 20 mg, then max. 40 mg daily; CHILD and ADOLESCENT under 18 years, not recommended.

**Dynastat** (Pharmacia) ▪ Pharmacodynamic
Injection, powder for reconstitution, parecoxib (as sodium salt), net price 40-mg vial = £4.96, 40-mg vial (with solvent) = £5.67.

**RAPifen** (Janssen-Cilag) ▪ Pharmacodynamic
Injection, alfentanil (as hydrochloride) 500 micrograms/mL, net price 2-mL amp = £67 p; 10-mL amp = £3.08

**Intensive care injection, alfentanil (as hydrochloride)** 5 mg/mL. To be diluted before use. Net price 1-mL amp = £2.46.

**FENTANYL**

**Indications** analgesia during operation, enhancement of anaesthesia; respiratory depressant in assisted respiration; analgesia in other situations (section 4.7.2)

**Cautions** section 4.7.2 and notes above

**Contra-indications** section 4.7.2

**Side-effects** section 4.7.2 and notes above; also myoclonic movements; less commonly laryngospasm; rarely asystole, insomnia

**Dose**

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

- By slow intravenous injection, with spontaneous respiration, ADULT over 12 years, initially 50–100 micrograms (max. 200 micrograms on specialist advice), then 50 micrograms as required; CHILD 2–12 years, initially 2–3 micrograms/kg, then 1 microgram/kg as required.

- With assisted ventilation, ADULT and CHILD over 12 years, initially 0.3–3.5 mg, then 100–200 micrograms as required; CHILD 2–12 years, initially 2–3 micrograms/kg, then 1 microgram/kg as required.

- By intravenous infusion, with spontaneous respiration, ADULT, 50–80 nanograms/kg/minute adjusted according to response.

- With assisted ventilation, ADULT, initially 10 micrograms/kg over 10 minutes then 100 nanograms/kg/minute adjusted according to response; may require

**ALFENTANIL**

**Indications** analgesia especially during short operative procedure and outpatient surgery; enhancement of anaesthesia; analgesia and suppression of respiratory activity in patients receiving intensive care, with assisted ventilation, for up to 4 days.

**Cautions** section 4.7.2 and notes above

**Contra-indications** section 4.7.2

**Side-effects** section 4.7.2 and notes above; also hypotension, myoclonic movements; less commonly arrhythmias, cough, hiccup, laryngospasm, visual disturbances

**Dose**

To avoid excessive dosage in obese patients, dose may need to be calculated on the basis of ideal body-weight.

- By intravenous injection, spontaneous respiration, ADULT, initially up to 500 micrograms over 30 seconds; supplemental, 250 micrograms.

- With assisted ventilation, ADULT over 18 years, initially 30–50 micrograms/kg; supplemental, 15 micrograms/kg; CHILD 1 month–18 years, initially 10–20 micrograms/kg; supplemental doses up to 10 micrograms/kg.

- By intravenous infusion, with assisted ventilation, ADULT and CHILD, initially 50–100 micrograms/kg over 10 minutes or as a bolus, followed by maintenance of 0.5–1 micrograms/kg/minute.

- Analgesia and suppression of respiratory activity during intensive care, with assisted ventilation, by intravenous infusion, initially 2 mg/hour subsequently adjusted according to response (usual range 0.5–10 mg/hour); more rapid initial control may be obtained with an intravenous dose of 5 mg given in divided portions over 10 minutes (slowing if hypotension or bradycardia occur); additional doses of 0.5–1 mg may be given by intravenous injection during short painful procedures.
15.1.5 Neuromuscular blocking drugs

Neuromuscular blocking drugs used in anaesthesia are also known as muscle relaxants. By specific blockade of the neuromuscular junction they enable light anaesthesia to be used with adequate relaxation of the muscles of the abdomen and diaphragm. They also relax the vocal cords and allow the passage of a tracheal tube. Their action differs from the muscle relaxants used in musculoskeletal disorders (section 10.2.2) that act on the spinal cord or brain.

Patients who have received a neuromuscular blocking drug should always have their respiration assisted or controlled until the drug has been inactivated or antagonised (section 15.1.6). They should also receive sufficient concomitant inhalational or intravenous anaesthetic or sedative drugs to prevent awareness.

Non-depolarising neuromuscular blocking drugs

Non-depolarising neuromuscular blocking drugs (also known as competitive muscle relaxants) compete with acetylcholine for receptor sites at the neuromuscular junction and their action can be reversed with anticholinesterases such as neostigmine (section 15.1.6). Non-depolarising neuromuscular blocking drugs can be divided into the aminosteroid group, comprising pancuronium, rocuronium, and vecuronium, and the benzylisoquinolinium group, comprising atracurium, cisatracurium, and mivacurium.

Non-depolarising neuromuscular blocking drugs have a slower onset of action than suxamethonium. These drugs can be classified by their duration of action as short-acting (15–30 minutes), intermediate-acting (30–40 minutes), and long-acting (60–120 minutes), although duration of action is dose-dependent. Drugs with a shorter or intermediate duration of action, such as atracurium and vecuronium, are more widely used than those with a longer duration of action, such as pancuronium.

Non-depolarising neuromuscular blocking drugs have no sedative or analgesic effects and are not considered to trigger malignant hyperthermia.

For patients receiving intensive care and who require tracheal intubation and mechanical ventilation, a non-depolarising neuromuscular blocking drug is chosen according to its onset of effect, duration of action, and infusion rate of at least 100 nanograms/kg/minute for at least 5 minutes before procedure and adjust every 2–5 minutes according to requirements, usual range 250–750 nanograms/kg/minute.

- Cardiac surgery, consult product literature

**Note** Remifentanil doses in BNF may differ from those in product literature

Ultiva® (GSK)  
**Injection**, powder for reconstitution, remifentanil (as hydrochloride), net price 1-mg vial = £5.12; 2-mg vial = £10.23; 5-mg vial = £25.58

## REMIFENTANIL

**Indications** supplementation of general anaesthesia during induction and analgesia during maintenance of anaesthesia (consult product literature for use in patients undergoing cardiac surgery); analgesia and sedation in ventilated, intensive care patients

**Contra-indications** section 4.7.2 (but no dose adjustment necessary in renal impairment) and notes above

**Side-effects** section 4.7.2 and notes above; left ventricular dysfunction

**Dose**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- Induction of anaesthesia, **ADULT** and **CHILD** over 12 years, by intravenous infusion, 0.5–1 micrograms/kg/minute, **with or without** an initial dose by intravenous injection of 0.25–1 microgram/kg over at least 30 seconds

  **Note** If patient to be intubated more than 8 minutes after start of intravenous infusion, initial intravenous injection dose is not necessary

- Maintenance of anaesthesia in ventilated patients, **ADULT** and **CHILD** over 12 years, by intravenous infusion, 0.05–2 micrograms/kg/minute **with or without** an initial dose by intravenous injection of 0.25–1 micrograms/kg over at least 30 seconds according to anaesthetic technique and adjusted according to response; in light anaesthesia supplemental doses by intravenous injection every 2–5 minutes

- Maintenance of anaesthesia with spontaneous respiration, **ADULT** and **CHILD** over 12 years, by intravenous infusion, initially 40 nanograms/kg/minute adjusted according to response, usual range 25–100 nanograms/kg/minute

- Maintenance of anaesthesia, **CHILD** 1–12 years, by intravenous infusion, 0.05–1.3 micrograms/kg/minute **with or without** an initial dose by intravenous injection of 0.1–1 microgram/kg over at least 30 seconds according to anaesthetic technique and adjusted according to response

- Analgesia and sedation in ventilated, intensive-care patients, by intravenous infusion, **ADULT** over 18 years, initially 100–150 nanograms/kg/minute adjusted according to response in steps of 25 nanograms/kg/minute (allow at least 5 minutes between dose adjustments); usual range 6–740 nanograms/kg/minute; if an infusion rate of 200 nanograms/kg/minute does not produce adequate sedation add another sedative (consult product literature for details)

- Additional analgesia during stimulating or painful procedures in ventilated, intensive-care patients, by intravenous infusion, **ADULT** over 18 years, maintain

**Fentanyl** (Non-proprietary)  
**Injection**, fentanyl (as citrate) 50 micrograms/mL, net price 2-mL amp = 54p, 10-mL amp = £1.11

**Sublimaze®** (Janssen-Cilag)  
**Injection**, fentanyl (as citrate) 50 micrograms/mL, net price 2-mL amp = 22p, 10-mL amp = £1.11

**BNF 57 15 Anaesthesia**
side-effects. Rocuronium, with a rapid onset of effect, may facilitate intubation. Atracurium or cisatracurium may be suitable for long-term neuromuscular blockade since their duration of action is not dependent on elimination by the liver or the kidneys.

**Cautions** Allergic cross-reactivity between neuromuscular blocking drugs has been reported; caution is advised in cases of hypersensitivity to these drugs. Their activity is prolonged in patients with myasthenia gravis and in hypothermia, and lower doses are required. Non-depolarising neuromuscular blocking drugs should be used with great care in those with other neuromuscular disorders and those with fluid and electrolyte disturbances, as response is unpredictable. Resistance can develop in patients with burns, who may require increased doses; low plasma cholinesterase activity in these patients requires dose titration for mivacurium.

**Interactions:** Appendix 1 (muscle relaxants).

**Side-effects** Benzylisoquinolinium non-depolarising neuromuscular blocking drugs (except cisatracurium) are associated with histamine release, which can cause skin flushing, hypotension, tachycardia, bronchospasm, and very rarely anaphylactoid reactions. Most aminosteroid neuromuscular blocking drugs produce minimal histamine release. Drugs with vagolytic activity can counteract any bradycardia that occurs during surgery. Acute myopathy has also been reported after prolonged use in intensive care.

Atracurium, a mixture of 10 isomers, is a benzylisoquinolinium neuromuscular blocking drug with an intermediate duration of action. It undergoes non-enzymatic metabolism which is independent of liver and kidney function, thus allowing its use in patients with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release.

Cisatracurium is a single isomer of atracurium. It is more potent and has a slightly longer duration of action than atracurium and provides greater cardiovascular stability because cisatracurium lacks histamine-releasing effects.

Mivacurium, a benzylisoquinolinium neuromuscular blocking drug, has a short duration of action. It is metabolised by plasma cholinesterase and muscle paralysis is prolonged in individuals deficient in this enzyme. It is not associated with vagolytic activity or ganglionic blockade although histamine release can occur, particularly with rapid injection.

Pancuronium, an aminosteroid neuromuscular blocking drug, has a long duration of action and is often used in patients receiving long-term mechanical ventilation in intensive care units. It lacks a histamine-releasing effect, but vagolytic and sympathomimetic effects can cause tachycardia and hypertension.

Rocuronium exerts an effect within 2 minutes and has the most rapid onset of any of the non-depolarising neuromuscular blocking drugs. It is an aminosteroid neuromuscular blocking drug with an intermediate duration of action. It is reported to have minimal cardiovascular effects; high doses produce mild vagolytic activity.

Vecuronium, an aminosteroid neuromuscular blocking drug, has an intermediate duration of action. It does not generally produce histamine release and lacks cardiovascular effects.

### atracurium besylate

**Indications** neuromuscular blockade (short to intermediate duration) for surgery or during intensive care

**Cautions** see notes above; pregnancy (Appendix 4); breast-feeding (Appendix 5)

**Side-effects** see notes above; seizures also reported

**Dose**

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- Surgery or intubation, ADULT and CHILD over 1 month, by intravenous injection, initially 300–600 micrograms/kg; maintenance, by intravenous injection, 100–200 micrograms/kg as required or by intravenous infusion, 5–10 micrograms/kg/minute (300–600 micrograms/kg/hour)

- Intensive care, ADULT and CHILD over 1 month, by intravenous injection, initially 300–600 micrograms/kg (optional) then by intravenous infusion 4.5–29.5 micrograms/kg/minute (usual dose 11–13 micrograms/kg/minute)

**Atracurium** (Non-proprietary)

**Injection** atracurium besilate 10 mg/mL, net price 2.5-mL amp = £1.85; 5-mL amp = £3.37; 25-mL amp = £14.45

**Tracrium** (GSK)

**Injection** atracurium besilate 10 mg/mL, net price 2.5-mL amp = £1.86; 5-mL amp = £3.00; 25-mL amp = £12.91

### cisatracurium

**Indications** neuromuscular blockade (intermediate duration) for surgery or during intensive care

**Cautions** see notes above; pregnancy (Appendix 4); breast-feeding

**Side-effects** see notes above

**Dose**

- To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- Intubation, by intravenous injection, ADULT and CHILD over 1 month, initially 150 micrograms/kg; maintenance, by intravenous injection, 30 micrograms/kg approx. every 20 minutes; CHILD 2–12 years, 20 micrograms/kg approx. every 9 minutes; or maintenance, by intravenous infusion, ADULT and CHILD over 2 years, initially, 3 micrograms/kg/minute, then after stabilisation, 1–2 micrograms/kg/minute; dose reduced by up to 40% if used with isoflurane

- Intensive care, by intravenous infusion, ADULT 0.5–10.2 micrograms/kg/minute (usual dose 3 micrograms/kg/minute)

**Note** Lower doses can be used for children over 2 years when not for intubation

**Nimbex** (GSK)

**Injection** cisatracurium (as besilate) 2 mg/mL, net price 10-mL amp = £7.55, 50-mL amp = £36.5

**Forte injection** cisatracurium (as besilate) 5 mg/mL, net price 30-mL vial = £31.09
**MIVACURIAM**

**Indications** neuromuscular blockade (short duration) for surgery

**Cautions** see notes above; low plasma cholinesterase activity; elderly; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4)

**Side-effects** see notes above

**Dose**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- By intravenous injection, 70–250 micrograms/kg; maintenance 100 micrograms/kg every 15 minutes; CHILD 2–6 months initially 150 micrograms/kg, 7 months–12 years initially 200 micrograms/kg; maintenance (CHILD 2 months–12 years) 100 micrograms/kg every 6–9 minutes

**Note** Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In patients with asthma, cardiovascular disease or those who are sensitive to falls in arterial blood pressure give over 60 seconds

- By intravenous infusion, maintenance of block, 8–10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose of 6–7 micrograms/kg/minute; CHILD 2 months–12 years, usual dose 11–14 micrograms/kg/minute

**Mivacurium** (GSK) (UK)

Injection, mivacurium (as chloride) 2 mg/mL, net price 5-mL amp = £2.79; 10-mL amp = £4.51

**PANCURONIUM BROMIDE**

**Indications** neuromuscular blockade (long duration) for surgery or during intensive care

**Cautions** see notes above; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4) and breast-feeding (Appendix 5)

**Side-effects** see notes above

**Dose**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- Intubation, **ADULT** and **CHILD** over 1 month, by intravenous injection, initially 600 micrograms/kg; maintenance by intravenous injection, 150 micrograms/kg (ELDERLY 75–100 micrograms/kg) or maintenance by intravenous infusion, 300–600 micrograms/kg/hour (ELDERLY up to 400 micrograms/kg/hour) adjusted according to response

- Intensive care, by intravenous injection, **ADULT** initially 600 micrograms/kg; maintenance by intravenous infusion, 300–600 micrograms/kg/hour for first hour, then adjusted according to response

**Esmeron** (Organon) (UK)

Injection, rocuronium bromide 10 mg/mL, net price 5-mL vial = £3.01, 10-mL vial = £6.01

**VECURONIUM BROMIDE**

**Indications** neuromuscular blockade (intermediate duration) for surgery

**Cautions** see notes above; pregnancy (Appendix 4)

**Side-effects** see notes above

**Dose**

To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- By intravenous injection, intubation, **ADULT** and **CHILD** over 5 months, 80–100 micrograms/kg (CHILD under 1 year, onset more rapid and high intubation dose may not be required); maintenance 20–30 micrograms/kg adjusted according to response; **NEONATE** and **CHILD** up to 4 months, initial test dose 10–20 micrograms/kg then incremental doses to achieve response

- By intravenous infusion, 0.8–1.4 micrograms/kg/minute (after initial intravenous injection of 40–100 micrograms/kg)

**Norcuron** (Organon) (UK)

Injection, powder for reconstitution, vecuronium bromide, net price 10-mg vial = £3.95 (with water for injections)

**Depolarising neuromuscular blocking drugs**

Suxamethonium has the most rapid onset of action of any of the neuromuscular blocking drugs and is ideal if fast onset and brief duration of action are required e.g. with tracheal intubation. Its duration of action is about 2 to 6 minutes after intravenous doses of about 1 mg/kg; repeated doses can be used for longer procedures.

Suxamethonium acts by mimicking acetylcholine at the neuromuscular junction but hydrolysis is much slower than for acetylcholine; depolarisation is therefore prolonged, resulting in neuromuscular blockade. Unlike the non-depolarising neuromuscular blocking drugs, its action cannot be reversed and recovery is spontaneous; anticholinesterases such as neostigmine potentiate the neuromuscular block.

Suxamethonium should be given after anaesthetic induction because paralysis is usually preceded by pain.
ful muscle fasciculations. While tachycardia occurs with single use, bradycardia may occur with repeated doses in adults and with the first dose in children. Premedication with atropine reduces bradycardia as well as the excessive salivation associated with suxamethonium use.

Prolonged paralysis may occur in dual block, which occurs with high or repeated doses of suxamethonium and is caused by the development of a non-depolarising block following the initial depolarising block; edrophonium (section 15.1.6) may be used to confirm the diagnosis of dual block. Individuals with myasthenia gravis are resistant to suxamethonium but can develop dual block resulting in delayed recovery. Prolonged paralysis may also occur in those with low or atypical plasma cholinesterase. Assisted ventilation should be continued until muscle function is restored.

SUXAMETHONIUM CHLORIDE (Succinylcholine chloride)

**Indications** neumorscular blockade (rapid onset, short duration)

**Cautions** see notes above; hypersensitivity to other neuromuscular blocking drugs; patients with cardiac, respiratory or neuromuscular disease; raised intraocular pressure (avoid in penetrating eye injury); severe sepsis (risk of hyperkalaemia); pregnancy (Appendix 4); **Interactions**: Appendix 1 (muscle relaxants)

**Contra-indications** family history of malignant hyperthermia, hyperkalaemia; major trauma, severe burns, neurological disease involving acute wasting of major muscle, prolonged immobility—risk of hyperkalaemia, personal or family history of congenital myotonic disease, Duchenne muscular dystrophy, low plasma-cholinesterase activity (including severe liver disease) (Appendix 2)

**Side-effects** see notes above; also increased gastric pressure; hyperkalaemia; postoperative muscle pain, myoglobinuria, myoglobinemia; increased intraocular pressure; flushing, rash; rarely arrhythmias, cardiac arrest; bronchospasm, apnoea, prolonged respiratory depression; limited jaw mobility; very rarely anaphylactic reactions, malignant hyperthermia; also reported hypertension, hypotension, rhabdomyolysis

**Dose**
- By intravenous injection, initially 1 mg/kg; maintenance, usually 0.5–1 mg/kg at 5–10 minute intervals; max. 500 mg/hour; **NEONATE** and **INFANT** under 1 year, 2 mg/kg; **CHILD** over 1 year, 1 mg/kg
- By intravenous infusion of a solution containing 1–2 mg/mL (0.1–0.2%), 2.5–4 mg/minute; max. 500 mg/hour; **CHILD** reduce infusion rate according to body-weight
- By intramuscular injection, **INFANT** under 1 year, up to 4–5 mg/kg; **CHILD** over 1 year, up to 4 mg/kg; max. 150 mg

**Suxamethonium Chloride (Non-proprietary) [75]**

**Injection**, suxamethonium chloride 50 mg/mL, net price 2-mL amp = 64p, 2-mL prefilled syringe = £7.35

**Anectine® (GSK) [75]**

**Injection**, suxamethonium chloride 50 mg/mL, net price 2-mL amp = 71p

---

**15.1.6 Drugs for reversal of neuromuscular blockade**

**Anticholinesterases**

Anticholinesterases reverse the effects of the non-depolarising (competitive) neuromuscular blocking drugs such as pancuronium but they prolong the action of the depolarising neuromuscular blocking drug suxamethonium.

**Edrophonium** has a transient action and may be used in the diagnosis of suspected dual block due to suxamethonium. Atropine (section 15.1.3) is given before or with edrophonium to prevent muscarinic effects when given for reversal of non-depolarising neuromuscular blockade.

**Neostigmine** has a longer duration of action than edrophonium and is used specifically for reversal of non-depolarising (competitive) blockade. It acts within one minute of intravenous injection and its effects last for 20 to 30 minutes; a second dose may then be necessary. Glycopyrronium or alternatively atropine (section 15.1.3), given before or with neostigmine, prevent bradycardia, excessive salivation, and other muscarinic effects of neostigmine.

**EDROPONIUM CHLORIDE**

**Indications** see under Dose; myasthenia gravis (section 10.2.1)

**Cautions** section 10.2.1; atropine should also be given

**Contra-indications** section 10.2.1

**Side-effects** section 10.2.1

**Dose**
- Brief reversal of non-depolarising neuromuscular blockade, by intravenous injection over several minutes, 500–700 micrograms/kg (after or with atropine)
- Diagnosis of dual block, by intravenous injection, 10 mg

**Edrophonium** (Cambridge) [94]

**Injection**, edrophonium chloride 10 mg/mL, net price 1-mL amp = £8.35

**NEOSTIGMINE METILSULFATE** (Neostigmine methylsulphate)

**Indications** see under Dose

**Cautions** section 10.2.1 and notes above; glycopyrronium or atropine should also be given

**Contra-indications** section 10.2.1 and notes above

**Side-effects** section 10.2.1 and notes above

**Dose**
- Reversal of non-depolarising neuromuscular blockade, by intravenous injection over 1 minute, 50–70 micrograms/kg (max. 5 mg) after or with glycopyrronium or atropine
- Myasthenia gravis, see section 10.2.1

**Neostigmine** (Non-proprietary) [94]

**Injection**, neostigmine metilsulfate 2.5 mg/mL, net price 1-mL amp = 58p
With glycopyrronium

Robinitul-Neostigmine (Anpharm) \(^{(a)}\) Injection, neostigmine metilsulfate 2.5 mg, glycopyrronium bromide 500 micrograms/mL, net price 1-ml amp = £15.15

Dose reversal of non-depolarising neuromuscular blockade by intravenous injection over 10–30 seconds; 1–2 mL or 0.02 mL/kg, dose may be repeated if required (total max. 2 mL); CHILD 0.02 mL/kg (or 0.2 mL/kg of a 1 in 10 dilution using water for injections or sodium chloride injection 0.9%), dose may be repeated if required (total max. 2 mL).

Note May be difficult to obtain

Other drugs for reversal of neuromuscular blockade

Sugammadex is a modified gamma cyclodextrin used for reversal of neuromuscular blockade induced by rocuronium or vecuronium (section 15.1.5).

SUGAMMADEX

Indications reversal of neuromuscular blockade induced by rocuronium or vecuronium

Cautions recurrence of neuromuscular blockade—monitor respiratory function until fully recovered; recovery may be delayed in cardiovascular disease and elderly; wait 24 hours before re-administering rocuronium or vecuronium; renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (sugammadex)

Side-effects taste disturbances; less commonly allergic reactions; bronchospasm also reported

Dose To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body-weight

- Routine reversal of neuromuscular blockade induced by rocuronium or vecuronium, by intravenous injection, ADULT over 18 years, 2–4 mg/kg (consult product literature); a further dose of 4 mg/kg may be required if recurrence of neuromuscular blockade occurs
- Routine reversal of neuromuscular blockade induced by rocuronium, by intravenous injection, CHILD 2–18 years, 2 mg/kg (consult product literature)
- Immediate reversal of neuromuscular blockade induced by rocuronium, by intravenous injection, ADULT over 18 years, 16 mg/kg (consult product literature)

Bridion (Schering-Plough) \(^{(a)}\) Injection, sugammadex (as sodium salt) 100 mg/mL, net price 2-mL amp = £59.64, 5-mL amp = £149.10

Electrolytes Na 0.42 mmol/mL

15.1.7 Antagonists for central and respiratory depression

Respiratory depression is a major concern with opioid analgesics and it may be treated by artificial ventilation or be reversed by naloxone. Naloxone will immediately reverse opioid-induced respiratory depression but the dose may have to be repeated because of the short duration of action of naloxone; however, naloxone will also antagonise the analgesic effect.

Flumazenil is a benzodiazepine antagonist for the reversal of the central sedative effects of benzodiazepines after anaesthetic and similar procedures. Flumazenil has a shorter half-life and duration of action than diazepam or midazolam so patients may become reseedated.

Doxapram (section 3.5.1) is a central and respiratory stimulant but is of limited value in anaesthesia.

FLUMAZENIL

Indications reversal of sedative effects of benzodiazepines in anaesthetic, intensive care, and diagnostic procedures

Cautions short-acting (repeat doses may be necessary)—benzodiazepine effects may persist for at least 24 hours; benzodiazepine dependence (may precipitate withdrawal symptoms); prolonged benzodiazepine therapy for epilepsy (risk of convulsions); history of panic disorders (risk of recurrence); ensure neuromuscular blockade cleared before giving; avoid rapid injection in high-risk or anxious patients and following major surgery; head injury (rapid reversal of benzodiazepine sedation may cause convulsions); elderly; children; hepatic impairment (Appendix 2); pregnancy (Appendix 4); breast-feeding

Contra-indications life-threatening condition (e.g. raised intracranial pressure, status epilepticus) controlled by benzodiazepines

Side-effects nausea, vomiting, and flushing; if waking too rapid, agitation, anxiety, and fear; transient increase in blood pressure and heart-rate in intensive care patients; very rarely convulsions (particularly in those with epilepsy), hypersensitivity reactions including anaphylaxis

Dose

- By intravenous injection, 200 micrograms over 15 seconds, then 100 micrograms at 60-second intervals if required; usual dose range, 300–600 micrograms; max. total dose 1 mg (2 mg in intensive care); question aetiology if no response to repeated doses
- By intravenous infusion, if drowsiness recurs after injection, 100–400 micrograms/hour, adjusted according to level of arousal

Flumazenil (Non-proprietary) \(^{(a)}\) Injection, flumazenil 100 micrograms/mL, net price 5-mL amp = £14.49

Anexate (Roche) \(^{(a)}\) Injection, flumazenil 100 micrograms/mL, net price 5-mL amp = £14.49

NALOXONE HYDROCHLORIDE

Indications reversal of opioid-induced respiratory depression; reversal of neonatal respiratory depression resulting from opioid administration to mother during labour; overdosage with opioids (see Emergency Treatment of Poisoning)

Cautions cardiovascular disease or those receiving cardioactive drugs (serious adverse cardiovascular effects reported); physical dependence on opioids (precipitates withdrawal); pain (see also under Titration of Dose, below); has short duration of action
15.1.8 Drugs for malignant hyperthermia

Malignant hyperthermia is a rare but potentially lethal complication of anaesthesia. It is characterised by a rapid rise in temperature, increased muscle rigidity, tachycardia, and acidosis. The most common triggers of malignant hyperthermia are volatile anaesthetics. Suxamethonium has also been implicated, but malignant hyperthermia is more likely if it is given following a volatile anaesthetic. Volatile anaesthetics and suxamethonium should be avoided during anaesthesia in patients at high risk of malignant hyperthermia.

Dantrolene is used in the treatment of malignant hyperthermia. It acts on skeletal muscle cells by interfering with calcium efflux, thereby stopping the contractile process.

**DANTROLENE SODIUM**

**Indications** malignant hyperthermia; chronic severe spasticity of voluntary muscle (section 10.2.2)

**Cautions** avoid extravasation (risk of tissue necrosis); pregnancy (Appendix 4); breast-feeding (Appendix 5); interactions: Appendix 1 (muscle relaxants)

**Side-effects** hepatotoxicity, pulmonary oedema, dizziness, weakness, and injection-site reactions including erythema, rash, swelling, and thrombophlebitis

**Dose**
- By rapid intravenous injection, 1 mg/kg, repeated as required to a cumulative max. of 10 mg/kg

**Dantrolene Intravenous** (Procter & Gamble Pharm.)

**Injection**, powder for reconstitution, dantrolene sodium, net price 20-mg vial = £15.08 (hosp. only)

15.2 Local anaesthesia

The use of local anaesthetics by injection or by application to mucous membranes to produce local analgesia is discussed in this section.

See also section 1.7 (anus), section 11.7 (eye), section 12.3 (oropharynx), and section 13.3 (skin).

**Use of local anaesthetics** Local anaesthetic drugs act by causing a reversible block to conduction along nerve fibres. The drugs used vary widely in their potency, toxicity, duration of action, stability, solubility in water, and ability to penetrate mucous membranes. These variations determine their suitability for use by various routes, e.g. topical (surface), infiltration, peripheral nerve block, intravenous regional anaesthesia (Bier’s block), plexus, epidural (extradural) or spinal block. Local anaesthetics may also be used for postoperative pain relief, thereby reducing the need for analgesics such as opioids.

**Administration** In estimating the safe dosage of these drugs it is important to take account of the rate at which they are absorbed and excreted as well as their potency. The patient’s age, weight, physique, and clinical condition, the degree of vascularity of the area to which the drug is to be applied, and the duration of administration are other factors which must be taken into account.

Local anaesthetics do not rely on the circulation to transport them to their sites of action, but uptake into the systemic circulation is important in terminating their action and producing toxicity. Following most regional anaesthetic procedures, maximum arterial plasma concentrations of anaesthetic develop within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection. Great care must be taken to avoid accidental intravascular injection. Local anaesthesia around the oral cavity may impair swallowing and therefore increase the risk of aspiration.

Epidural anaesthesia is commonly used during surgery, often combined with general anaesthesia, because of its protective effect against the stress response of surgery. It is often used when good postoperative pain relief is essential (e.g. major thoracic or intra-abdominal surgery).

**Toxicity** Toxic effects associated with local anaesthetics usually result from excessively high plasma concentrations; single application of topical lidocaine preparations does not generally cause systemic side-effects. Effects initially include a feeling of inebriation and lightheadedness followed by sedation, circumsoral paraesthesia and twitching; convulsions can occur in severe reactions. On intravenous injection convulsions and cardiovascular collapse may occur very rapidly. Hypersensitivity reactions occur mainly with the exter-
type local anaesthetics such as benzocaine, cocaine, procaine, and tetracaine (amethocaine); reactions are less frequent with the amide types such as lidocaine (lignocaine), bupivacaine, levobupivacaine, prilocaine, and ropivacaine. Local anaesthetics may be associated with methaemoglobinaemia; prilocaine and benzocaine have been implicated.

When prolonged analgesia is required, a long-acting local anaesthetic is preferred to minimise the likelihood of cumulative systemic toxicity. Local anaesthetic injections should be given slowly in order to detect inadvertent intravascular administration. Local anaesthetics should not be injected into inflamed or infected tissues nor should they be applied to the traumatised urethra. In such cases absorption into the blood may increase the possibility of systemic side-effects. The local anaesthetic effect may also be reduced by the altered local pH. Local anaesthetics can also be otoxic and should not be applied to the middle ear.

Use of vasoconstrictors Most local anaesthetics, with the exception of cocaine, cause dilation of blood vessels. The addition of a vasoconstrictor such as adrenaline (epinephrine) diminishes local blood flow, slows the rate of absorption of the local anaesthetic, and prolongs its local effect. Adrenaline must be used in a low concentration (e.g. 1 in 200 000) for this purpose and it should not be given with a local anaesthetic injection in digits and appendages; it may produce ischaemic necrosis.

When adrenaline is included the final concentration should be 1 in 200 000 (5 micrograms/mL), but see also Dental Anaesthesia below.

The total dose of adrenaline should not exceed 500 micrograms and it is essential not to exceed a concentration of 1 in 200 000 (5 micrograms/mL) if more than 50 mL of the mixture is to be injected. Care must also be taken to calculate a safe maximum dose of local anaesthetic when using combination products. For general cautions associated with the use of adrenaline, see section 2.7.3. For drug interactions, see Appendix 1 (sympathomimetics).

Dental anaesthesia Lidocaine (lignocaine) is widely used in dental procedures; it is most often used in combination with adrenaline (epinephrine). Lidocaine 2% combined with adrenaline 1 in 80 000 (12.5 micrograms/mL) is a safe and effective preparation; there is no justification for using higher concentrations of adrenaline.

The local anaesthetics articaine (carticaine) and mepivacaine are also used in dentistry; they are available in cartridges suitable for dental use. Mepivacaine is available with or without adrenaline (as Scandonest®) and articaine is available with adrenaline (as Septanest®).

In patients with severe hypertension or unstable cardiac rhythm, the use of adrenaline in a local anaesthetic may be hazardous. For these patients prilocaine with or without felypressin can be used but there is no evidence that it is any safer. Felypressin can cause coronary vasoconstriction when used at high doses; limit dose in patients with coronary artery disease.

Great care should be taken to avoid inadvertent intravenous administration of a preparation containing adrenaline.

---

**Lidocaine**

Lidocaine (lignocaine) is effectively absorbed from mucous membranes and is a useful surface anaesthetic in concentrations up to 10%. Except for surface anaesthesia and dental anaesthesia, solutions should not usually exceed 1% in strength. The duration of the block (with adrenaline) is about 90 minutes.

---

**LIDOCAINE HYDROCHLORIDE**

(Lignocaine hydrochloride)

**Indications** see under Dose; also dental anaesthesia (see p. 704); ventricular arrhythmias (section 2.3.2)

**Cautions** see notes above; see section 2.3.2 for effects on heart; epilepsy, respiratory impairment, impaired cardiac conduction, bradycardia, severe shock; acute porphyria (section 9.8.2); myasthenia gravis; reduce dose in elderly or debilitated; resuscitative equipment should be available; hepatic impairment (Appendix 2); renal impairment (Appendix 3); pregnancy (Appendix 4); interactions: Appendix 1 (lidocaine)

**Contra-indications** see notes above; hypovolaemia, complete heart block; do not use solutions containing adrenaline for anaesthesia in appendages

**Side-effects** see notes above and section 2.3.2; also CNS effects include confusion, respiratory depression and convulsions; hypotension and bradycardia (may lead to cardiac arrest); rarely hypersensitivity reported

**Dose**

- Infiltration anaesthesia, by injection, according to patient’s weight and nature of procedure, max. 200 mg (or 500 mg if given in solutions containing adrenaline)—see also Administration on p. 702 and see also important warning below

- Intravenous regional anaesthesia and nerve blocks, seek expert advice

- Surface anaesthesia, usual strengths 2–4%, see preparations below

---

**Lidocaine hydrochloride injections**

**Lidocaine** (Non-proprietary) ( BN 78p)

Injection 0.5%, lidocaine hydrochloride 5 mg/mL, net price 10-mL amp = 35p

Injection 1%, lidocaine hydrochloride 10 mg/mL, net price 2-mL amp = 21p; 5-mL amp = 25p; 10-mL amp = 38p; 10-mL prefilled syringe = £1.04; 20-mL amp = 78p

Injection 2%, lidocaine hydrochloride 20 mg/mL, net price 2-mL amp = 27p; 5-mL amp = 28p

**Xylocaine** (AstraZeneca) ( BN 78p)

Injection 1% with adrenaline 1 in 200 000, anhydrous lidocaine hydrochloride 10 mg/mL, adrenaline 1 in 200 000 (5 micrograms/mL), net price 20-mL vial = 99p

Injection 2% with adrenaline 1 in 200 000, anhydrous lidocaine hydrochloride 20 mg/mL, adrenaline 1 in 200 000 (5 micrograms/mL), net price 20-mL vial = £1.04
Lidocaine injections for dental use

Note Consult expert dental sources for specific advice in relation to dose of lidocaine for dental anaesthesia

A variety of lidocaine injections with adrenaline is available in dental cartridges; brands include Lignospan Special®, Rexocaine® and Xylocaine®

Lidocaine for surface anaesthesia

Important Rapid and extensive absorption may result in systemic side-effects

Lidocaine (Non-proprietary)

Ointment Lidocaine hydrochloride 5%, net price 15 g = £88p

Dose dental practice, rub gently into dry gum

Sore nipples from breast-feeding, apply using gauze and wash off immediately before feed

Pain relief (in anal fissures, haemorrhoids, pruritus ani, pruritus vulvae, herpes zoster, or herpes labialis), 1–2 mL applied when necessary, avoid long-term use

Solution Lidocaine hydrochloride 4%, net price 25 mL = £1.35

Dose biopsy in mouth, 3–4 mL with suitable spray (with adrenaline if necessary); max. 5 mL, ELDERLY lower max. dose, CHILD max. 3 mg/kg

Puncture of maxillary sinus or polyectomy, apply with spray for 2–3 minutes (with adrenaline); max. 5 mL ELDERLY lower max. dose, CHILD max. 3 mg/kg

Bronchoscopy and bronchography, 2–3 mL with suitable spray, max. 5 mL ELDERLY lower max. dose, CHILD max. 3 mg/kg

EMLA® (AstraZeneca)

Drug Tariff cream Lidocaine 2.5%, prilocaine 2.5%, net price 5-g tube = £1.73

Surgical pack cream Lidocaine 2.5%, prilocaine 2.5%, net price 30-g tube = £10.25

Premedication pack cream Lidocaine 2.5%, prilocaine 2.5%, net price 5 × 5-g tube with 12 occlusive dressings = £9.75

Cautions not for preterm neonates, children under 1 year receiving treatment with methaemoglobin-inducing agents, wounds, mucous membranes (except genital mucosa in adults), or atopic dermatitis; avoid use near eyes or middle ear; although systemic absorption low, caution in anaemia, in congenital or acquired methaemoglobinemia or in G6PD deficiency (see also Prilocaine, p. 706)

Side-effects include administration site reactions such as transient paleness, redness, oedema, itching, burning sensation, and localised lesions

Dose ADULT and CHILD over 1 year, anaesthesia before minor skin procedures including venepuncture, apply thick layer under occlusive dressing 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting); NEONATE and CHILD under 3 months or body-weight less than 5 kg, single application max. 1 g under occlusive dressing for max. 1 hour, CHILD 3–12 months and body-weight over 5 kg, apply max. 2 g under occlusive dressing for max. 4 hours

Anaesthesia on genital skin before injection of local anaesthetics in adult men, apply under occlusive dressing for max. 4 hours

Anaesthesia before surgical treatment of lesions on genital skin in adults, apply up to 10 g 5–10 minutes before procedure

Instillagel® (Climed)

Gel Lidocaine hydrochloride 2%, chlorhexidine gluconate solution 0.25%, in a sterile lubricant basis in disposable syringe, net price 6–11 mL syringe = £1.41, 11–50 mL syringe = £1.58

Excipients include hydroxybenzoates (parabens)

Dose 6–11 mL into urethra

Laryngojet® (UCB Pharma) Medicated plaster, lidocaine 70 mg, tetracaine 70 mg, net price 25 = £98.00

Excipients include hydroxybenzoates (parabens)

Dose needle puncture or superficial surgical procedures, ADULT over 18 years, apply 1–4 plasters to intact skin 30 minutes before needle puncture or procedure; max. 4 plasters daily, CHILD 3–18 years, needle puncture, apply 1–2 plasters to intact skin 30 minutes before needle puncture; max. 2 plasters daily

The Scottish Medicines Consortium (p. 3) has advised (May 2008) that lidocaine 70 mg/tetracaine 70 mg (Rapydan medicated plaster) is not recommended for use within NHS Scotland for surface anaesthesia of the skin in connection with needle puncture or for cases of superficial surgical procedures on normal skin in adults or children over 3 years

Versatis® (Grünenthal) Medicated plaster, lidocaine 5% (700 mg/medicated plaster), net price 30 = £72.40

Excipients include hydroxybenzoates (parabens), propylene glycol

Cautions should not be applied to mucous membranes

Side-effects include administration site reactions such as skin lesions or injury

Dose postherpetic neuralgia, ADULT over 18 years, apply to intact, dry, non-hairy, non-irritated skin once daily for up to 12 hours, followed by a 12-hour plaster-free period; discontinue if no response after 4 weeks

Note Up to 3 plasters may be used to cover large areas; plasters may be cut

The Scottish Medicines Consortium has advised (December 2006) that Versatis is not recommended for the treatment of postherpetic neuralgia

Xylocaine® (AstraZeneca)

Spray (= pump spray), lidocaine 10% (100 mg/g) supplying 10 mg lidocaine/dose; 500 spray doses per container. Net price 50-g bottle = £3.13

Dose dental practice, 1–5 doses

Maxillary sinus puncture, 3 doses

During delivery in obstetrics, up to 20 doses

Bronchoscopy, laryngoscopy, oesophagoscopy, entodrateschial intubation, up to 20 doses; CHILD up to 3 mg/kg

Note Lidocaine can damage plastic cuffs of entodrateschial tubes

Lidocaine for ear, nose, and oropharyngeal use For cautions, contra-indications and side-effects of phenylephrine, see section 2.7.2

Lidocaine with Phenylephrine (Non-proprietary)

Topical solution, lidocaine hydrochloride 5%, phenylephrine hydrochloride 0.5%, net price 2.5 mL (with nasal applicator) = £9.60.

Bupivacaine

The advantage of bupivacaine over other local anaesthetics is its longer duration of action. It has a slow onset of action, taking up to 30 minutes for full effect. It is often used in lumbar epidural blockade and is particularly suitable for continuous epidural analgesia in labour, or for postoperative pain relief. It is the principal drug used for spinal anaesthesia.
**Bupivacaine Hydrochloride**

**Indications** see under Dose

**Cautions** see under Lidocaine Hydrochloride and notes above; myocardial depression may be more severe and more resistant to treatment; **interactions:** Appendix 1 (bupivacaine)

**Contra-indications** see under Lidocaine Hydrochloride and notes above; intravenous regional anaesthesia (Bier’s block)

**Side-effects** see under Lidocaine Hydrochloride and notes above

**Dose**

**Note** Doses should be adjusted according to patient’s physical status and nature of procedure—**important:** see also under Administration, p. 702

- **Local infiltration**, max. 60 mL, using a 2.5 mg/mL (0.25%) solution
- **Peripheral nerve block**, max. 60 mL, using a 2.5 mg/mL (0.25%) solution; max. 30 mL, using a 5 mg/mL (0.5%) solution
- **Epidural block**
  - Surgery, lumbar, max. 20 mL, using a 5 mg/mL (0.5%) solution
  - Surgery, caudal, max. 30 mL, using a 5 mg/mL (0.5%) solution; **CHILD** (up to 10 years) using a 2.5 mg/mL (0.25%) solution, up to lower-thoracic (T10) 0.3–0.4 mL/kg, up to mid-thoracic (T6) 0.4–0.8 mL/kg
  - Labour, lumbar, max. 12 mL, using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution; **caudal** (but rarely used) max. 20 mL, using a 2.5 mg/mL (0.25%) or 5 mg/mL (0.5%) solution
- **Sympathetic block**, max. 50 mL, using a 2.5 mg/mL (0.25%) solution
- **Intrathecal anaesthesia**, see under preparations

**Important**
The licensed doses stated above may not be appropriate in some settings and expert advice should be sought

**Bupivacaine** (Non-proprietary) [P][M]

**Injection**, anhydrous bupivacaine hydrochloride 2.5 mg/mL (0.25%), net price 10 mL = £62p; 5 mg/mL (0.5%), 10 mL = £94p

**Note** Bupivacaine hydrochloride injection 0.25% and 0.5% are available in glass or plastic ampoules, and sterile-wrapped glass ampoules

**Infusion**, anhydrous bupivacaine hydrochloride 1 mg/mL (0.1%), net price 100 mL = £8.41, 250 mL = £10.59; 1.25 mg/mL (0.125%), 250 mL = £10.80

**Dose**

Continuous lumbar epidural infusion during labour (once epidural block established), 10–15 mg/hour of 0.1% or 0.125% solution, max. 2 mg/kg over 4 hours and total of 400 mg in 24 hours

Continuous thoracic, upper abdominal, or lower abdominal epidural infusion for postoperative pain (once epidural block established), 4–15 mg/hour of 0.1% or 0.125% solution; max. 2 mg/kg over 4 hours and total of 400 mg in 24 hours; not recommended for use in children

**Marcain**® (AstraZeneca) [P][M]

**Injection**, anhydrous bupivacaine hydrochloride 2.5 mg/mL (Marcain® 0.25%), net price 10-mL Polymamp® = £1.06; 5 mg/mL (Marcain® 0.5%), 10-mL Polymamp® = £1.21

**Marcain Heavy**® (AstraZeneca) [P][M]

**Injection**, anhydrous bupivacaine hydrochloride 5 mg/mL, glucose 80 mg/mL, net price 4-mL amp = £1.21

**Dose**

Intrathecal anaesthesia for surgery; 2–4 mL (dose may need to be reduced in elderly and in late pregnancy)

**With adrenaline**

**Bupivacaine and Adrenaline** (Non-proprietary) [P][M]

**Injection**, anhydrous bupivacaine hydrochloride 2.5 mg/mL (0.25%), adrenaline 1 in 200 000 (5 micrograms/mL), net price 10-mL amp = £1.23

**Injection**, anhydrous bupivacaine hydrochloride 5 mg/mL (0.5%), adrenaline 1 in 200 000 (5 micrograms/mL), net price 10-mL amp = £1.40

**Levobupivacaine**

Levobupivacaine, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine, but is thought to have fewer adverse effects.

**LEVOBUPIVACAINE**

**Note** Levobupivacaine is an isomer of bupivacaine

**Indications** see under Dose

**Cautions** see under Lidocaine Hydrochloride and notes above; **interactions:** Appendix 1 (levobupivacaine)

**Contra-indications** see under Lidocaine Hydrochloride and notes above; intravenous regional anaesthesia (Bier’s block); paracervical block in obstetrics; do not use 7.5 mg/mL strength in obstetrics

**Side-effects** see under Lidocaine Hydrochloride and notes above

**Dose**

**Note** Doses should be adjusted according to patient’s physical status and nature of procedure—**important:** see also under Administration, p. 702

- **Surgical anaesthesia**
  - Lumbar epidural, 10–20 mL (50–150 mg) of 5 mg/mL or 7.5 mg/mL solution over 5 minutes; caesarean section, 15–30 mL (75–150 mg) of 5 mg/mL solution over 15–20 minutes
  - Intrathecal, 3 mL (15 mg) of 5 mg/mL solution
  - Periperal nerve block, 1–40 mL of 2.5 mg/mL or 5 mg/mL solution (max. 150 mg); ilioinguinal/iliohypogastric block, **CHILD** under 12 years 0.25–0.5 mL/kg (0.625–2.5 mg/kg) of a 2.5 mg/mL or 5 mg/mL solution
  - Peribulbar block, 5–15 mL (37.5–112.5 mg) of 7.5 mg/mL solution
  - Local infiltration, 1–60 mL (max. 150 mg) of 2.5 mg/mL solution
  - **Acute pain**
    - Lumbar epidural, labour pain, 6–10 mL (15–25 mg) of 2.5 mg/mL solution at intervals of at least 15 minutes or 5–12.5 mg/hour as a continuous epidural infusion, postoperative pain, 12.5–18.75 mg/hour as a continuous epidural infusion; max. 400 mg in 24 hours

**Important**
The licensed doses stated above may not be appropriate in some settings and expert advice should be sought

**Chirocaine**® (Abbott) [P][M]

**Injection**, levobupivacaine (as hydrochloride) 2.5 mg/mL, net price 10-mL amp = £1.66; 5 mg/mL, 10-mL amp = £1.90; 7.5 mg/mL, 10-mL amp = £2.85

**Note** For 1.25 mg/mL concentration dilute standard solutions with sodium chloride 0.9%
**Procaine**

Procaine is now seldom used. It is as potent as lidocaine (lidocaine) but has a shorter duration of action. It provides less intense analgesia because of reduced spread through the tissues. It is of no value as a surface anaesthetic.

**Prilocaine**

Prilocaine is a local anaesthetic of low toxicity which is similar to lidocaine (lidocaine). If used in high doses, methaemoglobinemia may occur which can be treated with intravenous injection of methylenblum chloride (methylene blue) 1% using a dose of 1 mg/kg. Infants under 6 months are particularly susceptible to methaemoglobinemia.

**PRIOCAINE HYDROCHLORIDE**

**Indications** infiltration anaesthesia (higher strengths for dental use only), nerve block

**Cautions** see under Lidocaine Hydrochloride and notes above; severe or untreated hypertension, severe heart disease; concomitant drugs which cause methaemoglobinemia; reduce dose in elderly or debilitated; pregnancy (Appendix 4); interactions: Appendix 1 (prilocaine)

**Contra-indications** see under Lidocaine Hydrochloride and notes above; anaemia or congenital or acquired methaemoglobinemia

**Side-effects** see under Lidocaine Hydrochloride and notes above; ocular toxicity (including blindness) reported with excessively high strengths used for ophthalmic procedures

**Dose**

- See under preparations—important: see also under Administration, p. 702

**Citranest® (AstraZeneca)**

Injection 1%, prilocaine hydrochloride 10 mg/mL, net price 50-mL multidose vial = £0.02

**Dose** adjusted according to site of administration and response, 100–200 mg/minute, or in incremental doses, to max. total dose 400 mg; CHILD over 6 months up to 5 mg/kg

**With lidocaine**

**EMLA®** see Lidocaine, p. 704

**For dental use**

**Note** Consult expert dental sources for specific advice in relation to dose of prilocaine for dental anaesthesia.

**Citranest® (Dentsply)**

Injection 4%, prilocaine hydrochloride 40 mg/mL, net price 2.2-mL cartridge = £0.17p

**Citranest with Octapressin® (Dentsply)**

Injection 3%, prilocaine hydrochloride 30 mg/mL, felypressin 0.03 unit/mL net price 1.8-mL cartridge and self-aspirating cartridge (both) = £0.15p

**Ropivacaine**

Ropivacaine is an amide-type local anaesthetic agent similar to bupivacaine. It is less cardiotoxic than bupivacaine, but also less potent.

**ROPIVACAINE HYDROCHLORIDE**

**Indications** see under Dose

**Cautions** see under Lidocaine Hydrochloride and notes above; interactions: Appendix 1 (ropivacaine)

**Contra-indications** see under Lidocaine Hydrochloride and notes above; intravenous regional anaesthesia (Bier’s block); paracervical block in obstetrics

**Side-effects** see under Lidocaine Hydrochloride and notes above; also nausea, vomiting; hypertension, tachycardia; headache, rigors, impaired temperature regulation; urinary retention; back pain; less commonly syncope, dyspnoea, anxiety; rarely arrhythmia

**Dose**

- See under preparations—important: see also under Administration on p. 702

**Note** Doses should be adjusted according to patient’s physical status and nature of procedure—important: see also under Administration, p. 702

- By injection, up to 1 g (200 mL of 0.5% solution or 100 mL of 1%) with adrenaline 1 in 200 000

**Procaine** (Martindale)

**Injection**, procaine hydrochloride 2% (20 mg/mL) in sodium chloride intravenous infusion, net price 2-mL amp = £0.127

**For lumbar epidural**

- Lumbar epidural injection 3% procaine hydrochloride 6–10 mL/hour of 2 mg/mL solution as a continuous epidural infusion for labour pain

**For thoracic epidural**

- Thoracic epidural incremental doses (max. total dose 150 mg)

**For major nerve block**

- Major nerve block (brachial plexus block), ADULT and CHILD over 12 years, 30–40 mL of 7.5 mg/mL solution

**For field block**

- Field block, ADULT and CHILD over 12 years, 1–30 mL of 7.5 mg/mL solution

**Acute pain**

- Lumbar epidural, ADULT and CHILD over 12 years, 10–20 mL of 2 mg/mL solution followed by 10–15 mL of 2 mg/mL solution at intervals of at least 30 minutes or 6–10 mL/hour of 2 mg/mL solution as a continuous epidural infusion for labour pain or 6–14 mL/hour of 2 mg/mL solution as a continuous epidural infusion for postoperative pain

**For intravenous regional anaesthesia**

- Intravenous regional anaesthesia (but see notes above)

**Pharmacology**

- Important:

  - Lumbar epidural, ADULT and CHILD over 12 years, 15–20 mL of 10 mg/mL solution or 15–25 mL of 7.5 mg/mL solution (max. total dose 200 mg); caesarean section, 15–20 mL of 7.5 mg/mL solution in incremental doses (max. total dose 150 mg)

  - Thoracic epidural (to establish block for postoperative pain), ADULT and CHILD over 12 years, 5–15 mL of 7.5 mg/mL solution

**For major nerve block**

- Major nerve block (brachial plexus block), ADULT and CHILD over 12 years, 30–40 mL of 7.5 mg/mL solution

**For field block**

- Field block, ADULT and CHILD over 12 years, 1–30 mL of 7.5 mg/mL solution

**For acute pain**

- Lumbar epidural, ADULT and CHILD over 12 years, 10–20 mL of 2 mg/mL solution followed by 10–15 mL of 2 mg/mL solution at intervals of at least 30 minutes or 6–10 mL/hour of 2 mg/mL solution as a continuous epidural infusion for labour pain or 6–14 mL/hour of 2 mg/mL solution as a continuous epidural infusion for postoperative pain

**Infusion**, levobupivacaine (as hydrochloride)

- 625 micrograms/mL, net price 100 mL = £7.80, 200 mL = £10.40, 1.25 mg/mL, net price 100 mL = £8.54, 200 mL = £12.20

**Side-effects**

- See notes above; pregnancy (Appendix 4); interactions: Appendix 1 (procaine)

**Contra-indications** see notes above; pregnancy (Appendix 4); interactions: Appendix 1 (procaine)

**Procaine** (Martindale)

**Injection**, procaine hydrochloride 2% (20 mg/mL) in sodium chloride intravenous infusion, net price 2-mL amp = £0.127

**For lumbar epidural**

- Lumbar epidural injection 3% procaine hydrochloride 6–10 mL/hour of 2 mg/mL solution as a continuous epidural infusion for labour pain

**For thoracic epidural**

- Thoracic epidural incremental doses (max. total dose 150 mg)

**For major nerve block**

- Major nerve block (brachial plexus block), ADULT and CHILD over 12 years, 30–40 mL of 7.5 mg/mL solution

**For field block**

- Field block, ADULT and CHILD over 12 years, 1–30 mL of 7.5 mg/mL solution

**Acute pain**

- Lumbar epidural, ADULT and CHILD over 12 years, 10–20 mL of 2 mg/mL solution followed by 10–15 mL of 2 mg/mL solution at intervals of at least 30 minutes or 6–10 mL/hour of 2 mg/mL solution as a continuous epidural infusion for labour pain or 6–14 mL/hour of 2 mg/mL solution as a continuous epidural infusion for postoperative pain

**Pharmacology**

- Important:

  - Lumbar epidural, ADULT and CHILD over 12 years, 15–20 mL of 10 mg/mL solution or 15–25 mL of 7.5 mg/mL solution (max. total dose 200 mg); caesarean section, 15–20 mL of 7.5 mg/mL solution in incremental doses (max. total dose 150 mg)

  - Thoracic epidural (to establish block for postoperative pain), ADULT and CHILD over 12 years, 5–15 mL of 7.5 mg/mL solution

**For major nerve block**

- Major nerve block (brachial plexus block), ADULT and CHILD over 12 years, 30–40 mL of 7.5 mg/mL solution

**For field block**

- Field block, ADULT and CHILD over 12 years, 1–30 mL of 7.5 mg/mL solution

**For acute pain**

- Lumbar epidural, ADULT and CHILD over 12 years, 10–20 mL of 2 mg/mL solution followed by 10–15 mL of 2 mg/mL solution at intervals of at least 30 minutes or 6–10 mL/hour of 2 mg/mL solution as a continuous epidural infusion for labour pain or 6–14 mL/hour of 2 mg/mL solution as a continuous epidural infusion for postoperative pain

**Infusion**, levobupivacaine (as hydrochloride)

- 625 micrograms/mL, net price 100 mL = £7.80, 200 mL = £10.40, 1.25 mg/mL, net price 100 mL = £8.54, 200 mL = £12.20
Thoracic epidural, **ADULT** and **CHILD** over 12 years, 6–14 mL/hour of 2 mg/mL solution as a continuous infusion

Field block, **ADULT** and **CHILD** over 12 years, 1–100 mL of 2 mg/mL solution

Peripheral nerve block, **ADULT** and **CHILD** over 12 years, 5–10 mL/hour of 2 mg/mL solution as a continuous infusion or by intermittent injection

**CHILD** under 12 years, consult product literature

**Naropin**® (AstraZeneca) ®

**Injection**, ropivacaine hydrochloride 2 mg/mL, net price 10-mL Polyamp® = £1.78; 7.5 mg/mL, 10-mL Polyamp® = £2.65; 10 mg/mL, 10-mL Polyamp® = £3.20

**Electrolytes** Na < 0.5 mmol/mL

**Infusion**, ropivacaine hydrochloride 2 mg/mL, net price 200-mL Polybag® = £14.45

**Electrolytes** Na < 0.5 mmol/mL

**TETRACAINE**

Tetracaine (amethocaine) is an effective local anaesthetic for topical application; a 4% gel is indicated for anaesthesia prior to venepuncture or venous cannulation. It is rapidly absorbed from mucous membranes and should never be applied to inflamed, traumatised, or highly vascular surfaces. It should never be used to provide anaesthesia for bronchoscopy or cystoscopy, as lidocaine (lignocaine) is a safer alternative. It is used in ophthalmology (section 11.7) and in skin preparations (section 13.3). Hypersensitivity to tetracaine has been reported.

**TETRACAINE**

(Amethocaine)

**Indications** see under preparation below

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; also erythema, oedema and pruritus; very rarely blistering

**Important**. Rapid and extensive absorption may result in systemic side-effects (see also notes above)

**Ametop**® (S&N Hlth.)

**Gel**, tetracaine 4%, net price 1.5-g tube = £1.08

**Dose** **ADULT** and **CHILD** over 1 month, apply contents of tube to site of venepuncture or venous cannulation and cover with occlusive dressing; remove gel and dressing after 30 minutes for venepuncture and after 45 minutes for venous cannulation

**Note** **ADULT** and **CHILD** over 5 years, max. 5 tubes applied at separate sites at a single time, **CHILD** 1 month–5 years, max. 1 tube applied at separate sites at a single time. Max. in a 24-hour period, **ADULT** 7 tubes, **CHILD** 2 tubes

**NEONATE** see BNF for Children

**With lidocaine**

Rapydan® see Lidocaine, p. 704

**Other local anaesthetics**

Benzocaine is a local anaesthetic of low potency and toxicity. It is used in concentrations of up to 20% for topical anaesthesia of the oral mucosa before injection. It is an ingredient of some proprietary topical preparations for musculoskeletal conditions (section 10.3.2), mouth-ulcer preparations (section 12.3.1), and throat lozenges (section 12.3.3). Benzocaine sprays used in the mouth and throat have been associated with methaemoglobinemia.

Cocaine readily penetrates mucous membranes and is an effective surface anaesthetic with an intense vasoconstrictor action. However, apart from its use in otolaryngology (see below), it has now been replaced by less toxic alternatives. It has marked sympathomimetic activity and should never be given by injection because of its toxicity. As a result of its intense stimulant effect it is a drug of addiction. In otolaryngology cocaine is applied to the nasal mucosa in concentrations of 4 to 10% (40–100 mg/mL); an oromucosal solution and nasal spray both containing cocaine hydrochloride 10% are available (Aurum). In order to avoid systemic effects, the maximum dose recommended for application to the nasal mucosa in fit adults is a total of 1.5 mg/kg, which is equivalent to a total topical dose of approximately 100 mg for an adult male; this dose relates to direct application of cocaine (application on gauze may reduce systemic absorption). It should be used only by those skilled in the precautions needed to minimize absorption and the consequent risk of arrhythmias. Although cocaine interacts with other drugs liable to induce arrhythmias, including adrenaline, some otolaryngologists consider that combined use of topical cocaine with topical adrenaline (in the form of a paste or a solution) improves the operative field and may possibly reduce absorption. Cocaine is a mydriatic as well as a local anaesthetic but owing to corneal toxicity it is now little used in ophthalmology. Cocaine should be avoided in acute porphyria (section 9.8.2).
Appendix 1: Interactions

Two or more drugs given at the same time may exert their effects independently or may interact. The interaction may be potentiation or antagonism of one drug by another, or occasionally some other effect. Adverse drug interactions should be reported to the CHM as for other adverse drug reactions.

Drug interactions may be pharmacodynamic or pharmacokinetic.

Pharmacodynamic interactions

These are interactions between drugs which have similar or antagonistic pharmacological effects or side-effects. They may be due to competition at receptor sites, or occur between drugs acting on the same physiological system. They are usually predictable from a knowledge of the pharmacology of the interacting drugs; in general, those demonstrated with one drug are likely to occur with related drugs. They occur to a greater or lesser extent in most patients who receive the interacting drugs.

Pharmacokinetic interactions

These occur when one drug alters the absorption, distribution, metabolism, or excretion of another, thus increasing or reducing the amount of drug available to produce its pharmacological effects. They are not easily predicted and many of them affect only a small proportion of patients taking the combination of drugs. Pharmacokinetic interactions occurring with one drug cannot be assumed to occur with related drugs unless their pharmacokinetic properties are known to be similar.

Pharmacokinetic interactions are of several types:

Affecting absorption The rate of absorption or the total amount absorbed can both be altered by drug interactions. Delayed absorption is rarely of clinical importance unless high peak plasma concentrations are required (e.g. when giving an analgesic). Reduction in the total amount absorbed, however, may result in ineffective therapy.

Due to changes in protein binding To a variable extent most drugs are loosely bound to plasma proteins. Protein-binding sites are non-specific and one drug can displace another thereby increasing its proportion free to diffuse from plasma to its site of action. This only produces a detectable increase in effect if it is an extensively bound drug (more than 90%) that is not widely distributed throughout the body. Even so displacement rarely produces more than transient potentiation because this increased concentration of free drug results in an increased rate of elimination.

Displacement from protein binding plays a part in the potentiation of warfarin by sulphonamides and tolbutamide but the importance of these interactions is due mainly to the fact that warfarin metabolism is also inhibited.

Affecting metabolism Many drugs are metabolised in the liver. Induction of the hepatic microsomal enzyme system by one drug can gradually increase the rate of metabolism of another, resulting in lower plasma concentrations and a reduced effect. On withdrawal of the inducer plasma concentrations increase and toxicity may occur. Barbiturates, griseofulvin, many antiepileptics, and rifampicin are the most important enzyme inducers. Drugs affected include warfarin and the oral contraceptives.

Conversely when one drug inhibits the metabolism of another higher plasma concentrations are produced, rapidly resulting in an increased effect with risk of toxicity. Some drugs which potentiate warfarin and phenytoin do so by this mechanism.

Isoenzymes of the hepatic cytochrome P450 system interact with a wide range of drugs. Drugs may be substrates, inducers or inhibitors of the different isoenzymes. A great deal of in-vitro information is available on the effect of drugs on the isoenzymes; however, since drugs are eliminated by a number of different metabolic routes as well as renal excretion, the clinical effects of interactions cannot be predicted accurately from laboratory data on the cytochrome P450 isoenzymes. Except where a combination of drugs is specifically contra-indicated, the BNF presents only interactions that have been reported in clinical practice. In all cases the possibility of an interaction must be considered if toxic effects occur or if the activity of a drug diminishes.

Affecting renal excretion Drugs are eliminated through the kidney both by glomerular filtration and by active tubular secretion. Competition occurs between those which share active transport mechanisms in the proximal tubule. For example, salicylates and some other NSAIDs delay the excretion of methotrexate; serious methotrexate toxicity is possible.

Relative importance of interactions

Many drug interactions are harmless and many of those which are potentially harmful only occur in a small proportion of patients; moreover, the severity of an interaction varies from one patient to another. Drugs with a small therapeutic ratio (e.g. phenytoin) and those which require careful control of dosage (e.g. anticoagulants, antihypertensives, and antidiabetics) are most often involved.

Patients at increased risk from drug interactions include the elderly and those with impaired renal or liver function.

Hazardous interactions The symbol ● has been placed against interactions that are potentially hazardous and where combined administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring).

Interactions that have no symbol do not usually have serious consequences.
ACE Inhibitors

Clonidine: enhanced hypotensive effect when ACE inhibitors given with clonidine; antihypertensive effect of captopril possibly delayed by previous treatment with clonidine

Corticosteroids: hypotensive effect of ACE inhibitors antagonised by corticosteroids

Cytotoxics: increased risk of anaemia or leucopenia when captopril given with azathioprine especially in renal impairment; increased risk of anaemia when enalapril given with azathioprine especially in renal impairment

Diazoxide: enhanced hypotensive effect when ACE inhibitors given with diazoxide

Diuretics: enhanced hypotensive effect when ACE inhibitors given with diuretics: increased risk of severe hyperkalaemia when ACE inhibitors given with potassium-sparing diuretics and aldosterone antagonists (monitor potassium concentration with low-dose spironolactone in heart failure)

Dopaminergics: enhanced hypotensive effect when ACE inhibitors given with levodopa

Lithium: ACE inhibitors reduce excretion of lithium (increased plasma concentration)

Methyldopa: enhanced hypotensive effect when ACE inhibitors given with methyldopa

Moxisylyte (thymoxamine): enhanced hypotensive effect when ACE inhibitors given with moxisylyte

Moxonidine: enhanced hypotensive effect when ACE inhibitors given with moxonidine

Muscle Relaxants: enhanced hypotensive effect when ACE inhibitors given with baclofen or tizanidine

Nitrates: enhanced hypotensive effect when ACE inhibitors given with nitrates

Oestrogens: hypotensive effect of ACE inhibitors antagonised by oestrogens

Potassium Salts: increased risk of severe hyperkalaemia when ACE inhibitors given with potassium salts

Probenecid: excretion of captopril reduced by probenecid

Progestogens: risk of hyperkalaemia when ACE inhibitors given with drospirenone (monitor serum potassium during first cycle)

Prostaglandins: enhanced hypotensive effect when ACE inhibitors given with alprostadil

Vasodilator Antihypertensives: enhanced hypotensive effect when ACE inhibitors given with hydralazine, minoxidil or sodium nitroprusside

ACE Inhibitors (continued)

Abacavir:
- Absorption of abacavir possibly reduced by rifampicin
- Increased risk of side-effects when abacavir given with rifampicin
- Values for abacavir interactions as for aciclovir

Aciclovir:
- Increased risk of severe hyperkalaemia when ACE inhibitors given with aciclovir

Adefovir:
- Absorption of adefovir possibly reduced by rifampicin
- Values for adefovir interactions as for aciclovir

Aciclovir, see Aciclovir interactions as for aciclovir

Acenocoumarol (nicoumalone): see Anticoagulants

Acetazolamide: see Diuretics

Aciclovir: see Antiviral
corticosteroids

Anakinra: see Antidiabetics

Anasthetics, General: enhanced hypotensive effect when ACE inhibitors given with general anaesthetics

Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when ACE inhibitors given with angiotensin-II receptor antagonists

Antacids: absorption of ACE inhibitors possibly reduced by antacids; absorption of captopril, enalapril and fosinopril reduced by antacids

Anticoagulants: increased risk of hyperkalaemia when ACE inhibitors given with anticoagulants

Antidepressants: increased hypotensive effect of ACE inhibitors possibly enhanced by MAOIs

Antidiabetics: ACE inhibitors possibly enhance hypoglycaemic effect of insulin, metformin and sulphonylureas

Antipsychotics: enhanced hypotensive effect when ACE inhibitors given with antipsychotics

Antidiabetics: see Antidiabetics

Beta-blockers: enhanced hypotensive effect when ACE inhibitors given with beta-blockers

Calcium-channel Blockers: enhanced hypotensive effect when ACE inhibitors given with calcium-channel blockers

Captopril possibly increases plasma concentration of digoxin

Clonidine: enhanced hypotensive effect when ACE inhibitors given with clonidine; antihypertensive effect of captopril possibly delayed by previous treatment with clonidine

Corticosteroids: hypotensive effect of ACE inhibitors antagonised by corticosteroids

Cytotoxics: increased risk of anaemia or leucopenia when captopril given with azathioprine especially in renal impairment; increased risk of anaemia when enalapril given with azathioprine especially in renal impairment

Diazoxide: enhanced hypotensive effect when ACE inhibitors given with diazoxide

Diuretics: enhanced hypotensive effect when ACE inhibitors given with diuretics: increased risk of severe hyperkalaemia when ACE inhibitors given with potassium-sparing diuretics and aldosterone antagonists (monitor potassium concentration with low-dose spironolactone in heart failure)

Dopaminergics: enhanced hypotensive effect when ACE inhibitors given with levodopa

Lithium: ACE inhibitors reduce excretion of lithium (increased plasma concentration)

Methyldopa: enhanced hypotensive effect when ACE inhibitors given with methyldopa

Moxisylyte (thymoxamine): enhanced hypotensive effect when ACE inhibitors given with moxisylyte

Moxonidine: enhanced hypotensive effect when ACE inhibitors given with moxonidine

Muscle Relaxants: enhanced hypotensive effect when ACE inhibitors given with baclofen or tizanidine

Nitrates: enhanced hypotensive effect when ACE inhibitors given with nitrates

Oestrogens: hypotensive effect of ACE inhibitors antagonised by oestrogens

Potassium Salts: increased risk of severe hyperkalaemia when ACE inhibitors given with potassium salts

Probenecid: excretion of captopril reduced by probenecid

Progestogens: risk of hyperkalaemia when ACE inhibitors given with drospirenone (monitor serum potassium during first cycle)

Prostaglandins: enhanced hypotensive effect when ACE inhibitors given with alprostadil

Vasodilator Antihypertensives: enhanced hypotensive effect when ACE inhibitors given with hydralazine, minoxidil or sodium nitroprusside

Acebutolol: see Beta-blockers

Adefovir: see Antiviral
corticosteroids

Anakinra: see Antidiabetics
Adenosine

Note: Possibility of interaction with drugs tending to impair myocardial condition.

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with bupivacaine, levobupivacaine, prilocaine or ropivacaine.

- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics.
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval.

Beta-blockers: increased myocardial depression when anti-arrhythmics given with beta-blockers.

Dipyridamole: effect of adenosine enhanced and extended by dipyridamole (important risk of toxicity).

Theophylline: anti-arrhythmic effect of adenosine antagonised by theophylline.

Adrenaline (epinephrine) see Sympathomimetics.

Adrenergic Neurone Blockers

Alcohol: enhanced hypotensive effect when adrenergic neurone blockers given with alcohol.

- Alpha-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with alpha-blockers.
- Beta-blockers: enhanced hypotensive effect when adrenergic neurone blockers antagonised by beta-blockers.
- General anaesthetics: enhanced hypotensive effect of adrenergic neurone blockers antagonised by NSAIDs.

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when adrenergic neurone blockers given with angiotensin-II receptor antagonists.

Beta-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with alpha-blockers.

Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by tricyclics.

Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by haloperidol; enhanced hypotensive effect of adrenergic neurone blockers given with chlorpromazine; enhanced hypotensive effect when adrenergic neurone blockers given with phenothiazines.

Anxiolytics and Hypnotics: enhanced hypotensive effect when adrenergic neurone blockers given with anxiolytics and hypnotics.

Betaxolol: enhanced hypotensive effect when adrenergic neurone blockers given with beta-blockers.

Calcium-channel Blockers: enhanced hypotensive effect when adrenergic neurone blockers given with calcium-channel blockers.

Clonidine: enhanced hypotensive effect when adrenergic neurone blockers given with clonidine.

Corticosteroids: hypotensive effect of adrenergic neurone blockers antagonised by corticosteroids.

Diazoxide: enhanced hypotensive effect when adrenergic neurone blockers given with diazoxide.

Diuretics: enhanced hypotensive effect when adrenergic neurone blockers given with diuretics.

Dopaminergics: enhanced hypotensive effect when adrenergic neurone blockers given with levodopa.

Methyl dopa: enhanced hypotensive effect when adrenergic neurone blockers given with methyl dopa.

Moxisylyte (thymoxamine): enhanced hypotensive effect when adrenergic neurone blockers given with moxisylyte.

Maxidone: enhanced hypotensive effect when adrenergic neurone blockers given with maxidone.

Muscle Relaxants: enhanced hypotensive effect when adrenergic neurone blockers given with baclofen or tizanidine.

Nitrates: enhanced hypotensive effect when adrenergic neurone blockers given with nitrates.

Opioids: hypotensive effect of adrenergic neurone blockers antagonised by oestrogens.

Pizotifen: hypotensive effect of adrenergic neurone blockers antagonised by pizotifen.

Adrenergic Neurone Blockers (continued)

Prostaglandins: enhanced hypotensive effect when adrenergic neurone blockers given with alprostadil.

- Symptoms (chronic): hypotensive effect of adrenergic neurone blockers antagonised by ephedrine, isometheptene, metaraminol, methyphenidate, noradrenaline (norepinephrine), oxytazolone, phenylephrine, phenylpropanolamine, pseudoephedrine and xylometazoline.

Vasodilators: Hypotensive effect of adrenergic neurone blockers given with hydralazine, minoxidil or sodium nitroprusside.

Adsorbents see Kaolin.

Agalsidase Alfa and Beta

Anti-arrhythmics: effects of agalsidase alfa and beta possibly inhibited by amiodarone (manufacturers of agalsidase alfa and beta advise avoid concomitant use).

Antibacterials: effects of agalsidase alfa and beta possibly inhibited by gentamicin (manufacturers of agalsidase alfa and beta advise avoid concomitant use).

Antimalarials: effects of agalsidase alfa and beta possibly inhibited by chloroquine and hydroxychloroquine (manufacturers of agalsidase alfa and beta advise avoid concomitant use).

Alpha-blockers: enhanced hypotensive effect when adrenergic neurone blockers given with alpha-blockers.

Alcohol

ACE Inhibitors: enhanced hypotensive effect when alcohol given with ACE inhibitors.

Adrenergic Neurone Blockers: enhanced hypotensive effect when alcohol given with adrenergic neurone blockers.

Alpha-blockers: increased sedative effect when alcohol given with indoramin; enhanced hypotensive effect when alcohol given with alpha-blockers.

Anxiolytics and Hypnotics: enhanced hypotensive and sedative effects when alcohol given with opioid analgesics.

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alcohol given with angiotensin-receptor antagonists.

Antibacterials: disulfiram-like reaction when alcohol given with metronidazole; possibility of disulfiram-like reaction when alcohol given with tinidazole; increased risk of convulsions when alcohol given with cycloserine.

Anticoagulants: major changes in consumption of alcohol may affect anticoagulant control with coumarins or ephedrine.

Antidepressants: some beverages containing alcohol and some dealcoholised beverages contain tyramine which interacts with MAOIs (hypertensive crisis)—if no tyramine, enhanced hypotensive effect; sedative effects possibly increased when alcohol given with SSRIs; increased sedative effect when alcohol given with mitrazapine, tricyclic-related antidepressants or tricyclics.

Antidiabetics: alcohol enhances hypoglycaemic effect of antidiabetics; increased risk of lactic acidosis when alcohol given with metformin; flushing, in susceptible subjects, when alcohol given with chlorpropamide.

Antiepileptics: alcohol possibly increases CNS side-effects, increased sedative effect when alcohol given with primidone.

Antifungals: effects of alcohol possibly enhanced by griseofulvin.

Antihistamines: increased sedative effect when alcohol given with antihistamines (possibly less effect with non-sedating antihistamines).

Antimuscarinics: increased sedative effect when alcohol given with hyoscine.

Antipsychotics: increased sedative effect when alcohol given with antipsychotics.

Anxiolytics and Hypnotics: increased sedative effect when alcohol given with anxiolytics and hypnotics.

Barbiturates: increased sedative effect when alcohol given with barbiturates.

Beta-blockers: enhanced hypotensive effect when alcohol given with beta-blockers.
Alcohol (continued)
Calcium-channel Blockers: enhanced hypotensive effect when alcohol given with calcium-channel blockers; plasma concentration of alcohol possibly increased by verapamil
Clonidine: enhanced hypotensive effect when alcohol given with clonidine
Cytotoxics: disulfiram-like reaction when alcohol given with paraldehyde
Diazoxide: enhanced hypotensive effect when alcohol given with diazoxide
Disulfiram: disulfiram reaction when alcohol given with disulfiram (see p. 275)
Diuretics: enhanced hypotensive effect when alcohol given with diuretics
Dopaminergics: alcohol reduces tolerance to bromocriptine
Levamisole: possibility of disulfiram-like reaction when alcohol given with levamisole
Lofexidine: increased sedative effect when alcohol given with lofexidine
Methyldopa: enhanced hypotensive effect when alcohol given with methyldopa
Moxonidine: enhanced hypotensive effect when alcohol given with moxonidine
Muscle Relaxants: increased sedative effect when alcohol given with baclofen, methocarbamol or tizanidine
Nabnilone: increased sedative effect when alcohol given with nabnilone
Nicorandil: alcohol possibly enhances hypotensive effect of nicorandil
Nitrates: enhanced hypotensive effect when alcohol given with nitrates
Paraldehyde: increased sedative effect when alcohol given with paraldehyde
Retinoids: presence of alcohol causes eretinate to be formed from acitretin (increased risk of teratogenicity in women of child-bearing potential)
Vasodilator Antihypertensives: enhanced hypotensive effect when alcohol given with hydralazine, minoxidil or sodium nitroprusside
Aliskiren (continued)
Antifungals: plasma concentration of aliskiren increased by ketoconazole
Diuretics: aliskiren reduces plasma concentration of furosemide (frusemide); increased risk of hyperkalaemia when aliskiren given with potassium-sparing diuretics and aldosterone antagonists
Potassium Salts: increased risk of hyperkalaemia when aliskiren given with potassium salts
Alitretinoin see Retinoids
Antihypertensive Drugs see Bisulfan, Carmustine, Cyclophosphamide, Ifosamide, Lomustine, Methyldopa, and Thiopeta
Allopurinol
ACE Inhibitors: increased risk of leucopenia and hypersensitivity reactions when allopurinol given with ACE inhibitors especially in renal impairment
Antibacterials: increased risk of rash when allopurinol given with amoxicillin or ampicillin
Anticoagulants: allopurinol possibly enhances anti-coagulant effect of coumarins
α-Vinyls: allopurinol increases plasma concentration of zidovudine (risk of toxicity)—avoid concomitant use
Ciclosporin: allopurinol possibly increases plasma concentration of ciclosporin (risk of nephrotoxicity)
Cytotoxics: allopurinol enhances effects and increases toxicity of azathioprine and mercaptopurine (reduce dose of azathioprine and mercaptopurine to one quarter of usual dose); avoidance of allopurinol advised by manufacturer of mercaptopurine
Diuretics: increased risk of hypersensitivity when allopurinol given with thiazides and related diuretics especially in renal impairment
Theophylline: allopurinol possibly increases plasma concentration of theophylline
Almopitrapan see SHT Agonists
Alpha -adrenoceptor Stimulants see Apraclonidine, Brimonidine, Clonidine and Methyldopa
Alpha-blockers
ACE Inhibitors: enhanced hypotensive effect when alpha-blockers given with ACE inhibitors
Adrenergic Neurone Blockers: enhanced hypotensive effect when alpha-blockers given with adrenergic neurone blockers
Alcohol: enhanced hypotensive effect when alpha-blockers given with alcohol; increased sedative effect when inforamin given with alcohol
Aliskiren: enhanced hypotensive effect when alpha-blockers given with aliskiren
Anaesthetics, General: enhanced hypotensive effect when alpha-blockers given with general anaesthetics
Analgesics: hypotensive effect of alpha-blockers antagonised by NSAIDs
Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alpha-blockers given with angiotensin-II receptor antagonists
Antidepressants: enhanced hypotensive effect when alpha-blockers given with MAOIs; manufacturer of indomethacin advises avoid concomitant use with MAOIs
Antipsychotics: enhanced hypotensive effect when alpha-blockers given with antipsychotics
Antivirals: plasma concentration of alfuzosin possibly increased by ritonavir—avoid concomitant use
Anxiolytics and Hypnotics: enhanced hypotensive and sedative effects when alpha-blockers given with anxiolytics and hypnotics
Beta-blockers: enhanced hypotensive effect when alpha-blockers given with calcium-channel blockers, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
Captopril, Enalapril, Lisinopril, Perindopril, Ramipril anticongulants and other medications with hypertensive effects
Appendix 1: Interactions

Aminoglycosides

Agalsidase Alfa and Beta (continued) agalsidase alfa and beta advise avoid concomitant use

Analgesics: plasma concentration of amikacin and gentamicin in neonates possibly increased by indometacin

Antibacterials: neomycin reduces absorption of phenoxymethylinicillin; increased risk of nephrotoxicity when aminoglycosides given with colistin or polymyxins; increased risk of nephrotoxicity and ototoxicity when aminoglycosides given with capreomycin, teicoplanin or vancomycin; possible increased risk of nephrotoxicity when aminoglycosides given with cephalosporins

Anticoagulants: experience in anticoagulant clinics suggests that INR possibly altered when neomycin (given for local action on gut) is given with coumarins or ophenindione

Antidiabetics: neomycin possibly enhances hypoglycaemic effect of acarbose, also severity of gastrointestinal effects increased

Antifungals: increased risk of nephrotoxicity when aminoglycosides given with amphoterin

Bisphosphonates: increased risk of hypocalcaemia when aminoglycosides given with bisphosphonates

Cardiac Glycosides: neomycin reduces absorption of digoxin; gentamicin possibly increases plasma concentration of digoxin

Ciclosporin: increased risk of nephrotoxicity when aminoglycosides given with ciclosporin

Cytotoxics: neomycin possibly reduces absorption of methotrexate; increased risk of nephrotoxicity and possibly of ototoxicity when aminoglycosides given with platinum compounds

Diuretics: increased risk of ototoxicity when aminoglycosides given with deep diuretics

Muscle Relaxants: aminoglycosides enhance effects of non-depolarising muscle relaxants and suxamethonium

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)

Parasymptomimetics: aminoglycosides antagonise effects of neostigmine and pyridostigmine

Tacrolimus: increased risk of nephrotoxicity when aminoglycosides given with tacrolimus

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Vitamins: neomycin possibly reduces absorption of vitamin A

Aminophylline see Theophylline

Aminosaliclyates Cardiac Glycosides: sulfasalazine possibly reduces absorption of digoxin

Cytotoxics: possible increased risk of leucopenia when aminosalicylates given with azathioprine or mercaptopurine

Folates: sulfasalazine possibly reduces absorption of folic acid

Amiodarone Note Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped

Agalsidase Alfa and Beta: amiodarone possibly inhibits effects of agalsidase alfa and beta (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Anaesthetics, Local: increased myocardial depression when anti-arrhythmic given with bupivacaine, levobupivacaine, prilocaine or ropivacaine

Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics; increased risk of ventricular arrhythmias when amiodarone given with disopyramide—avoid concomitant use; amiodarone increases plasma concentration of flecainide (half dose of flecainide)

Antibacterials: increased risk of ventricular arrhythmias when amiodarone given with parenteral

Cardiac Glycosides: prazosin increases plasma concentration of digoxin

Clonidine: enhanced hypotensive effect when alpha-blockers given with clonidine

Corticosteroids: hypotensive effect of alpha-blockers antagonised by corticosteroids

Diapride: enhanced hypotensive effect when alpha-blockers given with diazoxide

Diuretics: enhanced hypotensive effect when alpha-blockers given with diuretics, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin

Dopaminergics: enhanced hypotensive effect when alpha-blockers given with levodopa

Methyldopa: enhanced hypotensive effect when alpha-blockers given with methyldopa

Metoprolol (thymoxamine): possible severe postural hypotension when alpha-blockers given with metoprolol

Moxonidine: enhanced hypotensive effect when alpha-blockers given with moxonidine

Muscle Relaxants: enhanced hypotensive effect when alpha-blockers given with nitrates

Oestrogens: hypotensive effect of alpha-blockers antagonised by oestrogens

Prostaglandins: enhanced hypotensive effect when alpha-blockers given with alprostadil

Sildenafil (avoid alpha-blockers for 4 hours after sildenafil)

Sympathomimetics: avoid concomitant use of tolazamide (tolazamide antagonised by oestrogens(risk probably small, see p. 439)

Vasodilator Antihypertensives: enhanced hypotensive effect when alpha-blockers given with hydralazine, minoxidil or sodium nitroprusside

Alpha-blockers (post-synaptic) see Alpha-blockers

Alprostadil see Prostaglandins

Aluminium Hydroxide see Antacids

Aminophylline see Theophylline

Aminosaliclyates Cardiac Glycosides: sulfasalazine possibly reduces absorption of digoxin

Cytotoxics: possible increased risk of leucopenia when aminosaliclyates given with azathioprine or mercaptopurine

Folates: sulfasalazine possibly reduces absorption of folic acid

Amiodarone Note Amiodarone has a long half-life; there is a potential for drug interactions to occur for several weeks (or even months) after treatment with it has been stopped

Agalsidase Alfa and Beta: amiodarone possibly inhibits effects of agalsidase alfa and beta (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with bupivacaine, levobupivacaine, prilocaine or ropivacaine

Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics; increased risk of ventricular arrhythmias when amiodarone given with disopyramide—avoid concomitant use; amiodarone increases plasma concentration of flecainide (half dose of flecainide)

Antibacterials: increased risk of ventricular arrhythmias when amiodarone given with parenteral
Antipsychotics: increased risk of ventricular arrhythmias when amiodarone given with

Cardiac Glycosides: increased risk of ventricular arrhythmias when amiodarone given with

Beta-blockers: increased plasma concentration of amiodarone (reduce dose of amiodarone ex ethinyl estradiol)

Anticoagulants: increased risk of ventricular arrhythmias when amiodarone given with

Antidepressants: increased risk of ventricular arrhythmias when amiodarone given with

Antiepileptics: increased plasma concentration of amiodarone possibly increased by

Antihistamines: increased risk of ventricular arrhythmias when amiodarone given with

Antimalarials: avoidance of amiodarone advised by manufacturer of artesunate

Antipsychotics: increased risk of ventricular arrhythmias when amiodarone given with

Antivirals: increased risk of ventricular arrhythmias when amiodarone given with

Amiodarone: increased plasma concentration of amiodarone possibly increased by

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Antibacterials: increased risk of nephrotoxicity when amphotericin given with

Antidepressants, Tricyclic: increased risk of nephrotoxicity when amphotericin given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Antidepressants: increased risk of ventricular arrhythmias when amiodarone given with

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Amphotericin: increased plasma concentration of amiodarone possibly increased by

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Amphotericin: increased plasma concentration of amiodarone possibly increased by

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia

Amphotericin: increased risk of ventricular arrhythmias when amiodarone given with

Anticoagulants: amiodarone antagonised by oral anticoagulants

Alpha-blockers: increased risk of Bradycardia
Appendix 1: Interactions

Anaesthetics, General
- Antidepressants (continued)
  Increased risk of arrhythmias and hypotension when general anaesthetics given with tricyclics
- Antipsychotics: enhanced hypotensive effect when general anaesthetics given with antipsychotics
- Anxiolytics and Hypnotics: increased sedative effect when general anaesthetics given with anxiolytics and hypnotics

Beta-blockers: enhanced hypotensive effect when general anaesthetics given with beta-blockers
- Calcium-channel Blockers: enhanced hypotensive effect when general anaesthetics or isoflurane given with calcium-channel blockers; general anaesthetics enhance hypotensive effect of everapamil (also AV delay)

Clonidine: enhanced hypotensive effect when general anaesthetics given with clonidine
- Cytotoxics: nitrous oxide increases antifolate effect of methotrexate—avoid concomitant use

Diazoxide: enhanced hypotensive effect when general anaesthetics given with diazoxide
- Diuretics: enhanced hypotensive effect when general anaesthetics given with diuretics
- Dopaminergics: increased risk of arrhythmias when volatile liquid general anaesthetics given with levodopa
- Ergot Alkaloids: halothane reduces effects of ergometrine on the parturient uterus
- Memantine: increased risk of CNS toxicity when ketamine given with memantine (manufacturer of memantine advises avoid concomitant use)
- Methylphenidate: enhanced hypotensive effect when general anaesthetics given with methylphenidate
- Muscle Relaxants: increased risk of myocardial depression and bradycardia when propofol given with suxamethonium; volatile liquid general anaesthetics enhance effects of non-depolarising muscle relaxants and suxamethonium
- Nitrites: enhanced hypotensive effect when general anaesthetics given with nitrites
- Oxytocin: oxytocic effect possibly reduced, also enhanced hypotensive effect and risk of arrhythmias when volatile liquid general anaesthetics given with oxytocin
- Probencid: effects of thiopteral possibly enhanced by probencid
- Sympathomimetics: increased risk of arrhythmias when volatile liquid general anaesthetics given with adrenaline (epinephrine); increased risk of hypertensive effect when volatile liquid general anaesthetics given with methylphenidate
- Theophylline: increased risk of convulsions when ketamine given with theophylline; increased risk of arrhythmias when halothane given with theophylline
- Vasodilator Antihypertensives: enhanced hypotensive effect when general anaesthetics given with hydralazine, minoxidil or sodium nitroprusside

Anaesthetics, General (intravenous) see Anaesthetics, General

Anaesthetics, General, Local see Bupivacaine, Levobupivacaine, Lidocaine (lignocaine), Prilocaine, Procaine, and Ropivacaine

Angiotensin-II Receptor Antagonists
- ACE Inhibitors: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with ACE inhibitors
- Adrenergic Neurone Blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with alcohol
- Alcohol: enhanced hypotensive effect when angiotensin-II receptor antagonists given with alcohol
- Aldesleukin: enhanced hypotensive effect when angiotensin-II receptor antagonists given with aldesleukin
- Alliskiren: irbesartan possibly reduces plasma concentration of alliskiren
- Alpha-blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with alpha-blockers
- Anaesthetics, General: enhanced hypotensive effect when angiotensin-II receptor antagonists given with general anaesthetics
- Analgesics: increased risk of renal impairment when angiotensin-II receptor antagonists given with NSAIDs, also hypotensive effect antagonised
- Anticoagulants: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with heparin
- Antidepressants: hypotensive effect of angiotensin-II receptor antagonists possibly enhanced by MAOIs
- Antipsychotics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with antipsychotics
- Anxiolytics and Hypnotics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with anxiolytics and hypnotics
- Beta-blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with beta-blockers
- Calcium-channel Blockers: enhanced hypotensive effect when angiotensin-II receptor antagonists given with calcium-channel blockers
- Ciclosporin: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with ciclosporin
- Clonidine: enhanced hypotensive effect when angiotensin-II receptor antagonists given with clonidine
- Corticosteroids: hypotensive effect of angiotensin-II receptor antagonists antagonised by corticosteroids
- Diazoxide: enhanced hypotensive effect when angiotensin-II receptor antagonists given with diazoxide
- Diuretics: enhanced hypotensive effect when angiotensin-II receptor antagonists given with diuretics
- Dopaminergics: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with dopamine
- Lamotrigine: enhanced hypotensive effect when angiotensin-II receptor antagonists given with lamotrigine
- Lithium: angiotensin-II receptor antagonists reduce excretion of lithium (increased plasma concentration)
- Methylprednisolone: enhanced hypotensive effect when angiotensin-II receptor antagonists given with methylprednisolone
- Moxisylyte (thymoxamine): enhanced hypotensive effect when angiotensin-II receptor antagonists given with moxisylyte
- Moxifloxacin: enhanced hypotensive effect when angiotensin-II receptor antagonists given with moxifloxacin
- Muscle Relaxants: enhanced hypotensive effect when angiotensin-II receptor antagonists given with baclofen or tizanidine
Antipsychotics: see Antazoline.

Antacids

• Potassium Salts: increased risk of hyperkalaemia when antipsychotic-II receptor antagonists given with potassium salts

Prostaglandins: risk of hyperkalaemia when antipsychotic-II receptor antagonists given with drosperinone (monitor serum potassium during first cycle)

Prostaglandins: enhanced hypotensive effect when antipsychotic-II receptor antagonists given with alprostadil

Tacrolimus: increased risk of hyperkalaemia when antipsychotic-II receptor antagonists given with tacrolimus

Vasodilator Antihypertensives: enhanced hypotensive effect when antipsychotic-II receptor antagonists given with hydralazine, minoxidil or sodium nitroprusside

Antacids

Note Antacids should preferably not be taken at the same time as other drugs since they may impair absorption

ACE inhibitors: antacids possibly reduce absorption of captopril, enalapril and fosinopril

Analgesics: alkaline urine due to some antacids increases excretion of aspirin

Antibacterials: antacids reduce absorption of azithromycin, cefaclor, cepodoxime, ciprofloxacin, isoniazid, levofloxacin, moxifloxacin, ofloxacin, rifampicin and tetracyclines; oral magnesium salts (as magnesium trisilicate) reduce absorption of nitrofurantoin

Antiepileptics: antacids reduce absorption of gabapentin and phenytoin

Antifungals: antacids reduce absorption of imipenem and cilastatin, amoxicillin and clavulanate, and tetracyclines

Antihistamines: antacids reduce absorption of fexofenadine

Antimalarials: antacids reduce absorption of chloroquine and hydroxychloroquine; oral magnesium salts (as magnesium trisilicate) reduce absorption of proguanil

Antipsychotics: antacids reduce absorption of phenothiazines and sulpiride

Antivirals: antacids possibly reduce plasma concentration of atazanavir; antacids possibly reduce absorption of fosamprenavir; antacids reduce absorption of tipranavir

Bile Acids: antacids possibly reduce absorption of bile acids

Bisphosphonates: antacids reduce absorption of bisphosphonates

Cardiac Glycosides: antacids possibly reduce absorption of digoxin

Corticosteroids: antacids reduce absorption of deflazacort

Cytotoxics: antacids reduce absorption of mycophenolate

Deferasirox: antacids containing aluminium possibly reduce absorption of deferasirox (manufacturer of deferasirox advises avoid concomitant use)

Dipyriramole: antacids possibly reduce absorption of dipyriramole

Iron: oral magnesium salts (as magnesium trisilicate) reduce absorption of oral iron

Lipid-regulating Drugs: antacids reduce absorption of rosuvastatin

Lithium: sodium bicarbonate increases excretion of lithium (reduced plasma concentration)

Penicillamine: antacids reduce absorption of penicillamine

Thyroid Hormones: antacids possibly reduce absorption of levothyroxine (thyroxine)

Ulcercalulating Drugs: antacids possibly reduce absorption of lansoprazole

Antazoline see Antihistamines

Anti-arrhythmics see Adenosine, Amiodarone, Disopyramide, Flecaïnide, Lidocaine (lignocaine), and Propafenone.

Antibacterials see individual drugs.

Antibiotics (cytotoxic) see Bleomycin, Doxorubicin, Epirubicin, Mitomycin.

Anticoagulants see Coumarins, Dabigatran etexilate, Heparins, Phenindione, and Rivaroxaban

Antidepressants see Antidepressants, SSRI; Antidepressants, Tricyclic; Antidepressants, Tricyclic (related); MAOIs; Mirtazapine; Moclobemide; Reboxetine; St John’s Wort; Tryptophan; Venlafaxine

Antidepressants, Noradrenaline Re-uptake Inhibitors see Reboxetine

Antidepressants, SSRIs

Alcohol: sedative effects possibly increased when SSRIs given with alcohol

Anaesthetics, Local: fluvoxamine inhibits metabolism of ropivacaine—avoid prolonged administration of ropivacaine

Analgesics: increased risk of bleeding when SSRIs given with nSAIDs or aspirin; fluvoxamine possibly increases plasma concentration of methadone; increased risk of CNS toxicity when SSRIs given with tramadol

Anti-arrhythmics: fluoxetine increases plasma concentration of flecainide; paroxetine possibly inhibits metabolism of propafenone (increased risk of toxicity)

Anticoagulants: SSRIs possibly enhance anticoagulant effect of warfarin

Antidepressants: avoidance of fluvoxamine advised by manufacturer of reboxetine; possible increased serotonergic effects when SSRIs given with duloxetine; fluvoxamine inhibits metabolism of mirtazapine—avoid concomitant use; citalopram, escitalopram, fluoxetine, paroxetine or sertraline should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 1 week after stopping citalopram, escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs increased by MAOIs (risk of serious toxicity); sertraline should not be started until 2 weeks after stopping fluoxetine; fluoxetine and paroxetine or sertraline: CNS effects of SSRIs increased by MAOIs; also MAOIs should not be started until at least 5 weeks after stopping citalopram, escitalopram, fluvoxamine or paroxetine do not start until 2 weeks after stopping fluoxetine; fluoxetine should not be started until 2 weeks after stopping fluoxetine; increased risk of CNS toxicity when escitalopram given with moclobemide, preferably avoid concomitant use; after stopping citalopram, fluvoxamine or paroxetine do not start moclobemide for at least 1 week; after stopping fluoxetine do not start moclobemide for 5 weeks; after stopping sertraline do not start moclobemide for 2 weeks; increased serotonergic effects when SSRIs given with St John’s wort—avoid concomitant use; SSRIs increase plasma concentration of some tricyclics; agitation and nausea may occur when SSRIs given with tryptophan

Antiepileptics: SSRIs antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); fluvoxamine inhibits fluvoxamine increase plasma concentration of carbamazepine; plasma concentration of paroxetine reduced by carbamazepine, phenytoin and primidone; fluoxetine and fluvoxamine increase plasma concentration of ophenytoin Antithistamines: antidepressant effect of SSRIs possibly antagonised by cyproheptadine

Antimicrobials: avoidance of antidepressants advised by manufacturer of ciprofloxacin/levofloxacin

Antithrombotic: aspirin reduces antiplatelet effect of SSRIs

Antipsychotics: fluoxetine increases plasma concentration of clozapine, haloperidol, risperidone, sulpiride and ziprasidone (paroxetine inhibits metabolism of perphenazine (reduce dose of perphenazine); fluoxetine and paroxetine possibly inhibit metabolism of warfarin—reduce dose of aspiri-
Antidepressants, SSRI
- Antipsychotics (continued)
  - prazepam; fluvoxamine, paroxetine and sertraline increase plasma concentration of clozapine (increased risk of toxicity); fluvoxamine increases plasma concentration of olanzapine; SSRIs possibly increase plasma concentration of pimozone (increased risk of ventricular arrhythmias—avoid concomitant use); paroxetine possibly increases plasma concentration of risperidone (increased risk of toxicity); paroxetine increases plasma concentration of sertindole
- Antivirals: plasma concentration of paroxetine and sertraline possibly reduced by darunavir; plasma concentration of paroxetine reduced by efavirenz; plasma concentration of paroxetine possibly reduced by ritonavir; plasma concentration of SSRIs possibly increased by ritonavir
- Anxiolytics and Hypnotics: fluvoxamine increases plasma concentration of some benzodiazepines; fluvoxamine increases plasma concentration of melatonin—avoid concomitant use; sedative effects possibly increased when sertraline given with zolpidem
- Bupropion: plasma concentration of citalopram possibly increased by bupropion
- Calcium-channel Blockers: fluoxetine possibly inhibits metabolism of nifedipine (increased plasma concentration)
- Dopaminergics: caution with paroxetine advised by manufacturer of entacapone; increased risk of CNS toxicity when SSRIs given with rasagiline; fluvoxamine should not be started until 2 weeks after stopping rasagiline; fluoxetine should not be started until 2 weeks after stopping rasagiline, also rasagiline should not be started until at least 5 weeks after stopping fluoxetine; increased risk of hypotension and CNS excitation when paroxetine or sertraline given with selegiline; selegiline should not be started until 2 weeks after stopping paroxetine or sertraline, avoid paroxetine or sertraline for 2 weeks after stopping selegiline; increased risk of hyperpnea and CNS excitation when fluvoxamine given with selegiline (selegiline should not be started until 1 week after stopping fluvoxamine, avoid fluvoxamine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when fluoxetine given with selegiline (selegiline should be not started until 1 week after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); theorectical risk of serotonin syndrome if citalopram given with selegline (especially if dose of selegline exceeds 10 mg daily); manufacturer of escitalopram advises caution with selegline
- 5HT Agonists: possible increased serotonergic effects when SSRIs given with troleandomycin; fluvoxamine inhibits the metabolism of troleandomycin; increased risk of CNS toxicity when citalopram, escitalopram, fluoxetine, fluvoxamine or paroxetine given with sumatriptan; increased risk of CNS toxicity when sertraline given with sumatriptan (manufacturer of sertraline advises avoid concomitant use); fluvoxamine possibly inhibits metabolism of zolmitriptan; increased risk of CNS toxicity when citalopram given with fluoxetine, escitalopram, and paroxetine increases plasma concentration of clozapine (increased risk of toxicity); fluvoxamine increases plasma concentration of olanzapine; SSRIs possibly increase plasma concentration of pimozone (increased risk of ventricular arrhythmias—avoid concomitant use); paroxetine possibly increases plasma concentration of risperidone (increased risk of toxicity); paroxetine increases plasma concentration of sertindole
- Antidepressants, SSRI
- 5HT Agonists (continued)
  - amine possibly inhibits metabolism of zolmitriptan
  - Lithium: increased risk of CNS effects when SSRIs given with lithium (lithium toxicity reported)
  - Muscle Relaxants: fluvoxamine increases plasma concentration of izoxidine (increased risk of toxicity)—avoid concomitant use
  - Parasympathomimetics: paroxetine increases plasma concentration of galantamine
  - Sympathomimetics: metabolism of SSRIs possibly inhibited by methylphenidate
- Theophylline: fluvoxamine increases plasma concentration of theophylline (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration)
- Antidepressants, Tricyclic
  - Adrenergic Neurone Blockers: tricyclics antagonise anticonvulsant effect of neurotransmitters
  - Alcohol: increased sedative effect when tricyclics given with alcohol
  - Alpha-adrenergic Stimulants: avoidance of tricyclics by manufacturer of aripiprazole and brimonidine
  - Anaesthetics, General: increased risk of arrhythmias and hypotension when tricyclics given with general anaesthetics
  - Analgesics: increased risk of CNS toxicity when tricyclics given with tramadol; side-effects possibly increased when tricyclics given with nefopam; sedative effects possibly increased when tricyclics given with opioid analgesics
  - Anti-arrhythmics: increased risk of ventricular arrhythmias when tricyclics given with amiodarone—avoid concomitant use; increased risk of ventricular arrhythmias when tricyclics given with disopyramide or lefacainide; increased risk of arrhythmias when tricyclics given with propafenone
  - Antibacterials: increased risk of ventricular arrhythmias when tricyclics given with moxifloxacin—avoid concomitant use; plasma concentration of tricyclics possibly reduced by rifampicin
  - Anticoagulants: tricyclics may enhance or reduce anticoagulant effect of coumarins
  - Antidepressants: possible increased serotonergic effects when tricyclics given with amitriptyline or clomipramine given with duloxetine; increased risk of hypertension and CNS excitation when tricyclics given with MAOIs, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine); after stopping tricyclics do not start moclobemide for at least 1 week; plasma concentration of some tricyclics increased by SSRIs; plasma concentration of amitriptyline increased by St John’s wort
  - Antiepileptics: tricyclics antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); metabolism of tricyclics accelerated by carbamazepine (reduced plasma concentration and reduced effect); plasma concentration of tricyclics possibly reduced by phenytoin; tricyclics antagonise anticonvulsant effect of primidone (convulsive threshold lowered), also metabolism of tricyclics possibly accelerated (reduced plasma concentration)
Antidepressants, Tricyclic (continued)

Sympathomimetics (continued) of hypertension and arrhythmias when tricyclics given with

Thyroid Hormones: effects of tricyclics possibly enhanced by thyroid hormones; effects of amitriptyline and imipramine enhanced by thyroid hormones

Ulcer-healing Drugs: plasma concentration of tricyclics possibly increased by cimetidine; metabolism of amitriptyline, doxepin, imipramine and nortriptyline inhibited by cimetidine (increased plasma concentration)

Antidepressants, Tricyclic (related)

- Alcohol: increased sedative effect when tricyclic-related antidepressants given with alcohol
- Alpha-adrenoceptor Stimulants: avoidance of antidepressants advised by manufacturer of atomoxetine; possible increased antimuscarinic and sedative effects when tricyclic-related antidepressants given with atomoxetine

Antihistamines: increased antimuscarinic and sedative effects when tricyclic-related antidepressants given with antihistamines

Antimalarials: avoidance of antidepressants advised by manufacturer of artether/lumefantrine

Antimuscarinics: increased risk of antimuscarinic side-effects when tricyclics given with antimuscarinics

Anxiolytics and Hypnotics: increased sedative effect when tricyclics given with anxiolytics and hypnotics

Atomoxetine: increased risk of venricular arrhythmias when tricyclics given with atomoxetine; possible increased risk of convulsions when antidepressants given with atomoxetine

Barbiturates: tricyclics antagonise anticonvulsant effect of barbiturates (convulsive threshold lowered), also metabolism of tricyclics possibly accelerated (reduced plasma concentration)

Beta-blockers: plasma concentration of imipramine increased by labetalol and propranolol; increased risk of venricular arrhythmias when tricyclics given with sotalol

Calcium-channel Blockers: plasma concentration of imipramine increased by diltiazem and verapamil; plasma concentration of tricyclics possibly increased by diltiazem and verapamil

Clonidine: tricyclics antagonise hypotensive effect of clonidine, also increased risk of hypertension on clonidine withdrawal

Disulfiram: metabolism of tricyclics inhibited by disulfiram (increased plasma concentration); concommitant amitriptyline reported to increase disulfiram reaction with alcohol

Dihydropyridine calcium antagonists: increased risk of postural hypotension when tricyclics given with diuretics

Dopaminergics: caution with tricyclics advised by manufacturer of entacapone; increased risk of CNS toxicity when tricyclics given with rasagiline; CNS toxicity reported when tricyclics given with selegiline

Lithium: risk of toxicity when tricyclics given with lithium

Muscle Relaxants: tricyclics enhance muscle relaxant effect of baclofen

Nicorandil: tricyclics possibly enhance hypotensive effect of nicorandil

Nitrates: tricyclics reduce effects of sublingual tablets of nitrates (failure to dissolve under tongue owing to dry mouth)

Oestrogens: increased risk of CNS toxicity when tricyclics given with oestrogens (but side-effects of tricyclics possibly increased due to increased plasma concentration)

Pentamidine Isetionate: increased risk of venricular arrhythmias when tricyclics given with pentamidine isetionate

Sibutramine: increased risk of CNS toxicity when tricyclics given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Sodium Oxybate: increased risk of side-effects when tricyclics given with sodium oxybate

Sympathomimetics: increased risk of hypertension and arrhythmias when tricyclics given with dopamine (epinephrine) (but local anaesthetics with adrenaline appear to be safe); metabolism of tricyclics possibly inhibited by methylphenidate; increased risk

Antifungals, Tricyclic (continued)

Antifungals: plasma concentration of imipramine and norimipramine possibly increased by terbinafine

Antihistamines: increased antimuscarinic and sedative effects when tricyclics given with antihistamines

Antimalaria Drugs: plasma concentration of tricyclics possibly increased by meprofoliate (norephedrine) (but local anaesthetics with adrenaline appear to be safe); metabolism of tricyclics possibly inhibited by methylphenidate; increased risk

Antimalarials: avoidance of antidepressants advised by manufacturer of artether/lumefantrine

Antimuscarinics: increased risk of antimuscarinic side-effects when tricyclics given with antimuscarinics

Antipsychotics: plasma concentration of tricyclics increased by antipsychotics—possibly increased risk of venricular arrhythmias; possibly increased antimuscarinic side-effects when tricyclics given with clozapine; increased risk of antimuscarinic side-effects when tricyclics given with phenothiazines; increased risk of venricular arrhythmias when tricyclics given with pipemidone—avoid concomitant use

Antivirals: side-effects of tricyclics possibly increased by fosamprenavir; plasma concentration of tricyclics possibly increased by ritonavir

Anxiolytics and Hypnotics: increased sedative effect when tricyclics given with anxiolytics and hypnotics

Atomoxetine: increased risk of venricular arrhythmias when tricyclics given with atomoxetine; possible increased risk of convulsions when antidepressants given with atomoxetine

Barbiturates: tricyclics antagonise anticonvulsant effect of barbiturates (convulsive threshold lowered), also metabolism of tricyclics possibly accelerated (reduced plasma concentration)

Beta-blockers: plasma concentration of imipramine increased by labetalol and propranolol; increased risk of venricular arrhythmias when tricyclics given with sotalol

Calcium-channel Blockers: plasma concentration of imipramine increased by diltiazem and verapamil; plasma concentration of tricyclics possibly increased by diltiazem and verapamil

Clonidine: tricyclics antagonise hypotensive effect of clonidine, also increased risk of hypertension on clonidine withdrawal

Disulfiram: metabolism of tricyclics inhibited by disulfiram (increased plasma concentration); concommitant amitriptyline reported to increase disulfiram reaction with alcohol

Dihydropyridine calcium antagonists: increased risk of postural hypotension when tricyclics given with diuretics

Dopaminergics: caution with tricyclics advised by manufacturer of entacapone; increased risk of CNS toxicity when tricyclics given with rasagiline; CNS toxicity reported when tricyclics given with selegiline

Lithium: risk of toxicity when tricyclics given with lithium

Muscle Relaxants: tricyclics enhance muscle relaxant effect of baclofen

Nicorandil: tricyclics possibly enhance hypotensive effect of nicorandil

Nitrates: tricyclics reduce effects of sublingual tablets of nitrates (failure to dissolve under tongue owing to dry mouth)

Oestrogens: increased risk of CNS toxicity when tricyclics given with oestrogens (but side-effects of tricyclics possibly increased due to increased plasma concentration)

Pentamidine Isetionate: increased risk of venricular arrhythmias when tricyclics given with pentamidine isetionate

Sibutramine: increased risk of CNS toxicity when tricyclics given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Sodium Oxybate: increased risk of side-effects when tricyclics given with sodium oxybate

Sympathomimetics: increased risk of hypertension and arrhythmias when tricyclics given with dopamine (epinephrine) (but local anaesthetics with adrenaline appear to be safe); metabolism of tricyclics possibly inhibited by methylphenidate; increased risk

Antidepressants, Tricyclic

- Sympathomimetics (continued) of hypertension and arrhythmias when tricyclics given with

Thyroid Hormones: effects of tricyclics possibly enhanced by thyroid hormones; effects of amitriptyline and imipramine enhanced by thyroid hormones

Ulcer-healing Drugs: plasma concentration of tricyclics possibly increased by cimetidine; metabolism of amitriptyline, doxepin, imipramine and nortriptyline inhibited by cimetidine (increased plasma concentration)

Antidepressants, Tricyclic (related)

- Alcohol: increased sedative effect when tricyclic-related antidepressants given with alcohol
- Alpha-adrenoceptor Stimulants: avoidance of tricyclic-related antidepressants advised by manufacturer of apraclonidine and brimonidine

Antidepressants: tricyclic-related antidepressants should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; after stopping tricyclic-related antidepressants do not start emoclomide for at least 1 week

Antiepileptics: tricyclic-related antidepressants possibly antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); plasma concentration of mianserin reduced by carbamazepine and phenytoin; metabolism of mianserin accelerated by primidone (reduced plasma concentration)

Antihistamines: possible increased antimuscarinic and sedative effects when tricyclic-related antidepressants given with antihistamines

Antimalarials: avoidance of antidepressants advised by manufacturer of artether/lumefantrine

Antimuscarinics: possibly increased antimuscarinic side-effects when tricyclic-related antidepressants given with antimuscarinics

Antivirals: side-effects possibly increased when trazodone given with ritonavir

Anxiolytics and Hypnotics: increased sedative effect when tricyclic-related antidepressants given with anxiolytics and hypnotics

Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine

Barbiturates: tricyclic-related antidepressants possibly antagonise anticonvulsant effect of barbiturates (convulsive threshold lowered); plasma concentration of mianserin reduced by carbamazepine and phenytoin; metabolism of mianserin accelerated by primidone (reduced plasma concentration)

Diazoxide: enhanced hypotensive effect when tricyclic-related antidepressants given with diazoxide

Nitrates: tricyclic-related antidepressants possibly reduce effects of sublingual tablets of nitrates (failure to dissolve under tongue owing to dry mouth)

Sibutramine: increased risk of CNS toxicity when tricyclic-related antidepressants given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Vasodilator Antihypertensives: enhanced hypotensive effect when tricyclic-related antidepressants given with hydralazine or sodium nitroprusside

Antidiabetics

Note Other oral drugs may be taken at least 1 hour before or 4 hours after exenatide injection, or taken with a meal when exenatide is not administered, to minimise possible interference with absorption

ACE inhibitors: hypoglycaemic effect of insulin, metformin and sulphonylureas possibly enhanced by ACE inhibitors

Alcohol: hypoglycaemic effect of antidepressants enhanced by alcohol; increased risk of lactic acidosis when metformin given with alcohol; flushing, in susceptible subjects, when chlorpropamide given with alcohol

Anabolic Steroids: hypoglycaemic effect of anti-diabetes possibly enhanced by anabolic steroids
Antidiabetics (continued)

- Analgesics: effects of sulphonylureas possibly enhanced by NSAIDs; effects of tolbutamide enhanced by disopyramide (avoid concomitant use)

- Anti-arhythmics: hypoglycaemic effect of glitazides, insulin and metformin possibly enhanced by disopyramide

- Antibacterials: hypoglycaemic effect of acarbose possibly enhanced by neomycin; also severity of gastrointestinal effects increased; effects of repaglinide enhanced by daptomycin; effects of glibenclamide possibly enhanced by ciprofloxacin and norfloxacin; plasma concentration of nateglinide reduced by rifampicin; hypoglycaemic effect of repaglinide possibly antagonised by rifampicin; plasma concentration of rosiglitazone reduced by sulphonylureas possibly reduced by trimethoprim—manufacturer advises avoid concomitant use

- Anticoagulants: exenatide possibly enhances anticoagulant effect of warfarin; hypoglycaemic effect of sulphonylureas possibly enhanced by coenzymes, also possible changes to anticoagulant effect

- Antidepressants: hypoglycaemic effect of insulin, metformin and sulphonylureas enhanced by MAOIs; hypoglycaemic effect of antidiabetics possibly enhanced by MAOIs

- Antiepileptics: tolbutamide transiently increases plasma concentration of phenytoin (possibility of toxicity); plasma concentration of gliclazide and glipizide enhanced by sulfinpyrazone; effects of sulphonylureas enhanced by phenothiazines; metabolism of chlorpropamide and tolbutamide accelerated by neflamycins (reduced effect); metabolism of sulphonylureas possibly accelerated by neflamycins (reduced effect); effects of sulphonylureas rarely enhanced by sulphonamides and trimethoprim with hypoglycaemic effect of repaglinide possibly enhanced by trimethoprim—manufacturer advises avoid concomitant use

- Anti-influenzal: hypoglycaemic effect of insulin, metformin and sulphonylureas enhanced by MAOIs; hypoglycaemic effect of antidiabetics possibly enhanced by MAOIs

- Antifungals: plasma concentration of sulphonylureas increased by fluconazole and micafungone; hypoglycaemic effect of glitazides and glipizide enhanced by micafungone—avoid concomitant use; hypoglycaemic effect of nateglinide possibly enhanced by posaconazole; plasma concentration of sulphonylureas possibly increased by voriconazole

- Antihistamines: thrombocyte count depressed when metformin given with ketotifen (manufacturer of ketotifen advises avoid concomitant use)

- Antivirals: hypoglycaemic effect of sulphonylureas possibly antagonised by phenothiazines

- Antivirals: plasma concentration of tolbutamide possibly increased by ritonavir

- Aprepitant: plasma concentration of tolbutamide reduced by aprepitant

- Beta-blockers: warning signs of hypoglycaemia (such as tremor) with antidiabetics may be masked when β-blockers given; hypoglycaemic effect of insulin enhanced by β-blockers

- Bosentan: increased risk of hepatotoxicity when glibenclamide given with bosentan—avoid concomitant use

- Calcium-channel blockers: glucose tolerance occasionally impaired when insulin given with nifedipine

- Cardiac Glycosides: sitagliptin increases plasma concentration of digoxin; acarbose possibly reduces plasma concentration of digoxin

- Ciclosporin: hypoglycaemic effect of repaglinide possibly enhanced by ciclosporin

- Corticosteroids: hypoglycaemic effect of antidiabetics antagonised by corticosteroids

- Cytotoxics: avoidance of repaglinide advised by manufacturer of lapatinib; metabolism of rosiglitazone possibly inhibited by paclitaxel

- Diazoxide: hypoglycaemic effect of antidiabetics antagonised by diazoxide

Antidiabetics (continued)

- Diuretics: hypoglycaemic effect of antidiabetics antagonised by loop diuretics and thiazides and related diuretics; increased risk of hypokalaemia when chlorpropamide given with potassium-sparing diuretics and aldosterone antagonists plus thiazide; increased risk of hyponatraemia when chlorpropamide given with thiazides and related diuretics plus potassium-sparing diuretic

- Hormone Antagonists: requirements for insulin, metformin, glibenclamide and sulphonylureas possibly reduced by lanreotide; requirements for insulin, metformin, repaglinide and sulphonylureas possibly reduced by octreotide

- Leflunomide: hypoglycaemic effect of tolbutamide possibly enhanced by lefunomide

- Lipid-regulating Drugs: hypoglycaemic effect of acarbose possibly enhanced by colchicine; hypoglycaemic effect of nateglinide possibly enhanced by gemfibrozil; increased risk of severe hypoglycaemia when repaglinide given with gemfibrozil—avoid concomitant use; plasma concentration of rosiglitazone increased by gemfibrozil (consider reducing dose of rosiglitazone); plasma concentration of glibenclamide possibly increased by fluvastatin; may be improved glucose tolerance and an additive effect when insulin or sulphonylureas given with fibrates

- Oestrogens: hypoglycaemic effect of antidiabetics antagonised by oestrogens

- Orlistat: avoidance of acarbose advised by manufacturer of orlistat

- Pancreatins: hypoglycaemic effect of acarbose antagonised by panreatin

- Probenecid: hypoglycaemic effect of chlorpropamide possibly enhanced by probenecid

- Progestogens: hypoglycaemic effect of antidiabetics antagonised by progestogens

- Sulfinpyrazone: effects of sulphonylureas enhanced by sulfinpyrazone

- Testosterone: hypoglycaemic effect of antidiabetics possibly enhanced by testosterone

- Ulcer-healing Drugs: excroion of metformin reduced by cimetidine (increased plasma concentration); hypoglycaemic effect of sulphonylureas enhanced by cimetidine

Antiepileptics see Carbamazepine, Ethosuximide, Gaba-pentin, Lacosamide, Lamotrigin, Levetiracetam, Oxcarebezpine, Phenytoin, Primidon, Rufinamide, Tiagabine, Topiramate, Valproate, Vigabatrin, and Zonisamide

Antifungals see Amphotericin; Antifungals, Imidazole; Antifungals, Triazole; Cefsporin; Flucytosine; Griseofulvin; Micafungin; Terbinafine

Antifungals, Imidazole

- Aliskiren: ketonozonate increases plasma concentration of aliskiren

- Analgesics: ketonozonate inhibits metabolism of suprenorphine (reduce dose of buprenorphine)

- Antacids: absorption of ketonozonate reduced by antacids

- Anti-arhythmics: increased risk of ventricular arrhyth-mias when ketonozonate given with disopyramide—avoid concomitant use

- Antibacterials: metabolism of ketonozonate accelerated by rifampicin (reduced plasma concentration), also plasma concentration of rifampicin may be reduced; plasma concentration of ketonozonate possibly reduced by isoniazid; avoidance of concomitant ketonozonate in severe renal and hepatic impairment advised by manufacturer of telithromycin

- Anticoagulants: ketonozonate enhances anticoagulant effect of coenuramins (micazone oral gel and possibly vaginal formulations absorbed); ketonozonate increases plasma concentration of rivaroxaban—avoid concomitant use
Antifungals, Imidazole (continued)

- Antidepressants: avoidance of imidazoles advised by manufacturer of paroxetine; ketoconazole increases plasma concentration of mirtazapine.

- Anti-inflammatory: miconazole enhances hypoglycaemic effect of glimepiride and glipizide—avoid concomitant use; miconazole increases plasma concentration of sulphonylureas.

- Antiepileptics: ketoconazole and miconazole possibly increase plasma concentration of carbamazepine; plasma concentration of ketoconazole reduced by phenytoin; miconazole enhances anticonvulsant effect of phenytoin (plasma concentration of phenytoin increased) Antifungals: imidazoles possibly antagonise effects of amphotericin.

- Antihistamines: manufacturer of loratadine advises ketoconazole possibly increases plasma concentration of loratadine; imidazoles possibly inhibit metabolism of emozolastine (avoid concomitant use); ketoconazole inhibits metabolism of emozolastine—avoid concomitant use.

- Antimalarials: avoidance of imidazoles advised by manufacturer of artether/luemetanfotin.

- Antimycobacterics: absorption of ketoconazole reduced by antismycobacterics; ketoconazole increases plasma concentration of darifenacin—avoid concomitant use; manufacturer of fosoterodine advises dose reduction when ketoconazole given with fosoterodine—avoid concomitant use; ketoconazole increases plasma concentration of solifenacin; avoidance of ketoconazole advised by manufacturer of tolterodine.

- Antipsychotics: ketoconazole inhibits metabolism of aripiprazole (reduce dose of aripiprazole); increased risk of ventricular arrhythmias when imidazoles given with eperozide—avoid concomitant use; imidazoles possibly increase plasma concentration of quetiapine (reduce dose of quetiapine); increased risk of ventricular arrhythmias when ketoconazole given with sertindole—avoid concomitant use; possible increased risk of ventricular arrhythmias when imidazoles given with sertindole—avoid concomitant use.

- Antivirals: plasma concentration of both drugs increased when ketoconazole given with darunavir; plasma concentration of ketoconazole increased by fosamprenavir; ketoconazole increases plasma concentration of indinavir and maraviroc (consider reducing dose of indinavir and maraviroc); plasma concentration of ketoconazole reduced by nevirapine—avoid concomitant use; combination of ketoconazole with ritonavir may increase plasma concentration of either drug (or both); ketoconazole increases plasma concentration of saquinavir; imidazoles possibly increase plasma concentration of saquinavir.

- Anxiolytics and Hypnotics: ketoconazole increases plasma concentration of alprazolam; miconazole increases plasma concentration of midazolam (risk of prolonged sedation) Aprepitant: ketoconazole increases plasma concentration of aprepitant.

- Bosentan: ketoconazole increases plasma concentration of bosentan.

- Calcium-channel Blockers: ketoconazole inhibits metabolism of diltiazem (increased plasma concentration); avoidance of ketoconazole advised by manufacturer of diltiazem; ketoconazole possibly inhibits metabolism of dihydropyridines (increased plasma concentration).

- Ciclosporin: ketoconazole inhibits metabolism of ciclosporin (increased plasma concentration); miconazole possibly inhibits metabolism of ciclosporin (increased plasma concentration).

- Clobetasol: ketoconazole possibly increases plasma concentration of clobetasol—avoid concomitant use.

- Cinacalcet: ketoconazole inhibits metabolism of cinacalcet (increased plasma concentration).

Antifungals, Imidazole (continued)

- Corticosteroids: ketoconazole possibly inhibits metabolism of dexamethasone; ketoconazole increases plasma concentration of inhaled and oral budesonide; ketoconazole increases plasma concentration of active metabolite of ciclesonide; ketoconazole inhibits the metabolism of methylprednisolone; ketoconazole increases plasma concentration of inhaled mometasone furoate.

- Cytochrome P450: ketoconazole inhibits metabolism of erlotinib and sunitinib (increased plasma concentration); ketoconazole increases plasma concentration of bortezomib and imatinib; ketoconazole increases plasma concentration of elapatinib and nilotinib—avoid concomitant use; ketoconazole increases plasma concentration of active metabolite of temsirolimus—avoid concomitant use; in vitro studies suggest a possible interaction between ketoconazole and docetaxel (consult docetaxel product literature); ketoconazole reduces plasma concentration of irinotecan (but concentration of active metabolite of irinotecan increased)—avoid concomitant use.

- Diuretics: ketoconazole increases plasma concentration of spironolactone—avoid concomitant use.

- Dopemidine: ketoconazole possibly increases risk of arrhythmias with domperidone.

- Ergot Alkaloids: increased risk of ergotism when imidazoles given with ergotamine and methysergide—avoid concomitant use.

- 5HT Agonists: ketoconazole increases plasma concentration of almotriptan (increased risk of toxicity); ketoconazole increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use.

- Ibravadin: ketoconazole increases plasma concentration of ibravadin—avoid concomitant use. Lanthanum: absorption of ketoconazole possibly reduced by lanthanum (give at least 2 hours apart).

- Lipid-Regulating Drugs: possible increased risk of myopathy when imidazoles given with atorvastatin or simvastatin; increased risk of myopathy when ketoconazole given with simvastatin (avoid concomitant use); possible increased risk of myopathy when miconazole given with simvastatin—avoid concomitant use.

- Oestrogens: anecdotal reports of contraceptive failure when imidazoles or ketoconazole given with oestrogens.

- Parasympathomimetics: ketoconazole increases plasma concentration of galantamine.

- Retinoids: ketoconazole increases plasma concentration of allretinoin.

- Rimonabant: ketoconazole increases plasma concentration of rimonabant.

- Sildenafil: ketoconazole increases plasma concentration of sildenafil.

- Sirolimus: ketoconazole increases plasma concentration of sirolimus—avoid concomitant use; miconazole increases plasma concentration of sirolimus.

- Tacrolimus: imidazoles possibly increase plasma concentration of tacrolimus; ketoconazole increases plasma concentration of tacrolimus.

- Tadalafil: ketoconazole increases plasma concentration of tadalafil.

- Theophylline: ketoconazole possibly increases plasma concentration of theophylline.

- Ulcer-healing Drugs: absorption of ketoconazole reduced by histamine H₂-antagonists, proton pump inhibitors and sucralfate.

- Vardenafil: ketoconazole increases plasma concentration of vardenafil—avoid concomitant use.

- Vitamins: ketoconazole possibly increases plasma concentration of paricalcitol.

Antifungals, Polyene see Amphotericin.

Antifungals, Triazole

- Note: In general, fluconazole interactions relate to multiple-dose treatment.

- Analgesics: fluconazole increases plasma concentration of celecoxib (halve dose of celecoxib); flucon-
Antifungals, Triazole
- Analgesics (continued)
aazole increases plasma concentration of parecoxib (parecoxib). Voriconazole increases plasma concentration of alfentanil and methadone (consider reducing dose of alfentanil and methadone); fluconazole inhibits metabolism of alfentanil (risk of prolonged or delayed respiratory depression); itraconazole possibly inhibits metabolism of alfentanil; fluconazole and itraconazole possibly increase plasma concentration of fentanyl.

Antacids: absorption of itraconazole reduced by antacids.
- Anti-arhythmic: manufacturer of itraconazole advises avoid concomitant use with disopyramide.
- Antimicrobials: plasma concentration of itraconazole increased by clarithromycin; triazoles possibly increase plasma concentration of erlubutin (increased risk of uveitis—reduce rifabutin dose); posaconazole increases plasma concentration of rifabutin (also plasma concentration of posaconazole reduced); voriconazole increases plasma concentration of rifabutin; itraconazole and voriconazole possibly reduced by rifabutin; plasma concentration of posaconazole reduced by rifabutin—avoid concomitant use; plasma concentration of posaconazole reduced by rifampicin; plasma concentration of voriconazole reduced by rifampicin—avoid concomitant use; metabolism of fluconazole and itraconazole accelerated by rifampicin.
- Anticoagulants: fluconazole, itraconazole and voriconazole enhance anticoagulant effect of coumarins; avoidance of itraconazole, posaconazole and voriconazole advised by manufacturer of rivaroxaban.
- Antidepressants: avoidance of triazoles advised by manufacturer of esketamine; plasma concentration of voriconazole reduced by St John’s wort—avoid concomitant use.
- Antidiabetics: posaconazole possibly increases hypoglycaemic effect of glipizide; fluconazole possibly enhances hypoglycaemic effect of nateglinide; itraconazole possibly enhances hypoglycaemic effect of repaglinide; fluconazole increases plasma concentration of sulphonylureas; voriconazole possibly increases plasma concentration of sulphonylureas.
- Antiepileptics: plasma concentration of itraconazole and posaconazole possibly reduced by carbamazepine; fluconazole possibly increases plasma concentration of carbamazepine; plasma concentration of voriconazole possibly reduced by carbamazepine and erimidine—avoid concomitant use; voriconazole increases plasma concentration of phenytoin, also phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity); plasma concentration of posaconazole reduced by carbamazepine and erimidine; plasma concentration of itraconazole reduced by erimidine—avoid concomitant use; fluconazole increases plasma concentration of phenytoin (consider reducing dose of phenytoin); plasma concentration of posaconazole possibly reduced by erimidine.
- Antifungals: triazoles possibly antagonise effects of amphotericin; plasma concentration of itraconazole increased by micafungin (consider reducing dose of itraconazole).
- Antihistamines: itraconazole inhibits metabolism of mizolastine—avoid concomitant use.
- Antimalarias: avoidance of triazoles advised by manufacturer of darifenacin and tolterodine; manufacturer of fosoterodine advises dose reduction when itraconazole given with fosoterodine consult fosoterodine package literature; itraconazole increases plasma concentration of solifenacin.

Antipsychotics: itraconazole possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); itraconazole increases risk of ventricular arrhythmias when triazoles given with pimozide—avoid concomitant use; triazoles possibly increase plasma concentration of quetiapine (reduce dose of quetiapine); possible increased risk of ventricular arrhythmias when triazoles given with sertindole—avoid concomitant use; increased risk of ventricular arrhythmias when itraconazole given with sertindole—avoid concomitant use.
- Antivirals: posaconazole increases plasma concentration of efavirenz; plasma concentration of voriconazole and posaconazole reduced by efavirenz; plasma concentration of voriconazole possibly increased by fosamprenavir, atazanavir and also monitor for rifabutin toxicity); itraconazole increases plasma concentration of efavirenz (consider increasing voriconazole dose and reducing efavirenz dose); plasma concentration of itraconazole possibly increased by fosamprenavir; voriconazole increases plasma concentration of indinavir (consider reducing dose of indinavir); fluconazole increases plasma concentration of nevirapine, ritonavir and tipranavir; plasma concentration of voriconazole reduced by ritonavir—avoid concomitant use; combination of itraconazole with ritonavir may increase plasma concentration of either drug (or both); voriconazole possibly increase plasma concentration of saquinavir; fluconazole increases plasma concentration of zidovudine (increased risk of toxicity).
- Anxiolytics and Hypnotics: itraconazole increases plasma concentration of alprazolam; posaconazole increases plasma concentration of midazolam; fluconazole and itraconazole increase plasma concentration of ziprasidone; voriconazole and also monitor for phenytoin toxicity); voriconazole and also monitor for phenytoin toxicity); voriconazole increases plasma concentration of ziprasidone; itraconazole and voriconazole advised by manufacturer of fesoterodine—consult fesoterodine package literature; itraconazole increases plasma concentration of solifenacin.

Antifungals, Triazole
- Antimuscarinics (continued)
itraconazole given with fesoterodine consult fesoterodine package literature; itraconazole increases plasma concentration of solifenacin.
- Antipsychotics: itraconazole possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); itraconazole increases risk of ventricular arrhythmias when triazoles given with pimozide—avoid concomitant use; triazoles possibly increase plasma concentration of quetiapine (reduce dose of quetiapine); possible increased risk of ventricular arrhythmias when triazoles given with sertindole—avoid concomitant use; increased risk of ventricular arrhythmias when itraconazole given with sertindole—avoid concomitant use.
- Antivirals: posaconazole increases plasma concentration of efavirenz; plasma concentration of voriconazole and posaconazole reduced by efavirenz; plasma concentration of voriconazole possibly increased by fosamprenavir; voriconazole increases plasma concentration of indinavir (consider reducing dose of indinavir); fluconazole increases plasma concentration of nevirapine, ritonavir and tipranavir; plasma concentration of voriconazole reduced by ritonavir—avoid concomitant use; combination of itraconazole with ritonavir may increase plasma concentration of either drug (or both); voriconazole possibly increase plasma concentration of saquinavir; fluconazole increases plasma concentration of zidovudine (increased risk of toxicity).
- Anxiolytics and Hypnotics: itraconazole increases plasma concentration of alprazolam; posaconazole increases plasma concentration of midazolam; fluconazole and itraconazole increase plasma concentration of ziprasidone; voriconazole and also monitor for phenytoin toxicity); voriconazole increases plasma concentration of ziprasidone; itraconazole and voriconazole advised by manufacturer of fesoterodine—consult fesoterodine package literature; itraconazole increases plasma concentration of solifenacin.

Antifungals, Triazole
- Antimuscarinics (continued)
itraconazole given with fesoterodine consult fesoterodine package literature; itraconazole increases plasma concentration of solifenacin.
- Antipsychotics: itraconazole possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); itraconazole increases risk of ventricular arrhythmias when triazoles given with pimozide—avoid concomitant use; triazoles possibly increase plasma concentration of quetiapine (reduce dose of quetiapine); possible increased risk of ventricular arrhythmias when triazoles given with sertindole—avoid concomitant use; increased risk of ventricular arrhythmias when itraconazole given with sertindole—avoid concomitant use.
- Antivirals: posaconazole increases plasma concentration of efavirenz; plasma concentration of voriconazole and posaconazole reduced by efavirenz; plasma concentration of voriconazole possibly increased by fosamprenavir; voriconazole increases plasma concentration of indinavir (consider reducing dose of indinavir); fluconazole increases plasma concentration of nevirapine, ritonavir and tipranavir; plasma concentration of voriconazole reduced by ritonavir—avoid concomitant use; combination of itraconazole with ritonavir may increase plasma concentration of either drug (or both); voriconazole possibly increase plasma concentration of saquinavir; fluconazole increases plasma concentration of zidovudine (increased risk of toxicity).
- Anxiolytics and Hypnotics: itraconazole increases plasma concentration of alprazolam; posaconazole increases plasma concentration of midazolam; fluconazole and itraconazole increase plasma concentration of ziprasidone; voriconazole and also monitor for phenytoin toxicity); voriconazole increases plasma concentration of ziprasidone; itraconazole and voriconazole advised by manufacturer of fesoterodine—consult fesoterodine package literature; itraconazole increases plasma concentration of solifenacin.

Antifungals, Triazole
- Antimuscarinics (continued)
itraconazole given with fesoterodine consult fesoterodine package literature; itraconazole increases plasma concentration of solifenacin.
Antifungals, Triazole (continued)

- Diuretics: fluconazole increases plasma concentration of thiazides (reduce dose of thiazide); itraconazole increases plasma concentration of spironolactone—avoid concomitant use; plasma concentration of fluconazole increased by hydrochlorothiazide
- Ergot Alkaloids: increased risk of ergotism when triazoles given with ergotamine and methysergide—avoid concomitant use
- 5HT Agonists: itraconazole increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use
- Ixavudrine: fluconazole increases plasma concentration of ivabradine—reduce initial dose of ivabradine; itraconazole possibly increases plasma concentration of ivabradine—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when triazoles given with atorvastatin or simvastatin; increased risk of myopathy when itraconazole or posaconazole given with atorvastatin (avoid concomitant use); fluconazole increases plasma concentration of fluvastatin; itraconazole and voriconazole increase plasma concentration of simvastatin—avoid concomitant use
- Oestrogenergines: anecdotal reports of contraceptive failure when fluconazole or itraconazole given with oestrogenergines
- Sildenafil: itraconazole increases plasma concentration of sildenafil—reduce initial dose of sildenafil
- Sirolimus: posaconazole possibly increases plasma concentration of sirolimus; itraconazole and voriconazole increase plasma concentration of sirolimus—avoid concomitant use
- Tacrolimus: triazoles possibly increase plasma concentration of tacrolimus; posaconazole increases plasma concentration of tacrolimus (reduce dose of tacrolimus); fluconazole, itraconazole, and voriconazole increase plasma concentration of tacrolimus
- Tadalafil: itraconazole possibly increases plasma concentration of tadalafil
- Theophylline: fluconazole possibly increases plasma concentration of theophylline
- Ulcer-healing Drugs: plasma concentration of posaconazole reduced by cimetidine; voriconazole possibly increases plasma concentration of esomeprazole; voriconazole increases plasma concentration of omeprazole (consider reducing dose of omeprazole); absorption of itraconazole reduced by histamine H2 antagonists and proton pump inhibitors
- Vardenafil: itraconazole possibly increases plasma concentration of vardenafil—avoid concomitant use

Antihistamines

Note: Sedative interactions apply to a lesser extent to the non-sedating antihistamines. Interactions do not generally apply to antihistamines used for topical action (including inhalation)

Alcohol: increased sedative effect when antihistamines given with alcohol (possibly less effect with non-sedating antihistamines)

Analgesics: sedative effects possibly increased when antihistamines given with opioid analgesics

Antacids: absorption of fexofenadine reduced by antacids

Anti-arthritics: increased risk of ventricular arrhythmias when mizolastine given with amiodyarone, disopyramide or propafenone—avoid concomitant use

Antibacterials: manufacturer of loratadine advises plasma concentration possibly increased by erythromycin; metabolism of mizolastine inhibited by erythromycin—avoid concomitant use; increased risk of ventricular arrhythmias when mizolastine given with moxifloxacin—avoid concomitant use; metabolism of mizolastine possibly inhibited by macrolides (avoid concomitant use)

Antidepressants: increased antimuscarinic and sedative effects when antihistamines given with MAOIs or tricyclics; cyproheptadine possibly antagonises antidepressant effect of SSRIs; possible increased antimuscarinic and sedative effects when antihistamines given with tricyclic-related antidepressants

Antidiabetics: thrombocyte count depressed when ketotifen given with metformin (manufacturer of ketotifen advises avoid concomitant use)

Antifungals: manufacturer of loratadine advises plasma concentration possibly increased by ketoconazole; metabolism of mizolastine inhibited by itraconazole or ketoconazole—avoid concomitant use; metabolism of mizolastine possibly inhibited by imidazoles (avoid concomitant use)

Antimuscarinics: increased risk of antimuscarinic side-effects when antihistamines given with antimuscarinics

Antivirals: plasma concentration of loratadine possibly increased by fosamprenavir; plasma concentration of chlorphenamine (chlorpheniramine) possibly increased by lopinavir; plasma concentration of non-sedating antihistamines possibly increased by ritonavir

Anxiolytics and Hypnotics: increased sedative effect when antihistamines given with anxiolytics and hypnotics

Beta-blockers: increased risk of ventricular arrhythmias when mizolastine given with sotalol—avoid concomitant use

Betahistine: antimuscarinics theoretically antagonise effect of betahistine

Ulcet-healing Drugs: manufacturer of loratadine advises plasma concentration possibly increased by cimetidine

Antihistamines, Non-sedating: see Antihistamines

Antihistamines, Sedating: see Antihistamines

Antimalarials: manufacturer of Lumefantrine, Chloroquine and Hydroxychloroquine, Mefloquine, Primaquine, Proguanil, and Quinine

Antimetabolites: see Cytarabine, Fludarabine, Fluorouracil, Mercaptopurine, Methotrexate, and Thioguanine

Antimuscarinics

Note: Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase side-effects such as dry mouth, urine retention, and constipation; concomitant use can also lead to confusion in the elderly. Interactions do not generally apply to antimuscarinics used by inhalation

Alcohol: increased sedative effect when loratadine given with alcohol

Analgesics: increased risk of antimuscarinic side-effects when antihistamines given with nefopam

Anti-arthritics: increased risk of ventricular arrhythmias when tolterodine given with amiodyarone, disopyramide or propafenone—increased risk of antimuscarinic side-effects when antihistamines given with disopyramide

Antibacterials: manufacturer of fesoterodine advises dose reduction when fesoterodine given with clarithromycin and telithromycin—consult fesoterodine product literature; manufacturer of tolterodine advises avoid concomitant use with clarithromycin and erythromycin; plasma concentration of darifenacin possibly increased by erythromycin; plasma concentration of active metabolite of fesoterodine reduced by rifampicin

Antidepressants: plasma concentration of darifenacin and propoxyphene increased by paroxetine; increased risk of antimuscarinic side-effects when antimuscarinics given with MAOIs or tricyclics; possibly increased antimuscarinic side-effects when antimuscarinics given with tricyclic-related antidepressants

Antifungals: antimuscarinics reduce absorption of ketoconazole; manufacturer of fesoterodine advises dose reduction when fesoterodine given with itraconazole and ketoconazole—consult fesoterodine...
Anti-arrhythmics
Antifungals (continued)

Antipsychotics: increased risk of antimuscarinic side-effects when antimuscarinics given with antipsychotics (increased risk of antimuscarinic side-effects); possible increased risk of ventricular arrhythmias when amisulpride, haloperidol, phenothiazines, pimozide, sertindole or zuclopenthixol given with amisulpride or sertindole; increased risk of ventricular arrhythmias when sulpiride given with amisulpride or sulpiride; possible increased risk of ventricular arrhythmias when pimozide given with amisulpride or sulpiride; increased risk of ventricular arrhythmias when amisulpride or sulpiride given with paroxetine; plasma concentration of clozapine possibly increased by paroxetine; metabolism of aripiprazole possibly inhibited by paroxetine; concentration of clozapine possibly reduced by kaolin

Antipsychotics

Note
Increased risk of toxicity with myelosuppressive drugs
Note
Avoid concomitant use of clozapine with drugs that have a substantial potential for causing agranulocytosis
ACE inhibitors: enhanced hypotensive effect when antipsychotics given with ACE inhibitors
Adrenergic Neurone Blockers: enhanced hypotensive effect when phenothiazines given with adrenergic neurone blockers; higher doses of chlorpromazine antagonise hypotensive effect of adrenergic neurone blockers; haloperidol antagonises hypotensive effect of adrenergic neurone blockers

Antipsychotics

Analgesics (continued)

Analgesics: avoided concomitant use of clozapine with

Analgesics: avoided concomitant use of clozapine with

Antipsychotics with tramadol; enhanced hypotensive and sedative effects when antipsychotics given with opioid analgesics

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when antipsychotics given with angiotensin-II receptor antagonists

Antacids: absorption of phenothiazines and sulpiride reduced by antacids

Anti-arrhythmics: increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with anti-arrhythmics that prolong the QT interval; increased risk of ventricular arrhythmias when amisulpride, haloperidol, phenothiazines, pimozide, sertindole or zuclopenthixol given with amiodarone; avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with amiodarone; manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when sulpiride given with amiodarone or disopyramide; increased risk of ventricular arrhythmias when amisulpride, pimozide, sertindole or zuclopenthixol given with disopyramide; avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with amiodarone; increased risk of arrhythmias when clozapine given with disopyramide

Antibacterials: increased risk of ventricular arrhythmias when pimozide given with clarithromycin, moxifloxacin or telithromycin; avoid concomitant use; increased risk of ventricular arrhythmias when sertraline given with erythromycin or moxifloxacin; avoid concomitant use; increased risk of ventricular arrhythmias when amitriptyline given with erythromycin; possible increased risk of con-valusions; possible increased risk of ventricular arrhythmias when pimozide given with erythromycin; avoid concomitant use; increased risk of ventricular arrhythmias when sulpiride given with paroxetine; plasma concentration of clozapine possibly increased by ciprofloxacin; plasma concentration of olanzapine possibly increased by ciprofloxacin; increased risk of ventricular arrhythmias when haloperidol, phenothiazines or zuclopenthixol given with moxifloxacin; avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with moxifloxacin—manufacturer of benperidol advises avoid concomitant use; plasma concentration of aripiprazole possibly reduced by rifabutin and rifampicin—increase absorption of clozapine; plasma concentration of clozapine possibly reduced by rifampicin; metabolism of haloperidol accelerated by rifampicin (reduced plasma concentration); avoid concomitant use of clozapine with chloramphenicol or sulphonamides (increased risk of agranulocytosis); plasma concentration of quetiapine possibly increased by macrolides (reduce dose of quetiapine); possible increased risk of ventricular arrhythmias when sertraline given with macrolides—avoid concomitant use

Antidepressants: plasma concentration of clozapine possibly increased by citalopram (increased risk of toxicity); metabolism of aripiprazole possibly inhibited by fluoxetine and paroxetine (reduce dose of aripiprazole); plasma concentration of clozapine, haloperidol, risperidone, sertindole and zotepine increased by fluoxetine; plasma concentration of clozapine and olanzapine increased by fluvoxamine; plasma concentration of clozapine and sertindole increased by paroxetine; plasma concentration of risperidone possibly increased by paroxetine (increased risk of toxicity); metabolism of perphenazine inhibited by paroxetine (reduce dose of perphenazine); plasma concentration of clozapine
Antipsychotics

Antidepressants (continued)

Antidepressants: 
- Increased by: sertraline and venlafaxine; plasma concentration of haloperidol increased by venlafaxine; clozapine possibly increases CNS effects of MAOIs; plasma concentration of pimozide possibly increased by SSRI s (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of aripiprazole possibly reduced by St John's wort; increased dose of olanzapine; antipsychotics increase plasma concentration of tricyclics—possibly increased risk of ventricular arrhythmias; increased risk of antimuscarinic side-effects when phenothiazines given with tricyclics; increased risk of ventricular arrhythmias when pimozide given with tricyclics—avoid concomitant use; possibly increased antimuscarinic side-effects when clozapine given with tricyclics

Antidiabetics: phenothiazines possibly antagonise hypoglycaemic effect of sulphonylureas

Antiepileptics: metabolism of clozapine accelerated by carbamazepine (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; metabolism of haloperidol, olanzapine, quetiapine, risperidone and sertindole accelerated by carbamazepine (reduced plasma concentration); plasma concentration of aripiprazole reduced by carbamazepine; plasma concentration of pimozide reduced by carbamazepine; antipsychotics antagonise anticonvulsant effect of carbamazepine, ethosuximide, oxcarbazepine, phenytoin, primidone and valproate (convulsive threshold lowered); metabolism of clozapine, quetiapine and sertindole accelerated by phenytoin (reduced plasma concentration); plasma concentration of aripiprazole possibly reduced by phenytoin and valproate; increased dose of aripiprazole; metabolism of haloperidol accelerated by primidone (reduced plasma concentration); increased risk of neutropenia when olanzapine given with valproate

Antifungals: metabolism of aripiprazole inhibited by ketoconazole (reduce dose of aripiprazole); increased risk of ventricular arrhythmias when sertindole given withitraconazole; ketoconazole—avoid concomitant use; metabolism of aripiprazole possibly inhibited byitraconazole (reduce dose of aripiprazole); possible increased risk of ventricular arrhythmias when sertindole given with midazolam or etrizolam—avoid concomitant use; plasma concentration of quetiapine increased by idazoxane and triazolam (reduce dose of quetiapine); increased risk of ventricular arrhythmias when pimozide given with midazolam or triazolam—avoid concomitant use

Antimalarials: avoidance of antipsychotics advised by manufacturer of artether/lumefantrine; increased risk of ventricular arrhythmias when pimozide given with nefopam or quinine—avoid concomitant use

Antimuscarinics: increased risk of antimuscarinic side-effects when clozapine given with antimuscarinics; plasma concentration of phenothiazines reduced by antimuscarinics, but risk of antimuscarinic side-effects increased, effects of haloperidol possibly reduced by antimuscarinics

Antipsychotics: avoid concomitant use of clozapine with depot formulation of iloperidone, iloperidone, risperidone or zuclopenthixol as cannot be withdrawn quickly if neuropenia occurs; increased risk of ventricular arrhythmias when sulphide given with haloperidol; increased risk of ventricular arrhythmias when sertindole given with amisulpride—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with phenothiazines—avoid concomitant use; increased risk of ventricular arrhythmias when pimozide given with sulpiride

Antivirals: plasma concentration of pimozide possibly increased by atazanavir—avoid concomitant use; metabolism of aripiprazole possibly inhibited by atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (reduce dose of aripiprazole); plasma concentration of pimozide possibly increased by atazanavir and enveirapine—dose of aripiprazole; plasma concentration of pimozide and sertindole increased by fosamprenavir (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of aripiprazole possibly reduced by fosamprenavir; plasma concentration of sertindole increased by indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of clozapine possibly increased by fosamprenavir; plasma concentration of sertindole increased by indinavir, lopinavir, nelfinavir, ritonavir and saquinavir (increased risk of ventricular arrhythmias—avoid concomitant use)

Anxiolytics and Hypnotics: increased sedative effect when antipsychotics given with anxiolytics and hypnotics; plasma concentration of zotepine increased by diazepam; increased risk of hypotension, bradycardia and respiratory depression when intramuscular olanzapine given with parenteral benzodiazepines; plasma concentration of haloperidol increased by buspirone

Aprepitant: avoidance of pimozide advised by manufacturer of aprepitant

Atomoxetine: increased risk of ventricular arrhythmias when antipsychotics that prolong the QT interval given with atomoxetine

Barbiturates: antipsychotics antagonise anticonvulsant effect of barbiturates (convulsive threshold lowered); metabolism of haloperidol accelerated by phenobarbital (reduced plasma concentration); plasma concentration of aripiprazole possibly reduced by phenytoin and valproate; increased plasma concentration of clozapine increased by phenobarbital (increased risk of toxicity)—avoid concomitant use; plasma concentration of antipsychotics possibly increased by phenobarbital; plasma concentration of pimozide increased by phenobarbital (increased risk of ventricular arrhythmias—avoid concomitant use)

Beta-blockers: enhanced hypotensive effect when phenothiazines given with beta-blockers; plasma concentration of both drugs may increase when chlorpromazine given with propranolol; increased risk of ventricular arrhythmias when amisulpride, phenothiazines, pimozide, sertindole or sulpiride given with sotalol; increased risk of ventricular arrhythmias when zuclopenthixol given with sotalol—avoid concomitant use

Calcium-channel Blockers: enhanced hypotensive effect when antipsychotics given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when phenothiazines given with clonidine

Cytotoxics: avoid concomitant use of clozapine with cytotoxics (increased risk of agranulocytosis); avoidance of pimozide advised by manufacturer of lapatinib

Desferrioxamine: manufacturer of levmepromazine (methyltrimeprazine) advises avoid concomitant use with desferrioxamine; avoidance of prochlorperazine advised by manufacturer of desferrioxamine

Diazoxide: enhanced hypotensive effect when phenothiazines given with diazoxide
Antipsychotics (continued)

- Diuretics: risk of ventricular arrhythmias with amiloride or sertindole increased by hypokalaemia caused by Diuretics; risk of ventricular arrhythmias with pimozone increased by hypokalaemia caused by diuretics (avoid concomitant use); enhanced hypotensive effect when phenothiazines given with diuretics

Dopaminergics: increased risk of extrapyramidal side-effects when antipsychotics given with amisulpride; antipsychotics antagonise e.g. apomorphine, levodopa and pergolide; antipsychotics antagonise hypoprolactinaemia and antiparkinsonian effects of bromocriptine and cabergoline; manufacturer of amiludipe advises avoid concomitant use of levo-dopa (antagonism of effect); avoidance of antipsychotics caused by membrane effects of: amitriptyline, maprotiline, trazodone, zotepine (antagonism of effect)

- Ixabradine: increased risk of ventricular arrhythmias when pimozone or sertindole given with ixabradine

- Lithium: increased risk of ventricular arrhythmias when sertindole given with lithium—avoid concomitant use; increased risk of extrapyramidal side-effects and possible neuotoxicity when clozapine, flupentixol, haloperidol, phenothiazines or zuclopenthixol given with lithium; increased risk of extrapyramidal side-effects when sulpiride given with lithium

Mecamylamine: effects of antipsychotics possibly reduced by memantine

Methyldopa: enhanced hypotensive effect when antipsychotics given with methyldopa (also increased risk of extrapyramidal effects)

Metoclopramide: increased risk of extrapyramidal side-effects when antipsychotics given with metoclopramide

Moxonidine: enhanced hypotensive effect when phenothiazines given with moxonidine

Muscle Relaxants: promazine possibly enhances effects of sufamethoxine

Nitrates: enhanced hypotensive effect when phenothiazines given with nitrates

Penicillamine: avoid concomitant use of clozapine with penicillamine (increased risk of agranulocytosis)

Pentamidine Isetionate: increased risk of ventricular arrhythmias when amisulpride given with pentamidine isetionate—avoid concomitant use; increased risk of ventricular arrhythmias when phenothiazines given with pentamidine isetionate

Sibutramine: increased risk of CNS toxicity when antipsychotics given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

- Sodium Benzoate: haloperidol possibly reduces effects of sodium benzoate

Sodium Oxylate: antisepsis possibly enhance effects of sodium oxylate

Sodium Phenylbutyrate: haloperidol possibly reduces effects of sodium phenylbutyrate

Sympathomimetics: antipsychotics antagonise hyper-tensive effect of sympathomimetics

Tetrabenazine: increased risk of extrapyramidal side-effects when antipsychotics given with tetrabenazine

- Ultra-potent dopamine receptor antagonists: chlorpromazine and clozapine possibly enhanced by cimetidine; increased risk of ventricular arrhythmias when sertindole given with cimetidine—avoid concomitant use; plasma concentration of clozapine possibly reduced by omeprazole; absorption of sulphasalazine reduced by sucralfate

- Vasodilator: Antihypertensives: enhanced hypotensive effect when phenothiazines given with hydralazine, minoxidil or sodium nitroprusside

Antivirals see Abacavir, Aciclovir, Adefovir, Atazanavir, Cidofovir, Darunavir, Didanosine, Efavirenz, Emtricitabine, Etravirine, Famciclovir, Foscarnet, Ganciclovir, Indinavir, Lamivudine, Lopinavir, Maraviroc, Nelfina-vir, Nevirapine, Raltegravir, Ribavirin, Ritonavir, Saquinavir, Stavudine, Telbivudine, Tenofovir, Tipra-navir, Valaciclovir, and Zidovudine

Anxiolytics and Hypnotics

ACE Inhibitors; enhanced hypotensive effect when anxiolytics and hypnotics given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when anxiolytics and hypnotics given with adrenergic neurone blockers

Alcohol: increased sedative effect when anxiolytics and hypnotics given with alcohol

Alpha-blockers: enhanced hypotensive and sedative effect when anxiolytics and hypnotics given with alpha-blockers

Anaesthetics, General: increased sedative effect when anxiolytics and hypnotics given with general anaesthetics

Analgesics: increased sedative effect when anxiolytics and hypnotics given with opioid analgesics

Anxiolytics and Hypnotics: increased risk of extrapyramidal side-effects when anxiolytics and hypnotics given with angiotensin-II receptor antagonists

- Antibacterials: metabolism of midazolam inhibited by clarithromycin, erythromycin, quinupristin/ dalfopristin and telithromycin (increased plasma concentration with increased sedation); plasma concentration of midazolam increased by ritonavir given with angiotensin-II receptor antagonists; metabolism of benzodiazepines possibly accelerated by rifampicin (reduced plasma concentration); metabolism of diazepam accelerated by rifampicin (reduced plasma concentration); metabolism of buspirona and zaleplon possibly accelerated by rifampicin; metabolism of zopiclone accelerated by rifampicin (reduced plasma concentration and reduced effect); plasma concentration of zopiclone significantly reduced by rifampicin; metabolism of diazepam inhibited by aminoglycosides

- Antidepressants: chlorimipramine and tricloro may transiently enhance anticoagulant effect of coumarin

- Antidepressants: plasma concentration of melatonin increased by fluvoxamine—avoid concomitant use; plasma concentration of some benzodiazepines increased by fluvoxamine; sedative effects possibly increased when zolpidem given with sertraline; manufacturer of buspirona advises avoid concomitant use with MAOIs; plasma concentration of oral midazolam possibly reduced by St John's wort; increased sedative effect when anxiolytics and hypnotics given with mirtazapine, tricyclic-related antidepressants or tricycles

- Anxiolytics and Hypnotics: plasma concentration of midazolam reduced by carbamazepine; plasma concentration of clonazepam often reduced by carbamazepine, phenytoin and primidone; benzodiazepines possibly increase or decrease plasma concentration of phenytoin; diazepam increases or decreases plasma concentration of phenytoin; clobazam possibly increases plasma concentration of valproate; plasma concentration of diazepam and lorazepam possibly increased by valproate; increased risk of side-effects when clonazepam given with valproate

- Antifungals: plasma concentration of alprazolam increased by itraconazole and ketoconazole; plasma concentration of midazolam increased by itraconazole, ketoconazole and itraconazole (risk of prolonged sedation); plasma concentration of buspirona increased by itraconazole (reduce dose of buspirona); plasma concentration of midazolam increased by posaconazole

- Antihistamines: increased sedative effect when anxiolytics and hypnotics given with antihistamines

- Antipsychotics: increased sedative effect when anxiolytics and hypnotics given with antipsychotics; buspirona increases plasma concentration of haloperidol; increased risk of hypertension, bradycardia and respiratory depression when parenteral benzodiazepines or midazolam given with buspirona; diazepam increases plasma concentration of zolpidem

- Antivirals: plasma concentration of midazolam possibly increased by atazanavir—avoid concomitant use of
Anxiolytics and Hypnotics (continued)

- Antivirals (continued)
  oral midazolam; increased risk of prolonged sedation when midazolam given with 
  efavirenz—avoid concomitant use; increased risk of prolonged sedation and respiratory depression
  when alprazolam, clonazepam, diazepam, flurazepam or midazolam given with
  fosamprenavir; plasma concentration of midazolam possibly increased by
  indinavir, nelfinavir and ritonavir (risk of prolonged sedation—avoid concomitant use of oral midazolam); increased risk of prolonged sedation when alprazolam given with
  indinavir—avoid concomitant use; plasma concentration of alprazolam, diazepam, flurazepam and zolpidem possibly increased by
  ritonavir (risk of extreme sedation and respiratory depression—avoid concomitant use); plasma concentration of anxiolytics and hypnotics possibly increased by
  ritonavir; plasma concentration of buspiron increased by
  ritonavir (increased risk of toxicity); plasma concentration of midazolam increased by
  saquinavir (risk of prolonged sedation—avoid concomitant use of oral midazolam).

Aprepitant: plasma concentration of midazolam increased by aprepitant (risk of prolonged sedation)
Barbiturates: plasma concentration of clonazepam often reduced by phenobarbital
Beta-blockers: enhanced hypnotic effect when anxiolytics and hypnotics given with beta-blockers
Calcium-channel Blockers: enhanced hypnotic effect when anxiolytics and hypnotics given with calcium-channel blockers; midazolam increases absorption of lercanidipine; metabolism of midazolam inhibited by
diltiazem and verapamil (increased plasma concentration with increased sedation); plasma concentration of buspiron increased by
diltiazem and verapamil (reduce dose of buspiron)
Cardiac Glycosides: alprazolam increases plasma concentration of digoxin (increased risk of toxicity)
Clonidine: enhanced hypnotic effect when anxiolytics and hypnotics given with clonidine
Cytotoxics: plasma concentration of midazolam increased by nilotinib
Diferasirox: plasma concentration of midazolam possibly reduced by diferasirox
Diazoxide: enhanced hypnotic effect when anxiolytics and hypnotics given with diazoxide
Disulfiram: metabolism of benzodiazepines inhibited by
disulfiram (increased sedative effects); increased risk of temazepam toxicity when given with
disulfiram
Diuretics: enhanced hypnotic effect when anxiolytics and hypnotics given with diuretics; administration of chloral or triclofos with parenteral
furosemide (frusemide) may displace thyroid hormone from binding sites
Dopaminergics: benzodiazepines possibly antagonise effects of levodopa
Grapefruit Juice: plasma concentration of buspiron increased by grapefruit juice
Lofexidine: increased sedative effect when anxiolytics and hypnotics given with lofexidine
Methylhydrazine-enhanced hypnotic effect when anxiolytics and hypnotics given with methylhydrazine
Moxonidine: enhanced hypnotic effect when anxiolytics and hypnotics given with moxonidine
Muscle Relaxants: increased sedative effect when anxiolytics and hypnotics given with baclofen or tizanidine
Nabilone: increased sedative effect when anxiolytics and hypnotics given with nabilone
Nitrates: enhanced hypnotic effect when anxiolytics and hypnotics given with nitrates
Oestrogens: plasma concentration of melatonin increased by oestrogens
Probenecid: excretion of lorazepam reduced by probenecid (increased plasma concentration); excretion of nitrazepam possibly reduced by probenecid (increased plasma concentration)
Sodium Oxybate: benzodiazepines enhance effects of sodium oxybate (avoid concomitant use)
Theophylline: effects of benzodiazepines possibly reduced by theophylline
Ulcere-healing Drugs: plasma concentration of melatonin increased by cimetidine; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by
cimetidine (increased plasma concentration); metabolism of midazolam possibly inhibited by
esomeprazole and omeprazole (increased plasma concentration)
Vasodilator Antihypertensives: enhanced hypnotic effect when anxiolytics and hypnotics given with
dihydralazine, minoxidil or sodium nitroprusside

Apomorphine
Antipsychotics: effects of apomorphine antagonised by antipsychotics
Dopaminergics: effects of apomorphine possibly reduced by entacapone
Memantine: effects of dopaminergics possibly enhanced by memantine
Methylhydrazine: antiparkinsonian effect of dopaminergics antagonised by methylhydrazine

Aprepitant
Antidepressants: manufacturer of apraclonidine advises avoid concomitant use with MAOIs, tricyclic-related antidepressants and tricyclics

Aprepitant
Note: Foaprepitant is a prodrug of aprepitant
Antidepressants: plasma concentration of aprepirant possibly increased by clarithromycin and teithromycin; plasma concentration of aprepirant reduced by rifampicin
Anticoagulants: aprepirant possibly reduces anti-
coagulant effect of warfarin

Antidepressants; manufacturer of aprepirant advises avoid concomitant use with 
St John’s wort
Antidiabetics: aprepirant reduces plasma concentra-
tion of tolbutamide
Antiepileptics: plasma concentration of aprepirant possibly reduced by carbamazepine and phenytoin
Antifungals: plasma concentration of aprepirant increased by ketoconazole

Antipsychotics: manufacturer of aprepirant advises avoid concomitant use with

Antivirals: plasma concentration of aprepirant possibly increased significantly by

Anxiolytics and Hypnotics (continued)

Nitrates: enhanced hypnotic effect when anxiolytics and hypnotics given with nitrates
Oestrogens: plasma concentration of melatonin increased by nitrates
Probenecid: excretion of lorazepam reduced by probenecid (increased plasma concentration); excretion of nitrazepam possibly reduced by probenecid (increased plasma concentration)
Sodium Oxybate: benzodiazepines enhance effects of sodium oxybate (avoid concomitant use)
Theophylline: effects of benzodiazepines possibly reduced by theophylline
Ulcere-healing Drugs: plasma concentration of melatonin increased by cimetidine; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by cimetidine (increased plasma concentration); metabolism of midazolam possibly inhibited by esomeprazole and omeprazole (increased plasma concentration)
Vasodilator Antihypertensives: enhanced hypnotic effect when anxiolytics and hypnotics given with dihydralazine, minoxidil or sodium nitroprusside

Apomorphine
Antipsychotics: effects of apomorphine antagonised by antipsychotics
Dopaminergics: effects of apomorphine possibly reduced by entacapone
Memantine: effects of dopaminergics possibly enhanced by memantine
Methylhydrazine: antiparkinsonian effect of dopaminergics antagonised by methylhydrazine

Aprepitant
Antidepressants: manufacturer of apraclonidine advises avoid concomitant use with MAOIs, tricyclic-related antidepressants and tricyclics

Aprepitant
Note: Foaprepitant is a prodrug of aprepirant
Antidepressants: plasma concentration of aprepirant possibly increased by clarithromycin and teithromycin; plasma concentration of aprepirant reduced by rifampicin
Anticoagulants: aprepirant possibly reduces anti-
coagulant effect of warfarin

Antidepressants; manufacturer of aprepirant advises avoid concomitant use with 
St John’s wort
Antidiabetics: aprepirant reduces plasma concentra-
tion of tolbutamide
Antiepileptics: plasma concentration of aprepirant possibly reduced by carbamazepine and phenytoin
Antifungals: plasma concentration of aprepirant increased by ketoconazole

Antipsychotics: manufacturer of aprepirant advises avoid concomitant use with

Antivirals: plasma concentration of aprepirant possibly increased significantly by

Anxiolytics and Hypnotics (continued)

Nitrates: enhanced hypnotic effect when anxiolytics and hypnotics given with nitrates
Oestrogens: plasma concentration of melatonin increased by nitrates
Probenecid: excretion of lorazepam reduced by probenecid (increased plasma concentration); excretion of nitrazepam possibly reduced by probenecid (increased plasma concentration)
Sodium Oxybate: benzodiazepines enhance effects of sodium oxybate (avoid concomitant use)
Theophylline: effects of benzodiazepines possibly reduced by theophylline
Ulcere-healing Drugs: plasma concentration of melatonin increased by cimetidine; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by cimetidine (increased plasma concentration); metabolism of midazolam possibly inhibited by esomeprazole and omeprazole (increased plasma concentration)
Vasodilator Antihypertensives: enhanced hypnotic effect when anxiolytics and hypnotics given with dihydralazine, minoxidil or sodium nitroprusside

Apomorphine
Antipsychotics: effects of apomorphine antagonised by antipsychotics
Dopaminergics: effects of apomorphine possibly reduced by entacapone
Memantine: effects of dopaminergics possibly enhanced by memantine
Methylhydrazine: antiparkinsonian effect of dopaminergics antagonised by methylhydrazine

Aprepitant
Antidepressants: manufacturer of apraclonidine advises avoid concomitant use with MAOIs, tricyclic-related antidepressants and tricyclics

Aprepitant
Note: Foaprepitant is a prodrug of aprepirant
Antidepressants: plasma concentration of aprepirant possibly increased by clarithromycin and teithromycin; plasma concentration of aprepirant reduced by rifampicin
Anticoagulants: aprepirant possibly reduces anti-
coagulant effect of warfarin

Antidepressants; manufacturer of aprepirant advises avoid concomitant use with 
St John’s wort
Antidiabetics: aprepirant reduces plasma concentra-
tion of tolbutamide
Antiepileptics: plasma concentration of aprepirant possibly reduced by carbamazepine and phenytoin
Antifungals: plasma concentration of aprepirant increased by ketoconazole

Antipsychotics: manufacturer of aprepirant advises avoid concomitant use with

Antivirals: plasma concentration of aprepirant possibly increased significantly by

Appendix 1: Interactions 725

Appendix 1: Interactions
Antivirals:

Appendix 1: Interactions

Atazanavir

Antidepressants:

Anticoagulants:

Aspirin

Ulcer-healing Drugs:

Beta-blockers:

Antipsychotics:

Antibacterials:

Artemether with Lumefantrine (continued)

• Antibacterials: manufacturer of artemether/lumefantrine advises avoid concomitant use with macrolides and quinolones

• Antidepressants: manufacturer of artemether/lumefantrine advises avoid concomitant use with antidepressants

• Antifungals: manufacturer of artemether/lumefantrine advises avoid concomitant use with midazolams and azoles

• Antimalarials: manufacturer of artemether/lumefantrine advises avoid concomitant use with antimalarials; increased risk of ventricular arrhythmias when artemether/lumefantrine given with quinine

• Antipsychotics: manufacturer of artemether/lumefantrine advises avoid concomitant use with antipsychotics

• Antivirals: manufacturer of artemether/lumefantrine advises caution with atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir

• Beta-blockers: manufacturer of artemether/lumefantrine advises avoid concomitant use with metoprolol and etanol

Grapefruit juice: plasma concentration of artemether/lumefantrine possibly increased by grapefruit juice

• Ulcer-healing Drugs: manufacturer of artemether/lumefantrine advises avoid concomitant use with cimetidine

Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 679

Ascorbic acid see Vitamins

Aspirin

Adsortens: absorption of aspirin possibly reduced by kaolin

• Analgesics: avoid concomitant use of aspirin with NSAIDs (increased side-effects); antiplatelet effect of aspirin possibly reduced by ibuprofen

Antacid: excretion of aspirin increased by alkaline urine due to some antacids

• Anticoagulants: increased risk of bleeding when aspirin given with coumarins or phenindione (due to antiplatelet effect); aspirin enhances anticoagulant effect of leaseparin

• Antidepressants: increased risk of bleeding when aspirin given with SSRIs or venlafaxine

Antiepileptics: aspirin enhances effects of phenytoin and valproate

Cristolazo: manufacturer of cristolazo recommends dose of aspirin should not exceed 80 mg daily when given with cristolazo

Clodiropr: increased risk of bleeding when aspirin given with clodiprogel

Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when aspirin given with corticosteroids, also corticosteroids reduce plasma concentration of salicylate

• Cytotoxics: aspirin reduces excretion of methotrexate (increased risk of toxicity)—but for concomitant use in rheumatic disease see p. 568

Diuretics: aspirin antagonises diuretic effect of spironolactone; increased risk of toxicity when high-dose aspirin given with carbonic anhydrate inhibitors

Iloprost: increased risk of bleeding when aspirin given with iloprost

Leukotriene Antagonists: aspirin increases plasma concentration of zafirlukast

Metoclopramide: rate of absorption of aspirin increased by metoclopramide (enhanced effect)

Probenecid: aspirin antagonises effects of probenecid

Sibutramine: increased risk of bleeding when aspirin given with sibutramine

Sulfispyrazone: aspirin antagonises effects of sulfispyrazone

Atazanavir

Antacids: plasma concentration of atazanavir possibly reduced by antacids

Atazanavir (continued)

• Anti-arrhythmics: atazanavir possibly increases plasma concentration of brendamore and lidocaine (lignocaine)

• Antibacterials: plasma concentration of both drugs increased when atazanavir given with clarithromycin; atazanavir increases plasma concentration of rifabutin (reduce dose of rifabutin); plasma concentration of atazanavir reduced by lamiparin—avoid concomitant use; avoidance of concomitant atazanavir in severe renal and hepatic impairment advised by manufacturer of ertithromycin

Anticoagulants: atazanavir may enhance or reduce anticoagulant effect of warfarin; avoidance of atazanavir advised by manufacturer of rivaroxaban

• Antidepressants: plasma concentration of atazanavir reduced by SS John’s wort—avoid concomitant use

• Antifungals: plasma concentration of atazanavir increased by posaconazole

Antimalarials: caution with atazanavir advised by manufacturer of artemether/lumefantrine

Antimuscarinics: avoidance of atazanavir advised by manufacturer of darifenacin; manufacturer of fesoterodine advises dose reduction when atazanavir given with fesoterodine—consult fesoterodine product literature

Antipsychotics: atazanavir possibly inhibits metabolism of arzipiprazole (reduce dose of arzipiprazole); atazanavir possibly increases plasma concentration of rifapentine—avoid concomitant use

Antivirals: manufacturer of atazanavir advises avoid concomitant use with efavirenz (plasma concentration of atazanavir reduced); avoid concomitant use of atazanavir with indinavir; atazanavir increases plasma concentration of maravir (consider reducing dose of maravir); plasma concentration of atazanavir possibly reduced by nefaviramine—avoid concomitant use; atazanavir increases plasma concentration of saquinavir; plasma concentration of atazanavir reduced by tenofovir, also plasma concentration of tenofovir possibly increased; atazanavir increases plasma concentration of tipranavir (also plasma concentration of atazanavir reduced)

• Anxiolytics and Hypnotics: atazanavir possibly increases plasma concentration of midazolam—avoid concomitant use of oral midazolam

Calcium-channel Blockers: atazanavir increases plasma concentration of dilisiazem (reduce dose of dilisazem); atazanavir possibly increases plasma concentration of verapamil

Ciclosporin: atazanavir possibly increases plasma concentration of ciclosporin

Cytotoxics: atazanavir possibly enhances metabolism of irinotecan (increased risk of toxicity)

Ergot Alkaloids: atazanavir possibly increases plasma concentration of ergot alkaloids—avoid concomitant use

Lipid-regulating Drugs: possible increased risk of myopathy when atazanavir given with atorvastatin; possible increased risk of myopathy when atazanavir given with rosuvastatin—avoid concomitant use; increased risk of myopathy when atazanavir given with simvastatin (avoid concomitant use)

Oestrogens: atazanavir increases plasma concentration of ethinylestradiol—avoid concomitant use

Sildenafil: atazanavir possibly increases side-effects of sildenafil

Sirolimus: atazanavir possibly increases plasma concentration of sirolimus

Tacroflum: atazanavir possibly increases plasma concentration of tacrolimus

Ulcer-healing Drugs: plasma concentration of atazanavir possibly reduced by histamine H2-antagonists; plasma concentration of atazanavir reduced by proton pump inhibitors

Atenolol see Beta-blockers

Atomoxetine

• Analgesics: increased risk of ventricular arrhythmias when atomoxetine given with methadone; possible
Antivirals: Azithromycin

Antibacterials: Azelastine

Antipsychotics: increased risk of ventricular arrhythmias when atomoxetine given with amiodarone or disopyramide

Antibacterials: increased risk of ventricular arrhythmias when atomoxetine given with erythromycin; increased risk of ventricular arrhythmias when atomoxetine given with moxifloxacin

Antidepressants: metabolism of atomoxetine possibly inhibited by fluoxetine and paroxetine; possible increased risk of convulsions when atomoxetine given with antidepressants; atomoxetine should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; increased risk of ventricular arrhythmias when atomoxetine given with tricyclics

Antimalarials: increased risk of ventricular arrhythmias when atomoxetine given with mefloquine

Antipsychotics: increased risk of ventricular arrhythmias when atomoxetine given with antipsychotics that prolong the QT interval

Beta-blockers: increased risk of ventricular arrhythmias when atomoxetine given with metoprolol

Bupropion: possible increased risk of convulsions when atomoxetine given with bupropion

Diuretics: risk of ventricular arrhythmias with atomoxetine increased by hypokalaemia caused by diuretics

Sympathomimetics, Beta: Increased risk of cardiovascular side-effects when atomoxetine given with parenteral salbutamol

Azatovastatin see Statins

Atovaquone

Antibacterials: plasma concentration of atovaquone reduced by erafabin and rifampicin (possible therapeutic failure of atovaquone); plasma concentration of atovaquone reduced by tetracycline

Antivirals: atovaquone possibly reduces plasma concentration of indinavir; atovaquone possibly inhibits metabolism of zidovudine (increased plasma concentration)

Metoclopramide: plasma concentration of atovaquone reduced by metoclopramide

Atracurium see Muscle Relaxants

Atropine see Antimuscarinics

Auranofin see Gold

Azapropazone see NSAIDs

Azathioprine

ACE inhibitors: increased risk of anaemia or leucopenia when azathioprine given with captopril especially in renal impairment; increased risk of anaemia when azathioprine given with enalapril especially in renal impairment

Allopurinol: enhanced effects and increased toxicity of azathioprine when given with allopurinol; allopurinol (reduce dose of azathioprine to one quarter of usual dose) Aminosaliclylates: possible increased risk of leucopenia when azathioprine given with aminosalicylates

Antibacterials: increased risk of haematological toxicity when azathioprine given with sulfamethoxazole (as co-trimoxazole); increased risk of haematological toxicity when azathioprine given with trimethoprim (also with co-trimoxazole)

Anticoagulants: azathioprine possibly reduces anti-coagulant effect of coumarins

Antiepileptics: cytotoxics possibly reduce absorption of phenytoin

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Azelastine see Antihistamines

Azithromycin see Macrolides

Aztreonam

Anticoagulants: aztreonam possibly enhances anti-coagulant effect of coumarins

Antimicrobial antibiotics that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Baclofen see Muscle Relaxants

Balsalazide see Aminosalicylates

Bambuterol see Sympathomimetics, Beta

Barbiturates

Alcohol: increased sedative effect when barbiturates given with alcohol

Antidepressants: barbiturates accelerate metabolism of disopyramide (reduced plasma concentration)

Antibacterials: barbiturates accelerate metabolism of chloramphenicol, doxycycline and metronidazole (reduced plasma concentration); phenobarbital possibly reduces plasma concentration of rifampicin; phenobarbital reduces plasma concentration of telithromycin (avoid during and for 2 weeks after phenobarbital)

Anticoagulants: barbiturates accelerate metabolism of coumarins (reduced anticoagulant effect)

Antidepressants: phenobarbital reduces plasma concentration of paroxetine; phenobarbital accelerates metabolism of aripiprazole; phenobarbital increases plasma concentration of telithromycin, and reduces plasma concentration of SSRIs (convulsive threshold lowered); anti-convulsant effect of barbiturates antagonised by SSRIs, controlled by phenobarbital with co-treatment of barbiturates given with primidone; plasma concentration of phenobarbital increased by valproate (also plasma concentration of valproate reduced); plasma concentration of phenobarbital possibly reduced by vigabatrin

Antifungals: phenobarbital possibly reduces plasma concentration of itraconazole and posaconazole; phenobarbital possibly reduces plasma concentration of voriconazole—avoid concomitant use; phenobarbital reduces absorption of griseofulvin (reduced effect)

Antipsychotics: anticonvulsant effect of barbiturates antagonised by antipsychotics (convulsive threshold lowered); phenobarbital accelerates metabolism of haloperidol (reduced plasma concentration); plasma concentration of both drugs reduced when pheno- barbital given with chlorpromazine; phenobarbital possibly reduces plasma concentration of aripiprazole—increased dose of aripiprazole

Antivirals: phenobarbital possibly reduces plasma concentration of abacavir, darunavir, fosamprenavir and lopinavir; avoidance of phenobarbital advised by manufacturer of etravirine; barbiturates possibly reduce plasma concentration of indinavir, nelfinavir and saquinavir; phenobarbital possibly reduces plasma concentration of indinavir, also plasma concentration of phenobarbital possibly reduced

Anxiolytics and Hypnotics: phenobarbital often reduces plasma concentration of clonazepam
Barbiturates (continued)

Aprepitant: phenobarbital possibly reduces plasma concentration of aprepitant

Beta-blockers: barbiturates reduce plasma concentration of metoprolol and timolol; barbiturates possibly reduce plasma concentration of propranolol

- Calcium-channel Blockers: barbiturates reduce effects of verapamil; plasma concentration of diltiazem and isradipine; barbiturates possibly reduce plasma concentration of trinitocain and its active metabolite

Cardiac Glycosides: barbiturates accelerate metabolism of digoxin (reduced effect)

Ciclosporin: barbiturates accelerate metabolism of ciclosporin (reduced effect)

Corticosteroids: barbiturates accelerate metabolism of corticosteroids (reduced effect)

Cytotoxics: phenobarbital possibly reduces plasma concentration of etoposide; phenobarbital reduces plasma concentration of ifosfamide and its active metabolite

Diuretics: phenobarbital reduces plasma concentration of spironolactone—avoid concomitant use; increased risk of osteomalacia when phenobarbital given with carbonic anhydrase inhibitors

Folates: plasma concentration of phenobarbital possibly reduced by folates

Hormone Antagonists: barbiturates accelerate metabolism of gestrinone (reduced plasma concentration); barbiturates possibly accelerate metabolism of torsemide (reduced plasma concentration)

Leukotriene Antagonists: phenobarbital reduces plasma concentration of mephenytoin

Lofexidine: increased sedative effect when barbiturates given with lofexidine

Mannetmine: effects of barbiturates possibly reduced by memantine

Oestrogens: barbiturates accelerate metabolism of oestrogens (reduced contraceptive effect—see p. 439)

Progestogens: barbiturates accelerate metabolism of progestogens (reduced contraceptive effect—see p. 439)

Sodium Oxybate: barbiturates enhance effects of sodium oxybate (avoid concomitant use)

Symptomimetics: plasma concentration of phenothiazines possibly increased by mexitelidate

Tacrolimus: phenobarbital reduces plasma concentration of tacrolimus

Theophylline: barbiturates accelerate metabolism of theophylline (reduced effect)

Thyroid Hormones: barbiturates accelerate metabolism of thyroid hormones (may increase requirements for thyroid hormones in hypothyroidism)

This action on barbiturates accelerates metabolism of fentanyl (reduced plasma concentration)

Vitamins: barbiturates possibly increase requirements for vitamin D

Beclometasone see Corticosteroids

Belladonna Alkaloids see Antimuscarinics

Benepinar see Heparins

Bendrofluazide (bendrofluazide) see Diuretics

Benfentanill see Antipsychotics

Benzoprine (benzoprin) see Antimuscarinics

Benzodiazepines see Anxiolytics and Hypnotics

Benzthiazide see Diuretics

Benzylminillin see Penicillins

Beta-blockers

Note Since systemic absorption may follow topical application of beta-blockers to the eye the possibility of interaction, in particular, with drugs such as venepamil should be borne in mind

ACE Inhibitors: enhanced hypotensive effect when beta-blockers given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when beta-blockers given with adrenergic neurone blockers

Alcohol: enhanced hypotensive effect when beta-blockers given with alcohol

Beta-blockers (continued)

Aldesleukin: enhanced hypotensive effect when beta-blockers given with aldesleukin

- Alpha-blockers: enhanced hypotensive effect when beta-blockers given with alpha-blockers, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin

Anaesthetic, General: enhanced hypotensive effect when beta-blockers given with general anaesthetics

Anaesthetic, Local: propranolol increases risk of neuraxial toxicity

Analgesics: increased risk of beta-blockers antagonised by NSAIDs; plasma concentration of esmolol possibly increased by morphine

Antiangiotensin-II Receptor Antagonists: enhanced hypotensive effect when beta-blockers given with angiotensin-II receptor antagonists

- Anti-arrhythmics: increased risk of ventricular arrhythmias when beta-blockers given with anti-arrhythmics; increased risk of ventricular arrhythmias when sotalol given with amiodarone or disopyramide—avoid concomitant use; increased risk of atrioventricular block, AV block and myocardial depression when beta-blockers given with flecainide; increased risk of myocardial depression and bradycardia when beta-blockers given with amiodarone; increased risk of myocardial depression and bradycardia when beta-blockers given with sotalol and propranolol accelerated by rifampicin (plasma concentration significantly reduced); plasma concentration of carvedilol, celiprolol and metoprolol reduced by rifampicin

- Antidepressants: plasma concentration of metoprolol increased by citalopram and escitalopram; plasma concentration of propranolol increased by fluvoxamine; plasma concentration of metoprolol possibly increased by paroxetine (enhanced effect); labetalol and propranolol increase plasma concentration of imipramine; increased risk of myocardial infarction when beta-blockers given with MAOIs; increased risk of ventricular arrhythmias when sotalol given with tricyclics

Antidiabetics: beta-blockers may mask warning signs of hypoglycaemia (such as tremor) with antidiabetics; beta-blockers enhance hypoglycaemic effect of insulin

- Antihistamines: increased risk of ventricular arrhythmias when sotalol given with mizolastine—avoid concomitant use

- Antimalariaid: avoidance of metoprolol for heart failure advised by manufacturer of arteether/lumefantrine; increased risk of bradycardia when beta-blockers given with mefloquine

- Antimuscarinics: increased risk of ventricular arrhythmias when sotalol given with tiotidine

- Antipsychotics: plasma concentration of both drugs may be increased when propranolol given with chlorpromazine; increased risk of ventricular arrhythmias when sotalol given with zuclopenthixol;avoid concomitant use; increased risk of ventricular arrhythmias when sotalol given with amisulpride, phenothiazines, pimozide, sertrindole or sulpiride; enhanced hypotensive effect when beta-blockers given with phenothiazines

- Antivirals: avoidance of metoprolol for heart failure advised by manufacturer of epilavir

Anxiolytics and Hypnotics: enhanced hypotensive effect when beta-blockers given with anxiolytics and hypnotics

Anxiolytics: enhanced hypotensive effect when sotalol given with atenoloxetin

Barbiturates: plasma concentration of metoprolol and timolol reduced by barbiturates; plasma concentration of propranolol possibly reduced by barbiturates

Appendix 1: Interactions
Beta-blockers (continued)

- Calcium-channel blockers: enhanced hypotensive effect when beta-blockers with calcium-channel blockers; possible severe hypotension and heart failure when beta-blockers with nifedipine; increased risk of AV block and bradycardia when beta-blockers with diltiazem; astyrole, severe hypotension and heart failure when beta-blockers with verapamil (see p. 118).

Cardiac Glycosides: increased risk of AV block and bradycardia when beta-blockers with cardiac glycosides.

- Ciclosporin: carvedilol increases plasma concentration of ciclosporin.

- Clonidine: increased risk of withdrawal hypertension when beta-blockers with carvedilol increases plasma concentration of labetalol; increased risk of severe hypertension and bradycardia when beta-blockers with clonidine.

Corticosteroids: hypotensive effect of beta-blockers antagonised by corticosteroids.

Diazoxide: enhanced hypotensive effect when beta-blockers with diazoxide.

- Diuretics: enhanced hypotensive effect when beta-blockers with diuretics; risk of ventricular arrhythmias with sotalol increased by hypokalaemia caused by loop diuretics or thiazides and related diuretics.

Dopaminergics: enhanced hypotensive effect when beta-blockers with levodopa.

Ergot Alkaloids: increased peripheral vasoconstriction when beta-blockers with ergotamine and methysergide.

5HT Agonists: propranolol increases plasma concentration of 5HT agonists.

- Moxonidine: enhanced hypotensive effect when beta-blockers with moxonidine.

Nitrates: enhanced hypotensive effect when beta-blockers with nitrates.

Oestrogens: hypotensive effect of beta-blockers antagonised by oestrogens.

Parasympathomimetics: propranolol antagonises effects of neostigmine and pyridostigmine; increased risk of arrhythmias when beta-blockers with pyridostigmine.

Prostaglandins: enhanced hypotensive effect when beta-blockers with prostaglandins.

- Sympathomimetics: increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers with adrenaline (epinephrine), also reponse to adrenaline (epinephrine) may be reduced; increased risk of severe hypotension and bradycardia when non-cardioselective beta-blockers with dobutamine; possible increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers with norepinephrine (norepinephrine).

Thyroid Hormones: metabolism of propranolol accelerated by levothyroxine (thyroxine).

Ulcer-healing Drugs: plasma concentration of labetalol, metoprolol and propranolol increased by cimetidine.

Beta-blockers (continued)

Vasodilator Antihypertensives: enhanced hypotensive effect when beta-blockers with hydralazine, minoxidil or sodium nitroprusside.

Betahistine

Antihistamines: effect of betahistine theoretically antagonised by antihistamines.

Betamethasone see Corticosteroids.

Betaxolol see Beta-blockers.

Betanechol see Parasympathomimetics.

Bexarotene

Antiepileptics: cytotoxics possibly reduce absorption of phenytoin.

- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis).

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets.

- Lipid-regulating Drugs: plasma concentration of bexarotene increased by gemfibrozil—avoid concomitant use.

Betazole see Fibrates.

Biclutamide

Anticoagulants: bicalutamide possibly enhances anticoagulant effect of coumarins.

Biganuine see Antidiabetics.

Bile Acid Sequestrants see Colesevelam, Colestipol, and Colestyramine.

Bile Acids see Ursodeoxycholic Acid.

Bispironol see Beta-blockers.

Bisphosphonates

Analgesics: bioavailability of tiduronic acid increased by indometacin.

Antacids: absorption of bisphosphonates reduced by antacids.

Antibacterials: increased risk of hypocalcaemia when bisphosphonates given with aminoglycosides.

- Calcium Salts: absorption of bisphosphonates reduced by calcium salts.

Iron: absorption of bisphosphonates reduced by oral iron.

Bleomycin

Antiepileptics: cytotoxics possibly reduce absorption of phenytoin.

- Antipsychotics: avoid concomitant use of cytotoxics with clozapine.

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets.

- Antihistamines: cytotoxics possibly reduce absorption of phenytoin.

Antifungals: plasma concentration of bortezomib increased by ketoconazole.

- Antipsychotics: avoid concomitant use of cytotoxics with clozapine.

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets.

Bosantan

- Antibacterials: plasma concentration of bosantan reduced by rifampicin—avoid concomitant use.

Anticoagulants: manufacturer of bosantan recommends monitoring anticoagulant effect of coumarins.

- Antidiabetics: increased risk of hepatotoxicity when bosantan given with cephalexin—avoid concomitant use.

Antifungals: plasma concentration of bosantan increased by ketoconazole—avoid concomitant use.

Antivirals: plasma concentration of bosantan possibly increased by ritonavir.

- Ciclosporin: plasma concentration of bosantan increased by ciclosporin (also plasma concentration of ciclosporin reduced—avoid concomitant use).

Lipid-regulating Drugs: bosantan reduces plasma concentration of simvastatin.
**Antivirals:**
- Oestrogens: bosantan possibly causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended).
- Progestogens: bosantan possibly causes contraceptive failure of hormonal contraceptives containing progestogens (alternative contraception recommended).
- Sildenafil: bosantan reduces plasma concentration of sildenafil.

**Brimonidine**
Antidepressants: manufacturer of brimonidine advises avoid concomitant use with MAOIs, tricyclic-related antidepressants and tricyclics.

**Brinzolamide** see Diuretics

**Bromocriptine**
- Analgesics: plasma concentration of bromocriptine increased by citalopram; manufacturer of bupropion advises caution within 72 hours of busulfan advises caution within 72 hours of paracetamol (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol).
- Antibacterials: plasma concentration of busulfan possibly inhibited by paracetamol (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol).
- Antidepressants: plasma concentration of busulfan possibly increased by metronidazole (increased risk of toxicity).
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin; plasma concentration of busulfan possibly reduced by phenytoin.

**Bosentan** (continued)
- Antifungals: metabolism of bosantan inhibited by itraconazole (increased risk of toxicity).
- Antipsychotics: avoid concomitant use of cytoxics with clozapine (increased risk of agranulocytosis).
- Cardiac Glycosides: cytoxics reduce absorption of digoxin tablets.
- Cytotoxics: increased risk of hepatotoxicity when busulfan given with tioguanine.

**Busulfan**
- Antibacterials: plasma concentration of busulfan increased by erythromycin (increased risk of toxicity); plasma concentration of busulfan possibly increased by macrolides (increased risk of toxicity).
- Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of busulfan antagonised by antipsychotics.
- Domperidone: hypoprolactinaemic effect of busulfan possibly antagonised by domperidone.
- Hormone Antagonists: plasma concentration of bromocriptine increased by octreotide.
- Memantine: effects of dopaminergics possibly enhanced by memantine.
- Methyldopa: antiparkinsonian effect of dopaminergics antagonised by methyldopa.
- Metoclopramide: hypoprolactinaemic effect of busulfan antagonised by metoclopramide.
- Sympathomimetics: risk of toxicity when bromocriptine given with omeprazole or phenylpropanolamine.

**Buclizine** see Antihistamines

**Bumetanide** see Diuretics

**Bupivacaine** see Antivaricella Zoster Virus

**Bupropion**
- Alcohol: plasma concentration of bupropion possibly increased by alcohol.
- Antivirals: plasma concentration of bupropion increased by antivirals.
- Antidepressants: plasma concentration of bupropion possibly increased by atomoxetine.
- Anti-arrhythmics: increased myocardial depression when bupivacaine given with anti-arrhythmics.
- Beta-blockers: increased risk of bupivacaine toxicity when given with propranolol.
- Antipsychotics: plasma concentration of cabergoline increased by antipsychotics.
- Calcium Salts: increased risk of hypercalcaemia when calcium salts given with thiazides and related diuretics.
- Calcium-channel Blockers: increased hypotensive effect when calcium-channel blockers given with ACE inhibitors.
- Calcium-channel Blockers: increased risk of first-dose hypotension with calcium-channel blockers.
- Calcium-channel Blockers: increased hypotensive effect when calcium-channel blockers given with adrenergic neurone blockers.
- Alcohol: increased hypotensive effect when calcium-channel blockers given with alcohol; verapamil possibly increases plasma concentration of alcohol.
- Alpha-blockers: decreased hypotensive effect when calcium-channel blockers given with angiotensin-II receptor antagonists.
- Antihypertensives: increased risk of bradycardia, AV block and myocardial depression when diltiazem or verapamil given with amiodarone; increased risk of...
Calcium-channel Blockers (continued)

- Beta-blockers: enhanced hypotensive effect when calcium-channel blockers given with beta-blockers; increased risk of AV block and bradycardia when diltiazem given with beta-blockers; astyole, severe hypotension and heart failure when verapamil given with beta-blockers (see p. 118); possible severe hypotension and heart failure when nifedipine given with beta-blockers.

Calcium-channel Blockers: plasma concentration of both drugs may increase when diltiazem given with nifedipine.

- Cardiac Glycosides: nifedipine possibly increases plasma concentration of digoxin; diltiazem, lercanidipine and nicardipine increase plasma concentration of digoxin; verapamil increases plasma concentration of digoxin, also increased risk of AV block and bradycardia.

- Ciclosporin: diltiazem, nicardipine and verapamil increase plasma concentration of ciclosporin; combination of lercanidipine with ciclosporin may increase plasma concentration of either drug (or both)—avoid concomitant use; plasma concentration of nifedipine possibly increased by ciclosporin (increased risk of toxicity including gingival hyperplasia).

- Cilostazol: diltiazem increases plasma concentration of cilostazol—avoid concomitant use.

- Corticosteroids: hypotensive effect of calcium-channel blockers antagonised by corticosteroids.

- Cytoxotics: nifedipine possibly inhibits metabolism of vincristine.

- Diazoxide: enhanced hypotensive effect when calcium-channel blockers given with diazoxide.

- Diuretics: enhanced hypotensive effect when calcium-channel blockers given with diuretics; diltiazem and verapamil increase plasma concentration of eplerenone (reduce dose of eplerenone).

- Dopaminergics: enhanced hypotensive effect when calcium-channel blockers given with levodopa.

- Grapefruit Juice: plasma concentration of felodipine, nimodipine and verapamil increased by grapefruit juice.

- Hormone Antagonists: diltiazem and verapamil increase plasma concentration of dutasteride.

- Ibradilide: diltiazem and verapamil increase plasma concentration of atrasivastatin; possible increased risk of myopathy when diltiazem given with simvastatin; increased risk of myopathy when verapamil given with simvastatin.

- Lithium: neurotoxicity may occur when diltiazem or verapamil given with lithium without increased plasma concentration of lithium.

- Magnesium (parenteral): profound hypotension reported with concomitant use of nifedipine and magnesium in pre-eclampsia.

- Mefloquine: avoidance of verapamil advised by manufacturer of darifenacin.

- Antipsychotics: enhanced hypotensive effect when calcium-channel blockers given with antipsychotics.

- Antivirals: plasma concentration of verapamil possibly increased by atazanavir which causes significant increase of diltiazem increased by ritazavir (reduce dose of diltiazem); plasma concentration of diltiazem reduced by efavirenz; manufacturer of lercanidipine advises avoid concomitant use with atazanavir and ritonavir; manufacturer of ciclosporin; combination of lercanidipine with ciclosporin increases risk of AV block and bradycardia.

- Antimuscarinics: effects of dihydropropyrindines, diltiazem and nifedipine probably reduced by antimuscarinics.

- Antihistaminics: possible increased risk of bradycardia when calcium-channel blockers given with mefloquine.

- Antifungals: metabolism of itraconazole and ketoconazole (increased plasma concentration); manufacturer of lercanidipine advises avoid concomitant use with itraconazole and ketoconazole; negative inotropic effect possibly increased when calcium-channel blockers given with itraconazole; plasma concentration of nifedipine increased by miconafungin.

- Antihypertensives: increase plasma concentration of atorvasivatin; possible increased risk of myopathy when diltiazem given with simvastatin; increased risk of myopathy when verapamil given with simvastatin.

- Antiparkinsonism: enhanced hypotensive effect when calcium-channel blockers given with mexitridine.

- Muscle Relaxants: verapamil enhances effects of non-depolarising muscle relaxants and suxamethonium; enhanced hypotensive effect when calcium-channel blockers given with beta-blockers; increased risk of AV block and bradycardia when diltiazem given with beta-blockers; astyole, severe hypotension and heart failure when verapamil given with beta-blockers; possible severe hypotension and heart failure when nifedipine given with beta-blockers.
Calcium-channel Blockers (continued)

Nitrates: enhanced hypotensive effect when calcium-channel blockers given with nitrates.

Oestro gens: hypotensive effect of calcium-channel blockers antagonised by oestro gens.

Prostaglandins: enhanced hypotensive effect when calcium-channel blockers given with alprostadil.

Sildenafil: enhanced hypotensive effect when amloidipine given with sildenafil.

- Sildenafil: diltiazem increases plasma concentration of sirolimus; plasma concentration of both drugs increased when verapamil given with sirolimus.

- Tacrolimus: diltiazem and nifedipine increase plasma concentration of tacrolimus; felodipine, nicardipine and verapamil possibly increase plasma concentration of tacrolimus.

- Theophylline: calcium-channel blockers possibly increase plasma concentration of theophylline (enhanced effect); diltiazem increases plasma concentration of theophylline; verapamil increases plasma concentration of theophylline (enhanced effect).

Ultra-healing Drugs: metabolism of calcium-channel blockers possibly inhibited by cimetidine (increased plasma concentration); plasma concentration of isradipine increased by cimetidine (halve dose of isradipine).

Vardenafil: enhanced hypotensive effect when nifedipine given with vardenafil.

Vasodilator Antihypertensives: enhanced hypotensive effect when calcium-channel blockers given with hydralazine, minoxidil or sodium nitroprusside.

Calcium-channel Blockers (dihydropyridines) see Calcium-channel Blockers.

Candesartan see Angiotensin-II Receptor Antagonists.

Capcetabine see Fluorouracil.

Cyclosporin see Cyclosporins.

Antibacterials: increased risk of nephrotoxicity when capreomycin given with colistin or polymyxins; increased risk of nephrotoxicity and ototoxicity when capreomycin given with aminoglycosides or vancomycin.

Cytotoxics: increased risk of nephrotoxicity and ototoxicity when capreomycin given with platinum compounds.

Oestro gens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestro gens (risk probably small, see p. 439).

Vaccines: antibacterials inactivate oral typhoid vaccine.

Captopril see ACE Inhibitors.

Carbamazepine

Alcohol: CNS side-effects of carbamazepine possibly increased by alcohol.

- Analgesics: effects of carbamazepine enhanced by dextropropoxyphene; carbamazepine reduces plasma concentration of methadone; carbamazepine reduces effects of tramadol; carbamazepine possibly accelerates metabolism of paracetamol.

- Antibacterials: plasma concentration of carbamazepine increased by eflornithine and erythromycin; plasma concentration of carbamazepine reduced by efavirenz; carbamazepine accelerates metabolism of doxycycline (reduced effect); plasma concentration of carbamazepine increased by isoniazid (also possibly increased isoniazid hepatotoxicity); carbamazepine reduces plasma concentration of ethinyl oestradiol (avoid during and for 2 weeks after carbamazepine).

- Anticonvulsants: carbamazepine possibly accelerates metabolism of ecmuarin (reduced anticonvulsant effect).

- Antidepressants: plasma concentration of carbamazepine increased by nefazodone and fluvoxamine; carbamazepine reduces plasma concentration of mianserin, mirtazapine and paroxetine; manufacturer of carbamazepine advises avoid for 2 weeks after stopping MAOIs, also antagonism of anti-convulsant effect; anticonvulsant effect of anti-epileptics possibly antagonised by MAOIs and antimycotics.

Carbamazepine

- Antidepressants (continued)

- Tricyclic-related antidepressants (conversible threshold lowered); avoid concomitant use of anti-epileptics (reduced plasma concentration and reduced effect).

Antiepileptics: carbamazepine possibly reduces plasma concentration of ethosuximide; carbamazepine often reduces plasma concentration of lamotrigine, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); plasma concentration of carbamazepine sometimes reduced by oxcarbazepine (but concentration of an active metabolite of carbamazepine may be increased), also plasma concentration of an active metabolite of oxcarbazepine often reduced; plasma concentration of both drugs often reduced when carbamazepine given with phenytoin, also plasma concentration of phenytoin may be increased; plasma concentration of carbamazepine often reduced by primidone, also plasma concentration of primidone sometimes reduced (but concentration of an active metabolite of primidone often increased); carbamazepine reduces plasma concentration of tiagabine and zonisamide; carbamazepine often reduces plasma concentration of topiramate; carbamazepine reduces plasma concentration of valproate, also plasma concentration of an active metabolite of carbamazepine increased.

- Antifungals: plasma concentration of carbamazepine possibly increased by fluconazole and ketoconazole; carbamazepine possibly reduces plasma concentration of itraconazole and posaconazole; carbamazepine possibly reduces plasma concentration of voriconazole—avoid concomitant use; carbamazepine possibly reduces plasma concentration of caspofungin—consider increasing dose of caspofungin.

- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine.

- Antipsychotics: anticonvulsant effect of carbamazepine antagonised by antipsychotics (conversible threshold lowered); carbamazepine accelerates metabolism of haloperidol, olanzapine, quetiapine, risperidone and zoledol (reduced plasma concentration); carbamazepine reduces plasma concentration of aripiprazole—increase dose of aripiprazole; carbamazepine accelerates metabolism of clozapine (reduced plasma concentration), also avoid concomitant use of drugs with substantial potential for causing agranulocytosis; carbamazepine reduces plasma concentration of paliperidone.

- Antivirals: carbamazepine possibly reduces plasma concentration of darunavir, fosamprenavir, lopinavir, nelfinavir, saquinavir and tipranavir; plasma concentration of both drugs reduced when carbamazepine given with efavirenz; avoidance of carbamazepine advocated with nelfinavir, ritonavir, saquinavir and tipranavir; plasma concentration of efavirenz, darunavir, fosamprenavir, lopinavir, ritonavir and etravirine (reduced plasma concentration); also avoidance of drugs with substantial potential for causing agranulocytosis; carbamazepine reduces plasma concentration of indinavir, also plasma concentration of carbamazepine possibly increased; plasma concentration of carbamazepine possibly increased by ritonavir.

- Antioxidants: carbamazepine reduces plasma concentration of midazolam.

Aprepitant: carbamazepine possibly reduces plasma concentration of aprepitant.

Barbiturates: plasma concentration of carbamazepine reduced by phenobarbital.

Bupropion: carbamazepine reduces plasma concentration of bupropion.

- Calcium-channel Blockers: carbamazepine reduces effects of felodipine and isradipine; carbamazepine...
Carbamazepine
- Calcium-channel blockers (continued)
  - probably reduces effects of dihydropryridines, nifedipine and nicardipine; effects of carbamazepine enhanced by diltiazem and verapamil

Cardiac Glycosides: carbamazepine accelerates metabolism of digitoxin (reduced effect)
- Ciclosporin: carbamazepine accelerates metabolism of ciclosporin (reduced plasma concentration)
- Corticosteroids: carbamazepine accelerates metabolism of eprostenoids (reduced plasma concentration)
- Cytotoxics: carbamazepine reduces plasma concentration of tamoxifen and lapatinib—avoid concomitant use; carbamazepine reduces plasma concentration of irinotecan and its active metabolite
- Diuretics: increased risk of hyponatraemia when carbamazepine given with diuretics; plasma concentration of carbamazepine increased by acetazolamide; carbamazepine reduces plasma concentration of spironolactone—avoid concomitant use
- Hormone Antagonists: metabolism of carbamazepine inhibited by danazol (increased risk of toxicity); carbamazepine accelerates metabolism of gestrinone (reduced plasma concentration); carbamazepine possibly accelerates metabolism of toremifene (reduced plasma concentration)
- 5HT Antagonists: carbamazepine accelerates metabolism of ondansetron (reduced effect)
- Lithium: neurotoxicity may occur when carbamazepine given with lithium without increased plasma concentration of lithium
- Muscle Relaxants: carbamazepine antagonises muscle relaxant effect of non-depolarising muscle relaxants (accelerated recovery from neuromuscular blockade)
- Oestrogens: carbamazepine accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 439)
- Progestogens: carbamazepine accelerates metabolism of progestogens (reduced contraceptive effect—see p. 439)
- Retinoids: plasma concentration of carbamazepine possibly reduced by isotretinoin
- Theophylline: carbamazepine accelerates metabolism of theophylline (reduced effect)
- Thyroid Hormones: carbamazepine accelerates metabolism of thyroid hormones (may increase requirements for thyroid hormones in hypothyroidism)
- Tobilone: carbamazepine accelerates metabolism of tibilone (reduced plasma concentration)
- Ulcer-healing Drugs: metabolism of carbamazepine increased by amitriptyline (increased plasma concentration)
- Vitamins: carbamazepine possibly increases requirements for vitamin D

Carbapenems
- see Doripenem, Ertapenem, Imipenem with Clastatin, and Meropenem

Carbonic Anhydrase Inhibitors
- see Diuretics

Carboplatin
- see Platinum Compounds

Carprofos
- see Prostaglandins

Cardiac Glycosides
- ACE Inhibitors: plasma concentration of digoxin possibly increased by captopril
- Alpha-blockers: plasma concentration of digoxin increased by prazosin
- Aminosaliclate: absorption of digoxin possibly reduced by salicylates
- Analgesics: plasma concentration of cardiac glycosides possibly increased by NSAIDs, also possible exacerbation of heart failure and reduction of renal function
- Antacids: absorption of digoxin possibly reduced by antacids
- Anti-arrhythmics: plasma concentration of digoxin increased by amiodarone and propafenone (halve dose of digoxin)
- Antibacterials: plasma concentration of digoxin possibly increased by gentamicin, telithromycin and clarithromycin

Cardiac Glycosides
- Antibacterials (continued)
  - trimethoprim: absorption of digoxin reduced by neomycin, plasma concentration of digoxin possibly reduced by rifampicin; plasma concentration of digoxin increased by macrolides (increased risk of toxicity); metabolism of digitoxin accelerated by rifamycins (reduced effect)
- Antidepressants: plasma concentration of digoxin reduced by St John’s wort—avoid concomitant use
- Antidiabetics: plasma concentration of digoxin possibly reduced by acarbose; plasma concentration of digoxin increased by sitagliptin
- Antiepileptics: metabolism of digitoxin accelerated by carbamazepine, phenytoin and primidone (reduced effect); plasma concentration of digoxin possibly reduced by phenytoin
- Antifungals: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with amphotericin; plasma concentration of digoxin increased by itraconazole
- Antimalarials: plasma concentration of digoxin possibly increased by chloroquine and hydroxychloroquine; possible increased risk of bradycardia when digoxin given with mefloquine; plasma concentration of digoxin increased by quinine
- Antimuscarinics: plasma concentration of digoxin possibly increased by darifenacin
- Antivirals: plasma concentration of digoxin increased by etravirine; plasma concentration of digoxin possibly increased by ritonavir
- Anxiolytics and Hypnotics: plasma concentration of digoxin increased by alprazolam (increased risk of toxicity)
- Barbiturates: metabolism of digitoxin accelerated by barbiturates (reduced effect)
- Beta-blockers: increased risk of AV block and bradycardia when cardiac glycosides given with beta-blockers
- Calcium Salts: arrhythmias can be precipitated when cardiac glycosides given with large intravenous doses of calcium salts
- Calcium-channel Blockers: plasma concentration of digoxin increased by diltiazem, lercanidipine and nicardipine; plasma concentration of digoxin possibly increased by nifedipine; plasma concentration of digoxin increased by diltiazem and verapamil, also increased risk of AV block and bradycardia
- Ciclosporin: plasma concentration of digoxin increased by ciclosporin (increased risk of toxicity)
- Corticosteroids: increased risk of hypokalaemia when cardiac glycosides given with corticosteroids
- Cytotoxics: absorption of digoxin tablets reduced by cytotoxics
- Diuretics: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with acetazolamide, loop diuretics or thiazides and related diuretics; plasma concentration of digoxin possibly increased by potassium carnenate; plasma concentration of digoxin possibly affected by spironolactone; plasma concentration of digoxin increased by spironolactone
- Lenalidomide: plasma concentration of digoxin possibly increased by lenalidomide
- Lipid-regulating Drugs: absorption of cardiac glycosides possibly reduced by colesterol and colestyramine; plasma concentration of digoxin possibly increased by atorvastatin
- Muscle Relaxants: risk of ventricular arrhythmias when cardiac glycosides given with suxamethonium; possible increased risk of bradycardia when cardiac glycosides given with tizanidine
- Penicillamine: plasma concentration of digoxin possibly increased by penicillamine
- Symptomaticinetics, Beta- plasma concentration of digoxin possibly increased by salbutamol
- Ulcer-healing Drugs: plasma concentration of digoxin possibly slightly increased by proton pump inhibitors;
Appendix 1: Interactions

Cardiac Glycosides

Ulcer-healing Drugs (continued)

absorption of cardiac glycosides possibly reduced by sucralfate

Carmustine

Antiepileptics: cytotoxics possibly reduce absorption of phenytoin

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Ciclosporin: possible increased risk of nephrotoxicity when ciclosporin given with azathioprine (increased risk of toxicity)

Ciclosporin: metabolism of ciclosporin possibly reduced by antileptics—consider increasing dose of ciclosporin

Chloramphenicol

Antiepileptics: avoid concomitant use of chloramphenicol with phenytoin (increased risk of agranulocytosis)

Barbiturates: metabolism of chloramphenicol accelerated by barbiturates (reduced plasma concentration)

Ciclosporin: chloramphenicol possibly increases plasma concentration of ciclosporin

Hydroxocobalamin: chloramphenicol reduces plasma concentration of hydroxocobalamin

Oestrogens: that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)

Tacrolimus: chloramphenicol possibly increases plasma concentration of tacrolimus

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Chloridiazepoxide see Anxiolytics and Hypnotics

Chloroquine and Hydroxychloroquine

Adenoptes: absorption of chloroquine and hydroxychloroquine reduced by kaolin

Agalsidase Alfa and Beta: chloroquine and hydroxychloroquine possibly inhibit effects of agalsidase alfa and beta (manufacturers of agalsidase alfa and beta advise avoid concomitant use)

Antacids: absorption of chloroquine and hydroxychloroquine reduced by antacids

Anti-arrhythmics: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with amiodarone—avoid concomitant use

Antibacterials: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with moxifloxacin—avoid concomitant use

Antiepileptics: possible increased risk of convulsions when chloroquine and hydroxychloroquine given with antiepileptics

Antimalarials: avoidance of antimalarials advised by manufacturer of artmether/lumefantrine; increased risk of convulsions when chloroquine and hydroxychloroquine given with mefloquine

Cardiac Glycosides: chloroquine and hydroxychloroquine possibly increase plasma concentration of digoxin

Ciclosporin: chloroquine and hydroxychloroquine increase plasma concentration of ciclosporin (increased risk of toxicity)

Lanthanum: absorption of chloroquine and hydroxychloroquine possibly reduced by lanthanum (give at least 2 hours apart)

Laronidase: chloroquine and hydroxychloroquine possibly inhibit effects of laronidase (manufacturer of laronidase advises avoid concomitant use)

Parasympathomimetics: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine and pyridostigmine

Ulcer-healing Drugs: metabolism of chloroquine and hydroxychloroquine inhibited by cineminidine (increased plasma concentration)

Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 679

Chlorothiazide see Diuretics

Chlorphenamine (chlorpheniramine) see Antihistamines

Chlorpromazine see Antipsychotics

Chlorpropamide see Antidiabetics

Chlorotaldione see Diuretics

Chlorotetracycline see Tetracyclines

Ciclesonide see Corticosteroids

Ciclosporin

ACE Inhibitors: increased risk of hyperkalaemia when ciclosporin given with ACE inhibitors

Allopurinol: plasma concentration of ciclosporin possibly increased by allopurinol (risk of nephrotoxicity)

Analgesics: increased risk of nephrotoxicity when ciclosporin given with NSAIDs; ciclosporin increases plasma concentration of diclofenac (halve dose of diclofenac)
Ciclosporin (continued)

- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when ciclosporin given with angio-
tensin-II receptor antagonists

- Anti-arthrythmics: plasma concentration of ciclosporin possibly increased by amiodarone and propafenone

- Antibacterials: metabolism of ciclosporin inhibited by clarithromycin and erythromycin (increased plasma concentration); metabolism of ciclosporin accelerated by rifampicin (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by saquinavir; plasma concentration of ciclosporin possibly increased by clarithromycin and erythromycin (increased plasma concentration); metabolism of ciclosporin possibly increased by rifampicin; metabolism of ciclosporin possibly increased by diltiazem

- Barbiturates: metabolism of ciclosporin accelerated by phenobarbital

- Bile Acids: metabolism of ciclosporin possibly increased by cholestyramine

- Calcium-channel Blockers: metabolism of ciclosporin possibly increased by nifedipine

- Calcium-channel Blockers: combination of ciclosporin with nifedipine may increase plasma concentra-
tion of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by nifedipine; plasma concentration of ciclosporin increased by amlodipine; plasma concentration of ciclosporin increased by nifedipine (increased risk of toxicity including gingival hyper-
plasia)

- Cardiac Glycosides: ciclosporin increases plasma concentration of digoxin (increased risk of toxicity)

- Corticosteroids: increased risk of nephrotoxicity when ciclosporin given with corticosteroids (increased risk of toxicity)

- Corticosteroids: Plasma concentration of ciclosporin increased by high-dose methylprednisolone (risk of convulsions); ciclosporin increases plasma concentration of methylprednisolone

- Cytotoxic: increased risk of nephrotoxicity when ciclosporin given with melphalan; increased risk of neurotoxicity when ciclosporin given with doxorubicin; risk of toxicity when ciclosporin given with methotrexate; plasma concentration of ciclosporin possibly increased by imatinib; in vitro studies suggest a possible interaction between ciclosporin and docetaxel (consult docetaxel product literature); ciclosporin possibly increases plasma concentration of etoposide (increased risk of toxicity)

- Diuretics: increased risk of hyperkalaemia when ciclosporin given with potassium-sparing diuretics and aldosterone antagonists; increased risk of nephrotoxicity and possibly hypermagnesaemia when ciclosporin given with thiazides and related diuretics

- Grapefruit Juice: plasma concentration of ciclosporin increased by grapefruit juice (increased risk of toxicity)

- Hormone Antagonists: metabolism of ciclosporin inhibited by danazol (increased plasma concentration); metabolism of ciclosporin accelerated by tamoxifen (reduced plasma concentration); increased risk of nephrotoxicity when ciclosporin given with tamoxifen, also plasma concentration of ciclosporin reduced by intravenous trimethoprim

- Antidepressants: plasma concentration of ciclosporin reduced by St John’s Wort—avoid concomitant use Antidiabetics: ciclosporin possibly enhances hypogly-
caeic effect of repaglinide

- Antiepileptics: metabolism of ciclosporin accelerated by carbamazepine and phenytoin (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by oxcarbazepine; metabolism of ciclosporin accelerated by primidone (reduced effect)

- Antifungals: metabolism of ciclosporin inhibited by fluconazole, itraconazole, ketoconazole, miconazole, and voriconazole (increased risk of toxicity); metabolism of ciclosporin possibly inhibited by miconazole (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with amphotericin; ciclosporin increases plasma concentration of caspofungin (manufacturer of caspofungin recommends monitoring liver enzymes); plasma concentration of ciclo-
sporin possibly reduced by griseofulvin; plasma concentration of ciclosporin possibly increased by micafungin

- Antimalarials: plasma concentration of ciclosporin increased by chloroquine and hydroxychloroquine (increased risk of toxicity)

- Antithrombins: plasma concentration of ciclosporin advised by manufacturer of darifenacin

- Anti-infectives: risk of ciclosporin advised by manufacturer of saquinavir

- Antivirals: increased risk of nephrotoxicity when ciclosporin given with aciclovir; plasma concentration of ciclosporin possibly increased by atazanavir, nelfinavir and ritonavir; plasma concentration of ciclosporin increased by indinavir; plasma concentration of both drugs increased when ciclosporin given with saquinavir

- Barbiturates: metabolism of ciclosporin accelerated by barbiturates (reduced effect)

- Beta-blockers: plasma concentration of ciclosporin increased by carvedilol

- Bile Acids: absorption of ciclosporin increased by ursodeoxycholic acid

- Breastfeeding: ciclosporin increases plasma concentration of omeprazole (also plasma concentration of ciclo-
sporin reduced—avoid concomitant use)

- Calcium-channel Blockers: combination of ciclosporin with lercanidipine may increase plasma concentra-
tion of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by lercanidipine; plasma concentration of ciclosporin increased by nifedipine (increased risk of toxicity including gingival hyper-
plasia)

- Cardiac Glycosides: ciclosporin increases plasma concentration of digoxin (increased risk of toxicity)

- Corticosteroids: Plasma concentration of ciclosporin increased by high-dose methylprednisolone (risk of convulsions); ciclosporin increases plasma concentration of methylprednisolone

- Cytotoxic: increased risk of nephrotoxicity when ciclosporin given with melphalan; increased risk of neurotoxicity when ciclosporin given with doxorubicin; risk of toxicity when ciclosporin given with methotrexate; plasma concentration of ciclosporin possibly increased by imatinib; in vitro studies suggest a possible interaction between ciclosporin and docetaxel (consult docetaxel product literature); ciclosporin possibly increases plasma concentration of etoposide (increased risk of toxicity)

- Diuretics: increased risk of hyperkalaemia when ciclosporin given with potassium-sparing diuretics and aldosterone antagonists; increased risk of nephrotoxicity and possibly hypermagnesaemia when ciclosporin given with thiazides and related diuretics

- Grapefruit Juice: plasma concentration of ciclosporin increased by grapefruit juice (increased risk of toxicity)

- Hormone Antagonists: metabolism of ciclosporin inhibited by danazol (increased plasma concentration); metabolism of ciclosporin accelerated by tamoxifen (reduced plasma concentration); increased risk of nephrotoxicity when ciclosporin given with tamoxifen, also plasma concentration of ciclosporin reduced by intravenous trimethoprim

- Antidepressants: plasma concentration of ciclosporin reduced by St John’s Wort—avoid concomitant use Antidiabetics: ciclosporin possibly enhances hypogly-
caeic effect of repaglinide

- Antiepileptics: metabolism of ciclosporin accelerated by carbamazepine and phenytoin (reduced plasma concentration); plasma concentration of ciclosporin possibly reduced by oxcarbazepine; metabolism of ciclosporin accelerated by primidone (reduced effect)

- Antifungals: metabolism of ciclosporin inhibited by fluconazole, itraconazole, ketoconazole, miconazole, and voriconazole (increased risk of toxicity); metabolism of ciclosporin possibly inhibited by miconazole (increased plasma concentration); increased risk of nephrotoxicity when ciclosporin given with amphotericin; ciclosporin increases plasma concentration of caspofungin (manufacturer of caspofungin recommends monitoring liver enzymes); plasma concentration of ciclo-
sporin possibly reduced by griseofulvin; plasma concentration of ciclosporin possibly increased by micafungin

- Antimalarials: plasma concentration of ciclosporin increased by chloroquine and hydroxychloroquine (increased risk of toxicity)

- Antithrombins: plasma concentration of ciclosporin advised by manufacturer of darifenacin

- Anti-infectives: risk of ciclosporin advised by manufacturer of saquinavir

- Antivirals: increased risk of nephrotoxicity when ciclosporin given with aciclovir; plasma concentration of ciclosporin possibly increased by atazanavir, nelfinavir and ritonavir; plasma concentration of ciclosporin increased by indinavir; plasma concentration of both drugs increased when ciclosporin given with saquinavir

- Barbiturates: metabolism of ciclosporin accelerated by barbiturates (reduced effect)

- Beta-blockers: plasma concentration of ciclosporin increased by carvedilol

- Bile Acids: absorption of ciclosporin increased by ursodeoxycholic acid

- Breastfeeding: ciclosporin increases plasma concentration of omeprazole (also plasma concentration of ciclo-
sporin reduced—avoid concomitant use)

- Calcium-channel Blockers: combination of ciclosporin with lercanidipine may increase plasma concentra-
tion of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by lercanidipine; plasma concentration of ciclosporin increased by nifedipine (increased risk of toxicity including gingival hyper-
plasia)
Appendix 1: Interactions

Clonazepam
- Increased risk of withdrawal hypertension when clonazepam given with betablockers

Clomipramine
- Increased risk of rhabdomyolysis when clomipramine given with cimetidine

Clomethiazole
- Increased risk of rhabdomyolysis when clomethiazole given with cimetidine

Co-careldopa
- Increased risk of rhabdomyolysis when co-careldopa given with cimetidine

Co-beneldopa
- Increased risk of rhabdomyolysis when co-beneldopa given with cimetidine

Cobampicil
- Increased risk of rhabdomyolysis when cobampicil given with cimetidine

Co-amoxiclav
- Increased risk of rhabdomyolysis when co-amoxiclav given with cimetidine

Citrin (quinidine)
- Increased risk of rhabdomyolysis when citrin given with cimetidine

Clindamycin
- Increased risk of rhabdomyolysis when clindamycin given with cimetidine

Cimetidine
- Increased risk of rhabdomyolysis when cimetidine given with clopidogrel

Ciprofibrate
- Increased risk of rhabdomyolysis when ciprofibrate given with cimetidine

Cinnarizine
- Increased risk of rhabdomyolysis when cinnarizine given with cimetidine

Cinacalcet
- Increased risk of rhabdomyolysis when cinacalcet given with cimetidine

Cimetidine
- Increased risk of rhabdomyolysis when cimetidine given with clopidogrel

Clopamide
- Increased risk of rhabdomyolysis when clopamide given with cimetidine

Clonazepam
- Increased risk of rhabdomyolysis when clonazepam given with cimetidine

Clonidine
- Increased risk of rhabdomyolysis when clonidine given with cimetidine

Clonidine (continued)
- Antipsychotics: enhanced hypotensive effect when clonidine given with phenothiazines

Clonidine (continued)
- Beta-blockers: increased risk of withdrawal hypertension when clonidine given with beta-blockers

Calcium-channel Blockers
- Increased risk of withdrawal hypertension when clonidine given with calcium-channel blockers

Corticosteroids
- Increased risk of withdrawal hypertension when clonidine given with corticosteroids

Diazoxide
- Increased risk of withdrawal hypertension when clonidine given with diazoxide

Diuretics
- Increased risk of withdrawal hypertension when clonidine given with diuretics

Methyl dopa
- Increased risk of withdrawal hypertension when clonidine given with methyl dopa

Moxisylyte (thymoxamine)
- Increased risk of withdrawal hypertension when clonidine given with moxisylyte

Muscle Relaxants
- Increased risk of withdrawal hypertension when clonidine given with muscle relaxants

Nalbufin
- Increased risk of withdrawal hypertension when clonidine given with nalbufin

Nalbuphine
- Increased risk of withdrawal hypertension when clonidine given with nalbuphine

Noradrenaline (norepinephrine)
- Increased risk of withdrawal hypertension when clonidine given with noradrenaline (norepinephrine)

Opioid Analgesics
- Increased risk of withdrawal hypertension when clonidine given with opioid analgesics

Oxycodone
- Increased risk of withdrawal hypertension when clonidine given with oxycodone

Penicillin
- Increased risk of withdrawal hypertension when clonidine given with penicillin

Penicillins
- Increased risk of withdrawal hypertension when clonidine given with penicillins

Phenelzine
- Increased risk of withdrawal hypertension when clonidine given with phenelzine

Phenindione
- Increased risk of withdrawal hypertension when clonidine given with phenindione

Phenobarbital
- Increased risk of withdrawal hypertension when clonidine given with phenobarbital

Phenytoin
- Increased risk of withdrawal hypertension when clonidine given with phenytoin

Piroxicam
- Increased risk of withdrawal hypertension when clonidine given with piroxicam

Prostaglandins
- Increased risk of withdrawal hypertension when clonidine given with prostaglandins

Propoxyphene
- Increased risk of withdrawal hypertension when clonidine given with propoxyphene

Quinidine
- Increased risk of withdrawal hypertension when clonidine given with quinidine

Rifampicin
- Increased risk of withdrawal hypertension when clonidine given with rifampicin

Rifabutin
- Increased risk of withdrawal hypertension when clonidine given with rifabutin

Ritonavir
- Increased risk of withdrawal hypertension when clonidine given with ritonavir

Ritonavir and saquinavir
- Increased risk of withdrawal hypertension when clonidine given with ritonavir and saquinavir

Sildenafil
- Increased risk of withdrawal hypertension when clonidine given with sildenafil

Terfenadine
- Increased risk of withdrawal hypertension when clonidine given with terfenadine

Thalidomide
- Increased risk of withdrawal hypertension when clonidine given with thalidomide

Tramadol
- Increased risk of withdrawal hypertension when clonidine given with tramadol

Trichloroethylene
- Increased risk of withdrawal hypertension when clonidine given with trichloroethylene

Tobol
- Increased risk of withdrawal hypertension when clonidine given with tobol

Triglycerides
- Increased risk of withdrawal hypertension when clonidine given with triglycerides

Tramadol
- Increased risk of withdrawal hypertension when clonidine given with tramadol

Tramadol hydrochloride
- Increased risk of withdrawal hypertension when clonidine given with tramadol hydrochloride

Ursodeoxycholic acid
- Increased risk of withdrawal hypertension when clonidine given with ursodeoxycholic acid

Valproate
- Increased risk of withdrawal hypertension when clonidine given with valproate

Vasodilator Antihypertensives
- Increased risk of withdrawal hypertension when clonidine given with vasodilator antihypertensives

Vasopressin
- Increased risk of withdrawal hypertension when clonidine given with vasopressin

Warfarin
- Increased risk of withdrawal hypertension when clonidine given with warfarin

Zopiclone
- Increased risk of withdrawal hypertension when clonidine given with zopiclone

Zolpidem
- Increased risk of withdrawal hypertension when clonidine given with zolpidem

Zonisamide
- Increased risk of withdrawal hypertension when clonidine given with zonisamide

Zotepine
- Increased risk of withdrawal hypertension when clonidine given with zotepine

Zuclopenthixol
- Increased risk of withdrawal hypertension when clonidine given with zuclopenthixol

Zulifem
- Increased risk of withdrawal hypertension when clonidine given with zulifem
**Antibacterials**: reduce plasma concentration of isoniazid; metabolism of corticosteroids accelerated by rifampicins (reduced effect)

**Anticoagulants**: corticosteroids may enhance or reduce anticoagulant effect of coumarins (high-dose corticosteroids enhance anticoagulant effect)

**Antidiabetics**: corticosteroids antagonise hypoglycaemic effect of antidiabetics

**Antiepileptics**: metabolism of corticosteroids accelerated by carbamazepine, phenytoin and primidone (reduced effect)

**Antifungals**: metabolism of corticosteroids possibly inhibited by itraconazole, ketoconazole; plasma concentration of active metabolite of ciclosporin increased by ketoconazole; plasma concentration of inhaled mometasone increased by ketoconazole; metabolism of methylprednisolone inhibited by ketoconazole; increased risk of hypokalaemia when corticosteroids given with amphotericin—avoid concomitant use unless corticosteroids needed to control reactions; plasma concentration of inhaled budesonide increased by ketoconazole; plasma concentration of inhaled and oral budesonide increased by ketoconazole; plasma concentration of inhaled and oral budesonide and fluticasone increased by ritonavir; concentration of inhaled and intranasal budesonide and fluticasone increased by ritonavir; metabolism of dexamethasone and methylprednisolone increased by aprepitant (reduce dose of dexamethasone and methylprednisolone)

**Barbiturates**: metabolism of corticosteroids accelerated by barbiturates (reduced effect)

**Beta-blockers**: corticosteroids antagonise hypotensive effect of beta-blockers

**Calcium-channel Blockers**: corticosteroids antagonise hypotensive effect of calcium-channel blockers

**Cardiac Glycosides**: increased risk of hypokalaemia when corticosteroids given with cardiac glycosides

**Calcium Salts**: corticosteroids reduce absorption of calcium salts

**Calcium-channel Blockers**: corticosteroids antagonise hypotensive effect of calcium-channel blockers

**Diuretics**: corticosteroids antagonise hypotensive effect of diuretics

**Diazoxide**: corticosteroids antagonise hypotensive effect of diazoxide

**Diazoxide**: metabolism of corticosteroids possibly inhibited by diazoxide

**Diuretics**: corticosteroids antagonise diuretic effect of diuretics; increased risk of hypokalaemia when corticosteroids given with acetazolamide, loop diuretics or thiazides and related diuretics

**Diazoxide**: metabolism of corticosteroids possibly inhibited by diazoxide

**Methylprednisolone**: metabolism of corticosteroids possibly inhibited by methylprednisolone

**Mepivacaine**: effect of corticosteroids (including inhaled corticosteroids) may be reduced for 3–4 days after mepivacaine

**Moxonidine**: corticosteroids antagonise hypotensive effect of moxonidine

**Nitrates**: corticosteroids antagonise hypotensive effect of nitrates

**Oestrogens**: plasma concentration of corticosteroids increased by oral contraceptives containing oestrogens
Appendix 1: Interactions

Corticosteroids (continued)

- Sodium Benzoate: corticosteroids possibly reduce effects of sodium benzoate
- Sodium Phenylbutyrate: corticosteroids possibly reduce effects of sodium phenylbutyrate

Somatropin: corticosteroids may inhibit growth-promoting effect of somatropin

- Sympathomimetics: metabolism of dexamethasone accelerated by ephedrine

Sympathomimetics, Beta: increased risk of hypokalaemia when corticosteroids given with high doses of beta sympathomimetics—for CSM advice (hypokalaemia) see p. 153

Phenytoine: increased risk of hypokalaemia when corticosteroids given with phenytoine

- Vaccines: high doses of corticosteroids impair immune response to vaccines, avoid concomitant use with live vaccines (see p. 660)

Vasodilator Antihypertensives: corticosteroids antagonise hypotensive effect of hydralazine, minoxidil and sodium nitroprusside

Cortisone see Corticosteroids

Co-trimoxazole see Trimethoprim and Sulfamethoxazole

Cumarins

- Note: Change in patient’s clinical condition, particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially including salads and vegetables) and in alcohol consumption may also affect anticoagulant control.

- Alcohol: anticoagulant control with cumarins may be affected by major changes in consumption of alcohol

- Allopurinol: anticoagulant effect of cumarins possibly enhanced by allopurinol

- Anabolic Steroids: anticoagulant effect of cumarins possibly enhanced by anabolic steroids

- Analgesics: anticoagulant effect of cumarins possibly enhanced by NSAIDs, celecoxib, dextropropoxyphene, etodolac, etoricoxib, flurbiprofen, ibuprofen, mefenamic acid, meclozine, parecoxib, piroxicam and sulindac; anticoagulant effect of cumarins enhanced by azaproprazone (avoid concomitant use); anticoagulant effect of cumarins possibly enhanced by diclofenac, also increased risk of haemorrhage with intravenous diclofenac (avoid concomitant use); increased risk of bleeding when cumarins given with ketorolac (avoid concomitant use); anticoagulant effect of cumarins enhanced by aspirin (due to antiplatelet effect); anticoagulant effect of cumarins possibly enhanced by prolonged regular use of paracetamol

- Anti-arrhythmics: metabolism of cumarins inhibited by amiodarone (enhanced anticoagulant effect); anticoagulant effect of cumarins enhanced by propafenone

- Antibacterials: experience in anticoagulant clinics suggests that INR possibly altered when cumarins are given with enemycin, enoxacin, etozymycin, etyronycin, ephalexoporina, levofloxacin, metacrystycines, tigecycline and trimethoprim; anticoagulant effect of cumarins enhanced by chloramphenicol, ciprofloxacin, clarithromycin, erythromycin, metronidazole, nalidixic acid, norfloxacain, ofloxacin and sulphonamides; studies have failed to demonstrate an interaction with cumarins, but common experience in anticoagulant clinics is that INR can be altered by a course of broad-spectrum penicillins such as ampicillin; metabolism of cumarins accelerated by rifampicin (reduced anticoagulant effect)

Antidepressants: anticoagulant effect of warfarin possibly enhanced by venlafaxine; anticoagulant effect of cumarins possibly enhanced by SSRI; anticoagulant effect of cumarins reduced by St

- Antidepressants (continued)

- John’s WO™ (avoid concomitant use); anticoagulant effect of warfarin enhanced by mirtazapine; anticoagulant effect of cumarins may be enhanced or reduced by tricyclics

- Antidiabetics: anticoagulant effect of warfarin possibly enhanced by exenatide; cumarins possibly enhance hypoglycaemic effect of sitagliptin; also possible changes to anticoagulant effect

- Antiepileptics: metabolism of cumarins accelerated by carbamazepine and primidone (reduced anticoagulant effect); metabolism of cumarins accelerated by phenytoin (possibility of reduced anticoagulant effect, but enhancement also reported); anticoagulant effect of cumarins possibly enhanced by valproate

- Antifungals: anticoagulant effect of cumarins enhanced by fluconazole, itraconazole, ketoconazole and voriconazole; anticoagulant effect of cumarins enhanced by miconazole (miconazole oral gel and possibly vaginal formulations absorbed); anticoagulant effect of cumarins enhanced by ergotryptophan

- Antimalarials: isolated reports that anticoagulant effect of warfarin may be enhanced by proguanil

- Antivirals: anticoagulant effect of warfarin may be enhanced or reduced by azithromycin, clarithromycin and itraconazole; anticoagulant effect of cumarins may be enhanced or reduced by fosamprenavir; anti-coagulant effect of cumarins possibly enhanced by ritonavir; anticoagulant effect of warfarin possibly enhanced by saquinavir

- Anxiolytics and Hypnotics: anticoagulant effect of cumarins may transiently be enhanced by chloral and triclofos

- Appetisers: anticoagulant effect of warfarin possibly reduced by aprepitant

- Barbiturates: metabolism of cumarins accelerated by barbiturates (reduced anticoagulant effect)

- Bosentan: monitoring anticoagulant effect of cumarins recommended by manufacturer of bosentan

- Clopidogrel: anticoagulant effect of cumarins enhanced due to antiplatelet action of clopidogrel; avoidance of warfarin advised by manufacturer of clopidogrel

- Corticosteroids: anticoagulant effect of cumarins may be enhanced or reduced by corticosteroids (high-dose corticosteroids enhance anticoagulant effect)

- Cranberry Juice: anticoagulant effect of cumarins possibly enhanced by cranberry juice—avoid concomitant use

- Cytotoxics: anticoagulant effect of cumarins possibly enhanced by etoposide, ifosfamide and sorafenib; anticoagulant effect of cumarins enhanced by fluorouracil; anticoagulant effect of cumarins possibly reduced by z胎thioprine, mitotane; increased risk of bleeding when cumarins given with erlotinib; replacement of warfarin with a heparin advised by manufacturer of imatinib (possibility of enhanced warfarin effect)

- Diprydamole: anticoagulant effect of cumarins enhanced due to antiplatelet action of diprydamole

- Diallyliflam: anticoagulant effect of cumarins enhanced by diallyliflam

- Dopamine agonists: anticoagulant effect of warfarin enhanced by entacapone

- Enteral Foods: anticoagulant effect of cumarins antagonised by vitamin K (present in some enteral feeds)

- Glucosamine: anticoagulant effect of warfarin enhanced by glucosamine (avoid concomitant use)

- Hormone Antagonists: anticoagulant effect of cumarins possibly enhanced by bicalutamide and lormifene; metabolism of cumarins inhibited by danazol (enhanced anticoagulant effect); anti-
Cyclophosphamide (continued)
- Cytoxotics: increased toxicity when high-dose cyclophosphamide given with penicillamine—avoid concomitant use
Muscle Relaxants: cyclophosphamide enhances effects of suxamethonium

Cylopteralin
- Alcohol: increased risk of convulsions when cyclophosphamide given with alcohol
Antibacterials: increased risk of CNS toxicity when cyclophosphamide given with isoniazid
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Cyclopyrine see Antihistamines

Cytaibrate
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
Antifungals: cytarabine possibly reduces plasma concentration of fluconazole
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Cytotoxics: intracellular concentration of cytarabine increased by fludarabine

Dabigatran etexilate
- Analgesics: possible increased risk of bleeding when dabigatran etexilate given with NSAIDs
- Anti-arrhythmics: plasma concentration of dabigatan etexilate increased by amiodarone (reduce dose of dabigatran etexilate)
Sibutramine: increased risk of bleeding when anticoagulants given with sibutramine

Dairy Products
Antibacterials: dairy products reduces absorption of ciprofloxacin and norfloxacin; dairy products reduces absorption of tetracyclines (except doxycycline and minocycline)

Dalfopristin see Heparins

Danazol
- Anticoagulants: danazol inhibits metabolism of warfarin (enhanced anticoagulant effect)
- Antiepileptics: danazol inhibits metabolism of carbamazepine (increased risk of toxicity)
- Ciclosporin: danazol inhibits metabolism of ciclosporin (increased plasma concentration)
- Lipid-regulating Drugs: possible increased risk of myopathy when danazol given with simvastatin
Tacrolimus: danazol possibly increases plasma concentration of tacrolimus

Dantrolene see Muscle Relaxants

Dapsone
Antibacterials: plasma concentration of dapsone reduced by rifampicin; plasma concentration of both drugs may increase when dapsone given with trimethoprim
Antivirals: plasma concentration of dapsone possibly increased by fosamprenavir
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Probencid: excretion of dapsone reduced by probenecid (increased risk of side-effects)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Daptomycin
- Ciclosporin: increased risk of myopathy when daptomycin given with ciclosporin (preferably avoid concomitant use)
- Lipid-regulating Drugs: increased risk of myopathy when daptomycin given with fibrates or statins
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Antivirals (continued)

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Darifenacin see Antimuscarinics

Darunavir

Anti-arrhythmics: darunavir possibly increases plasma concentration of lidocaine (lignocaine)—avoid concomitant use

Antibacterials: darunavir increases plasma concentration of efavirenz (reduce dose of efavirenz); plasma concentration of darunavir unexpectedly reduced by rifampicin—avoid concomitant use

Anticoagulants: avoidance of darunavir advised by manufacturer of rivaroxaban

Antidepressants: darunavir possibly reduces plasma concentration of paroxetine and sertraline; plasma concentration of efavirenz reduced by manufacturer of artemether/lumefantrine

Antivirals: plasma concentration of darunavir reduced by efavirenz and saquinavir; plasma concentration of both drugs increased when darunavir given with ketoconazole Antimalarials: caution with darunavir advised by St John’s wort—avoid concomitant use

Antipleptics: plasma concentration of darunavir possibly reduced by carbamazepine and phenytoin

Antifungals: plasma concentration of both drugs increased when darunavir given with indinavir; plasma concentration of darunavir reduced by lopinavir, also plasma concentration of lopinavir increased (avoid concomitant use); darunavir increases plasma concentration of maraviroc (consider reducing dose of maraviroc)

Barbiturates: plasma concentration of darunavir possibly reduced by phenobarbital

Lipid-regulating Drugs: darunavir possibly increases plasma concentration of pravastatin; possible increased risk of myopathy when darunavir given with rosuvastatin—avoid concomitant use

Dasatinib

Antibacterials: metabolism of dasatinib accelerated by rifampicin (reduced plasma concentration—avoid concomitant use)

Antipleptics: cytotoxics possibly reduce absorption of phenytoin

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Lipid-regulating Drugs: dasatinib possibly increases plasma concentration of simvastatin; possible enhanced hypotensive effect when dasatinib given with rosuvastatin—avoid concomitant use

Deferasirox

Antacids: absorption of deferasirox possibly reduced by antacids containing aluminium (manufacturer of deferasirox advises avoid concomitant use)

Antipleptics and Hypnotics: deferasirox possibly reduces plasma concentration of midazolam

Deflazacort see Corticosteroids

Demeclocycline see Tetracyclines

Desferrioxamine

Antipsychotics: avoidance of desferrioxamine advised by manufacturer of levonorgestrel (metho-trimeprazine); manufacturer of desferrioxamine advises avoid concomitant use with prochlorperazine

Desflurane see Anaesthetics, General

Desloratadine see Antihistamines

Desmopressin see Opioid Analgesics

Dexamethasone see Corticosteroids

Dexprofetone see NSAIDs

Dextketoprofen see NSAIDs

Dextromethorphan see Opioid Analgesics

Dextropropoxyphene see Opioid Analgesics

Diamorphine see Opioid Analgesics

Diazepam see Anxiolytics and Hypnotics

Diazoxide

ACE Inhibitors: enhanced hypotensive effect when diazoxide given with ACE inhibitors Adrenergic Neurone Blockers: enhanced hypotensive effect when diazoxide given with adrenergic neurone blockers

Alcohol: enhanced hypotensive effect when diazoxide given with alcohol

Aldesleukin: enhanced hypotensive effect when diazoxide given with aldesleukin

Alpha-blockers: enhanced hypotensive effect when diazoxide given with alpha-blockers

Anaesthetics, General: enhanced hypotensive effect when diazoxide given with general anaesthetics

Anticoagulants: the enhanced hypotensive effect of diazoxide antagonised by NSAIDs

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diazoxide given with angiotensin-II receptor antagonists

Antidepressants: enhanced hypotensive effect when diazoxide given with MAOIs or tricyclic-related antidepressants

Antidiabetics: diazoxide antagonises hypoglycaemic effect of antidiabetics

Antipleptics: diazoxide reduces plasma concentration of phenytoin, also effect of diazoxide may be reduced

Antipsychotics: enhanced hypotensive effect when diazoxide given with phenothiazines

Anxiolytics and Hypnotics: enhanced hypotensive effect when diazoxide given with anxiolytics and hypnotics

Beta-blockers: enhanced hypotensive effect when diazoxide given with beta-blockers

Calcium-channel Blockers: enhanced hypotensive effect when diazoxide given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when diazoxide given with clonidine

Corticosteroids: hypotensive effect of diazoxide antagonised by corticosteroids

Diuretics: enhanced hypotensive and hyperglycaemic effects when diazoxide given with diuretics

Dopaminergics: enhanced hypotensive effect when diazoxide given with levodopa

Methylxypoxid: enhanced hypotensive effect when diazoxide given with methylxypoxid

Moxisylyte (thymoxamine): enhanced hypotensive effect when diazoxide given with moxisylyte

Moxonidine: enhanced hypotensive effect when diazoxide given with moxonidine

Muscle Relaxants: enhanced hypotensive effect when diazoxide given with baclofen or tizanidine

Nitrates: enhanced hypotensive effect when diazoxide given with nitrates

Oestrogens: hypotensive effect of diazoxide antagonised by oestrogens

Prostaglandins: enhanced hypotensive effect when diazoxide given with alprostadil

Vasodilators Antihypertensives: enhanced hypotensive effect when diazoxide given with hydralazine, minoxidil or sodium nitroprusside

Diclofenac see NSAIDs

Dicycloverine (dicyclomine) see Antimuscarinics

Didanosine

Note Antacids in tablet formulation may affect absorption of other drugs

Allopurinol: plasma concentration of didanosine increased by allopurinol (risk of toxicity)—avoid concomitant use

Antivirals: plasma concentration of didanosine possibly increased by ganciclovir; increased risk of side-effects when didanosine given with zidovudine—augment concomitant use; increased risk of side-effects when didanosine given with stavudine; plasma concentration of didanosine increased by tenofovir (increased risk of toxicity)—avoid concomitant use;
Antivirals

- **Disopyramide**
  - **Antipsychotics** (continued)
    - interval given with **antipsychotics** that prolong the QT interval; increased risk of ventricular arrhythmias when disopyramide given with **amisulpiride**, **oipmozide**, **sertindole** or **zuclopenthixol**—avoid concomitant use; increased risk of ventricular arrhythmias when disopyramide given with **phenothiazines** or **sulpiride**

- **Antivirals**: plasma concentration of disopyramide possibly increased by **nonavir** (increased risk of toxicity)

- **Arometoxine**: increased risk of ventricular arrhythmias when disopyramide given with **arometoxine** Barbiturates: metabolism of disopyramide accelerated by **barbiturates** (reduced plasma concentration)

- **Beta-blockers**: increased myocardial depression when anti-arrhythmics given with **beta-blockers**; increased risk of ventricular arrhythmias when disopyramide given with **calcium-channel Blockers**: increased risk of myocardial depression and asystole when disopyramide given with **verapamil**

- **Diuretics**: increased cardiac toxicity with disopyramide if hypokalaemia occurs with **aceazolamide**, **loop diuretics** and related diuretics

- **5HT Antagonists**: increased risk of ventricular arrhythmias when disopyramide given with **dolasetron**—avoid concomitant use

- **Ivabradine**: increased risk of ventricular arrhythmias when disopyramide given with **ivabradine**

- **Nitrates**: disopyramide reduces effects of sublingual tablets of **nitrates** (failure to dissolve under tongue owing to dry mouth)

- **Distigmine**: see Parasympathomimetics

**Disulfram**

- Alcohol: disulfram reaction when disulfram given with **alcohol** (see p. 275)

- **Antibacterials**: psychiatric reaction reported when disulfram given with **metronidazole**

- **Anticoagulants**: disulfram enhances anticoagulant effect of **warfarin**—avoid concomitant use

- **Antidepressants**: increased disulfram reaction with alcohol reported with concomitant amitriptyline; disulfram inhibits metabolism of **tricyclics** (increased plasma concentration)

- **Antiepileptics**: disulfram inhibits metabolism of **phenytoin**; disulfram inhibits metabolism of **benzodiazepines** (increased sedative effects)

- **Paraldehyde**: risk of toxicity when disulfram given with **paraldehyde**

- **Theophylline**: disulfram inhibits metabolism of **theophylline** (increased risk of toxicity)

**Diuretics**

- **Note** Since systemic absorption may follow topical application of brinzolamide to the eye, the possibility of interactions should be borne in mind

- **Note** Since systemic absorption may follow topical application of brinzolamide to the eye, the possibility of interactions should be borne in mind

- **ACE Inhibitors**: enhanced hypotensive effect when diuretics given with **ACE inhibitors**; increased risk of severe hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with **ACE inhibitors** (monitor potassium concentration with low-dose spironolactone in heart failure)

- **Adrenergic Neurone Blockers**: enhanced hypotensive effect when diuretics given with adrenergic neurone blockers

- **Alcohol**: enhanced hypotensive effect when diuretics given with **alcohol**

- **Aldesleukin**: enhanced hypotensive effect when diuretics given with **aldesleukin**

- **Alliskiren**: plasma concentration of furosemide (frusemide) reduced by **aliskiren**; increased risk of hyper-
Diuretics
Aliskiren (continued)
kalaemia when potassium-sparing diuretics and aldosterone antagonists given with aliskiren
Allopurinol: increased risk of hypersensitivity when thiazides and related diuretics given with allopurinol especially in renal impairment
• Alpha-blockers: enhanced hypotensive effect when diuretics given with alpha-blockers, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin
Anaesthetics, General: enhanced hypotensive effect when diuretics given with general anaesthetics
• Analgesics: Diuretic effect of potassium canrenoate possibly antagonised by NSAIDs; possibly increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with NSAIDs; diuretics increase risk of nephrotoxicity of NSAIDs, also antagonism of diuretic effect; effects of diuretics antagonised by indometacin and ketorolac; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with indometacin; occasional reports of reduced renal function when thiazide given with indometacin—avoid concomitant use; increased risk of toxicity when carbonic anhydride inhibitors given with high-dose aspirin; diuretic effect of spironolactone antagonised by aspirin
• Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when diuretics given with angiotensin-II receptor antagonists, increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with angiotensin-II receptor antagonists
• Anti-arrhythmics: plasma concentration of eplerenone increased by amiodarone (reduce dose of eplerenone); hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with amiodarone; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with diospyramide; hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics antagonises action of lidocaine (lignocaine)
• Antibacterials: plasma concentration of eplerenone increased by clarithromycin and telithromycin—avoid concomitant use; plasma concentration of eplerenone increased by erythromycin (reduce dose of eplerenone); plasma concentration of eplerenone reduced by erafampicin—avoid concomitant use; avoidance of diuretics advised by manufacturer of lymecycline; increased risk of ototoxicity when loop diuretics given with aminoglycosides; polymyxins or vancomycin; acetazolamide antagonises effects of methenamine; increased risk of hyperkalaemia when eplerenone given with trimethoprim
• Antidepressants: possible increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with reboxetine; enhanced hypotensive effect when diuretics given with MAOIs; plasma concentration of eplerenone reduced by St John’s wort—avoid concomitant use; increased risk of postural hypotension when diuretics given with tricyclics
Antidiabetics: loop diuretics and thiazides and related diuretics antagonise hypoglycaemic effect of anti-diabetics; increased risk of hypernatraemia when thiazides and related diuretics plus potassium-sparing diuretic given with chlorpropamide; increased risk of hyponatraemia when potassium-sparing diuretics and aldosterone antagonists plus thiazide given with MAOIs
• Antiepileptics: plasma concentration of eplerenone reduced by carbamazepine and phenytoin—avoid concomitant use; increased risk of hyponatraemia

Diuretics
• Antiepileptics (continued)
diuretics given with carbamazepine; acetazolamide increases plasma concentration of carbamazepine; effects of furosemide (frusemide) antagonised by phenytoin; increased risk of osteomalacia when carbonic anhydrase inhibitors given with phenytoin or primidone; acetazolamide possibly reduces plasma concentration of primidone
• Antifungals: plasma concentration of eplerenone increased byitraconazole and ketoconazole—avoid concomitant use; increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with amphotericin; hydrochlorothiazide increases plasma concentration of fluconazole; plasma concentration of eplerenone increased by fluconazole (reduce dose of eplerenone)
• Antipsychotics: hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with amisulpride or sertindole; enhanced hypotensive effect when diuretics given with phenothiazines; hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with pimozide (avoid concomitant use)
• Antivirals: plasma concentration of eplerenone increased by nelfinavir and ritonavir—avoid concomitant use; plasma concentration of eplerenone increased by saquinavir (reduce dose of eplerenone)
Anxiolytics and Hypnotics: enhanced hypotensive effect when diuretics given with anxiolytics and hypnotics; administration of parenteral furosemide (frusemide) with chloral or triclofos may displace thyroid hormone from binding sites
• Atomoxetine: hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with atomoxetine
• Barbiturates: increased risk of osteomalacia when carbonic anhydrase inhibitors given with phenobarbital; plasma concentration of eplerenone reduced by phenobarbital—avoid concomitant use
• Beta-blockers: enhanced hypotensive effect when diuretics given with beta-blockers; hypokalaemia caused by loop diuretics or thiazides and related diuretics increases risk of ventricular arrhythmias with sotalol
Calcium Salts: increased risk of hypercalcaemia when thiazides and related diuretics given with calcium salts
Calcium-channel Blockers: enhanced hypotensive effect when diuretics given with calcium-channel blockers; plasma concentration of eplerenone increased by diltiazem and verapamil (reduce dose of eplerenone)
• Cardiac Glycosides: hypokalaemia caused by acetazolamide, loop diuretics or thiazides and related diuretics increases cardiac toxicity with cardiac glycosides; spironolactone possibly affects plasma concentration of digoxin; potassium-sparing diuretics possibly increases plasma concentration of digoxin
• Ciclosporin: increased risk of nephrotoxicity and possibly hypermagnesaemia when thiazides and related diuretics given with ciclosporin; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with ciclosporin
Clonidine: enhanced hypotensive effect when diuretics given with clonidine
Corticosteroids: diuretic effect of diuretics antagonised by corticosteroids; increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with corticosteroids
• Corticotrophins: avoidance of spironolactone advised by manufacturer of mitotane (antagonism of effect); increased risk of nephrotoxicity and oto toxicity when diuretics given with platinum compounds
Diuretics (continued)

Diazoxide: enhanced hypotensive and hyperglycaemic action when diuretics given with diazoxide.

Diuretics: increased risk of hypokalaemia when loop diuretics or thiazides and related diuretics given with acetazolamide; profound diuresis possible when metolazone given with furosemide (frusemide); increased risk of hypokalaemia when thiazides and related diuretics given with loop diuretics.

Dopaminergics: enhanced hypotensive effect when diuretics given with levodopa.

Hormone Antagonists: increased risk of hypercalcaemia when thiazides and related diuretics given with toremifene; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with triostane.

Lithium: loop diuretics and thiazides and related diuretics reduce excretion of lithium (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides; potassium-sparing diuretics and aldosterone antagonists reduce excretion of lithium (increased plasma concentration and risk of toxicity); acetazolamide increases the excretion of lithium.

Methylidopa: enhanced hypotensive effect when diuretics given with methylidopa.

Moxisylyte (thymoxamine): enhanced hypotensive effect when diuretics given with moxisylyte.

Moxonidine: enhanced hypotensive effect when diuretics given with moxonidine.

Muscle Relaxants: enhanced hypotensive effect when diuretics given with baclofen or tizanidine.

Nitrates: enhanced hypotensive effect when diuretics given with nitrates.

Oestrogens: diuretic effect of diuretics antagonised by oestrogens.

Potassium Salts: increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with potassium salts.

Progestogens: risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with drospirenone (monitor serum potassium during first cycle).

Prostaglandins: enhanced hypotensive effect when diuretics given with alprostadil.

Sympathomimetics, Beta: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with high doses of beta sympathomimetics—for CSM advice (hypokalaemia) see p. 153.

Tacrolimus: increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with tacrolimus.

Theophylline: increased risk of hypokalaemia when acetazolamide, loop diuretics or thiazides and related diuretics given with theophylline.

Vasodilator Antihypertensives: enhanced hypotensive effect when diuretics given with hydralazine, minoxidil or sodium nitroprusside.

Vitamins: increased risk of hypercalcaemia when thiazides and related diuretics given with vitamin D.

Docetaxel (continued)

Antipsychotics: avoid concomitant use of cytoxotics with stiripentol (increased risk of agranulocytosis) Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets.

Ciclosporin: in vitro studies suggest a possible interaction between docetaxel and ciclosporin (consult docetaxel product literature).

Cytotoxics: plasma concentration of docetaxel increased by sorafenib.

Dolasetron see 5HT Antagonists.

Dopem

Antiepileptics: lorazepam possibly reduces plasma concentration of valproate.

Oestrogens: antibiotics that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439).

Probenecid: excretion of dopem reduced by probenecid (manufacturers of dopem advise avoid concomitant use).

Vaccines: antibiotics inactivate oral typhoid vaccine—see p. 679.

Dorzolamide see Diuretics.

Dosulepin (dothiepin) see Antidepressants, Tricyclic.

Doxapram

Antidepressants: effects of doxapram enhanced by MAOIs.

Sympathomimetics: increased risk of hypertension when doxapram given with sympathomimetics.

Theophylline: increased CNS stimulation when doxapram given with theophylline.

Doxazosin see Alpha-blockers.

Doxepin see Antidepressants, Tricyclic.

Doxorubicin

Antiepileptics: cytoxotics possibly reduce absorption of phenytoin.

Antipsychotics: avoid concomitant use of cytoxotics with clobazam (increased risk of agranulocytosis) Antivirals: doxurubicin possibly inhibits effects of stavudine.

Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets.

Ciclosporin: increased risk of neurotoxicity when doxurubicin given with ciclosporin.

Cytoxotics: plasma concentration of doxurubicin possibly increased by sorafenib.

Doxycycline see Tetracyclines.

Drospirenone see Progestogens.

Drotrecogin Alfa

Anticoagulants: manufacturer of drotrecogin alfa advises avoid concomitant use with high doses of warfarin in—consult product literature.

Duloxetine: possible increased serotoninergic effects when duloxetine given with pethidine or tramadol.

Antibacterials: metabolism of duloxetine inhibited by ciprofloxacin—avoid concomitant use.

Antidepressants: metabolism of duloxetine inhibited by fluvoxamine—avoid concomitant use; possible increased serotoninergic effects when duloxetine given with SSRIs, St John’s wort, amitriptyline, clomipa-
Duloxetine

- Antidepressants (continued)
  - nortriptyline, maprotiline, trimipramine; duloxetine should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 5 days after stopping duloxetine; after stopping SSR1-related antidepressants do not start moclobemide for at least 1 week
- Antimalarials: avoidance of antidepressants advised by manufacturer of arteether/ Lumefantrine
- Ergot alkaloids: increased risk of convulsions when antidepressants given with at least 1 week
- Antipsychotics: increased risk of ergotism when SSR1-related antidepressants given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Appendix 1: Interactions

Dutasteride
- Calcium-channel blockers: plasma concentration of dutasteride increased by diltiazem and verapamil

Erythromycin: increased risk of rash when efavirenz given with clarithromycin; efavirenz reduces plasma concentration of rifabutin—increase dose of rifabutin; plasma concentration of efavirenz reduced by rifampicin—increase dose of efavirenz
- Antidepressants: efavirenz plasma concentration of sertraline; plasma concentration of efavirenz reduced by St John's wort—avoid concomitant use
- Antiepileptics: plasma concentration of both drugs reduced when efavirenz given with carbamazepine
- Antifungals: efavirenz reduces plasma concentration of itraconazole and posaconazole; efavirenz reduces plasma concentration of voriconazole, also plasma concentration of efavirenz increased (consider increasing voriconazole dose and reducing efavirenz dose); efavirenz possibly reduces plasma concentration of caspofungin—consider increasing dose of caspofungin
- Antipsychotics: efavirenz possibly reduces plasma concentration of aripiprazole—increase dose of aripiprazole; efavirenz possibly increases plasma concentration of apomorphine; efavirenz increased (risk of ventricular arrhythmias—avoid concomitant use)
- Antivirals: avoidance of efavirenz advised by manufacturer of atazanavir (plasma concentration of efavirenz reduced); efavirenz reduces plasma concentration of darunavir, fosamprenavir and indinavir; efavirenz possibly reduces plasma concentration of stavudine—avoid concomitant use; efavirenz reduces plasma concentration of lopinavir—consider increasing dose of lopinavir; efavirenz possibly reduces plasma concentration of maraviroc—consider increasing dose of maraviroc; plasma concentration of efavirenz reduced by nevirapine; toxicity of efavirenz increased by ritonavir; monitor liver function tests; efavirenz significantly reduces plasma concentration of saquinavir
- Anxiolytics and Hypnotics: increased risk of prolonged sedation when efavirenz given with midazolam—avoid concomitant use
- Ergot alkaloids: increased risk of ergotism when efavirenz given with ergot alkaloids—avoid concomitant use

Efavirenz (continued)

- Grapefruit juice: plasma concentration of efavirenz possibly increased by grapefruit juice
- Lipid-regulating Drugs: efavirenz reduces plasma concentration of atorvastatin, pravastatin and simvastatin
- Oestrogens: efavirenz possibly reduces contraceptive effect of oestrogens
- Eletriptan: see SHT Agonists

Emtricitabine
- Anticoagulants: manufacturer of emtricitabine advises avoid concomitant use with lamivudine
- Antidepressants: manufacturer of emtricitabine advises caution with moclobemide, paroxetine, tricyclics and venlafaxine; avoid concomitant use of antidepressants with non-selective MAOIs
- Dopaminergics: efavirenz possibly enhances effects of apomorphine; efavirenz possibly reduces plasma concentration of rasagiline; manufacturer of efavirenz advises max. dose of 10 mg selegiline if used concomitantly
- Iron: absorption of efavirenz reduced by oral iron

Enteral Foods
- Anticoagulants: the presence of vitamin K in some enteral feeds can antagonise the anticoagulant effect of coumarins and phenindione
- Antiepileptics: enteral feeds possibly reduce absorption of phenytoin

Ephedrine see Sympathomimetics
- Ephedrine (adrenaline) see Sympathomimetics
- Epirubicin
  - Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
  - Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
  - Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
  - Ulcer-healing Drugs: plasma concentration of epirubicin increased by cimetidine

Eplerenone see Diuretics
- Eprosartan see Angiotensin-I Receptor Antagonists
- Eptifibatide
  - Iloprost: increased risk of bleeding when eptifibatide given with iloprost

Ergometrine see Ergot Alkaloids
- Ergot Alkaloids
  - Anaesthetics, General: effects of ergometrine on the parturient uterus reduced by halothane
  - Antibacterials: increased risk of ergotism when ergotamine and methysergide given with macrolides or telithromycin—avoid concomitant use; avoidance of ergotamine and methysergide advised by manufacturer of quinupristin/dalfopristin; increased risk of ergotism when ergotamine and methysergide given with tetracyclines
  - Antiinfectives: possible risk of hypertension when ergotamine and methysergide given with reboxetine
  - Antibacterials: increased risk of ergotism when ergotamine and methysergide given with ergot alkaloids possibly increased by atazanavir—avoid concomitant use; increased risk of ergotism when ergot alkaloids given with efavirenz—avoid concomitant use; increased risk of ergotism when ergotamine and...
Ergot Alkaloids

- Antivirals (continued)
methysergid see Vaccines (continued)
- 5HT Agonists: increased risk of vasospasm when ergotamine and methysergid given with antimigraine agents or vasoconstrictors

Beta-blockers: increased peripheral vasocstriction when ergotamine and methysergid given with beta-blockers
- 5HT Agonists: increased risk of vasospasm when ergotamine and methysergid given with antimigraine agents or vasoconstrictors

Antidepressants: avoid concomitant use

Antimigraine agents: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of anti-epileptics antagonised by neflfoquine

Antipsychotics: anticonvulsant effect of ethosuximide antagonised by antipsychotics (convulsive threshold lowered)

Antidepressants (continued)

Antibacterials

Antivirals:

Antidepressants:

Antibacterials:

Ethinylestradiol see Vaccines (continued)

Vaccines:

Anakinra:

Estropipate see Vaccines (continued)

Oestrogens (risk probably small, see p. 439)

Antifungals:

Antibacterials:

Antivirals

Antidepressants:

Antibacterials inactivate oral typhoid vaccine—see p. 679

Antiepileptics:

Antidepressants (convulsive threshold lowered); avoid concomitant use with St John's wort

Antiepileptics: plasma concentration of ethosuximide possibly reduced by car bamazepine and primidone; plasma concentration of ethosuximide possibly reduced by phenytoin, also plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly increased by valproate

Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of anti-epileptics antagonised by neflfoquine

Antipsychotics: anticonvulsant effect of ethosuximide antagonised by antipsychotics (convulsive threshold lowered)

Barbiturates: plasma concentration of ethosuximide possibly reduced by phenobarbital

Etorodolac see NSAIDs

Etomideate see Anaesthetics, General

Etonogestrel see Progestogens

Etoposide

Anticoagulants: increased risk of bleeding when erlotinib given with COUMARINS

Anticonvulsants: increased risk of bleeding when erlotinib given with COUMARINS

Antiepileptics: cytopoietics possibly reduce absorption of phenytoin

Antifungals: metabolism of erlotinib inhibited by ketoconazole (increased plasma concentration)

Antipsychotics: avoid concomitant use of cytopoietics with clozapine (increased risk of agranulocytosis)

Cardiac Glycosides: cytopoietics reduce absorption of digoxin tablets

Cytotoxic: plasma concentration of erlotinib possibly increased by clozapine possibly increased by cimetidine—avoid concomitant use

Antiepileptics see Ergot Alkaloids

Erlotinib

Analgesics:

Antidepressants, SSRIs

Proton Pump Inhibitors

Bartumeliz:

Cardiovascular: plasma concentration of erlotinib possibly increased by smoking

Cytotoxic: plasma concentration of erlotinib possibly increased by smoking

Ertapenem

Antiepileptics: ertapenem possibly reduces plasma concentration of valproate

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Erythromycin see Macrolides

Escitalopram see Antidepressants, SSRI

Esmolol see Beta-blockers

Esomeprazole see Proton Pump Inhibitors

Estradiol see Oestrogens

Estradiol see Oestrogens

Estrone see Oestrogens

Estrone see Oestrogens

Estradiol see Oestrogens

Estradiol see Oestrogens

Estradiol see Oestrogens

Etoradiv see Oestrogens

Etoposide

Antibacterials: metabolism of etoposide inhibited by ketoconazole (increased plasma concentration and risk of toxicity)

Antidepressants: antimconvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anti-...
Ezetimibe
Anticoagulants: ezetimibe possibly enhances anticoagulant effect of coumarins and phenindione.
- Ciclosporin: plasma concentration of both drugs may increase when ezetimibe given with ciclosporin.
Lipid-regulating Drugs: increased risk of cholelithiasis and gallbladder disease when ezetimibe given with fibrates—discontinue if suspected.

Famciclovir
Probenecid: excretion of famciclovir possibly reduced by probenecid (increased plasma concentration).

Famotidine see Histamine H-antagonists
Felodipine see Calcium-channel Blockers
Fenbufen see NSAIDs
Fenofibrate see Fibrates
Fenoprofen see Anti-inflammatory Drugs
Fenofibrate see Sodium Channel Blockers
Fentanyl see Opioid Analogues
Ferrous Salts see Iron
Fexofenadine see Antihistamines
Flavoxate see Anti-muscarinics
Flecainide (continued)
- Beta-blockers: increased risk of myocardial depression and torsades de pointes when flecainide given with beta-blockers.
- Increased myocardial depression when anti-arrhythmics given with beta-blockers.
- Calcium-channel Blockers: increased risk of myocardial depression and asystole when flecainide given with verapamil.
- Diuretics: increased cardiac toxicity with flecainide if hypokalaemia occurs with loop diuretics or thiazides and related diuretics.
- 5HT Antagonists: increased risk of ventricular arrhythmias when flecainide given with dolasetron—avoid concomitant use.

Fibrates
Antibacterials: increased risk of myopathy when fibrates given with daptomycin (preferably avoid concomitant use).
- Anticoagulants: fibrates enhance anticoagulant effect of coumarins.
- Antidiabetics: gemfibrozil increases plasma concentration of rosiglitazone (consider reducing dose of rosiglitazone); fibrates may improve glucose tolerance and have an additive effect with insulin or sulphonylureas; gemfibrozil possibly enhances hypoglycaemic effect of metaglinide; increased risk of severe hypoglycaemia when fibrates given with repaglinide—avoid concomitant use.
- Ciclosporin: increased risk of renal impairment when bezafibrate or fenofibrate given with ciclosporin.
- Cytotoxics: gemfibrozil increases plasma concentration of bexarotene—avoid concomitant use.
- Lipid-regulating Drugs: increased risk of cholelithiasis and gallbladder disease when fibrates given with ezetimibe—discontinue if suspected; increased risk of myopathy when gemfibrozil given with statins; increased risk of myopathy when gemfibrozil given with fenofibrate—preferably avoid concomitant use.

Filgrastim
Note Pegfilgrastim interactions as for filgrastim.
Cytotoxics: neutropenia possibly exacerbated when filgrastim given with fluorouracil.
Flavoxate see Antimuscarinics
Flecainide
Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with bupivacaine, levobupivacaine, prilocaine or ropivacaine.
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics; plasma concentration of flecainide increased by amiodarone (halve dose of flecainide).
- Antidepressants: plasma concentration of flecainide increased by fluoxetine; increased risk of ventricular arrhythmias when flecainide given with tricyclics.
- Anti-histamines: increased risk of ventricular arrhythmias when flecainide given with mizolastine—avoid concomitant use.
- Antimalarials: avoidance of flecainide advised by manufacturer of artemether/lufanfaine (risk of ventricular arrhythmias); plasma concentration of flecainide increased by quinine.
- Antimuscarinics: increased risk of ventricular arrhythmias when flecainide given with tolterodine.
- Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval; increased risk of arrhythmias when flecainide given with clozapine.
- Antivirals: plasma concentration of flecainide possibly increased by osmapirennavir, indinavir, lopinavir and ritonavir (increased risk of ventricular arrhythmias—avoid concomitant use).

Flecainide (continued)
- Beta-blockers: increased risk of myocardial depression and torsades de pointes when flecainide given with beta-blockers.
- Calcium-channel Blockers: increased risk of myocardial depression and asystole when flecainide given with verapamil.
- Diuretics: increased cardiac toxicity with flecainide if hypokalaemia occurs with loop diuretics or thiazides and related diuretics.
- 5HT Antagonists: increased risk of ventricular arrhythmias when flecainide given with dolasetron—avoid concomitant use.

Floxacin see Corticosteroids
Fluvastatin see Antidepressants, SSRIs
Fluvastatin see Statins
Fluvoxamine see Antidepressants, SSRIs
Furosemide see Cardiac glycosides
Fusidic acid see Anti-infectives
Fusidic acid see Antibacterial Drugs
Fusidic acid see Cytotoxic Drugs
Fusidic acid see Cytotoxic Drugs
Folates
Aminosaliclylates: absorption of folic acid possibly reduced by rifampicin
Antiepileptics: folate possibly reduce plasma concentration of phenytoin and primidone
Barbiturates: folates possibly reduce plasma concentration of phenobarbital

Folic Acid see Folates
Folic Acid see Folates
Formoterol (eformoterol) see Sympathomimetics, Beta

Fosamprenavir
Note: Fosamprenavir is a prodrug of amprenavir
Analgesics: Fosamprenavir increases plasma concentration of methadone
Antacids: Fosamprenavir possibly reduced by antacids
- Antidipsptides: fosamprenavir possibly increases plasma concentration of amiodarone,
  flecainide and propafenone (increased risk of ventricular arrhythmias—avoid concomitant use);
  fosamprenavir possibly increases plasma concentration of dloicaine (lignocaine)—avoid concomitant use
Antibacterials: plasma concentration of both drugs increased when fosamprenavir given with erythromycin;
  fosamprenavir increases plasma concentration of rifabutin (reduce dose of rifabutin); plasma concentration of fosamprenavir significantly reduced by rifampicin—avoid concomitant use; fosamprenavir possibly increases plasma concentration of dapsone—avoid concomitant use fosamprenavir given with
- Antiallantin: fosamprenavir increases plasma concentration of tiroconazol; fosamprenavir possibly increases plasma concentration of itronatidine Antimalarials: caution with fosamprenavir advised by manufacturer of artemether/lumefantrine
Antimuscarinics: caution with fosamprenavir advised by manufacturer of darifencin and tolterodine

Antipsychotics: fosamprenavir possibly inhibits metabolism of etipiriprazol (reduce dose of ariprazole); fosamprenavir possibly increases plasma concentration of clozapine; fosamprenavir increases plasma concentration of imazodin and esertindol (increased risk of ventricular arrhythmias—avoid concomitant use)
Antivirals: plasma concentration of fosamprenavir reduced by efavirens and sipiravir; plasma concentration of fosamprenavir increased by etravirine (reduce dose of etravirine); plasma concentration of fosamprenavir reduced by lopinavir, effect on lopinavir plasma concentration not predictable—avoid concomitant use; plasma concentration of fosamprenavir possibly reduced by nevirapine
Anxiolytics and Hypnotics: increased risk of prolonged sedation and respiratory depression when fosamprenavir given with alprazolam, clonazepam,
  diaepam, efurarazep or emidazolam
Barbiturates: plasma concentration of fosamprenavir possibly reduced by phenobarbital
Cislostatol: fosamprenavir possibly increases plasma concentration of cislostatol—avoid concomitant use
Ergot Alkaloids: increased risk of ergotism when fosamprenavir given with ergotamine and methysergide—avoid concomitant use

Fosamprenavir (continued)
- Lipid-regulating Drugs: possible increased risk of myopathy when fosamprenavir given with atorvastatin; possible increased risk of myopathy when fosamprenavir given with rosuvastatin or simvastatin—avoid concomitant use
Oestrogens: fosamprenavir increases plasma concentration of oestrogens, also plasma concentration of fosamprenavir reduced—alternative contraception recommended
Progestogens: fosamprenavir increases plasma concentration of progestogens, also plasma concentration of fosamprenavir reduced—alternative contraception recommended
Sildenafil: fosamprenavir possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil
Tadalafil: fosamprenavir possibly increases plasma concentration of tadalafil
Ulcer-healing Drugs: fosamprenavir possibly increases plasma concentration of cicemidine
Vardenafil: fosamprenavir possibly increases plasma concentration of vardenafil

Fosaprepitant see Aprepitant
Foscarnet
Antivirals: avoidance of foscarnet advised by manufacturer of lamivudine
Fosinopril see ACE Inhibitors
Fosphenytoin see Phenytoin
Formyamin see Aminoglyceroids
Frovatiran see SHT Agonists
Furosemide (furosemide) see Diuretics
Fusidic Acid
- Antivirals: plasma concentration of both drugs increased when fusidic acid given with ritonavir—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when fusidic acid given with atorvastatin; increased risk of myopathy when fusidic acid given with simvastatin
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Sugammadex: fusidic acid possibly reduces response to sugammadex
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Gabapentin
Antitamins: avoidance of gabapentin reduced by manufacter
- Antidepressants: anticonvulsivant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anti-convulsivant effect of antiepileptics antagonised by SSRIIs and bretricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wart
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxylororoquine; antiepileptic effect of antiepileptics antagonised by mefloquine

Galantamine see Parasympathomimetics
Gancicllovir
Note: Increased risk of myelosuppression with other myelosuppressive drugs—consult product literature
- Antivirals: increased risk of convulsions when ganciclovir given with pimipen with cilastatin
- Antivirals: ganciclovir possibly increases plasma concentration of didanol; avoidance of intravenous ganciclovir advised by manufacturer of lamivudine; profound myelosuppression when ganciclovir given with zidovudine (if possible avoid concomitant administration, particularly during initial ganciclovir therapy)
Cytotoxins: plasma concentration of ganciclovir possibly increased by mycophenolate, also plasma concentration of inactive metabolite of mycophenolate possibly increased
Appendix 1: Interactions

Ganciclovir (continued)

Probencid: excretion of ganciclovir reduced by probenicid (increased plasma concentration and risk of toxicity)

Tacrolimus: possible increased risk of nephrotoxicity when ganciclovir given with tacrolimus

Gemeprost see Prostaglandins

Gemfibrozil see Fibrates

Gentamicin see Aminoglycosides

Gestodene see Progestogens

Gestrone

Antibacterials: metabolism of gestrione accelerated by rifampicin (reduced plasma concentration)

Antipileptics: metabolism of gestrione accelerated by carbamazepine, phenytoin and primidone (reduced plasma concentration)

Barbiturates: metabolism of gestrione accelerated by barbiturates (reduced plasma concentration)

Glucuronidase see Anti-diabetics

Gliclazide see Anti-diabetics

Glimepride see Anti-diabetics

Glipizide see Anti-diabetics

Glucosamine

• Anticoagulants: glucosamine enhances anticoagulant effect of warfarin (avoid concomitant use)

Glycerol Trinitrate see Nitrates

Glucopyronium see Antimuscarinics

Gold

Penicillamine: avoidance of gold advised by manufacturer of penicillamine (increased risk of toxicity)

Grapefruit Juice

Anti-arrhythmics: grapefruit juice increases plasma concentration of amiodarone

Antimalarials: grapefruit juice possibly increases plasma concentration of artemether/lumefantrine

Antivirals: grapefruit juice possibly increases plasma concentration of efavirenz

Anxiolytics and Hypnotics: grapefruit juice increases plasma concentration of buspirone

Calcium-channel Blockers: grapefruit juice increases plasma concentration of felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil

• Cislosporin: grapefruit juice increases plasma concentration of cislosporin (increased risk of toxicity)

• Cytotoxics: avoidance of grapefruit juice advised by manufacturer of lapatinib and nilotinib

Ivabradine: grapefruit juice increases plasma concentration of ivabradine

Lipid-regulating Drugs: grapefruit juice possibly increases plasma concentration of atorvastatin; grapefruit juice increases plasma concentration of simvastatin—avoid concomitant use

Sildenafil: grapefruit juice possibly increases plasma concentration of sildenafil

• Sirolimus: grapefruit juice increases plasma concentration of sirolimus—avoid concomitant use

• Tacrolimus: grapefruit juice increases plasma concentration of tacrolimus

Tadalafil: grapefruit juice possibly increases plasma concentration of tadalafil

Vardenafil: grapefruit juice possibly increases plasma concentration of vardenafil—avoid concomitant use

Griseofulvin (continued)

• Progestogens: griseofulvin accelerates metabolism of progestogens (reduced contraceptive effect—see p. 439)

Guanythidined see Adrenergic Neurone Blockers

Haloperidol see Antipsychotics

Halothane see Anaesthetics, General

Heparin see Heparins

Heparins

ACE inhibitors: increased risk of hyperkalaemia when heparins given with ACE inhibitors

Alikiren: increased risk of hyperkalaemia when heparins given with alikiren

Anticoagulants: possible increased risk of bleeding when heparins given with NSAIDs; increased risk of haemorrhage when heparins given with intravenous diolbenic (avoid concomitant use, including low-dose heparin); increased risk of haemorrhage when heparins given with metoprolol (avoid concomitant use, including low-dose heparin); anticoagulant effect of heparins enhanced by aspirin

Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when heparins given with angiotensin-II receptor antagonists

Clopidogrel: increased risk of bleeding when heparins given with clopidogrel

Dipyridamole: anticoagulant effect of heparins enhanced by dipyridamole

Drotrecogin Alfa: avoidance of concomitant use of high doses of heparin with drotrecogin alfa advised by manufacturer of drotrecogin alfa—consult product literature

Iloprost: anticoagulant effect of heparins possibly enhanced by iloprost

Nitrates: anticoagulant effect of heparins reduced by infusion of glycerol trinitrate

Sibutramine: increased risk of bleeding when anti-coagulants given with sibutramine

Histamine H-antagonists

• Alpha-blockers: cimetidine and ranitidine antagonise effects of propranolol

Analgesics: cimetidine possibly increases plasma concentration of azapropropazone; cimetidine inhibits metabolism of opioid analgesics (increased plasma concentration)

• Anti-arrhythmics: cimetidine increases plasma concentration of amiodarone and propafenone; cimetidine inhibits metabolism of flecainide (increased plasma concentration); cimetidine increases plasma concentration of lidocaine (lignocaine) (increased risk of toxicity)

Antibacterials: histamine H-antagonists reduce absorption of cefpodoxime; cimetidine increases plasma concentration of erythromycin (increased risk of toxicity, including deafness); cimetidine inhibits metabolism of metronidazole (increased plasma concentration); metabolism of cimetidine accelerated by rifampicin (reduced plasma concentration)

Anticoagulants: cimetidine inhibits metabolism of coumarins (enhanced anticoagulant effect)

Antidepressants: cimetidine increases plasma concentration of clonazepam, escitalopram, mirtazapine and sertraline; cimetidine inhibits metabolism of amitriptyline, doxepin, imipramine and nortriptyline (increased plasma concentration); cimetidine increases plasma concentration of moclobemide (halve dose of moclobemide); cimetidine possibly increases plasma concentration of tricyclics

Antidiabetics: cimetidine reduces excretion of metformin (increased plasma concentration); cimetidine enhances hypoglycaemic effect of sulphonylureas

Antipileptics: cimetidine inhibits metabolism of carbamazepine, phenytoin and valproate (increased plasma concentration)

Antifungals: histamine H-antagonists reduce absorption of itraconazole and ketoconazole; cimetidine reduces plasma concentration of posaconazole;
Histamine H₁-antagonists
- Antifungals (continued)
cimetidine increases plasma concentration of terbinafine
- Antihistamines: manufacturer of loratadine advises cimetidine possibly increases plasma concentration of loratadine
- Antimalarials: avoidance of cimetidine advised by manufacturer of arteether/luemfantrine; cimetidine inhibits metabolism of chloroquine and hydroxychloroquine and quinine (increased plasma concentration)
- Antipsychotics: cimetidine possibly enhances effects of antipsychotics, chlorpromazine and clozapine; increased risk of ventricular arrhythmias when cimetidine given with sertraline—avoid concomitant use
- Antivirals: histamine H₁-antagonists possibly reduce plasma concentration of atazanavir; plasma concentration of cimetidine possibly increased by fosamprenavir; histamine H₁-antagonists possibly increase plasma concentration of raltegravir—manufacturer of raltegravir advises avoid concomitant use
- Calcium-channel Blockers: cimetidine possibly inhibits metabolism of calcium-channel blockers (increased plasma concentration); cimetidine increases plasma concentration of melatonin
- Beta-blockers: cimetidine increases plasma concentration of labetalol, metoprolol and propranolol
- Calcium-channel Blockers: cimetidine possibly inhibits metabolism of calcium-channel blockers (increased plasma concentration); cimetidine increases plasma concentration of isradipine (halve dose of isradipine)
- Ciclosporin: cimetidine possibly increases plasma concentration of ciclosporin
- Cilostazol: cimetidine possibly increases plasma concentration of cilostazol—avoid concomitant use
- Cytoxics: cimetidine possibly enhances myelosuppressive effects of carmustine and lomustine; cimetidine increases plasma concentration of l-asparaginase; cimetidine inhibits metabolism of fluorouracil (increased plasma concentration); famotidine possibly reduces plasma concentration of daunorubicin; histamine H₁-antagonists possibly reduce absorption of lapatinib
- Dopaminergic: cimetidine reduces excretion of pramipexole (increased plasma concentration)
- Ergot Alkaloids: increased risk of ergotism when cimetidine given with ergotamine and methysergide; cimetidine possibly avoid concomitant use
- Hormone Antagonists: absorption of cimetidine possibly delayed by octracetide
- 5HT Agonists: cimetidine inhibits metabolism of zolmitriptan (reduce dose of zolmitriptan)
- Mebendazole: cimetidine possibly inhibits metabolism of mebendazole (increased plasma concentration)
- Sildenafil: cimetidine increases plasma concentration of sildenafil (reduce initial dose of sildenafil)
- Theophylline: cimetidine inhibits metabolism of theophylline (increased plasma concentration)
- Thyroid Hormones: cimetidine reduces absorption of levothyroxine (thyroxine)
- Homatropine see Antimuscarincs
- Hormone Antagonists see Bicalutamide, Danazol, Dutasteride, Exemestane, Flutamide, Gestrinone, Lanreotide, Orectotide, Tamoxifen, Toremifene, and Triostanol

5HT Agonists
- Antidepressants: plasma concentration of eltoprazin increased by citalopram, escitalopram, fluoxetine, fluvoxamine or paroxetine; metabolism of fluvoxamine possibly inhibited by fluoxetine; reduction of dose of zolmitriptan
- Antidepressants: increased risk of CNS toxicity when sumatriptan given with citalopram (manufacturer of sertraline advises avoid concomitant use); possible increased serotoninergic effects when 5HT agonists given with duloxetine; risk of CNS toxicity when rizatriptan or sumatriptan given with MAOIs (avoid rizatriptan or sumatriptan for 2 weeks after MAOIs); increased risk of CNS toxicity when zolmitriptan given with MAOIs; risk of CNS toxicity when rizatriptan or sumatriptan given with moclobemide (avoid rizatriptan or sumatriptan for 2 weeks after moclobemide); risk of CNS toxicity when zolmitriptan given with moclobemide (reduce dose of zolmitriptan); possible increased serotoninergic effects when sumatriptan given with SSRI; increased serotoninergic effects when 5HT agonists given with St John’s wort—avoid concomitant use
- Antifungals: plasma concentration of eltoprazin increased by itraconazole and ketoconazole (risk of toxicity)—avoid concomitant use; plasma concentration of almotriptan increased by ketoconazole (increased risk of toxicity)
- Antivirals: plasma concentration of eletriptan increased by indinavir, nelfinavir and ritonavir (risk of toxicity)—avoid concomitant use
- Beta-blockers: plasma concentration of rizatriptan increased by propranolol (manufacturer of rizatriptan advises halve dose and avoid within 2 hours of propranolol)
- Ergot Alkaloids: increased risk of vasospasm when eltoprazin or frotovatran given with ergotamine and methysergide (avoid ergotamine and methysergide for 24 hours after eltoprazin or frotovatran, avoid eltoprazin or frotovatran for 24 hours after ergotamine and methysergide); increased risk of vasospasm when almotriptan, rizatriptan, sumatriptan or zolmitriptan given with ergotamine and methysergide (avoid ergotamine and methysergide for 6 hours after almotriptan, rizatriptan, sumatriptan or zolmitriptan, avoid almotriptan, rizatriptan, sumatriptan or zolmitriptan for 24 hours after ergotamine and methysergide)
- Ulcer-healing Drugs: metabolism of zolmitriptan inhibited by cimetidine (reduce dose of zolmitriptan)

5HT Antagonists
- Analgesics: ondansetron possibly antagonises effects of tramadol
- Anti-arrhythmics: increased risk of ventricular arrhythmias when dolasetron given with amiodarone, disopyramide, flecainide, lidocaine (lignocaine) or propafenone—avoid concomitant use
- Antibacterials: metabolism of ondansetron accelerated by rifampicin (reduced effect)
- Antiepileptics: metabolism of ondansetron accelerated by carbamazepine and phenytoin (reduced effect)
- Beta-blockers: increased risk of ventricular arrhythmias when dolasetron given with esmolol—avoid concomitant use
- Hydralazine see Vasodilator Antihypertensives
- Hydrochlorothiazide see Diuretics
- Hydrocortisone see Corticosteroids
- Hydroflumethiazide see Diuretics
- Hydrocortisone see Opioid Analgesics
- Hydrochlorothiazide see Diuretics
- Hydrocortisone see Antacids
- Hydroxocobalamin
- Antibacterials: response to hydroxocobalamin reduced by chloramphenicol
- Hydroxyurea
- Antiepileptics: cytoxetics possibly reduce absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytoxetics with clozapine (increased risk of agranulocytosis)
Hydroxy carbamides (continued)
- Antivirals: increased risk of toxicity when hydroxy carbamides given with didanosine and stavudine—avoid concomitant use
Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets
Hydroxychloroquine see Chloroquine and Hydroxychloroquine
Hydroxyzine see Antihistamines
Hycosine see Antimuscarinics
Ibandronic Acid see Bisphosphonates
Ibuprofen see NSAIDs
Ilosfamide
- Anticoagulants: irosfamide possibly enhances anticoagulant effect of coumarins
Antiepileptics: cytoxotics possibly reduce absorption of phenytoin
- Antimycotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets
Iloprost
Analgesics: increased risk of bleeding when iloprost given with NSAIDs or aspirin
Anticoagulants: iloprost possibly enhances anticoagulant effect of coumarins and heparins; increased risk of bleeding when iloprost given with phenindione
Clopidogrel: increased risk of bleeding when iloprost given with clopidogrel
Eptifibatide: increased risk of bleeding when iloprost given with eptifibatide
Tirofiban: increased risk of bleeding when iloprost given with tirofiban
Imatinib
- Antibacterials: plasma concentration of imatinib reduced by rifampicin—avoid concomitant use
Anticoagulants: manufacturer of imatinib advises replacement of warfarin with a heparin (possibility of enhanced warfarin effect)
- Antidepressants: plasma concentration of imatinib reduced by St John’s wort—avoid concomitant use
Antiepileptics: plasma concentration of imatinib reduced by phenytoin—avoid concomitant use; cytoxotics possibly reduce absorption of phenytoin
Antifungals: plasma concentration of imatinib increased by ketoconazole
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets
Ciclosporin: imatinib possibly increases plasma concentration of ciclosporin
Lipid-regulating Drugs: imatinib increases plasma concentration of simvastatin
Thyroid Hormones: imatinib possibly reduces plasma concentration of levothyroxine (thyroxine)
Imidapril see ACE Inhibitors
Imipenem with Clastatin
- Antibacterials: increased risk of convulsions when imipenem with clastatin given with ganciclovir
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679
Impiramine see Antidepressants, Tricyclic
Immunoglobulins
Note For advice on immunoglobulins and live virus vaccines, see under Normal Immunoglobulin, p. 681
Immunosuppressants (antiproliferative) see Azathioprine and Mycophenolate Mofetil
Indapamide see Diuretics
Indinavir
- Anti-arrhythmics: indinavir possibly increases plasma concentration of amiiodarone—avoid concomitant use; indinavir possibly increases plasma concentra-
Indinavir (continued)
- Anti-arrhythmics (continued)
- Antiarrhythmics: increased risk of ventricular arrhythmias—avoid concomitant use
- Antibacterials: indinavir increases plasma concentration of rifampicin—avoid concomitant use; metabolism of indinavir accelerated by rifampicin (reduced plasma concentration—avoid concomitant use); avoidance of concomitant indinavir in severe renal and hepatic impairment advised by manufacturer of enfuvirtide
Anticoagulants: avoidance of indinavir advised by manufacturer of rivaroxaban
Antidepressants: plasma concentration of indinavir reduced by St John’s wort—avoid concomitant use
Antiepileptics: plasma concentration of indinavir possibly reduced by carbamazepine and phenytoin, also plasma concentration of carbamazepine and phenytoin possibly increased; plasma concentration of indinavir possibly reduced by primidone
Antifungals: plasma concentration of indinavir increased by itraconazole and ketoconazole (consider reducing dose of indinavir)
Antimycotics: caution with indinavir advised by manufacturer of artemether/lumefantrine
Antimuscarinics: avoidance of indinavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when indinavir given with fesoterodine—consult fesoterodine product literature
- Antipsychotics: indinavir possibly inhibits metabolism of arimiprazole (reduce dose of aripiprazole); indinavir possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias—avoid concomitant use); indinavir increases plasma concentration of sertraline (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antivirals: avoid concomitant use of indinavir with stavudine; plasma concentration of both drugs increased when indinavir given with darunavir; plasma concentration of indinavir reduced by efavirenz and nevirapine; plasma concentration of indinavir possibly reduced by maraviroc; combination of indinavir with nelfinavir may increase plasma concentration of either drug (or both); plasma concentration of indinavir increased by ritonavir; indinavir increases plasma concentration of saquinavir
- Anxiolytics and Hypnotics: increased risk of prolonged sedation when indinavir given with alprazolam—avoid concomitant use; indinavir possibly increases plasma concentration of midazolam (risk of prolonged sedation—avoid concomitant use of oral midazolam)
Atovaquone: plasma concentration of indinavir possibly reduced by atovaquone
- Barbiturates: plasma concentration of indinavir possibly reduced by barbiturates; plasma concentration of indinavir possibly reduced by phenobarbital, also plasma concentration of phenobarbital possibly increased
- Ciclosporin: indinavir increases plasma concentration of ciclosporin
Clarithromycin: indinavir possibly increases plasma concentration of clarithromycin—avoid concomitant use
Corticosteroids: plasma concentration of indinavir possibly reduced by dexamethasone
- Ergotalkaloids: increased risk of ergotism when indinavir given with ergotamine and methysergide—avoid concomitant use
- 5HT Agonists: indinavir increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when indinavir given with atorvastatin; possible increased risk of myopathy when indinavir given with rosuvastatin—avoid concomitant use;
Indinavir
- Lipid-regulating Drugs (continued)
  Increased risk of myopathy when indinavir given with simvastatin (avoid concomitant use)
- Sildenafil: indinavir increases plasma concentration of sildenafil—reduce initial dose of sildenafil
- Tadalafil: indinavir possibly increases plasma concentration of tadalafil
- Vardenafil: indinavir increases plasma concentration of vardenafil—avoid concomitant use

Indometacin see NSAIDs
Indoramin see Alpha-blockers

Infliximab
- Abatacept: increased risk of side-effects when infliximab given with abatacept
- Anakinra: avoid concomitant use of infliximab with anakinra
- Vaccines: avoid concomitant use of infliximab with live vaccines (see p. 650)

Influenza Vaccine see Vaccines
Insulin see Antidiabetics
Interferon Alfa see Interferons
Interferon Gamma see Interferons

Interferons
Note Peginterferon alfa interactions as for interferon alfa
- Antibiotics: increased risk of peripheral neuropathy when interferon alfa given with telbivudine
- Theophyline: interferon alfa inhibits metabolism of theophyline (increased plasma concentration)
- Vaccines: manufacturer of interferon gamma advises avoid concomitant use with vaccines

Ipratropium see Antimuscarinics
Ivermectin see Angiotensin-II Receptor Antagonists

Irinotecan
- Antidepressants: metabolism of irinotecan accelerated by St John’s wort (reduced plasma concentration—avoid concomitant use)
- Antiepileptics: plasma concentration of irinotecan and its active metabolite reduced by carbamazepine and phenytoin; cytochromes possibly reduce absorption of phenytoin
- Antifungals: plasma concentration of irinotecan reduced by ketoconazole (but concentration of active metabolite of irinotecan increased)—avoid concomitant use
- Antipsychotics: avoid concomitant use of cytochromes (increased risk of agranulocytosis)
- Antivirals: metabolism of irinotecan possibly inhibited by stavudine (increased risk of toxicity)
- Barbiturates: plasma concentration of irinotecan and its active metabolite reduced by phenobarbital
- Cardiac Glycosides: cytochromes reduce absorption of digoxin tablets
- Cytotoxic: plasma concentration of irinotecan possibly increased by sorafenib

Iron
- Antacids: absorption of oral iron reduced by oral magnesium salts (as magnesium trisilicate)
- Antibacterials: oral iron reduces absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin; oral iron reduces absorption of tetracyclines, also absorption of oral iron reduced by tetracyclines
- Bisphosphonates: oral iron reduces absorption of bisphosphonates
- Calcium Salts: absorption of oral iron reduced by calcium salts
- Cytotoxic: oral iron reduces absorption of mycophenolate
- Dimercaprol: avoid concomitant use of iron with dimercaprol
- Dopaminergics: oral iron reduces absorption of entacapone; oral iron possibly reduces absorption of levodopa
- Methyldopa: oral iron antagonises hypotensive effect of methyldopa
- Penicillamine: oral iron reduces absorption of penicillamine

Iron (continued)
- Thyroid Hormones: oral iron reduces absorption of levothyroxine (thyroxine) (give at least 2 hours apart)
- Trientine: absorption of oral iron reduced by trientine
- Zinc: oral iron reduces absorption of zinc, also absorption of oral iron reduced by zinc

Isocarboxazid see MAOIs
Isosfuran see Anaesthetics, General
Isomethyptene see Sympathomimetics

Isoniazid
Anaesthetics, General: hepatotoxicity of isoniazid possibly potentiated by general anaesthetics
- Antacids: absorption of isoniazid reduced by antacids
- Antibacterials: increased risk of CNS toxicity when isoniazid given with cycloserine
- Antiepileptics: isoniazid increases plasma concentration of carbamazepine (also possibly increased plasma hepatoxocity); isoniazid inhibits metabolism of ethoxzolamide (increased plasma concentration and risk of toxicity); isoniazid inhibits metabolism of ophenytoin (increased plasma concentration)
- Antifungals: isoniazid possibly reduces plasma concentration of ketoconazole
- Antihistamines and Sedative Hypnotics: isoniazid inhibits the metabolism of diazepam
- Corticosteroids: plasma concentration of isoniazid possibly reduced by corticosteroids
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
- Theophyline: isoniazid possibly increases plasma concentration of theophyline
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Isosorbide Dinitrate see Nitrates
Isosorbide Mononitrate see Nitrates
Isotretinoin see Retinoids
Isradipine see Calcium-channel Blockers
Itraconazole see Antifungals, Triazole

Ivabradine
- Anti-arrhythmics: increased risk of ventricular arrhythmias when ivabradine given with amiodarone or disopyramide
- Antibacterials: plasma concentration of ivabradine possibly increased by chloramphenicol and rifampicin; increased concomitant use; increased risk of ventricular arrhythmias when ivabradine given with erythromycin—avoid concomitant use
- Antidepressants: plasma concentration of ivabradine reduced by St John's wort—avoid concomitant use
- Antifungals: plasma concentration of ivabradine increased by ketoconazole—avoid concomitant use; plasma concentration of ivabradine increased by fluconazole—reduce initial dose of ivabradine; plasma concentration of ivabradine possibly increased byitraconazole—avoid concomitant use
- Antimalarials: increased risk of ventricular arrhythmias when ivabradine given with mefloquine
- Antipsychotics: increased risk of ventricular arrhythmias when ivabradine given with pimozide or sertindole
- Antivirals: plasma concentration of ivabradine possibly increased by nelfinavir and ritonavir—avoid concomitant use

Beta-blockers: increased risk of ventricular arrhythmias when ivabradine given with esmolol
Calcium-channel Blockers: plasma concentration of ivabradine increased by diltiazem and verapamil—avoid concomitant use
Grapefruit Juice: plasma concentration of ivabradine increased by grapefruit juice
Pentamidine isethionate: increased risk of ventricular arrhythmias when ivabradine given with pentamidine isethionate

Kaoalin
Analgesics: kaoalin possibly reduces absorption of aspirin
Appendix 1: Interactions

Kaopectate

Antibacterials: kaopectate possibly reduces absorption of tetracyclines

Antimalarials: kaopectate reduces absorption of chloroquine and hydroxychloroquine

Antipsychotics: kaopectate possibly reduces absorption of phenothiazines

Ketamine see Anaesthetics, General

Ketoconazole see Antifungals, Imidazole

Ketoprofen see NSAIDs

Ketotifen see Antihistamines

Labelalol see Beta-blockers

Lacidipine see Calcium-channel Blockers

Lacosamide

Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered; anti-convulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s Wort

Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by metoquine

Lactulose

Anticoagulants: lactulose possibly enhances anticoagulant effect of coumarins

Lamivudine

Antibacterials: plasma concentration of lamivudine increased by trimethoprim (as co-trimoxazole)—avoid concomitant use of high-dose co-trimoxazole

Antivirals: avoidance of lamivudine advised by manufacturer of emtricitabine; manufacturer of lamivudine advises avoid concomitant use with foscamet; manufacturer of lamivudine advises avoid concomitant use of intravenous ganciclovir

Lamotrigine

Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered; anti-convulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s Wort

Antiepileptics: plasma concentration of lamotrigine often reduced by carbamazepine, also plasma concentration of lamotrigine increased by valproate

Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by metoquine

Barbiturates: plasma concentration of lamotrigine reduced by phenobarbital

Oestrogens: plasma concentration of lamotrigine reduced by oestrogens

Progestogens: plasma concentration of lamotrigine reduced by progestogens

Lanreotide

Antidiabetics: lanreotide possibly reduces requirements for insulin, metformin, repaglinide and sulphonylureas

Ciclosporin: lanreotide reduces plasma concentration of ciclosporin

Lansoprazole see Proton Pump Inhibitors

Lanthanum

Antifungals: lanthanum possibly reduces absorption of ketoconazole (give at least 2 hours apart)

Antimalarials: lanthanum possibly reduces absorption of chloroquine and hydroxychloroquine (give at least 2 hours apart)

Lapatinib

Antibacterials: manufacturer of lapatinib advises avoid concomitant use with rifabutin, rifampicin and telithromycin

Antidepressants: manufacturer of lapatinib advises avoid concomitant use with St John’s Wort

Antidiabetics: manufacturer of lapatinib advises avoid concomitant use with repaglinide

Antiepileptics: plasma concentration of lapatinib reduced by carbamazepine—avoid concomitant use; cytotoxics possibly reduce absorption of phenytoin; manufacturer of lapatinib advises avoid concomitant use with phenytoin

Antifungals: plasma concentration of lapatinib increased by ketoconazole—avoid concomitant use; manufacturer of lapatinib advises avoid concomitant use with efavirenz, posaconazole and voriconazole

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis); manufacturer of lapatinib advises avoid concomitant use with valproate

Antivirals: manufacturer of lapatinib advises avoid concomitant use with ritonavir and saquinavir

Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets

Grapefruit juice: manufacturer of lapatinib advises avoid concomitant use with grapefruit juice

Laronidase

Anaesthetics, Local: effects of laronidase possibly inhibited by procaine (manufacturer of laronidase advises avoid concomitant use)

Antimalarials: effects of laronidase possibly inhibited by chloroquine and hydroxychloroquine (manufacturer of laronidase advises avoid concomitant use)

Leflunomide

Note Increased risk of toxicity with other haematotoxic and hepatotoxic drugs

Antibacterials: plasma concentration of active metabolite of leflunomide possibly increased by rifampicin

Anticoagulants: leflunomide possibly enhances anticoagulant effect of warfarin

Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of tolbutamide

Antiepileptics: leflunomide possibly increases plasma concentration of phenytoin

Lipid-regulating Drugs: the effect of leflunomide is significantly decreased by colestyramine (enhanced elimination)—avoid unless drug elimination desired

Vaccines: avoid concomitant use of leflunomide with live vaccines (see p. 660)

Lenalidomide

Cardiac Glycosides: lenalidomide possibly increases plasma concentration of digoxin

Lercanidipine see Calcium-channel Blockers

Leukotriene Antagonists

Analgesics: plasma concentration of zafirlukast increased by aspirin

Antibacterials: plasma concentration of zafirlukast reduced by erythromycin

Anticoagulants: zafirlukast enhances anticoagulant effect of warfarin

Antiepileptics: plasma concentration of montelukast reduced by primidone

Barbiturates: plasma concentration of montelukast reduced by phenobarbital

Theophylline: zafirlukast possibly increases plasma concentration of theophylline, also plasma concentration of zafirlukast reduced

Levamisole

Alcohol: possibility of disulfiram-like reaction when levamisole given with alcohol

Anticoagulants: levamisole possibly enhances anticoagulant effect of warfarin

Antiepileptics: levamisole possibly increases plasma concentration of phenytoin
Levetiracetam
- Anti-convulsants: anticonvulsant effect of antiepileptics antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anti-convulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of anti-epileptics antagonised by mefloquine

Levobupivacaine see Beta-blockers

Levodopa
Anti-arrhythmics: increased myocardial depression when levobupivacaine given with anti-arrhythmics

Levetiracetam see Antihistamines

Levodopa
ACE Inhibitors: enhanced hypotensive effect when levodopa given with ACE inhibitors
Adrenergic Neurone Blockers: enhanced hypotensive effect when levodopa given with adrenergic neurone blockers
Alpha-blockers: enhanced hypotensive effect when levodopa given with alpha-blockers
- Anaesthetics, General: increased risk of arrhythmias when levodopa given with volatile liquid general anaesthetics
Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when levodopa given with angiotensin-II receptor antagonists
- Antidepressants: risk of hypertensive crisis when levodopa given with antidepressants (convulsive threshold lowered); anti-convulsant effect of antiepileptics antagonised by MAOIs, avoid levodopa for at least 2 weeks after stopping MAOIs; increased risk of side-effects when levodopa given with moclobemide
Antiepileptics: effects of levodopa possibly reduced by phenytoin
Antimuscarinics: absorption of levodopa possibly reduced by antimuscarinics
Antipsychotics: effects of levodopa antagonised by antipsychotics; avoidance of levodopa advised by manufacturer of amisulpride (antagonism of effect)
Anxiolytics and Hypnotics: effects of levodopa possibly antagonised by benzodiazepines
Beta-blockers: enhanced hypotensive effect when levodopa given with beta-blockers
Bupropion: increased risk of side-effects when levodopa given with bupropion
Calcium-channel Blockers: enhanced hypotensive effect when levodopa given with calcium-channel blockers
Clonidine: enhanced hypotensive effect when levodopa given with clonidine
Diazoxide: enhanced hypotensive effect when levodopa given with diazoxide
Diuretics: enhanced hypotensive effect when levodopa given with diuretics
Dopaminergics: enhanced effects and increased toxicity of levodopa when given with selegiline (reduce dose of levodopa)
- Iron: absorption of levodopa possibly reduced by oral iron
Mecamylamine: effects of dopaminergics possibly enhanced by mecamylamine
Methylphenidate: enhanced hypotensive effect when levodopa given with methylphenidate; antiparkinsonian effect of dopaminergics antagonised by methylphenidate
Moxonidine: enhanced hypotensive effect when levodopa given with moxonidine
Muscle Relaxants: possible agitation, confusion and hallucinations when levodopa given with baclofen
Nitrates: enhanced hypotensive effect when levodopa given with nitrates
Vasodilator Antihypertensives: enhanced hypotensive effect when levodopa given with hydralazine, manidyl or sodium nitroprusside
Vitamins: effects of levodopa reduced by pyridoxine when given without dopa-decarboxylase inhibitor

Levofloxacin see Quinolones

Levopropamide (methotrimprazine) see Antipsychotics

Levopropamide (methotrimeprazine) see Antipsychotics

Lidocaine (lignocaine)
- Note Interactions less likely when lidocaine used topically
- Antidepressants: increased risk of ventricular arrhythmias when lidocaine (lignocaine) given with trazodone
- Antiepileptics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics
- Antibacterials: increased risk of ventricular arrhythmias when lidocaine (lignocaine) given with other anti-arrhythmics
- Anti-arrhythmics: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics
- Antihistamines: increased risk of CNS effects when lidocaine given with omeprazole
- Antipsychotics: enhanced hypotensive effect when levodopa given with calcium-channel blockers
- Beta-blockers: increased hypotensive effect when levodopa given with beta-blockers
- Beta-blockers: enhanced hypotensive effect when levodopa given with calcium-channel blockers
- Antifungals: possibly antagonised by amphotericin B; avoid concomitant use
- Erythromycin: possibly antagonised by fluoroquinolones, avoid concomitant use
- Macrolides: possibly antagonised by fluoroquinolones, avoid concomitant use
- Omeprazole: possibly antagonised by fluoroquinolones, avoid concomitant use
- Tricyclic antidepressants: possibly antagonised by fluoroquinolones, avoid concomitant use

Lidocaine (lignocaine) see Antipsychotics

Lidothecine

Lipid-regulating Drugs see Colestipol, Colestymarine, Ezetimibe, Fibrates, Nicotinic Acid, and Statins

Lisinopril see ACE Inhibitors

Lithium
- ACE Inhibitors: excretion of lithium reduced by ACE inhibitors (increased plasma concentration)
- Analgesics: excretion of lithium probably reduced by NSAIDs (increased risk of toxicity); excretion of lithium reduced by diclofenac, ibuprofen, indomethacin, mafenamic acid, naproxen, parecoxib and piroxicam (increased risk of toxicity); excretion of lithium reduced by ketorolac (increased risk of toxicity); avoid concomitant use
- Angiotensin-II Receptor Antagonists: excretion of lithium reduced by angiotensin-II receptor antagonists (increased plasma concentration)
- Antacids: excretion of lithium increased by sodium bicarbonate (reduced plasma concentration)
- Anti-arrhythmics: avoidance of lithium advised by manufacturer of amiodarone (risk of ventricular arrhythmias)
- Antibacterials: increased risk of lithium toxicity when given with metronidazole
- Antidepressants: possible increased serotonergic effects when lithium given with venlafaxine; increased risk of CNS effects when lithium given with SSRIs (lithium toxicity reported); risk of toxicity when lithium given with tricyclics
- Antiepileptics: neurotoxicity may occur when lithium given with carbamazepine or phenytoin without
Lithium
Antiepileptics (continued)
increased plasma concentration of lithium; plasma concentration of lithium possibly affected by lamotrigine.
■ Antipsychotics: increased risk of extrapyramidal side-effects and possibly neurotoxicity when lithium given with clozapine, flupenthixol, haloperidol, phenothiazines or zuclopenthixol; increased risk of ventricular arrhythmias when lithium given with sertindole—avoid concomitant use; increased risk of extrapyramidal side-effects when lithium given with sulpiride.
Calcium-channel Blockers: neurotoxicity may occur when lithium given with diltiazem or verapamil without increased plasma concentration of lithium.
■ Diuretics: excretion of lithium increased by loop diuretics and thiazides and related diuretics (increased plasma concentration and risk of toxicity)—loop diuretics—avoid concomitant use; increased risk of extrapyramidal side-effects when lithium given with sulpiride.
Methyldopa: neurotoxicity may occur when lithium given with methyldopa without increased plasma concentration of lithium.
Muscle Relaxants: lithium enhances effects of muscle relaxants; hyperkinesia caused by lithium possibly aggravated by baclofen.
Pathoanatomometrics: lithium antagonises effects of neostigmine and pyridostigmine.
Theophylline: excretion of lithium increased by theophylline (reduced plasma concentration).
Lofepramine see Antidepressants, Tricyclic.
Loratadine see Antihistamines.
Loperamide
Desmopressin: loperamide increases plasma concentration of oral desmopressin.
Lopinavir
Antimuscarinics: avoidance of lopinavir advised by manufacturer of darifenacin and tolterodine.
■ Antipsychotics: lopinavir possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); lopinavir increases plasma concentration of esetindole (increased risk of ventricular arrhythmias—avoid concomitant use).
■ Antivirals: lopinavir reduces plasma concentration of saquinavir (consider reducing dose of maraviro)—plasma concentration of lopinavir reduced by nefinavir, also plasma concentration of active metabolite of nelfinavir increased; plasma concentration of lopinavir possibly reduced by nevirapine—consider increasing dose of lopinavir; lopinavir increases plasma concentration of propranolol; plasma concentration of lopinavir reduced by ritonavir.
■ Barbiturates: plasma concentration of lopinavir possibly reduced by phenobarbital.
■ Cilostazol: lopinavir possibly increases plasma concentration of cilostazol—avoid concomitant use. Cilostazol and rifampicin: plasma concentration of lopinavir possibly reduced by dexamethasone.
■ Lipid-regulating Drugs: possible increased risk of myopathy when lopinavir given with atorvastatin; possible increased risk of myopathy when lopinavir given with rosuvastatin or simvastatin—avoid concomitant use.
■ Sirolimus: lopinavir possibly increases plasma concentration of sirolimus.
Lorazepam see Antihistamines. Lorzepam see Antihistamines. Lometazipam see Antihistamines. Losartan see Angiotensin-II Receptor Antagonists. Lumefantrine see Artemether with Lumefantrine. Lymecycline see Tetracyclines.
Macrolides
Note
Note Interactions do not apply to small amounts of erythromycin used topically.
Note: erythromycin increases plasma concentration of antifungal agents: absorption of azithromycin reduced by antacids.
■ Anti-arthromic: increased risk of ventricular arrhythmias when parenteral erythromycin given with amiodarone—avoid concomitant use; erythromycin increases plasma concentration of isosorbide (increased risk of toxicity); clarithromycin possibly increases plasma concentration of isosorbide (increased risk of toxicity).
■ Antibacterials: increased risk of ventricular arrhythmias when parenteral erythromycin given with metronidazole—avoid concomitant use; macrolides possibly increase plasma concentration of rifabutin (increased risk of uveitis—reduce rifabutin dose); clarithromycin increases plasma concentration of rifabutin (increased risk of uveitis—reduce rifabutin dose); plasma concentration of clarithromycin reduced by ritonavir.
■ Antifungals: azithromycin possibly enhances anticoagulant effect of coumarins; clarithromycin and erythromycin enhance anticoagulant effect of coumarins.
■ Antidepressants: avoidance of macrolides advised by manufacturer of ebeketine. Antiepileptics: clarithromycin enhances effects of carbamazepine.
Antiepileptics: clarithromycin and erythromycin increase plasma concentration of carbamazepine;
Macrolides
- Antiepileptics (continued)
  - Clarithromycin inhibits metabolism of phenytoin (increased plasma concentration); erythromycin possibly inhibits metabolism of valproate (increased plasma concentration)
- Antifungals: clarithromycin increases plasma concentration of itraconazole
- Antihistamines: manufacturer of loratadine advises erythromycin possibly increases plasma concentration of loratadine; macrolides possibly inhibit metabolism of emizolastine (avoid concomitant use); erythromycin inhibits metabolism of emizolastine—avoid concomitant use
- Antiarrhythmics: avoidance of macrolides advised by manufacturer of amtermether/leumfanetine
- Antimuscarnicics: erythromycin possibly increases plasma concentration of darifenacin; manufacturer of fosoterodine advises dose reduction when clarithromycin given with fosoterodine—consult fosoterodine product literature; avoidance of clarithromycin and erythromycin advised by manufacturer of tolterodine
- Antipsychotics: increased risk of ventricular arrhythmias when parenteral erythromycin given with amisulpride or zuclopenthixol—avoid concomitant use; erythromycin possibly increases plasma concentration of amisulpride (reduce dose of amisulpride); possible increased risk of convulsions; increased risk of ventricular arrhythmias when clarithromycin given with pipamuzide—avoid concomitant use; possible increased risk of ventricular arrhythmias when erythromycin given with pipamuzide—avoid concomitant use; macrolides possibly increase plasma concentration of quetiapine (reduce dose of quetiapine); possible increased risk of ventricular arrhythmias when macrolides given with sertindole—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with sertindole—avoid concomitant use; increased risk of ventricular arrhythmias when parenteral erythromycin given with olanzapine
- Antivirals: plasma concentration of both drugs increased when clarithromycin given with atazanavir; increased risk of rash when clarithromycin given with efavirenz; clarithromycin increases plasma concentration of etravirine, also plasma concentration of clarithromycin reduced; plasma concentration of both drugs increased when erythromycin given with fosamprenavir; clarithromycin possibly increases plasma concentration of maraviroc (consider reducing dose of maraviroc); plasma concentration of azithromycin and erythromycin possibly increased by ritonavir; plasma concentration of clarithromycin increased by ritonavir (reduce dose of clarithromycin in renal impairment); plasma concentration of clarithromycin increased by tipranavir (reduce dose of clarithromycin in renal impairment), also clarithromycin increases plasma concentration of tipranavir; clarithromycin tablets reduce absorption of zidovudine (give at least 2 hours apart)
- Antiarrhythmics: clarithromycin and erythromycin inhibit metabolism of midazolam (increased plasma concentration with increased sedation); erythromycin increases plasma concentration of buspirone (reduce dose of buspirone); erythromycin inhibits the metabolism of zopiclone
- Antiretrovirals: clarithromycin possibly increases plasma concentration of aprepitant
- Antituberculars: increased risk of ventricular arrhythmias when parenteral erythromycin given with atamoxetine
- Calcium-channel Blockers: erythromycin possibly inhibits metabolism of felodipine (increased plasma concentration); avoidance of erythromycin advised by manufacturer of lercanidipine; clarithromycin and erythromycin possibly inhibit metabolism of verapamil (increased risk of toxicity)
- Cardiac Glycosides: macrolides increase plasma concentration of digoxin (increased risk of toxicity)

Macrolides (continued)
- Ciclosporin: macrolides possibly inhibit metabolism of ciclosporin (increased plasma concentration); clarithromycin and erythromycin inhibit metabolism of ciclosporin (increased plasma concentration)
- Cilostazol: erythromycin increases plasma concentration of cilostazol (also plasma concentration of erythromycin reduced)—avoid concomitant use
- Colchicine: clarithromycin or erythromycin increase risk of colchicine toxicity
- Corticosteroids: erythromycin possibly inhibits metabolism of corticosteroids; clarithromycin possibly increases plasma concentration of methylprednisolone; erythromycin inhibits the metabolism of methylprednisolone
- Cytoxotics: avoidance of clarithromycin advised by manufacturer of olotinib; in vitro studies suggest a possible interaction between erythromycin and docetaxel (consult docetaxel product literature); erythromycin increases toxicity of vinblastine—avoid concomitant use
- Diuretics: clarithromycin increases plasma concentration of bumetanide—avoid concomitant use; erythromycin increases plasma concentration of eplerenone (reduce dose of eplerenone)
- Dopaminergics: macrolides possibly increase plasma concentration of bromocriptine and cabergoline (increased risk of toxicity); erythromycin increases plasma concentration of bromocriptine and cabergoline (increased risk of toxicity)
- Ergot Alkaloids: increased risk of ergotism when macrolides given with ergotamine and methysergide—avoid concomitant use
- 5HT Agonists: clarithromycin and erythromycin increase plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use
- Ibravatricum: clarithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ivabradine—avoid concomitant use
- Leukotriene Antagonists: erythromycin reduces plasma concentration of zafirlukast
- Lipid-regulating Drugs: clarithromycin increases plasma concentration of atorvastatin and pravastatin; possible increased risk of myopathy when erythromycin given with atorvastatin; erythromycin increases plasma concentration of pravastatin; erythromycin reduces plasma concentration of rosuvastatin; increased risk of myopathy when clarithromycin or erythromycin given with simvastatin (avoid concomitant use)
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
- Parasymphathomimetics: erythromycin increases plasma concentration of galantamine
- Pentamidine Isetionate: increased risk of ventricular arrhythmias when parenteral erythromycin given with pentamidine isetionate
- Sildenafil: clarithromycin possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil; clarithromycin increases plasma concentration of sildenafil—reduce initial dose of sildenafil
- Sirolimus: clarithromycin increases plasma concentration of sirolimus—avoid concomitant use; plasma concentration of both drugs increased when erythromycin given with sirolimus
- Tacrolimus: clarithromycin and erythromycin increase plasma concentration of tacrolimus
- Tadalafil: clarithromycin and erythromycin possibly increase plasma concentration of tadalafil
- Theophylline: azithromycin possibly increases plasma concentration of theophylline; clarithromycin inhibits metabolism of theophylline (increased plasma concentration); erythromycin inhibits metabolism of theophylline (increased plasma concentration), if erythromycin given by mouth, also decreased plasma-erythromycin concentration

Appendix 1: Interactions
Appendix 1: Interactions

**Macrolides (continued)**

Ulcer-healing Drugs: plasma concentration of erythromycin is increased by metronidazole (risk of toxicity, including deafness); plasma concentration of both drugs increased when clarithromycin given with omeprazole

Vaccines: antibiotics inactivate oral typhoid vaccine—see p. 679

Vardenafil: erythromycin increases plasma concentration of vardenafil (reduce dose of vardenafil)

**Magnesium (parenteral)**

- Calcium-channel Blockers: profound hypotension reported with concomitant use of parenteral magnesium and nifedipine in pre-ecclampsia

Muscle Relaxants: parenteral magnesium enhances effects of non-depolarising muscle relaxants and stopping magnesium and vincristine

**Magnesium Salts (oral)** see Antacids

**MAOIs**

Note For interactions of reversible MAO-A inhibitors (RIMA)s see Moclobemide, and for interactions of MAO-B inhibitors see Rasagline and Selegiline; the antibacterial Linezolid is a reversible, non-selective MAO inhibitor

ACE Inhibitors: MAOIs possibly enhance hypotensive effect of ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when MAOIs given with adrenergic neurone blockers

- Alcohol: MAOIs interact with tyramine found in some beverages containing alcohol and some decaffeinated beverages (hypertensive crisis)—if no tyramine, enhanced hypotensive effect

Alpha -adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of apraclonidine and brimonidine

- Alpha-blockers:: avoidance of MAOIs advised by manufacturer of indoramin; enhanced hypotensive effect when MAOIs given with alpha-blockers

- Anaesthetics, General: Because of hazardous interactions between MAOIs and general anaesthetics, MAOIs should normally be stopped 2 weeks before surgery

- Analgesics: CNS excitation or depression (hypertension or hypotension) when MAOIs given with pethidine—avoid concomitant use and for 2 weeks after stopping MAOIs; avoidance of MAOIs advised by manufacturer of nefopam; possible CNS excitation or depression (hypertension or hypotension) when MAOIs given with opioid analgesics—avoid concomitant use and for 2 weeks after stopping MAOIs

Angiotensin-II Receptor Antagonists: MAOIs possibly enhance hypotensive effect of angiotensin-II receptor antagonists

- Antidepressants: increased risk of hypertension and CNS excitation when MAOIs given with venlafaxine (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs); after stopping MAOIs do not start nortriptyline or fluoxetine for 2 weeks, also MAOIs should not be started until at least 1 week after stopping clomipramine or venlafaxine; increased risk of hypertension and CNS excitation when MAOIs given with other MAOIs (avoid for at least 2 weeks after stopping previous MAOIs and then start at a reduced dose); MAOIs

- Antidepressants (continued) after stopping MAOIs do not start moclobemide for at least 1 week; MAOIs increase CNS effects of SSRIs (risk of serious toxicity); after stopping MAOIs do not start tricyclic-related antidepressants for 2 weeks, also MAOIs should not be started until at least 1–2 weeks after stopping tricyclic-related antidepressants; increased risk of hypertension and CNS excitation when MAOIs given with tricyclics, tricyclics should not be started until 2 weeks after stopping MAOIs (3 weeks if starting clomipramine or imipramine), also MAOIs should not be started for at least 1–2 weeks after stopping tricyclics (3 weeks in the case of clomipramine or imipramine); CNS excitation and confusion when MAOIs given with tryptophan (reduce dose of tryptophan)

Antidiabetics: MAOIs possibly enhance hypoglycaemic effect of antidiabetics; MAOIs enhance hypoglycaemic effect of insulin, metformin and sulphonylureas

- Antiepileptics: MAOIs possibly antagonise anti-convulsant effect of antiepileptics (convulsive threshold lowered); avoidance for 2 weeks after stopping MAOIs advised by manufacturer of carbamazepine, also antagonism of anticonvulsant effect

Antihistamines: increased antimuscarinic and sedative effect when MAOIs given with antihistamines

- Antimalarials: avoidance of antidepressants advised by manufacturer of artemether/lumefantrine

Antimuscarinics: increased risk of antimuscarinic side-effects when MAOIs given with antimuscarinics

- Antipsychotics: CNS effects of MAOIs possibly increased by doxapram

Anxiolytics and Hypnotics: avoidance of MAOIs advised by manufacturer of buspirone

- Atomoxetine: after stopping MAOIs do not start atomoxetine for 2 weeks, also MAOIs should not be started until at least 2 weeks after stopping atomoxetine; possible increased risk of convulsions when antidepressants given with atomoxetine

Barbiturates: MAOIs possibly antagonise anti-convulsant effect of barbiturates (convulsive threshold lowered)

Beta-blockers: enhanced hypotensive effect when MAOIs given with beta-blockers

- Bupropion: avoidance of bupropion for 2 weeks after stopping MAOIs advised by manufacturer of bupropion

Calcium-channel Blockers: enhanced hypotensive effect when MAOIs given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when MAOIs given with clonidine

Diazoxide: enhanced hypotensive effect when MAOIs given with diazoxide

Diuretics: enhanced hypotensive effect when MAOIs given with diuretics

- Dopaminergics: avoid concomitant use of non-selective MAOIs with entacapone; risk of hypertensive crisis when MAOIs given with levodopa, avoid levodopa for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when MAOIs given with rasagline, avoid MAOIs for at least 2 weeks after stopping rasagline; enhanced hypotensive effect when MAOIs given with selegiline; avoid concomitant use of MAOIs with tolcapone

Doxapram: MAOIs enhance effects of doxapram

5HT Agonists: risk of CNS toxicity when MAOIs given with zolmitriptan or sumatriptan (avoid zolmitriptan or sumatriptan for 2 weeks after MAOIs); increased risk of CNS toxicity when MAOIs given with sumatriptan

Methyldopa: avoidance of MAOIs advised by manufacturer of methyldopa
MAOIs (continued)
Moxonidine: enhanced hypotensive effect when MAOIs given with moxonidine
Muscle Relaxants: phenelzine enhances effects of saxethamethonium
Nicorandil: enhanced hypotensive effect when MAOIs given with nicorandil
Nitrates: enhanced hypotensive effect when MAOIs given with nitrates
Sibutramine: increased CNS toxicity when MAOIs given with sibutramine (manufacturer of sibutramine advises avoid concomitant use), also avoid sibutramine for 2 weeks after stopping MAOIs
Sympathomimetis: risk of hypertensive crisis when MAOIs given with dexmetetamine, dopamine, dopexamine, ephedrine, somethetepine, phenylephrine, phenylpropanolamine, pseudoephedrine or sympathomimetis; risk of hypertensive crisis when MAOIs given with methylnephenide, some manufacturers advise avoid methylphenidate for at least 2 weeks after stopping MAOIs
Tetrazenazine: risk of CNS excitation and hypertension when MAOIs given with tetrazenazine

Antidepressants: plasma concentration of maraviroc possibly increased by atazanavir, darunavir, indinavir, lopinavir and saquinavir (consider reducing dose of maraviroc); plasma concentration of maraviroc reduced by rifampicin—consider increasing dose of maraviroc
Antidepressants: plasma concentration of maraviroc possibly reduced by St John's wort—avoid concomitant use
Antifungals: plasma concentration of maraviroc increased by itaconazole (consider reducing dose of maraviroc)
Antivirals: plasma concentration of maraviroc increased by zanamivir, zidovudine, lamivudine (consider reducing dose of maraviroc); plasma concentration of maraviroc possibly reduced by efavirenz—consider increasing dose of maraviroc; plasma concentration of maraviroc possibly reduced by etravirine; plasma concentration of maraviroc possibly increased by nefilnavir (consider reducing dose of maraviroc)

Mebendazole
Ulcer-healing Drugs: metabolism of mebendazole possibly inhibited by cimetidine (increased plasma concentration)
Medroxyprogesterone see Progestogens
Mefenamic Acid see NSAIDs
Mefloquine (continued)
Beta-blockers: increased risk of bradycardia when mefloquine given with beta-blockers
Calcium-channel Blockers: possible increased risk of bradycardia when mefloquine given with calcium-channel blockers
Cardiac Glycosides: possible increased risk of bradycardia when mefloquine given with digoxin
Ivabradine: increased risk of ventricular arrhythmias when mefloquine given with ivabradine
Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 679

Megestrol see Progestogens
Melatonin see Anxiolytics and Hypnotics
Meloxicam see NSAIDs
Melphalan
Antibacterials: increased risk of melphalan toxicity when given with nalidixic acid
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Ciclosporin: increased risk of nephrotoxicity when melphalan given with ciclosporin
Menantine
Anaesthetics, General: increased risk of CNS toxicity when memantine given with etometamine (manufacturer of memantine advises avoid concomitant use)
Analgesics: increased risk of CNS toxicity when memantine given with dextromethorphan (manufacturer of memantine advises avoid concomitant use)
Anticoagulants: memantine possibly enhances anti-coagulant effect of warfarin
Antiepileptics: memantine possibly reduces effects of pridimone
Antimuscarinics: memantine possibly enhances effects of antimuscarinics
Antipsychotics: memantine possibly reduces effects of antipsychotics
Barbiturates: memantine possibly reduces effects of barbiturates
Dopaminergics: memantine possibly enhances effects of dopaminergics and selegiline; increased risk of CNS toxicity when memantine given with amantadine (manufacturer of memantine advises avoid concomitant use)
Muscle Relaxants: memantine possibly modifies effects of baclofen and dantrolene
Mepacrine
Antimalarials: mepacrine increases plasma concentration of primaquine (increased risk of toxicity)
Meprobamate see Anxiolytics and Hypnotics
Meptazinol see Opioid Analgesics
Mecaptopurine
Allopurinol: enhanced effects and increased toxicity of mecaptopurine when given with allopurinol (reduce dose of mercaptopurine to one quarter of usual dose) Aminosaliclylates: possible increased risk of leukopenia when mercaptopurine given with aminosaliclylates
Antibacterials: increased risk of haematological toxicity when mercaptopurine given with
Allopurinol (as co-trimoxazole) increased risk of haematological toxicity when mercaptopurine given with trimethoprim (also with co-trimoxazole)
Anticoagulants: mercaptopurine possibly reduces anticoagulant effect of coumarins
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Appendix 1: Interactions

Meropenem
Antiepileptics: meropenem reduces plasma concentration of valproate
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Probencid: excretion of meropenem reduced by probenecid (manufacturers of meropenem advise avoid concomitant use)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Mesalazine see Aminosalicylates
Methotrexate see Oestrogens
Metaraminol see Sympathomimetics
Methformin see Antidiabetics
Methadone see Opioid Analgesics
Methyldopa
• Antibacterials: increased risk of crystalluria when methenamine given with sulphonamides
• Diuretics: effects of methenamide antagonised by acetazolamide
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
Potassium Salts: avoid concomitant use of methenamine with potassium citrate
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Methocarbamol see Muscle Relaxants
Methotrexate
• Anaesthetics, General: antifolate effect of methotrexate increased by nitrous oxide—avoid concomitant use
• Analgesics: excretion of methotrexate probably reduced by NSAIDs (increased risk of toxicity)—but for concomitant use in rheumatic disease see p. 568; excretion of methotrexate reduced by azapropazone (avoid concomitant use); excretion of methotrexate reduced by aspirin, diclofenac, ibuprofen, indometacin, ketoprofen, meloxicam and naproxen (increased risk of toxicity)—but for concomitant use in rheumatic disease see p. 568
• Antibacterials: absorption of methotrexate possibly reduced by neomycin; excretion of methotrexate possibly reduced by ciprofloxacin (increased risk of toxicity); increased risk of haematological toxicity when methotrexate given with sulfa methoxazole (as co-trimoxazole); increased risk of methotrexate toxicity when given with doxycycline, sulphonamides or tetracycline; excretion of methotrexate reduced by penicillins (increased risk of toxicity); increased risk of haematological toxicity when methotrexate given with trimethoprim (also with co-trimoxazole)
Antiepileptics: antifolate effect of methotrexate increased by phenytoin; cytoxotics possibly reduce absorption of phenytoin
• Antimalarials: antifolate effect of methotrexate increased by pyrimethamine
• Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets
Ciclosporin: risk of toxicity when methotrexate given with ciclosporin
Corticosteroids: increased risk of haematological toxicity when methotrexate given with corticosteroids
Cytotoxics: increased pulmonary toxicity when methotrexate given with cisplatin
Probencid: excretion of methotrexate reduced by probenecid (increased risk of toxicity)
• Retinoids: plasma concentration of methotrexate increased by acitretin (also increased risk of hepatotoxicity)—avoid concomitant use
• Theophylline: methotrexate possibly increases plasma concentration of theophylline
Ulcer-healing Drugs: excretion of methotrexate possibly reduced by omeprazole (increased risk of toxicity)

Methoxamine see Sympathomimetics
Methyldopa
ACE Inhibitors: enhanced hypotensive effect when methyldopa given with ACE inhibitors
Adrenergic Neurone Blockers: enhanced hypotensive effect when methyldopa given with adrenergic neurone blockers
Alcohol: enhanced hypotensive effect when methyldopa given with alcohol
Aldesleukin: enhanced hypotensive effect when methyldopa given with aldesleukin
Alpha-blockers: enhanced hypotensive effect when methyldopa given with alpha-blockers
Anasthesics, General: enhanced hypotensive effect when methyldopa given with general anaesthetics
Analgesics: hypotensive effect of methyldopa antagonised by NSAIDs
Antigenos-II Receptor Antagonists: enhanced hypotensive effect when methyldopa given with angiotensin-II receptor antagonists
• Antidepressants: manufacturer of methyldopa advises avoid concomitant use with MAOIs
Antipsychotics: enhanced hypotensive effect when methyldopa given with antipsychotics (also increased risk of extrapyramidal effects)
Anxiolytics and Hypnotics: enhanced hypotensive effect when methyldopa given with anxiolytics and hypnotics
Beta-blockers: enhanced hypotensive effect when methyldopa given with beta-blockers
Calcium-channel Blockers: enhanced hypotensive effect when methyldopa given with calcium-channel blockers
Clonidine: enhanced hypotensive effect when methyldopa given with clonidine
Corticosteroids: hypotensive effect of methyldopa antagonised by corticosteroids
Diazoxide: enhanced hypotensive effect when methyldopa given with diazoxide
Diuretics: enhanced hypotensive effect when methyldopa given with diuretics
Dopaminergics: methyldopa antagonises anti-parkinsonian effect of dopaminergics; increased risk of extrapyramidal side-effects when methyldopa given with amantadine; effects of methyldopa possibly antagonised by entacapone; enhanced hypotensive effect when methyldopa given with levodopa
Iron: hypotensive effect of methyldopa antagonised by oral iron
• Lithium: neurotoxicity may occur when methyldopa given with lithium without increased plasma concentration of lithium
Moxisylyte (thymoxamine): enhanced hypotensive effect when methyldopa given with moxisylyte
Moxonidine: enhanced hypotensive effect when methyldopa given with moxonidine
Muscle Relaxants: enhanced hypotensive effect when methyldopa given with baclofen or tizanidine
Nitrates: enhanced hypotensive effect when methyldopa given with nitrates
Oestrogens: hypotensive effect of methyldopa antagonised by oestrogens
Prostaglandins: enhanced hypotensive effect when methyldopa given with alprostadil
• Sympathomimetics, Beta: acute hypotension reported when methyldopa given with infusion of adrenaline
• Vasodilator Antihypertensives: enhanced hypotensive effect when methyldopa given with hydralazine, minoxidil or sodium nitroprusside
Methylphenidate see Sympathomimetics
Methylprednisolone see Corticosteroids
Methysergide see Ergot Alkaloids
Metoprolol see Beta-blockers
Metoclopramide
• Analgesics: metoclopramide increases rate of absorption of aspirin (enhanced effect); effects of metoclopramide on gastro-intestinal activity antagonised by...
Appendix 1: Interactions

Metoclopramide
- Analgesics (continued)
  - opioid analgesics; metoclopramide increases rate of absorption of paracetamol
- Antimuscarinics: effects of metoclopramide on gastrointestinal activity antagonised by antimuscarinics
- Antipsychotics: increased risk of extrapyramidal side-effects when metoclopramide given with antipsychotics
- Atovaquone: metoclopramide reduces plasma concentration of atovaquone
  - Ciclosporin: metoclopramide increases plasma concentration of ciclosporin
- Dopaminergics: increased risk of extrapyramidal side-effects when metoclopramide given with amantadine;
  - metoclopramide antagonises antiparkinsonian effect of pergolide; avoidance of metoclopramide advised by manufacturer of ropinirole and rotigotine (antagonism of effect)
- Muscle Relaxants: metoclopramide enhances effects of suxamethonium
- Tetrabenazine: increased risk of extrapyramidal side-effects when metoclopramide given with tetrabenazine

Metololone see Diuretics

Metoprolol see Beta-blockers

Metronidazole
- Note Interactions do not apply to topical metronidazole preparations
- Alcohol: disulfiram-like reaction when metronidazole given with alcohol
  - Anticoagulants: metronidazole enhances anticoagulant effect of coumarins
  - Antiepileptics: metronidazole inhibits metabolism of phenytoin (increased plasma concentration);
  - metabolism of metronidazole accelerated by primidone (reduced plasma concentration)
  - Barbiruates: metabolism of metronidazole accelerated by barbiturates (reduced plasma concentration)
- Cytotoxics: metronidazole increases plasma concentration of busulfan (increased risk of toxicity);
  - metronidazole inhibits metabolism of fluorouracil (increased toxicity); metronidazole possibly reduces bioavailability of mycophenolate
- Disulfiram: psychotic reaction reported when metronidazole given with disulfiram
- Lithium: metronidazole increases risk of lithium toxicity
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
- Ulcer-healing Drugs: metabolism of metronidazole accelerated by primidone (reduced plasma concentration)
- Vaccines: antibacterials inactive oral typhoid vaccine—see p. 679

Mianserin see Antidepressants, Tricyclic (related)

Mifgitamin
- Antiluflurans: mifgitamin increases plasma concentration of itraconazole (consider reducing dose of itraconazole)
- Calcium-channel Blockers: mifgitamin increases plasma concentration of nifedipine
- Ciclosporin: mifgitamin possibly increases plasma concentration of ciclosporin
- Sirolimus: mifgitamin increases plasma concentration of sirolimus

Miconazole see Anxiolytics and Hypnotics

Mifepristone
- Corticosteroids: mifepristone may reduce effect of corticosteroids (including inhaled corticosteroids) for 3–4 days

Milorinone see Phosphodiesterase Inhibitors

Minacycline see Tetracyclines

Minoxidil see Vasodilator Antihypertensives

Mirtazapine
- Alcohol: increased sedative effect when mirtazapine given with alcohol
- Anticoagulants: mirtazapine enhances anticoagulant effect of warfarin
- Antidepressants: mirtazapine should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 2 weeks after stopping mirtazapine, after stopping mirtazapine do not use moclobemide for at least 1 week
- Antiepileptics: plasma concentration of mirtazapine reduced by carbamazepine and phenytoin
- Antifungals: plasma concentration of mirtazapine increased by ketoconazole
- Antimalarials: avoidance of antidepressants advised by manufacturer of arteether/lumefantrine
- Anxiolytics and Hypnotics: increased sedative effect when mirtazapine given with anxiolytics and hypnotics
- Atorvastatin: possible increased risk of convulsions when antidepressants given with atorvastatin
- Bupropion: avoid concomitant use of alcohol
- Dopaminergics: caution with mirtazapine advised by manufacturer of entacapone; increased risk of side-effects when moclobemide given with levodopa; avoid concomitant use of moclobemide with selegiline
- 5HT Agonists: risk of CNS toxicity when moclobemide given with nizatidine or sumatriptan (avoid
Moxonidine

- 5HT Agonists (continued)
  - rizatRIPTan or sumatriptan for 2 weeks after moxonidine; risk of CNS toxicity when moxonidine given with rizatryptan (reduce dose of rizatryptan)
  - Sibutramine: increased CNS toxicity when moxonidine given with sibutramine (manufacturer of sibutramine advises avoid concomitant use), also avoid sibutramine for 2 weeks after stopping moxonidine
  - Sympathomimetics: risk of hypertensive crisis when moxonidine given with sympathomimetics

- Beta-blockers: 
  - Moxisylyte (thymoxamine)
  - see Moxifloxacin
  - see Morphine
  - Montelukast 
  - see see
  - see Monobactams
  - Mometasone
  - see Moexipril

- Oestrogens:

- Ciclosporin:

- Modafinil

- Sympathomimetics:

- Ulcer-healing Drugs: plasma concentration of moxonidine increased by cimetidine (halve dose of moxonidine)

Modafinil

- Antiepileptics: modafinil possibly increases plasma concentration of phenytoin

- Ciclosporin: modafinil reduces plasma concentration of ciclosporin

- Oestrogests: modafinil accelerates metabolism of oestrogests (reduced contraceptive effect—see p. 439)

- Moexipril see ACE Inhibitors

- Mometasone see Corticosteroids

- Monobactams see Aztreonam

- Montelukast see Leukotriene Antagonists

- Morphine see Opioid Analgesics

- Morflexacin see Quinolones

- Moxisylyte (thymoxamine)

  - ACE inhibitors: enhanced hypotensive effect when moxisylyte given with ACE inhibitors
  - Adrenergic Neurone Blockers: enhanced hypotensive effect when moxisylyte given with adrenergic neurone blockers
  - Alpha-blockers: possible severe postural hypotension when moxisylyte given with alpha-blockers
  - Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxisylyte given with angiotensin-II receptor antagonists
  - Beta-blockers: possible severe postural hypotension when moxisylyte given with beta-blockers
  - Calcium-channel Blockers: enhanced hypotensive effect when moxisylyte given with calcium-channel blockers
  - Clonidine: enhanced hypotensive effect when moxisylyte given with clonidine
  - Diazoxide: enhanced hypotensive effect when moxisylyte given with diazoxide
  - Diuretics: enhanced hypotensive effect when moxisylyte given with diuretics
  - Methylodopa: enhanced hypotensive effect when moxisylyte given with methylodopa
  - Moxonidine: enhanced hypotensive effect when moxisylyte given with moxonidine
  - Nitrates: enhanced hypotensive effect when moxisylyte given with nitrates
  - Vasodilator Antihypertensives: enhanced hypotensive effect when moxisylyte given with hydralazine, minoxidil or sodium nitroprusside

Moxonidine

- ACE inhibitors: enhanced hypotensive effect when moxonidine given with ACE inhibitors
  - Adrenergic Neurone Blockers: enhanced hypotensive effect when moxonidine given with adrenergic neurone blockers
  - Alcohol: enhanced hypotensive effect when moxonidine given with alcohol
  - Aldesleukin: enhanced hypotensive effect when moxonidine given with aldesleukin
  - Alpha-blockers: enhanced hypotensive effect when moxonidine given with alpha-blockers

Moxonidine (continued)

Anaesthetics, General: enhanced hypotensive effect when moxonidine given with general anaesthetics

Analgesics: hypotensive effect of moxonidine antagonised by NSAIDs

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when moxonidine given with angiotensin-II receptor antagonists

Antidepressants: enhanced hypotensive effect when moxonidine given with MAOIs

Antipsychotics: enhanced hypotensive effect when moxonidine given with phenothiazines

Anxiolytics and Hypnotics: enhanced hypotensive effect when moxonidine given with anxiolytics and hypnotics; sedative effects possibly increased when moxonidine given with benzodiazepines

Beta-blockers: enhanced hypotensive effect when moxonidine given with beta-blockers

Calcium-channel Blockers: enhanced hypotensive effect when moxonidine given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when moxonidine given with clonidine

Corticosteroids: hypotensive effect of moxonidine antagonised by corticosteroids

Diazoxide: enhanced hypotensive effect when moxonidine given with diazoxide

Diuretics: enhanced hypotensive effect when moxonidine given with diuretics

Dopaminergics: enhanced hypotensive effect when moxonidine given with levodopa

Methylodopa: enhanced hypotensive effect when moxonidine given with methylodopa

Moxisylyte (thymoxamine): enhanced hypotensive effect when moxonidine given with moxisylyte

Muscle Relaxants

ACE inhibitors: enhanced hypotensive effect when baclofen or tizanidine given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when baclofen or tizanidine given with adrenergic neurone blockers

Antidepressants: General: increased risk of myocardial depression and bradycardia when suxamethonium given with propofol; effects of non-depolarising muscle relaxants and suxamethonium enhanced by volatile liquid general anaesthetics

Anaesthetics, Local: neuromuscular blockade enhanced and prolonged when suxamethonium given with propofol

Analgesics: excetration of baclofen possibly reduced by NSAIDs (increased risk of toxicity); excetration of baclofen reduced by ibuprofen (increased risk of toxicity)

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when baclofen or tizanidine given with angiotensin-II receptor antagonists

Anti-arrhythmics: neuromuscular blockade enhanced and prolonged when suxamethonium given with lidocaine (lignocaine)

Antibacterials: effects of non-depolarising muscle relaxants and suxamethonium enhanced by piperacillin; plasma concentration of tizanidine increased by ciprofloxacin (increased risk of toxicity)—avoid concomitant use; effects of non-depolarising muscle

Appendix 1: Interactions
Muscle Relaxants

Antibacterials (continued)
- relaxants and suxamethonium enhanced by
- vancomycin (antagonism of non-depolarising muscle relaxants and suxamethonium enhanced by clindamycin; effects of non-depolarising muscle relaxants and suxamethonium enhanced by polymyxins; effects of suxamethonium enhanced by vancomycin
- Antidepressants: plasma concentration of tizanidine increased by fluvoxamine (increased risk of toxicity)—avoid concomitant use; effects of suxamethonium enhanced by phenelzine; muscle relaxant effect of baclofen enhanced by tricyclics
- Antiepileptics: muscle relaxant effect of non-depolarising muscle relaxants antagonised by carbamazepine and phenytoin (accelerated recovery from neuromuscular blockade)
- Antimalarials: effects of suxamethonium possibly enhanced by quinine
- Antipsychotics: effects of suxamethonium possibly enhanced by promazine
- Anxiolytics and Hypnotics: increased sedative effect when baclofen or tizanidine given with anxiolytics and hypnotics
- Beta-blockers: enhanced hypotensive effect when baclofen given with beta-blockers; possible enhanced hypotensive effect and bradycardia when tizanidine given with beta-blockers; effects of muscle relaxants enhanced by propranolol
- Calcium-channel Blockers: enhanced hypotensive effect when baclofen or tizanidine given with calcium-channel blockers; effects of non-depolarising muscle relaxants enhanced by nifedipine and verapamil; risk of arrhythmias when intravenous dantrolene given with diltiazem; hypotension, myocardial depression, and hyperkalaemia when intravenous dantrolene given with verapamil; effects of suxamethonium enhanced by verapamil
- Cardiac Glycosides: possible increased risk of bradycardia when tizanidine given with cardiac glycosides; risk of ventricular arrhythmias when suxamethonium given with cardiac glycosides
- Clonidine: enhanced hypotensive effect when baclofen or tizanidine given with clonidine
- Corticosteroids: effects of pancuronium and vecuronium possibly modified by corticosteroids
- Cytotoxics: effects of suxamethonium enhanced by cyclophosphamide and thiotapec
- Diazoxide: enhanced hypotensive effect when baclofen or tizanidine given with diazoxide
- Diuretics: enhanced hypotensive effect when baclofen or tizanidine given with diuretics
- Dopaminergics: possible agitation, confusion and hallucinations when baclofen given with levodopa
- Lithium: effects of muscle relaxants enhanced by lithium; baclofen possibly aggravates hyperkinesis caused by lithium
- Magnesium (parenteral): effects of non-depolarising muscle relaxants and suxamethonium enhanced by parenteral magnesium
- Memantine: effects of baclofen and dantrolene possibly modified by memantine
- Methyldopa: enhanced hypotensive effect when baclofen or tizanidine given with methyldopa
- Metoclopramide: effects of suxamethonium enhanced by metoclopramide
- Naloxonidine: enhanced hypotensive effect when baclofen or tizanidine given with naloxonidine
- Nitrates: enhanced hypotensive effect when baclofen or tizanidine given with nitrates
- Oestrogens: plasma concentration of tizanidine possibly increased by oestrogens (increased risk of toxicity)
- Parasympathomimetics: effects of non-depolarising muscle relaxants possibly antagonised by donepezil; effects of suxamethonium possibly enhanced by donepezil; effects of non-depolarising muscle relaxants and suxamethonium enhanced by donepezil; plasma concentration of tizanidine possibly increased by progestogens (increased risk of toxicity)
- Sympathomimetics, Beta: effects of suxamethonium enhanced by bambuterol
- Vasodilator Antihypertensives: enhanced hypotensive effect when baclofen or tizanidine given with hydralazine; enhanced hypotensive effect when baclofen or tizanidine given with minoxidil; enhanced hypotensive effect when baclofen or tizanidine given with sodium nitroprusside
- Muscle Relaxants, depolarising see Muscle Relaxants

Muscle Relaxants, non-depolarising see Muscle Relaxants

MycoPhenolate
- Antacids: absorption of mycoPhenolate reduced by antacids
- Antibacterials: bioavailability of mycoPhenolate possibly reduced by metronidazole and norfloxacin; plasma concentration of active metabolite of mycoPhenolate reduced by rifampicin
- Antiepileptics: cytotoxics possibly reduced absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
- Antivirals: mycoPhenolate increases plasma concentration of aciclovir, also plasma concentration of inactive metabolite of mycoPhenolate increased; mycoPhenolate possibly increases plasma concentration of ganciclovir, also plasma concentration of inactive metabolite of mycoPhenolate possibly increased
- Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
- Iron: absorption of mycoPhenolate reduced by oral iron
- Lipid-regulating Drugs: absorption of mycoPhenolate reduced by colestatyramine
- Sevelamer: plasma concentration of mycoPhenolate possibly reduced by sevelamer
- MycoPhenolate Monotel see MycoPhenolate
- MycoPhenolate Sodium see MycoPhenolate
- MycoPhenolic Acid see MycoPhenolate

Nalbione
- Alcohol: increased sedative effect when nabilone given with alcohol
- Anxiolytics and Hypnotics: increased sedative effect when nabilone given with anxiolytics and hypnotics
- Nalbumeone see NSAIDs
- Nalodol see Beta-blockers
- Naldixidic Acid see Quinolones
- Nandrolone see Anabolic Steroids
- Naproxen see NSAIDs
- Naratriptan see 5HT Agonists
- Nateglinide see Antidiabetics
- Nebivolol see Beta-blockers
- Neofam
- Antidepressants: manufacturer of neofam advises avoid concomitant use with MAOIs; side-effects possibly increased when neofam given with tricyclics
- Antimuscarinics: increased risk of antimuscarinic side-effects when nefamopen given with antimuscarinics
- Nelfinavir
- Analgesics: nelfinavir reduces plasma concentration of methadone
- Anti-arrhythmics: increased risk of ventricular arrhythmias when nelfinavir given with amiodarone—avoid concomitant use
- Antibacterials: nelfinavir increases plasma concentration of rifabutin (halve dose of rifabutin); plasma concentration of nelfinavir significantly reduced by
Nelfinavir
- Antibacterials (continued)
  - rifampicin—avoid concomitant use; avoidance of concomitant nelfinavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
- Anticoagulants: avoidance of nelfinavir advised by manufacturer of rivaroxaban
- Antidepressants: plasma concentration of nelfinavir reduced by St John's worth—avoid concomitant use
- Antiepileptics: plasma concentration of nelfinavir possibly reduced by carbamazepine and primidone; nelfinavir reduces plasma concentration of phenytoin
- Antimalariials: caution with nelfinavir advised by manufacturer of arteether/lumeferantrine
- Antimuscarinics: avoidance of nelfinavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when nelfinavir given with fesoterodine—consult fesoterodine product literature; nelfinavir increases plasma concentration of solifenacin
- Antipsychotics: nelfinavir possibly inhibits metabolism of amisulpride (reduce dose of amisulpride); nelfinavir possibly increases plasma concentration of amitriptyline (increased risk of ventricular arrhythmias—avoid concomitant use); nelfinavir increases plasma concentration of aripiprazole (consider reducing dose of aripiprazole)
- Anxiolytics and Hypnotics: nelfinavir possibly increases plasma concentration of alprazolam (risk of prolonged sedation—avoid concomitant use of oral midazolam)
- Barbiturates: plasma concentration of nelfinavir possibly reduced by barbiturates
- Ciclosporin: nelfinavir possibly increases plasma concentration of ciclosporin
- Clotidazole: nelfinavir possibly increases plasma concentration of clotidazole—avoid concomitant use
- Diuretics: nelfinavir increases plasma concentration of spironolactone—avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when nelfinavir given with ergotamine and methysergide—avoid concomitant use
- 5HT Agonists: nelfinavir increases plasma concentration of sumatriptan (risk of toxicity)—avoid concomitant use
- Iverabidine: nelfinavir possibly increases plasma concentration of iverabidine—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when nelfinavir given with atorvastatin; possible increased risk of myopathy when nelfinavir given with rosuvastatin—avoid concomitant use; increased risk of myopathy when nelfinavir given with simvastatin (avoid concomitant use)
- Oestrogens: nelfinavir accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 439)
- Progestogens: nelfinavir possibly reduces contraceptve effect
- Sildenafil: nelfinavir possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil
- Tacrolimus: nelfinavir possibly increases plasma concentration of tacrolimus
- Ulcer-healing Drugs: plasma concentration of nelfinavir reduced by eomeprazole—avoid concomitant use

Nevirapine
- Analgesics: nevirapine possibly reduces plasma concentration of methadone
- Antibacterials: nevirapine possibly increases plasma concentration of rifabutin; plasma concentration of nevirapine reduced by rifampicin—avoid concomitant use
- Anticoagulants: nevirapine may enhance or reduce anticoagulant effect of warfarin
- Antidepressants: plasma concentration of nevirapine reduced by St John's worth—avoid concomitant use
- Antifungals: nevirapine reduces plasma concentration of ketoconazole—avoid concomitant use; plasma concentration of nevirapine increased by fluconazole; nevirapine possibly reduces plasma concentration of caspofungin—consider increasing dose of caspofungin
- Antipsychotics: nevirapine possibly reduces plasma concentration of aripiprazole—increase dose of aripiprazole
- Antivirals: nevirapine possibly reduces plasma concentration of etazanavir and etravirine—avoid concomitant use; nevirapine reduces plasma concentration of efavirenz and indinavir; nevirapine possibly reduces plasma concentration of fosamprenavir; nevirapine possibly reduces plasma concentration of olpanavir—consider increasing dose of olpanavir
- Oestrogens: nevirapine accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 439)
- Progestogens: nevirapine accelerates metabolism of progestogens (reduced contraceptive effect—see p. 439)

Nicardipine see Calcium-channel Blockers

Nicoardil
- Alcohol: hypotensive effect of nicoardil possibly enhanced by alcohol
- Antidepressants: enhanced hypotensive effect when nicoardil given with MAOIs; hypotensive effect of nicoardil possibly enhanced by tricyclics
- Sildenafil: hypotensive effect of nicoardil significantly enhanced by sildenafil (avoid concomitant use)
- Tadalafil: hypotensive effect of nicoardil significantly enhanced by tadalafil (avoid concomitant use)
- Vardenafil: possible increased hypotensive effect when nicoardil given with vardenafil—avoid concomitant use
- Vasodilator Antihypertensives: possible enhanced hypotensive effect when nicoardil given with hydralazine, minoxidil or sodium nitroprusside

Nitric Acid
- Note Interactions apply to lipid-regulating doses of nicotinic acid
- Lipid-regulating Drugs: increased risk of myopathy when atorvastatin with nicotinic acid given (applies to lipid regulating doses of nicotinic acid)

Nifedipine see Calcium-channel Blockers

Nilotinib
- Antibacterials: manufacturer of nilotinib advises avoid concomitant use with clarithromycin, moxifloxacin and telithromycin
- Antiepileptics: coadministration of cytoxotyks possibly reduce absorption of phenytoin
- Antifungals: plasma concentration of nilotinib increased by ketoconazole—avoid concomitant use; manufacturer of nilotinib advises avoid concomitant use with itraconazole and voriconazole
- Antipsychotics: avoid concomitant use of cytoxotyks with nilotinib (increased risk of agranulocytosis)
- Antivirals: manufacturer of nilotinib advises avoid concomitant use with ritonavir
- Anxiolytics and Hypnotics: nilotinib increases plasma concentration of midazolam
- Cardiac Glycosides: cytotoxicity reduce absorption of digoxin
- Grapefruit Juice: manufacturer of nilotinib advises avoid concomitant use with grapefruit juice

Nimodipine see Calcium-channel Blockers
Nitrates

ACE Inhibitors: enhanced hypotensive effect when nitrates given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when nitrates given with adrenergic neurone blockers

Alcohol: enhanced hypotensive effect when nitrates given with alcohol

Aldesleukin: enhanced hypotensive effect when nitrates given with aldesleukin

Alpha-blockers: enhanced hypotensive effect when nitrates given with alpha-blockers

Anaesthetics, General: enhanced hypotensive effect when nitrates given with general anaesthetics

Analgesics: hypotensive effect of nitrates antagonised by NSAIDs

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when nitrates given with angiotensin-II receptor antagonists

Anti-arythmics: effects of sublingual tablets of nitrates reduced by disopyramide (failure to dissolve under tongue owing to dry mouth)

• Anticoagulants: infusion of glycyrin trinitrate reduces anticoagulant effect of heparins

Antidepressants: enhanced hypotensive effect when nitrates given with MAOIs; effects of sublingual tablets of nitrates possibly reduced by tricyclic related antidepressants (failure to dissolve under tongue owing to dry mouth); effects of sublingual tablets of nitrates reduced by tricyclics (failure to dissolve under tongue owing to dry mouth)

Antimuscarinics: effects of sublingual tablets of nitrates possibly reduced by antimuscarinics (failure to dissolve under tongue owing to dry mouth)

Antipsychotics: enhanced hypotensive effect when nitrates given with phenothiazines

Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics

Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers

Calcium-channel Blockers: enhanced hypotensive effect when nitrates given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when nitrates given with clonidine

Corticosteroids: hypotensive effect of nitrates antagonised by corticosteroids

Diazoxide: enhanced hypotensive effect when nitrates given with diazoxide

Diuretics: enhanced hypotensive effect when nitrates given with diuretics

Dopaminergics: enhanced hypotensive effect when nitrates given with levodopa

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa

Moxisylyte (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyte

Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine

Muscle Relaxants: enhanced hypotensive effect when nitrates given with baclofen or tizanidine

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens

Prostaglandins: enhanced hypotensive effect when nitrates given with alprostadil

• Sildenafil: hypotensive effect of nitrates significantly enhanced by sildenafil (avoid concomitant use)

• Tadalafil: hypotensive effect of nitrates significantly enhanced by tadalafil (avoid concomitant use)

• Vardenafil: possible increased hypotensive effect when nitrates given with vardenafil—avoid concomitant use

Vasodilator Antihypertensives: enhanced hypotensive effect when nitrates given with hydralazine, minoxidil or sodium nitroprusside

Nitazepam see Anxiolytics and Hypnotics

Nitrofurantoin

Antacids: absorption of nitrofurantoin reduced by oral magnesium salts (as magnesium trisilicate)

Oestrogens: antibiotics that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)

Probencid: excretion of nitrofurantoin reduced by probencid (increased risk of side-effects)

Sulfinpyrazone: excretion of nitrofurantoin reduced by sulfinpyrazone (increased risk of toxicity)

Vaccines: antibacterial agents inactivate oral typhoid vaccine—see p. 879

Nitroimidazoles see Metronidazole and Tinidazole

Nitrous Oxide see Anaesthetics, General

Nizatidine see Histamine H1-antagonists

Noradrenaline (norepinephrine) see Sympathomimetics

Norapinephrine (noradrenaline) see Sympathomimetics

Norgesthromine see Progestogens

Norflaxacin see Quinolones

Norgestimate see Progestogens

Norgestrel see Progestogens

Nortriptyline see Antidepressants, Tricyclic

NSAIDs

Note See also Aspirin. Interactions do not generally apply to topical NSAIDs

ACE Inhibitors: increased risk of renal impairment when NSAIDs given with ACE inhibitors, also hypotensive effect antagonised

Adrenergic Neurone Blockers: NSAIDs antagonise hypotensive effect of adrenergic neurone blockers

Alpha-blockers: NSAIDs antagonise hypotensive effect of alpha-blockers

Analgesics: see Concomitant use of NSAIDs with

• Aspirin

Note

• NSAIDs or aspirin (increased side-effects)

Antidepressants: side-effects when NSAIDs given with MAOIs

Anticoagulants: anticoagulant effect of anticoagulants reduced by sulfinpyrazone (increased risk of toxicity)

Antihypertensives: hypotensive effect of antihypertensives antagonised by NSAIDs

Antimicrobials: inhibitors of bacterial growth may reduce effect of NSAIDs

Antipsychotics: enhanced hypotensive effect when nitrates given with phenothiazines

β-Blockers: enhanced hypotensive effect when nitrates given with β-blockers

Calcium-channel Blockers: enhanced hypotensive effect when nitrates given with calcium-channel blockers

Clonidine: enhanced hypotensive effect when nitrates given with clonidine

Corticosteroids: hypotensive effect of nitrates antagonised by corticosteroids

Diazoxide: enhanced hypotensive effect when nitrates given with diazoxide

Diuretics: enhanced hypotensive effect when nitrates given with diuretics

Dopaminergics: enhanced hypotensive effect when nitrates given with levodopa

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa

Moxisylyte (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyte

Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine

Muscle Relaxants: enhanced hypotensive effect when nitrates given with baclofen or tizanidine

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens

Prostaglandins: enhanced hypotensive effect when nitrates given with alprostadil

• Sildenafil: hypotensive effect of nitrates significantly enhanced by sildenafil (avoid concomitant use)

• Tadalafil: hypotensive effect of nitrates significantly enhanced by tadalafil (avoid concomitant use)

• Vardenafil: possible increased hypotensive effect when nitrates given with vardenafil—avoid concomitant use

Vasodilator Antihypertensives: enhanced hypotensive effect when nitrates given with hydralazine, minoxidil or sodium nitroprusside

Nitrazepam see Anxiolytics and Hypnotics

Appendix 1: Interactions 763

BNF 57
NSAIDs
- Antiepileptics (continued)
  * Monitor use; NSAIDs possibly enhance effects of
    * Carbamazepine, oxcarbazepine, phenytoin,
      trimidone, Rufinamide and topiramate (reduced

Antifungals: plasma concentration of piroxicam increased by flucanazole (reduce dose of piroxicam); plasma concentration of celecoxib increased by flucanazole (halve dose of celecoxib)
- Antipsychotics: possible severe drowsiness when indometacin given with haloperidol; avoid concomitant use of azapropazone with ciclosporin (increased risk of agranulocytosis)
- Antivirals: plasma concentration of NSAIDs possibly increased by ritonavir; plasma concentration of piroxicam increased by ritonavir (risk of toxicity)—avoid concomitant use; increased risk of haematological toxicity when NSAIDs given with zidovudine
- Beta-blockers: NSAIDs antagonise hypotensive effect of beta-blockers
- Bisphosphonates: indometacin increases bioavailability of iludronic acid
- Calcium-channel Blockers: NSAIDs antagonise hypotensive effect of calcium-channel blockers
- Cancer Glycosides: NSAIDs possibly increase plasma concentration of cardiac glycosides, also possible exacerbation of heart failure and reduction of renal function
- Ciclosporin: increased risk of nephrotoxicity when NSAIDs given with ciclosporin; plasma concentration of ciclofenac increased by ciclosporin (halve dose of ciclofenac)
- Clonidine: NSAIDs antagonise hypotensive effect of clonidine
- Clopidogrel: increased risk of bleeding when NSAIDs given with clopidogrel
- Corticosteroids: increased risk of gastro-intestinal bleeding and ulceration when NSAIDs given with corticosteroids
- Cytotoxics: NSAIDs probably reduce excretion of methotrexate (increased risk of toxicity)—but for concomitant use in rheumatic disease see p. 568; azapropazone reduces excretion of methotrexate (avoid concomitant use); ciclofenac, ibuprofen, indometacin, ketoprofen, meloxicam and naproxen reduce excretion of methotrexate (increased risk of toxicity)—but for concomitant use in rheumatic disease see p. 568; increased risk of bleeding when NSAIDs given with etorolcine
- Desmopressin: indometacin enhances effects of desmopressin
- Diazoxide: NSAIDs antagonise hypotensive effect of diazoxide
- Dimethyl sulfoxide: avoid concomitant use of sulindac with dimethyl sulfoxide
- Diuretics: risk of nephrotoxicity of NSAIDs increased by diuretics, also antagonism of diuretic effect; indometacin and ketorolac antagonise effects of diuretics; NSAIDs possibly antagonise diuretic effect of potassium canrenoate; occasional reports of reduced renal function when indometacin given with triamterene—avoid concomitant use; increased risk of hyperkalaemia when indometacin given with potassium-sparing diuretics and aldosterone antagonists; possibly increased risk of hyperkalaemia when NSAIDs given with potassium-sparing diuretics and aldosterone antagonists
- Iloprost: increased risk of bleeding when NSAIDs given with iloprost
- Lipid-regulating Drugs: excretion of meloxicam increased by colestevaline
- Lithium: NSAIDs probably reduce excretion of lithium (increased risk of toxicity); ciclofenac, ibuprofen, indometacin, mephenamic acid, naproxen, piroxicam and piroxicam reduce excretion of lithium (increased risk of toxicity); ketorolac reduces excretion of lithium (increased risk of toxicity)—avoid concomitant use
- Methyldopa: NSAIDs antagonise hypotensive effect of methyldopa

NSAIDs (continued)
- Moxonidine: NSAIDs antagonise hypotensive effect of moxonidine
- Muscle Relaxants: ibuprofen reduces excretion of baclofen (increased risk of toxicity); NSAIDs possibly reduce excretion of baclofen (increased risk of toxicity)
- Nitrates: NSAIDs antagonise hypotensive effect of nitrates
- Oestrogens: etoricoxib increases plasma concentration of ethinylestradiol
- Penicillamine: increased risk of nephrotoxicity when NSAIDs given with penicillamine
- Pentoxifylline (opentifylline): increased possible risk of bleeding when NSAIDs given with pentoxifylline (opentifylline); increased risk of bleeding when ketoprofen given with pentoxifylline (opentifylline) (avoid concomitant use)
- Probencid: excretion of desketoprofen, indometacin, ketoprofen and naproxen reduced by probencid (increased plasma concentration); excretion of ketorolac reduced by probencid (increased plasma concentration)—avoid concomitant use
- Progestogens: risk of hyperkalaemia when NSAIDs given with drospirenone (monitor serum potassium during first cycle)
- Sibutramine: increased risk of bleeding when NSAIDs given with sibutramine
- Tacrolimus: possible increased risk of nephrotoxicity when NSAIDs given with tacrolimus; increased risk of nephrotoxicity when ibuprofen given with tacrolimus
- Ulcer-healing Drugs: plasma concentration of azapropazone possibly increased by cimetidine
- Vasodilator Antihypertensives: NSAIDs antagonise hypotensive effect of hydralazine, minoxidil and sodium nitroprusside

Oestrogens
- Anti-diabetics: oestradiol possibly reduces requirements for insulin, metformin, repaglinide and sulphonylureas
- Ciclosporin: oestradiol reduces plasma concentration of ciclosporin
- Dopaminergics: oestradiol increases plasma concentration of bromocriptine
- Ulcer-healing Drugs: oestradiol possibly delays absorption of cimetidine

Oestrogens
- Note: Interactions of combined oral contraceptives may also apply to combined contraceptive patches
- ACE inhibitors: oestrogens antagonise hypotensive effect of ACE inhibitors
- Adrenergic Neurone Blockers: oestrogens antagonise hypotensive effect of adrenergic neurone blockers
- Alpha-blockers: oestrogens antagonise hypotensive effect of alpha-blockers
- Analogues: plasma concentration of ethinylestradiol increased by etoricoxib
- Angiotensin-II Receptor Antagonists: oestrogens antagonise hypotensive effect of angiotensin-II receptor antagonists
- Antibacterials: contraceptive effect of oestrogens possibly reduced by antibacterials that do not induce liver enzymes (risk probably small, see p. 439); metabolism of oestrogens accelerated by rifampicins (reduced contraceptive effect—see p. 439)
- Anticoagulants: oestrogens may enhance or reduce anticoagulant effect of coumarins; oestrogens antagonise anticoagulant effect of warfarin
- Antibiotics: contraceptive effect of oestrogens reduced by St John’s wort (avoid concomitant use); oestrogens antagonise antidepressant effect of tricyclics (but side-effects of tricyclics possibly increased due to increased plasma concentration)
- Anti-diabetics: oestrogens antagonise hypoglycaemic effect of insulin
- Antiepileptics: metabolism of oestrogens accelerated by carbamazepine, oxcarbazepine, phenytoin, primidone, rufinamide and topiramate (reduced
Oestrogens

- Antiepileptics (continued) contraceptive effect—see p. 439; oestrogens reduce plasma concentration of modafinil.
- Antifungals: anecdotial reports of contraceptive failure when oestrogens given with fluconazole, imidazoles, itraconazole or ketoconazole; metabolism of oestrogens accelerated by griseofulvin (reduced contraceptive effect—see p. 439); occasional reports of breakthrough bleeding when oestrogens (used for contraception) given with terbinafine.
- Antivirals: plasma concentration of ethinylestradiol increased by azatasanavir—avoid concomitant use; contraceptive effect of oestrogens possibly reduced by efavirenz; plasma concentration of oestrogens increased by fosamprenavir, also plasma concentration of fosamprenavir reduced—alternative contraception recommended; metabolism of oestrogens possibly accelerated by nefilnavir, nevirapine and ritonavir (reduced contraceptive effect—see p. 439).
- Anxiolytics and Hypnotics: oestrogens increase plasma concentration of melatonin.
- Appreitant: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with appreitant (alternative contraception recommended).
- Barbiturates: metabolism of oestrogens accelerated by barbiturates (reduced contraceptive effect—see p. 439).
- Beta-blockers: oestrogens antagonise hypotensive effect of beta-blockers.
- Bile Acid-Ads: elimination of cholesterol in bile increased when oestrogens given with bile acids.
- Bosentan: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with bosentan (alternative contraception recommended).
- Calcium-channel Blockers: oestrogens antagonise hypotensive effect of calcium-channel blockers.
- Ciclosporin: oestrogens possibly increase plasma concentration of ciclosporin.
- Clonidine: oestrogens antagonise hypotensive effect of clonidine.
- Corticosteroids: oral contraceptives containing oestrogens increase plasma concentration of corticosteroids.
- Diazoxide: oestrogens antagonise hypotensive effect of diazoxide.
- Diuretics: oestrogens antagonise diuretic effect of diuretics.
- Dopaminergics: oestrogens increase plasma concentration of ropinirole; oestrogens increase plasma concentration of selegiline (increased risk of toxicity).
- Lipid-regulating Drugs: plasma concentration of ethinylestradiol increased by atorvastatin and rosuvastatin.
- Methyldopa: oestrogens antagonise hypotensive effect of methyldopa.
- Modafinil: metabolism of oestrogens accelerated by modafinil (reduced contraceptive effect—see p. 439).
- Moxonidine: oestrogens antagonise hypotensive effect of moxonidine.
- Muscle Relaxants: oestrogens possibly increase plasma concentration of tizanidine (increased risk of toxicity).
- Nitrates: oestrogens antagonise hypotensive effect of nitrates.
- Sitaxentan: plasma concentration of oestrogens increased by sitaxentan.
- Somatropin: oestrogens (when used as oral replacement therapy) may increase dose requirements of somatropin.
- Sugammadex: plasma concentration of oestrogens possibly reduced by sugammadex.
- Tacrolimus: metabolism of oestrogens possibly inhibited by tacrolimus; ethinylestradiol possibly increases plasma concentration of tacrolimus.

Oestrogens (continued)

- Theophylline: oestrogens reduce excretion of theophylline (reduced plasma concentration).
- Thyroid Hormones: oestrogens may increase requirements for thyroid hormones in hypothyroidism.
- Vasodilator Antihypertensives: oestrogens antagonise hypotensive effect of hydralazine, minoxidil and sodium nitroprusside.
- Oestrogens, conjugated see Oestrogens.
- Olfoxacin see Quinolones.
- Olanzapine see Antipsychotics.
- Olmesartan see Angiotensin-II Receptor Antagonists.
- Olsalazine see Aminosalicylates.
- Omeprazole see Proton Pump Inhibitors.
- Ondansetron see 5HT Antagonists.

Opioid Analgesics

- Alcohol: metabolism of hypnotic and sedative effects when opioid analgesics given with alcohol.
- Antibacterials: plasma concentration of alfenaltanal increased by erythromycin; avoidance of premedication with opioid analgesics advised by manufacturer of ciprofloxacin (reduced plasma concentration of ciprofloxacin when ciprofloxacin used for surgical prophylaxis; metabolism of methadone accelerated by rifampicin (reduced effect).  
- Anticoagulants: tramadol enhances coagulant effect of ecoutamars; dextropropoxyphene possibly enhances anticoagulant effect of ecoutamars.
- Antidepressants: plasma concentration of methadone possibly increased by fluvoxamine; possible increased serotonergic effects when pethidine or tramadol given with duxoloxine; possible CNS excitation or depression (hypothesis or hypotension) when opioid analgesics given with MAOIs—avoid concomitant use and for 2 weeks after stopping MAOIs; CNS excitation or depression (hypothesis or hypotension) when pethidine given with MAOIs—avoid concomitant use and for 2 weeks after stopping MAOIs; possible CNS excitation or depression (hypothesis or hypotension) when dextromethorphan or pethidine given with moclobemide; possible CNS excitation or depression (hypothesis or hypotension) when tranylcyromel and pethidine given with tricyclics; sedative effects possibly increased when opioid analgesics given with tricyclics.
- Antiepileptics: plasma concentration of methadone reduced by carbamazepine; dextropropoxyphene enhances effects of carbamazepine; effects of tramadol reduced by carbamazepine; metabolism of methadone accelerated by phenytoin (reduced effect and risk of withdrawal effects).
- Antifungals: metabolism of buprenorphine inhibited by ketonozazole (reduce dose of buprenorphine); metabolism of alfenaltanal inhibited by fluconazole (risk of prolonged or delayed respiratory depression); plasma concentration of fentanyl possibly increased by fluconazole and itraconazole; metabolism of alfenaltanal possibly inhibited by itraconazole; plasma concentration of alfenaltanal and methadone increased by voriconazole (consider reducing dose of alfenaltanal and methadone).
- Antihistamines: sedative effects possibly increased when opioid analgesics given with sedating antihistamines.
- Antipsychotics: enhanced hypnotic and sedative effects when opioid analgesics given with antipsychotics; increased risk of convulsions when tramadol given with antipsychotics.
- Antivirals: plasma concentration of methadone possibly reduced by abacavir and nevirapine; plasma concentration of methadone reduced by efavirenz, fosamprenavir, nelfinavir and ritonavir; plasma concentration of dextropropoxyphene increased by ritonavir (risk of toxicity)—avoid concomitant use; plasma concentration of buprenorphine possibly increased by ritonavir; plasma concentration of...
Appendix 1: Interactions

Antimalarials:
- Antidepressants:
  - Oxcarbazepine
  - Oxazepam
  - see Oxandrolone
  - see Orciprenaline
  - see Sodium Oxybate
  - Memantine:
  - Atomoxetine:
  - Antivirals

Anticonvulsant effect of antiepileptics antagonised by:
- Antiepileptics:
  - Oxcarbazepine reduces plasma concentration of zidovudine
  - Anticoagulants:
    - Antimuscarinics
    - Antipsychotics (convulsive threshold lowered)
    - Barbiturates: oxcarbazepine increases plasma concentration of phenobarbital, also plasma concentration of an active metabolite of oxcarbazepine reduced
    - Clobazam: oxcarbazepine possibly reduces plasma concentration of clobazam
    - Cytotoxics: oxcarbazepine increases plasma concentration of omatinib—avoid concomitant use
    - Oestrogens: oxcarbazepine accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 349)
    - Progestogens: oxcarbazepine accelerates metabolism of progestogens (reduced contraceptive effect—see p. 349)

Oxprenolol see Beta-blockers
Oxybutynin see Antimuscarinics
Oxycodeone see Opioid Analgesics
Oxymetazoline see Sympathomimetics
Oxycodone see Lipid-regulating Drugs
Oxycycline see Tetracyclines
Oxycodone see Anxiolytics and Hypnotics
Oxcarbazepine (continued)
  - Antimarialarials (continued)
    - Antidepressants:
      - hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by
      - Antipsychotics: anticonvulsant effect of oxcarbazepine antagonised by
      - Barbiturates: oxcarbazepine increases plasma concentration of phenobarbital, also plasma concentration of an active metabolite of oxcarbazepine reduced
      - Clobazam: oxcarbazepine possibly reduces plasma concentration of clobazam
      - Cytotoxics: oxcarbazepine increases plasma concentration of omatinib—avoid concomitant use
      - Oestrogens: oxcarbazepine accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 349)
      - Progestogens: oxcarbazepine accelerates metabolism of progestogens (reduced contraceptive effect—see p. 349)
Parasymptomimetics

- Antibacterials (continued)
  - pyridostigmine antagonised by clindamycin; effects of neostigmine and pyridostigmine antagonised by polymyxins
- Antidepressants: plasma concentration of galantamine increased by paroxetine
- Antifungals: plasma concentration of galantamine increased by ketoconazole
- Antimalarials: effects of neostigmine and pyridostigmine may be diminished because of potential for chloroquine and hydroxychloroquine to increase symptoms of myasthenia gravis
- Antimuscarinics: effects of parasympathomimetics antagonised by antimuscarinics
- Beta-blockers: increased risk of arrhythmias when plicarpine given with beta-blockers; effects of neostigmine and pyridostigmine antagonised by propranolol
- Lithium: effects of neostigmine and pyridostigmine antagonised by lithium
- Muscle Relaxants: donepezil possibly enhances effects of suxamethonium; piperacillin, galantamine, neostigmine, pyridostigmine and rivastigmine enhance effects of suxamethonium; donepezil possibly antagonises effects of non-depolarising muscle relaxants; edrophonium, neostigmine, pyridostigmine and rivastigmine antagonise effects of non-depolarising muscle relaxants
- Paracetamol see NSAIDs
- Paroxetine see Vitamins
- Paroxetine see Antidepressants, SSRI
- Pegfilgrastim see Filgrastim
- Peginterferon Alfa see Interferons

Penicillamine

- Analgesics: possible increased risk of nephrotoxicity when penicillamine given with NSAIDs
- Antacids: absorption of penicillamine reduced by antacids
- Antipsychotics: avoid concomitant use of penicillamine with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: penicillamine possibly reduces plasma concentration of digoxin
- Gold: manufacturer of penicillamine advises avoid concomitant use with gold (increased risk of toxicity)
- Iron: absorption of penicillamine reduced by oral iron
- Zinc: penicillamine reduces absorption of zinc, also absorption of penicillamine reduced by zinc

Penicillins

- Allopurinol: increased risk of rash when amoxicillin or ampicillin given with allopurinol
- Antibacterials: absorption of phenoxymethylpenicillin reduced by neomycin
- Anticoagulants: common experience in anticoagulant clinics is that INR can be altered by a course of broad-spectrum penicillins such as ampicillin, although studies have failed to demonstrate an interaction with coumarins or phenindione
- Cytotoxics: penicillins reduce excretion of methotrexate (increased risk of toxicity)
- Muscle Relaxants: piperacillin enhances effects of non-depolarising muscle relaxants and suxamethonium
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
- Probencid: excretion of penicillins reduced by probenecid (increased plasma concentration)
- Sulfamethoxazole: fluoroquinoloxacin possibly reduces response to sulfamethoxazole
- Sulfapyrazine: excretion of penicillins reduced by sulfapyrazone
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Pentamidine Isethionate

- Anti-arrhythmics: increased risk of ventricular arrhythmias when pentamidine isethionate given with amiodarone—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when pentamidine isethionate given with parenteral erythromycin; increased risk of ventricular arrhythmias when pentamidine isethionate given with moxifloxacin—avoid concomitant use
- Antidepressants: increased risk of ventricular arrhythmias when pentamidine isethionate given with tricyclics
- Antifungals: possible increased risk of nephrotoxicity when pentamidine isethionate given with amphoterin
- Antipsychotics: increased risk of ventricular arrhythmias when pentamidine isethionate given with amisulpride—avoid concomitant use; increased risk of ventricular arrhythmias when pentamidine isethionate given with phenothiazines
- Ivalbridine: increased risk of ventricular arrhythmias when pentamidine isethionate given with ivermectin

Pentazocine see Opioid Analgesics

Pentoxifylline (oxpentifylline)

- Antiepileptics: cytoxotxically possibly reduce absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets
- Cytoxotics: increased toxicity when pentostatin given with high-dose cyclophosphamide—avoid concomitant use; increased pulmonary toxicity when pentostatin given with ifudarabine (unacceptably high incidence of fatalities)

Pentoxifylline (pentoxifylline)

- Analgesics: possible increased risk of bleeding when pentoxifylline (pentoxifylline) given with NSAIDs; increased risk of bleeding when pentoxifylline (pentoxifylline) given with ketorolac (avoid concomitant use)
- Theophylline: pentoxifylline (pentoxifylline) increases plasma concentration of theophylline

Pergolid

- Antipsychotics: effects of pergolide antagonised by antipsychotics
- Memantine: effects of dopaminergic possibly enhanced by memantine
- Metyldopa: antiparkinsonian effect of dopaminergic antagonised by metyldopa
- Metoclopramide: antiparkinsonian effect of pergolide antagonised by metoclopramide
- Pericyazine see Antipsychotics
- Perindopril see ACE Inhibitors
- Perphenazine see Antipsychotics
- Pethidine see Opioid Analgesics
- Phenozoene see Opioid Analgesics
- Phenerazine see MAOIs
- Phenindione
  - Note: Change in patient’s clinical condition particularly associated with liver disease, intercurrent illness, or drug administration, necessitates more frequent testing. Major changes in diet (especially involving salads and vegetables) and in alcohol consumption may also affect anticoagulant control
  - Alcohol: anticoagulant control with phenindione may be affected by major changes in consumption of alcohol
  - Anabolic Steroids: anticoagulant effect of phenindione enhanced by anabolic steroids
- Phenindione
  - Analgesics: anticoagulant effect of phenindione possibly enhanced by NSAIDs; anticoagulant effect of phenindione enhanced by diclofenac, also increased risk of haemorrhage with intravenous diclofenac (avoid concomitant use); anticoagulant effect of phenindione enhanced by ketorolac (increased risk of haemorrhage—avoid concomitant use); increased risk of bleeding when phenindione given with aspirin (due to antiplatelet effect)
Antivirals: metabolism of phenytoin inhibited by omeprazole (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of omeprazole (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of omeprazole.

Antibacterials: metabolism of phenytoin inhibited by clarithromycin, ciprofloxacin, and metronidazole (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of clarithromycin (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of ciprofloxacin (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of metronidazole (increased plasma concentration of phenytoin).

Antifungals: metabolism of phenytoin inhibited by fluconazole (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of fluconazole (increased plasma concentration of phenytoin).

Antiepileptics: metabolism of phenytoin inhibited by phenobarbital, phenytoin, phenytoin, phenytoin.

Anticoagulants: plasma concentration of phenytoin increased by clopidogrel—avoid concomitant use; plasma concentration of phenytoin increases when given with dipyridamole; plasma concentration of phenytoin increases when given with dipyridamole—avoid concomitant use; plasma concentration of phenytoin increases when given with dipyridamole.

Alpha-blockers: metabolism of phenytoin inhibited by clonidine (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of clonidine (increased plasma concentration of phenytoin); phenytoin reduces plasma concentration of clonidine (increased plasma concentration of phenytoin).
Phenytoin
- **Antivirals** (continued)
  - centration of phenytoin possibly affected; plasma concentration of phenytoin increased or decreased by zidovudine
- **Anxiolytics and Hypnotics**: phenytoin often reduces plasma concentration of clonazepam; plasma concentration of phenytoin increased or decreased by diazepam; plasma concentration of phenytoin possibly increased or decreased by benzodiazepines
- **Antiepileptics**: phenytoin possibly reduces plasma concentration of aminoglycosides; increased risk of ototoxicity when platinum compounds given with amphotericin or polymyxins; increased risk of ototoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin or polymyxins given with capreomycin; increased risk of nephrotoxicity and possibly of ototoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicoplanin; possibly of ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and oto-neurotoxicity when cisplatin given with vancomycin or teicopl
Appendix 1: Interactions

Polyoxymyxins (continued)

- Ciclosporin: increased risk of nephrotoxicity when polymyxins given with ciclosporin.
- Cytotoxics: increased risk of nephrotoxicity and possibly of ototoxicity when polymyxins given with platinum compounds.
- Diuretics: increased risk of ototoxicity when polymyxins given with loop diuretics.
- Muscle Relaxants: polymyxins enhance effects of non-depolarising muscle relaxants and aminoglycosides.
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439).
- Parasympathomimetics: polymyxins antagonise effects of oestrogens and mepiprostigmine.
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679.

Potassium Salts

- Potassium Citrate
- Potassium Chloride
- Potassium Aminobenzoate
- Potassium Canrenoate

Posaconazole

- Polystyrene Sulphonate Resins

Parasympathomimetics

- Diuretics

Ciclosporin:

(continued)

- Polymyxins
- Antimalarials:

- Avoidance of antimalarials inactivated by levofloxacin (thyroxine)

Potassium-sparing diuretics

- Antivirals:

- Antiallergics:

- Thyroid Hormones: polyxytene sulphonate resins reduce absorption of levothyroxine (thyroxine)

Posaconazole see Antifungals, Triazole

Potassium Canrenoate see Diuretics

Potassium Aminobenzoate

Antibacterials: potassium aminobenzoate inhibits effects of sulphonamides.

Potassium Bicarbonate see Potassium Salts

Potassium Chloride see Potassium Salts

Potassium Citrate see Potassium Salts

Potassium Salts

- Note: Includes salt substitutes.
- ACE Inhibitors: increased risk of severe hyperkalaemia when potassium salts given with ACE inhibitors.
- Aliskiren: increased risk of hyperkalaemia when potassium salts given with aliskiren.
- Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when potassium salts given with angiotensin-II receptor antagonists.
- Antibacterials: avoid concomitant use of potassium citrate with methenamine.
- Ciclosporin: increased risk of hyperkalaemia when potassium salts given with ciclosporin.
- Diuretics: increased risk of hyperkalaemia when potassium salts given with ciclosporin.
- Tacrolimus: increased risk of hyperkalaemia when potassium salts given with tacrolimus.

Pramipexole

- Antipsychotics: manufacturer of pramipexole advises avoidance concomitant use of antipsychotics (antagonism of effect).
- Memantine: effects of dopaminergics possibly enhanced by memantine.
- Metyldopa: antiparkinsonian effect of dopaminergics antagonised by metyldopa.
- Urease Inhibiting Drugs: excretion of pramipexole reduced by cimetidine (increased plasma concentration).

Prazastin see Statins

Prazosin see Alpha-blockers

Prednisolone see Corticosteroids

Pilocarpine

- Anti-arrhythmics: increased myocardial depression when pilocarpine given with anti-arrhythmics.
- Antibacterials: increased risk of methaemoglobinemia when pilocarpine given with sulphonamides.

Primadone

- Antibacterials: sometimes reduced (but concentration of an active metabolite of primadone often increased); primadone possibly reduces plasma concentration of etosuximide; primadone reduces plasma concentration of lamotrigine and tiagabine; plasma concentration of primadone possibly reduced by phenytoin (but concentration of an active metabolite increased); plasma concentration of phenytoin often reduced but may be increased; plasma concentration of primadone possibly increased by valproate (plasma concentration of active metabolite of primadone increased), also plasma concentration of valproate reduced; plasma concentration of primadone possibly reduced by vigabatrin.
- Antifungals: primadone possibly reduces plasma concentration of itraconazole; primadone possibly reduces plasma concentration of voriconazole—avoid concomitant use; primadone reduces absorption of griseofulvin (reduced effect).
- Antimarialis: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by antimalarial.
- Antipsychotics: anticonvulsant effect of primadone antagonised by antipsychotics (conversive threshold lowered); primadone antagonises mechanisms of haloperidol (reduced plasma concentration); primadone possibly reduces plasma concentration of aripiprazole—increase dose of aripiprazole.
- Antivirals: primadone possibly reduces plasma concentration of indinavir, efavirenz, nelfinavir and saquinavir.
- Antivirals and Hypnotics: primadone often reduces plasma concentration of carbamazepine.
- Barbiturates: increased sedative effect when primadone given with barbiturates.
- Calcium-channel Blockers: primadone reduces effects of felodipine and isradipine; primadone probably reduces effects of edhydropyridines, diltiazem and verapamil.
- Cardiac Glycosides: primadone accelerates metabolism of digoxin (reduced effect).
- Ciclosporin: primadone accelerates metabolism of ciclosporin (reduced effect).
- Corticosteroids: primadone accelerates metabolism of corticosteroids (reduced effect).
- Diuretics: plasma concentration of primadone possibly reduced by acetazolamide; increased risk of osteomalacia when primadone given with carbonic anhydrase inhibitors.
- Folates: plasma concentration of primadone possibly reduced by folates.
- Hormone Antagonists: primadone accelerates metabolism of gestrinone and toremifene (reduced plasma concentration).
Primidone (continued)
Leukotriene Antagonists: primidone reduces plasma concentration of montelukast
Memantine: effects of primidone possibly reduced by memantine
● Oestrogens: primidone accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 439)
● Progestogens: primidone accelerates metabolism of progestogens (reduced contraceptive effect—see p. 439)
Symptomatikism: plasma concentration of primidone possibly increased by methylphenidate
Thyroid Hormones: primidone accelerates metabolism of thyroxine (may increase requirements for thyroid hormones in hypothyroidism)
Tibolone: primidone accelerates metabolism of tibolone (reduced plasma concentration)
Vitamins: primidone possibly increases requirements for vitamin D
Probenecid
ACE Inhibitors: probenecid reduces excretion of captopril
Anaesthetics, General: probenecid possibly enhances effects of thiopental
● Analgesics: probenecid reduces excretion of
  ● dexketoprofen, indomethacin, ketoprofen and naproxen (increased plasma concentration); probenecid reduces excretion of ketorolac (increased plasma concentration)—avoid concomitant use; effects of probenecid antagonised by aspirin
Antibacterials: probenecid reduces excretion of doripenem and meropenem (manufacturers of doripenem and meropenem advise avoid concomitant use); probenecid reduces excretion of cephalosporins, ciprofloxacin, nalidixic acid, norfloxacin and penicillins (increased plasma concentration); probenecid reduces excretion of dapsone and nitrofurantoin (increased risk of side-effects); effects of probenecid antagonised by pyrazinamide
Antidiabetics: probenecid possibly enhances hypoglycaemic effect of chlorpropamide
● Antivirals: probenecid reduces excretion of aciclovir (increased plasma concentration); probenecid possibly reduces excretion of famiclovir (increased plasma concentration); probenecid reduces excretion of ganciclovir and acyclovir (increased plasma concentration and risk of toxicity)
Anxiolytics and Hypnotics: probenecid reduces excretion of lorazepam (increased plasma concentration); probenecid possibly reduces excretion of nitrazepam (increased plasma concentration)
● Cytotoxics: probenecid reduces excretion of mitoxantrone (increased risk of toxicity)
  Sodium Benzoate: probenecid possibly reduces excretion of conjugate formed by sodium benzoate
Sodium Phenylbutyrate: probenecid possibly reduces excretion of conjugate formed by sodium phenylbutyrate
Procarbazine
Alcohol: disulfiram-like reaction when procarbazine given with alcohol
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
● Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Prochlorperazine see Antipsychotics
Procyclidine see Antimuscarinics
Progesterone see Progestogens
Progestogens
Note Interactions of combined oral contraceptives may also apply to combined contraceptive patches
ACE Inhibitors: risk of hyperkalaemia when drospironone given with ACE inhibitors (monitor serum potassium during first cycle)
Analgesics: risk of hyperkalaemia when drospironone given with NSAIDs (monitor serum potassium during first cycle)
Angiotensin-II Receptor Antagonists: risk of hyperkalaemia when drospironone given with angiotensin-II receptor antagonists (monitor serum potassium during first cycle)
● Antibacterials: metabolism of progestogens accelerated by rifampicin (reduced contraceptive effect—see p. 439)
● Anticoagulants: progestogens may enhance or reduce anticoagulant effect of coumarins; progestogens antagonise anticoagulant effect of dexamethasone
● Antidepressants: metabolism of progestogens accelerated by St John’s Wort (avoid concomitant use)
Antidiabetics: progestogens antagonise hypoglycaemic effect of antidiabetics
● Antiepileptics: metabolism of progestogens accelerated by carbamazepine, oxcarbazepine, phenytoin, primidone, rufinamide and topiramate (reduced contraceptive effect—see p. 439); progestogens reduce plasma concentration of lamotrigine
● Antifungals: metabolism of progestogens accelerated by ketoconazole (reduced contraceptive effect—see p. 439); occasional reports of breakthrough bleeding when progestogens (used for contraception) given with terbinafine
● Antivirals: plasma concentration of progestogens increased by fosamprenavir, also plasma concentration of fosamprenavir reduced—alternative contraception recommended; contraceptive effect of progestogens possibly reduced by nelfinavir; metabolism of progestogens accelerated by nevirapine (reduced contraceptive effect—see p. 439)
● Aprepitant: possible contraceptive failure of hormonal contraceptives containing progestogens when given with aprepitant (alternative contraception recommended)
● Barbiturates: metabolism of progestogens accelerated by barbiturates (reduced contraceptive effect—see p. 439)
● Bosentan: possible contraceptive failure of hormonal contraceptives containing progestogens when given with bosentan (alternative contraception recommended)
● Ciclosporin: progestogens inhibit metabolism of ciclosporin (increased plasma concentration)
Diuretics: risk of hyperkalaemia when drospironone given with potassium-sparing diuretics and aldosterone antagonists (monitor serum potassium during first cycle)
Dopaminergic: progestogens increase plasma concentration of selegiline (increased risk of toxicity)
Lipid-regulating Drugs: plasma concentration of nor-ethisterone increased by atorvastatin; plasma concentration of norgestrel increased by rosuvastatin
Muscle Relaxants: progestogens possibly increase plasma concentration of tizanidine (increased risk of toxicity)
Sitaxentan: plasma concentration of progestogens increased by sitaxentan
Sugammadex: plasma concentration of progestogens possibly reduced by sugammadex
Tacrolimus: metabolism of progestogens possibly inhibited by tacrolimus
Progynova
Antacids: absorption of progynova reduced by oral magnesium salts (as magnesium trisilicate)
Anticoagulants: isolated reports that progynova may enhance anticoagulant effect of warfarin
Antivirals:
- Propranolol
- See Propiverine

Ulcer-healing Drugs:
- Beta-blockers
- Antihistamines
- Antibacterials
- Anti-arrhythmics
- Anticoagulants
- Antibacterials
- Antimalarials (continued)

Plasma concentration of propafenone possibly increased by time-related effects on plasma concentration of ciclosporin

Antidepressants:
- Anticoagulants: propafenone enhances anticoagulant effect of coumarins
- Antidepressants: metabolism of propafenone possibly inhibited by paroxetine

Anticoagulants:
- Increased risk of ventricular arrhythmias when propafenone given with nizoldipine—avoid concomitant use

Antipsychotics:
- Aconitum: plasma concentration of propafenone possibly increased by bosentan (increased risk of toxicity); plasma concentration of propafenone increased by itraconazole (increased risk of ventricular arrhythmias—avoid concomitant use)

Beta-blockers:
- Increased myocardial depression when anti-arrhythmics given with metoprolol and propranolol

Cardiac Glycosides:
- Increased myocardial depression when propafenone given with digoxin (halve dose of digoxin)

Ciclosporin: propafenone possibly increases plasma concentration of ciclosporin

5HT Antagonists: increased risk of ventricular arrhythmias when propafenone given with dolasetron—avoid concomitant use

Parasympathomimetics: propafenone possibly antagonises effects of neostigmine and pyridostigmine

Theophylline: propafenone increases plasma concentration of theophylline

Ulcer-healing Drugs: plasma concentration of propafenone increased by cimetidine

Propylthiouracil see Antimuscarnics

Propofol see Anaesthetics, General

Proparanol see Beta-blockers

Prostaglandins (continued)

Diuretics: enhanced hypotensive effect when alprostadil given with diuretics

Methyldopa: enhanced hypotensive effect when alprostadil given with methyldopa

Moxonidine: enhanced hypotensive effect when alprostadil given with moxonidine

Nitrates: enhanced hypotensive effect when alprostadil given with nitrates

Oxytocin: prostanoids potentiate uterine tonic effect of oxytocin

Vasodilator Antihypertensives: enhanced hypotensive effect when alprostadil given with hydralazine, minoxidil or sodium nitroprusside

Protein Kinase Inhibitors see Dasatinib, Erlotinib, Imatinib, Lapatinib, Nilotinib, Sorafenib, Sunitinib, and Temsirolimus

Proton Pump Inhibitors

Antacids: absorption of lansoprazole possibly reduced by antacids

Antibacterials: plasma concentration of both drugs increased when omeprazole given with clarithromycin

Anticoagulants: esomeprazole, omeprazole and pantoprazole possibly enhance anticoagulant effect of coumarins

Antidepressants: omeprazole increases plasma concentration of escitalopram; plasma concentration of lansoprazole possibly increased by fluvoxamine

Anti-inflammatory: esomeprazole enhances effects of phenytoin; omeprazole possibly enhances effects of phenytoin

Antifungals: proton pump inhibitors reduce absorption of itraconazole and ketoconazole; plasma concentration of esomeprazole possibly increased by voriconazole; plasma concentration of omeprazole increased by voriconazole (consider reducing dose of omeprazole)

Antipsychotics: omeprazole possibly reduces plasma concentration of clozapine

Antivirals: proton pump inhibitors reduce plasma concentration of azaferanavir; omeprazole reduces plasma concentration of melflufen—avoid concomitant use; proton pump inhibitors possibly increase plasma concentration of raltegravir—manufacturer of raltegravir advises avoid concomitant use; omeprazole increases plasma concentration of raltegravir—avoid concomitant use; omeprazole increases plasma concentration of saquinavir; plasma concentration of esomeprazole and omeprazole reduced by etipranavir

Anxiolytics and Hypnotics: esomeprazole and omeprazole possibly inhibit metabolism of diazepam (increased plasma concentration)

Cardiac Glycosides: proton pump inhibitors possibly slightly increase plasma concentration of digoxin

Ciclosporin: omeprazole possibly affects plasma concentration of ciclosporin

Cilostazol: omeprazole increases plasma concentration of cilostazol (risk of toxicity)—avoid concomitant use; lansoprazole possibly increases plasma concentration of cilostazol—avoid concomitant use; omeprazole increases plasma concentration of cilostazol (risk of toxicity); proton pump inhibitors possibly reduce absorption of lapatinib

Tacrolimus: omeprazole possibly increases plasma concentration of tacrolimus

Ulcer-healing Drugs: absorption of lansoprazole possibly reduced by omeprazole

Pseudoephedrine see Sympathomimetics

Pyrazinamide

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)

Probenecid: pyrazinamide antagonises effects of probenecid

Sulfonpyrazone: pyrazinamide antagonises effects of sulfonpyrazone
Antipsychotics:
- Increased antifolate effect when pyrimethamine given with quinoline; increased antifolate effect when pyrimethamine given with proguanil
- Increased antifolate effect when proguanil
- Increased antifolate effect when pyrimethamine given with zidovudine

Anticoagulants:
- Increased antifolate effect when pyrimethamine given with 
- Increased antifolate effect when pyrimethamine given with

Anti-arrhythmics:
- Increased antifolate effect when pyrimethamine given with
- Increased antifolate effect when quinoline given with pyridoxine
- Increased antifolate effect when quinoline given with pyridostigmine

Analgesics:
- Increased antifolate effect when pyrimethamine given with quinoline

Cardiac Glycosides:
- Increased antifolate effect when pyrimethamine given with quinidine

Antibacterials:
- Increased antifolate effect when pyrimethamine given with quinidine

Antimalarials:
- Increased antifolate effect when pyrimethamine given with quinidine

Cytotoxics:
- Increased antifolate effect when pyrimethamine given with quinidine

Antibacterials:
- Increased antifolate effect when pyrimethamine given with quinidine

Antiepileptics:
- Increased antifolate effect when pyrimethamine given with quinidine

Antipsychotics:
- Increased antifolate effect when pyrimethamine given with quinidine

Anticoagulants:
- Increased antifolate effect when pyrimethamine given with quinidine

Antihistamines:
- Increased antifolate effect when pyrimethamine given with quinidine

Vaccines:
- Increased antifolate effect when pyrimethamine given with quinidine

Ulcer-healing Drugs:
- Increased antifolate effect when pyrimethamine given with quinidine

Beta-blockers:
- Increased antifolate effect when pyrimethamine given with quinidine

Calcium Salts:
- Increased antifolate effect when pyrimethamine given with quinidine

Dairy Products:
- Increased antifolate effect when pyrimethamine given with quinidine

Oestrogens:
- Increased antifolate effect when pyrimethamine given with quinidine

Muscle Relaxants:
- Increased antifolate effect when pyrimethamine given with quinidine
Quinolones (continued)
Zinc: absorption of ciprofloxacin, levofloxacin, moxi-
foxacin, norfloxacin and ofloxacin reduced by zinc
Quinupristin with Dalfopristin
• Anti-arrhythmics: increased risk of ventricular arrhy-
thmias when quinupristin/dalfopristin given with
dipryamidine or lidocaine (lignocaine)—avoid concomitant use
Antibacterial: manufacturer: of quinupristin/dalfo-
pristin recommends monitoring liver function when
given with rifampicin
Antivirals: quinupristin/dalfopristin possibly increases
plasma concentration of saquinavir
• Anti-convulsants and Hypnotics: quinupristin/dalfopristin
inhibits metabolism of midazolam (increased
plasma concentration with increased sedation); quinupristin/dalfopristin inhibits the metabolism of
topoline
• Calcium-channel Blockers: quinupristin/dalfopristin
increases plasma concentration of nifedipine
• Ciclosporin: quinupristin/dalfopristin increases plasma
concentration of ciclosporin
• Ergot Alkaloids: manufacturer of quinupristin/dalfo-
pristin advises avoid concomitant use with ergot-
amine and methysergide
Oestrogens: antibacterials that do not induce liver
enzymes possibly reduce contraceptive effect of
Oestrogens (risk probably small, see p. 439)
• Tacroliumus: quinupristin/dalfopristin increases plasma
concentration of tacrolimus
Vaccines: antibacterials inactive oral typhoid
vaccine—see p. 679
Rabeprazole see Proton Pump Inhibitors
Rifaxifene
Anticoagulants: rifaxifene antagonises anticoagulant
effect of coumarins
Lipid-regulating Drugs: absorption of rifaxifene
reduced by colestyramine (manufacturer of rifaxifene
advises avoid concomitant administration)
Ralteglavir
• Antibacterials: plasma concentration of raltegravir
increased by enfuvirtide—consider increasing dose of
raltegravir
• Ulcer-healing Drugs: plasma concentration of rate-
gravir increased by omeprazole—avoid concomi-
tant use; plasma concentration of raltegravir possibly
increased by histamine H-antagonists and proton
pump inhibitors—manufacturer of raltegravir advises
avoid concomitant use
Ramipril see ACE Inhibitors
Ranitidine see Histamine H-antagonists
Rasagiline
Note Rasagiline is a MAO-B inhibitor
• Analgesics: avoid concomitant use of rasagiline with
dextromethorphan; risk of CNS toxicity when
rasagiline given with methadone (avoid methadone for 2
weeks after rasagiline)
• Antidepressants: after stopping rasagiline do not start
fluoxetine for 2 weeks, also rasagiline should not be
started until at least 5 weeks after stopping fluox-
etine; after stopping rasagiline do not start
fluvoxamine for 2 weeks; risk of hypertensive crisis
when rasagiline given with MAOs; avoid MAOs for
at least 2 weeks after stopping rasagiline; increased
risk of CNS toxicity when rasagiline given with
SSRIs or tricyclics
Dopaminergics: plasma concentration of rasagiline
possibly reduced by entacapone
Memantine: effects of dopaminergics possibly
enhanced by memantine
Methylodopa: antiparkinsonian effect of dopaminergics
antagonised by methylodopa
• Sympathomimetics: avoid concomitant use of rasagi-
line with sympathomimetics
Reboxetine
• Antibacterials: manufacturer of reboxetine advises
avoid concomitant use with macrolides
• Antidepressants: manufacturer of reboxetine advises
avoid concomitant use with fluvoxamine; increased
Reboxetine
• Antidepressants: manufacturer of reboxetine advises
avoid concomitant use with MAOs (MAOs should
not be started until 1 week after stopping
reboxetine, avoid reboxetine for 2 weeks after stopping
MAOs)
Antifungals: manufacturer of reboxetine advises avoid
concomitant use with imidazoles and triazoles
Antimalarials: avoidance of antidepressants advised by
manufacturer of recommends monitoring liver function when
given with reboxetine
Atomoxetine: possible increased risk of convulsions
when antidepressants given with atomoxetine
Diuretics: possible increased risk of hypokalaemia
when reboxetine given with loop diuretics or thia-
azes and related diuretics
Ergot Alkaloids: possible risk of hypertension when
reboxetine given with ergot alkaloids
Sibutramine: increased risk of CNS toxicity when
noradrenaline re-uptake inhibitors given with
sibutramine (manufacturer of sibutramine advises
avoid concomitant use)
Remifentanil see Opioid Analgesics
Repaglinide see Antidiabetics
Retinoids
• Alcohol: etretinate formed from acitretin in presence of
alcohol (increased risk of teratogenicity in women of
child-bearing potential)
Antibacterials: possible increased risk of benign
intracranial hypertension when retinoids given with
tetracyclines (avoid concomitant use)
Anticoagulants: acitretin possibly reduces anti-
coagulant effect of coumarins
Antiepileptics: isotretnoin possibly reduces plasma
concentration of carbamazepine
Antifungals: plasma concentration of alitretinoin
increased by ketoconazole
• Cytotoxics: acitretin increases plasma concentration of
methotrexate (also increased risk of hepatotoxic-
ity)—avoid concomitant use
• Lipid-regulating Drugs: alitretinoin reduces plasma
concentration of simvastatin
Vitamins: risk of hypervitaminosis A when retinoids
given with vitamin A
Ribavirin
• Antivirals: increased risk of side-effects when ribavirin
given with didanosine—avoid concomitant use; ribavirin possibly inhibits effects of etidronate; increased
risk of anaemia when ribavirin given with
zidovudine—avoid concomitant use
Ribafutin see Rifampicins
Rifampicin see Rifampicins
Rifamycins
ACE Inhibitors: rifampicin reduces plasma concentra-
tion of active metabolite of imidapril (reduced anti-
hypertensive effect)
Analgesics: rifampicin reduces plasma concentration of
ericorixib; rifampicin accelerates metabolism of
methadone (reduced effect)
Antacids: absorption of rifampicin reduced by antacids
Anti-arthrythmics: rifampicin accelerate metabolism of
clarithromycin (reduced plasma concentration); rif-
ampicin accelerates metabolism of clozapine
(reduced effect)
Antibacterials: rifampicin reduces plasma concentra-
tion of clarithromycin and dapsone; plasma concentra-
tion of rifabutin increased by clarithromycin
(1increased risk of uveitis—reduce rifabutin dose); rifampicin tolerates metabolism of chlorampheni-
ol (reduced plasma concentration); plasma concentra-
tion of rifabutin possibly increased by macrolides
(increased risk of uveitis—reduce rifabutin dose); monitoring of liver function with rifampicin recom-
manded by manufacturer of quinupristin/dalfopristin;
rifampicin reduces plasma concentration of
clarithromycin (avoid during and for 2 weeks after
rifampicin); rifampicin possibly reduces plasma concentra-
tion of trimethoprim
**Rifamycins (continued)**

- **Anticoagulants:** rifamycins accelerate metabolism of warfarin (increased anticoagulant effect); rifamycin reduces plasma concentration of warfarin.

- **Antidepressants:** rifamycin possibly reduces plasma concentration of tricyclics.

- **Antidiabetics:** rifamycins accelerate metabolism of tolbutamide, glibenclamide, and chlorpropamide (reduced effect); rifamycin reduces plasma concentration of glibenclamide and tolbutamide; rifamycin also reduces plasma concentration of acetohexamide (reduced effect).

- **Antiepileptics:** rifamycin reduces plasma concentration of phenytoin (reduced plasma concentration).

- **Antifungals:** rifamycin accelerates metabolism of itraconazole, voriconazole, and posaconazole (increased risk of hepatotoxicity).

- **Antipsychotics:** haloperidol (reduced plasma concentration) and also monitor for rifabutin toxicity; citalopram, escitalopram, and fluoxetine (increased metabolism by rifampicin); plasma concentration of citalopram possibly increased by concomitant use; rifampicin reduces plasma concentration of escitalopram and fluoxetine.

- **Antimalarials:** rifamycins affect metabolism of chloroquine (increased plasma concentration) and also monitor for rifabutin toxicity; rifampicin reduces plasma concentration of hydroxychloroquine.

- **Antivirals:** rifamycin reduces plasma concentration of lopinavir.

- **Calcium-channel Blockers:** rifampicin reduces plasma concentration of diltiazem, verapamil, felodipine, and isradipine; rifamycin possibly reduces plasma concentration of felodipine.

- **Ciclosporin:** rifamycins accelerate metabolism of ciclosporin; rifamycin possibly reduces plasma concentration of ciclosporin.

- **Corticosteroids:** rifamycins accelerate metabolism of cortisol.

- **Diuretics:** rifamycin reduces plasma concentration of spironolactone.

- **Hormone antagonists:** rifamycin reduces plasma concentration of exemestane; rifamycin accelerates metabolism of tamoxifen (reduced plasma concentration).

- **Hormone antagonists (continued):** rifamycin reduces plasma concentration of voriconazole; rifamycin reduces plasma concentration of voriconazole.

- **Lipid-regulating drugs:** atorvastatin and simvastatin (reduced effect) of atorvastatin and simvastatin.

- **Lipid-regulating drugs (continued):** fenofibrate reduces plasma concentration of atorvastatin and simvastatin (reduced effect) of atorvastatin and simvastatin.

- **Leflunomide:** rifamycin reduces plasma concentration of leflunomide.

- **Oestrogens:** rifamycins accelerate metabolism of oestrogens (reduced contraceptive effect—see p. 439); antibacterials that do not induce liver enzymes possibly reduces contraceptive effect of oestrogens (risk probably small, see p. 439).

**Rifamycins**

- **Antivirals (continued)**

- **Antiretrovirals:** rifabutin reduces plasma concentration of maraviroc; rifabutin reduces plasma concentration of raltegravir; rifabutin reduces plasma concentration of maraviroc and raltegravir; plasma concentration of rifabutin increased by nelfinavir (halve dose of rifabutin); plasma concentration of rifabutin possibly increased by nevirapine; plasma concentration of rifabutin increased by ritonavir (increased risk of toxicity); rifabutin reduces plasma concentration of saquinavir; rifamycin significantly reduces plasma concentration of saquinavir, also risk of hepatotoxicity—avoid concomitant use; rifampicin possibly reduces plasma concentration of elprapavir; rifampicin significantly reduces plasma concentration of atazanavir—avoid concomitant use.

- **Anxiolytics and Hypnotics:** rifamycin accelerates metabolism of diazepam (reduced plasma concentration); rifampicin possibly accelerates metabolism of benzodiazepines; rifamycin reduces plasma concentration of buspirone and zaleplon; rifampicin accelerates metabolism of zolpidem (reduced plasma concentration and reduced effect); rifampicin significantly reduces plasma concentration of zopiclone.

Barbiturates: plasma concentration of rifampicin possibly reduced by phenobarbital.

Betablockers: rifamycin accelerates metabolism of bisoprolol and propranolol (plasma concentration significantly reduced); rifampicin possibly reduces plasma concentration of carvedilol, celiprolol and metoprolol.

- **Beta-blockers:** rifamycin accelerates metabolism of metoprolol; plasma concentration of metoprolol increased by rifampicin; plasma concentration of atorvastatin and simvastatin (reduced effect) of atorvastatin and simvastatin.

- **Calcium-channel blockers:** rifamycin possibly accelerates metabolism of diltiazem and nicardipine (possible significantly reduced plasma concentration); rifamycin accelerates metabolism of felnidipine, nifedipine, nitrendipine and verapamil (plasma concentration significantly reduced).

Cardiac Glycosides: rifamycins accelerate metabolism of digoxin (reduced effect); rifampicin possibly reduces plasma concentration of digoxin.

- **Ciclosporin:** rifamycin accelerates metabolism of ciclosporin (reduced plasma concentration).

- **Corticosteroids:** rifamycins accelerate metabolism of corticosteroids (reduced effect).

- **Cytoxotics:** rifamycin reduces plasma concentration of active metabolite of mepacrine (reduced effect); rifamycin accelerates metabolism of ivermectin; rifamycin reduces plasma concentration of ivermectin.

- **Diuretics:** rifamycin reduces plasma concentration of spironolactone.

- **Hormone Antagonists:** rifamycin reduces plasma concentration of exemestane; rifamycin accelerates metabolism of tamoxifen (reduced plasma concentration).

- **Hormone Antagonists (continued):** rifamycin reduces plasma concentration of exemestane; rifamycin accelerates metabolism of tamoxifen (reduced plasma concentration).

- **Lipid-regulating drugs:** atorvastatin and simvastatin (reduced effect) of atorvastatin and simvastatin.

- **Lipid-regulating drugs (continued):** fenofibrate reduces plasma concentration of atorvastatin and simvastatin (reduced effect) of atorvastatin and simvastatin.

- **Leflunomide:** rifamycin reduces plasma concentration of leflunomide.

- **Oestrogens:** rifamycins accelerate metabolism of oestrogens (reduced contraceptive effect—see p. 439); antibacterials that do not induce liver enzymes possibly reduces contraceptive effect of oestrogens (risk probably small, see p. 439).
Anticoagulants: ritonavir possibly reduces plasma concentration of phenytoin—avoid concomitant use

Antiepileptics: ritonavir possibly reduces plasma concentration of phenytoin—avoid concomitant use

Antifungals: combination of ritonavir with itraconazole or ketoconazole may increase plasma concentration of either drug (or both); plasma concentration of ritonavir increased by fluconazole; ritonavir reduces plasma concentration of voriconazole—avoid concomitant use

Antihistamines: ritonavir possibly increases plasma concentration of non-sedating antihistamines

Antimaculins: avoidance of ritonavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when ritonavir given with fesoterodine consult fesoterodine product literature; ritonavir increases plasma concentration of solifenacin

Antipsychotics: ritonavir possibly increases plasma concentration of antipsychotics; ritonavir possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); ritonavir increases plasma concentration of olanzapine (increased risk of toxicity)—avoid concomitant use; ritonavir reduces plasma concentration of olanzapine—consider increasing dose of olanzapine; ritonavir increases plasma concentration of epimozide and esertidolone (increased risk of ventricular arrhythmias—avoid concomitant use)

Antivirals: ritonavir increases toxicity of efavirenz, nevirapine (function tests); ritonavir increases plasma concentration of indinavir and saquinavir; combination of ritonavir with nelfinavir may increase plasma concentration of either drug (or both)

Anxiolytics and Hypnotics: ritonavir possibly increases plasma concentration of anxiolytics and hypnotics; ritonavir possibly increases plasma concentration of alprazolam, diazepam, flurazepam and zolpidem (risk of extreme sedation and respiratory depression—avoid concomitant use); ritonavir possibly increases plasma concentration of midazolam (risk of prolonged sedation—avoid concomitant use of oral midazolam); ritonavir increases plasma concentration of bupropione (increased risk of toxicity)

Aprepitant: ritonavir possibly increases plasma concentration of aprepitant

Bosentan: ritonavir possibly increases plasma concentration of bosentan

Bupropion: ritonavir increases or decreases plasma concentration of bupropion

Calcium-channel Blockers: ritonavir possibly increases plasma concentration of calcium-channel blockers; avoidance of ritonavir advised by manufacturer of lercanidipine

Cardiac Glycosides: ritonavir possibly increases plasma concentration of digoxin

Ciclosporin: ritonavir possibly increases plasma concentration of ciclosporin

Cilostazol: ritonavir possibly increases plasma concentration of cilostazol—avoid concomitant use

Corticosteroids: ritonavir possibly increases plasma concentration of corticosteroids, dexamethasone and prednisolone; ritonavir increases plasma concentration of inhaled and intranasal budesonide and fluticasone

Cytochrome P450: avoidance of ritonavir advised by manufacturer of laptatinib and lolitnib; ritonavir increases plasma concentration of paxitaxel

Diuretics: ritonavir increases plasma concentration of spironolone—avoid concomitant use

Ergot Alkaloids: increased risk of ergotism when ritonavir given with ergotamine and methysergide—avoid concomitant use

5HT Agonists: ritonavir increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use
Ritonavir (continued)
- Ivermectin: ritonavir possibly increases plasma concentration of ivermectin—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when ritonavir given with atorvastatin; possible increased risk of myopathy when ritonavir given with rosuvastatin—avoid concomitant use; increased risk of myopathy when ritonavir given with simvastatin (avoid concomitant use)
- Oestrogens: ritonavir accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 439)
- Sildenafil: ritonavir significantly increases plasma concentration of sildenafil—avoid concomitant use
- Symptomimetics: ritonavir possibly increases plasma concentration of dexametidine
- Tacrolimus: ritonavir possibly increases plasma concentration of tacrolimus
- Tadalafil: ritonavir increases plasma concentration of tadalafil
- Theophylline: ritonavir accelerates metabolism of theophylline (reduced plasma concentration)
- Vardenafil: ritonavir possibly increases plasma concentration of vardenafil—avoid concomitant use

Rivaroxaban
- Antibacterials: plasma concentration of rivaroxaban reduced by rifampicin
- Antifungals: plasma concentration of rivaroxaban increased by ketoconazole—avoid concomitant use; manufacturer of rivaroxaban advises avoid concomitant use with itraconazole, posaconazole and voriconazole
- Antivirals: manufacturer of rivaroxaban advises avoid concomitant use with atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir; plasma concentration of rivaroxaban increased by ritonavir—manufacturer of rivaroxaban advises avoid concomitant use
- Sibutramine: increased risk of bleeding when anticoagulants given with sibutramine

Rivastigmine see Parasympathomimetics
Rizatriptan see 5HT Agonists
Rocuronium see Muscle Relaxants
Ropinirole
- Antibacterials: metabolism of ropinirole inhibited by ciprofloxacin (increased plasma concentration)
- Antipsychotics: manufacturer of ropinirole advises avoid concomitant use of antipsychotics (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by memantine
- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by methylodopa
- Metoclopramide: manufacturer of ropinirole advises avoid concomitant use of metoclopramide (antagonism of effect)
- Oestrogens: plasma concentration of ropinirole increased by oestrogens

Ropivacaine
- Anti-arhythmic: increased myocardial depression when ropivacaine given with anti-arhythmics
- Antidepressants: metabolism of ropivacaine inhibited by fluvoxamine—avoid prolonged administration of ropivacaine
- Rosiglitazone see Antidiabetics
- Rosuvastatin see Statins

Rotigotine
- Antipsychotics: manufacturer of rotigotine advises avoid concomitant use of antipsychotics (antagonism of effect)
- Memantine: effects of dopaminergics possibly enhanced by memantine
- Methylodopa: antiparkinsonian effect of dopaminergics antagonised by methylodopa
- Metoclopramide: manufacturer of rotigotine advises avoid concomitant use of metoclopramide (antagonism of effect)

Rowachol®
- Anticoagulants: Rowachol possibly reduces anticoagulant effect of coumarins

Rufinamide
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine
- Oestrogens: rufinamide accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 439)
- Progestogens: rufinamide accelerates metabolism of progestogens (reduced contraceptive effect—see p. 439)

St John’s Wort
- Antibacterials: St John’s wort reduces plasma concentration of tetracycline (avoid during and for 2 weeks after St John’s wort)
- Anticoagulants: St John’s wort reduces plasma concentration of coumarins (avoid concomitant use)
- Antidepressants: possible increased serotonergic effects when St John’s wort given with duloxetine; St John’s wort reduces plasma concentration of amitriptyline; increased serotonergic effects when St John’s wort given with SSRIs—avoid concomitant use
- Antiepileptics: avoid concomitant use of St John’s wort with antiepileptics
- Antifungals: St John’s wort reduces plasma concentration of voriconazole—avoid concomitant use
- Antimalarials: avoidance of antiepileptics advised by manufacturer of etravirine; St John’s wort possibly reduces plasma concentration of maraviroc and tipranavir—avoid concomitant use
- Antioxidants and Hypnotics: St John’s wort possibly reduces plasma concentration of oral midazolam
- Aprepitant: avoidance of St John’s wort advised by manufacturer of aprepitant
- Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine
- Barbiturates: avoid concomitant use of St John’s wort with phenobarbital
- Calcium-channel Blockers: manufacturer of amlodipine—avoid concomitant use; avoidance of St John’s wort advised by manufacturer of amlodipine
- Cardiac Glycosides: St John’s wort reduces plasma concentration of digoxin—avoid concomitant use
- Ciclosporin: St John’s wort reduces plasma concentration of ciclosporin—avoid concomitant use
- Cytoxotics: St John’s wort reduces plasma concentration of plerixafor—avoid concomitant use
- Diuretics: St John’s wort reduces plasma concentration of spironolactone—avoid concomitant use
- 5HT Agonists: increased serotonergic effects when St John’s wort given with 5HT agonists—avoid concomitant use
St John’s Wort (continued)

Ivabradine: St John’s wort reduces plasma concentration of ivabradine—avoid concomitant use
Lipid-regulating Drugs: St John’s wort reduces plasma concentration of simvastatin

• Oestrogens: St John’s wort reduces contraceptive effect of oestrogens (avoid concomitant use)
• Progestogens: St John’s wort reduces contraceptive effect of progestogens (avoid concomitant use)
• Tacrolimus: St John’s wort reduces plasma concentration of tacrolimus—avoid concomitant use
• Theophylline: St John’s wort reduces plasma concentration of theophylline—avoid concomitant use
Salbutamol see Sympathomimetics, Beta
Salmeterol see Sympathomimetics, Beta
Saquinavir

• Antibacterials: plasma concentration of saquinavir reduced by erafabutin; plasma concentration of saquinavir significantly reduced by imipenem, also risk of hepatotoxicity—avoid concomitant use; plasma concentration of saquinavir possibly increased by quinupristin/dalfopristin; avoidance of concomitant saquinavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
Anticoagulants: saquinavir possibly enhances anti-coagulant effect of warfarin; avoidance of saquinavir advised by manufacturer of rivaroxaban
• Antidepressants: plasma concentration of saquinavir reduced by St John’s wort—avoid concomitant use
• Antiepileptics: plasma concentration of saquinavir possibly reduced by carbamazepine, phenytoin and primidone
Antifungals: plasma concentration of saquinavir increased by ketoconazole; plasma concentration of saquinavir possibly increased by imidazoles and triazoles
Antimalarials: caution with saquinavir advised by manufacturer of arteether/lumefantrine
Antimuscarnics: avoidance of saquinavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when saquinavir given with fesoterodine—consult fesoterodine manufacturer of darifenacin and tolterodine; manufacturer of entacapone if used concomitantly
• Antipsychotics: saquinavir possibly inhibits metabolism of earipiprazole (reduce dose of earipiprazole); saquinavir possibly increases plasma concentration of amitriptyline (increased risk of ventricular arrhythmias—avoid concomitant use); saquinavir increases plasma concentration of sertindole (increased risk of extrastriate arhythmias—avoid concomitant use)
• Antivirals: plasma concentration of saquinavir increased by atazanavir, indinavir, lopinavir and ritonavir; saquinavir reduces plasma concentration of darunavir; plasma concentration of saquinavir significantly reduced by elaviren; saquinavir increases plasma concentration of maraviroc (consider reducing dose of maraviroc); combination of saquinavir with nelfinavir may increase plasma concentration of either drug (or both); plasma concentration of saquinavir reduced by tipranavir
• Anxiolytics and Hypnotics: saquinavir increases plasma concentration of midazolam (risk of prolonged sedation—avoid concomitant use of oral midazolam)
Barbiturates: plasma concentration of saquinavir possibly reduced by barbiturates
Ciclosporin: plasma concentration of both drugs increased when saquinavir given with ciclosporin
Cilostazol: saquinavir possibly increases plasma concentration of cilostazol—avoid concomitant use
Corticosteroids: plasma concentration of saquinavir possibly reduced by dexamethasone
Cytotoxics: avoidance of saquinavir advised by manufacturer of lapaatinib
Diuretics: saquinavir increases plasma concentration of eplerenone (reduce dose of eplerenone)

Saquinavir (continued)

• Ergot Alkaloids: increased risk of ergotism when saquinavir given with ergotamine and methysergide
• Lipid-regulating Drugs: possible increased risk of myopathy when saquinavir given with atorvastatin; possible increased risk of myopathy when saquinavir given with rosuvastatin—avoid concomitant use; increased risk of myopathy when saquinavir given with simvastatin—even in concomitant use; Sildenafil: saquinavir possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil

Tacrolimus: saquinavir increases plasma concentration of tacrolimus (consider reducing dose of tacrolimus)
Tadalafil: saquinavir possibly increases plasma concentration of tadalafil—reduce initial dose of tadalafil
Ulcer-healing Drugs: plasma concentration of saquinavir increased by omeprazole
Vardenafil: saquinavir possibly increases plasma concentration of vardenafil—reduce initial dose of vardenafil

Secobarbital see Barbiturates
SelgeLINE

Note SelgeLINE is a MAO-B inhibitor

• Analgesics: hypoxepirexia and CNS toxicity reported when selegiline given with pethidine (avoid concomitant use); manufacturer of selegiline advises caution with tramadol
• Antidepressants: theoretical risk of serotonin syndrome if selegiline given with citalopram (especially if dose of selegiline 10 mg daily); caution with selegiline advised by manufacturer of escitalopram; increased risk of hypertension and CNS excitation when selegiline given with lithium (selegiline should not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with fluvoxamine or venlafaxine; avoid fluvoxamine or venlafaxine for 2 weeks after stopping selegiline); increased risk of hypertension and CNS excitation when selegiline given with fluoxetine (selegiline should not be started until 2 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); enhanced hypnotic effect when selegiline given with MAOIs; avoid concomitant use of selegiline with moclobemide; CNS toxicity reported when selegiline given with tricyclics
Dopaminergics: max. dose of 10 mg selegiline advised by manufacturer of entacapone if used concomitantly; selegiline enhances effects and increases toxicity of levodopa (reduce dose of levodopa)
Mametane: effects of dopaminergics and selegiline possibly enhanced by memantine
Methyldopa: antiparkinsonian effect of dopaminergics antagonised by methyldopa
Oestrogens: plasma concentration of selegiline increased by oestrogens (increased risk of toxicity)
Progestogens: plasma concentration of selegiline increased by progestogens (increased risk of toxicity)
• Sympathomimetics: risk of hypertensive crisis when selegiline given with dopamine
Selenium

Vitamins: absorption of selenium possibly reduced by ascorbic acid (give at least 4 hours apart)
Stertindole see Antipsychotics
Sertaline see Antidepressants, SSRIs
Sevelamer

Antibacterials: sevelamer reduces bioavailability of ciprofloxacin
Ciclosporin: sevelamer possibly reduces plasma concentration of ciclosporin
Cytotoxics: sevelamer possibly reduces plasma concentration of mycophenolate

778 Appendix 1: Interactions BNF 57
Antivirals: sevelamer possibly reduces plasma concentration of tacrolimus
Sevelamer see Anaesthetics, General
Sibutramine Analgesics: increased risk of bleeding when sibutramine given with NSAIDs or aspirin
Non-steroidal anti-inflammatory drugs: increased risk of bleeding when sibutramine given with anticoagulants
• Antidepressants: increased CNS toxicity when sibutramine given with MAOIs or moclobemide (manufacturer of sibutramine advises avoid concomitant use), also avoid sibutramine for 2 weeks after stopping MAOIs or moclobemide; increased risk of CNS toxicity when sibutramine given with SSRI-related antidepressants, SSRIs, nortriptyline, imipramine, amitriptyline, tricyclic-related antidepressants, tricycles or tricycop (manufacturer of sibutramine advises avoid concomitant use)
• Antipsychotics: increased risk of CNS toxicity when sibutramine given with antipsychotics (manufacturer of sibutramine advises avoid concomitant use)

Sildenafil
Alpha-blockers: enhanced hypotensive effect when sildenafil given with alpha-blockers (avoid alpha-blockers for 4 hours after sildenafil)
Antibacterials: plasma concentration of sildenafil possibly increased by clarithromycin and telithromycin—reduce initial dose of sildenafil; plasma concentration of sildenafil increased by erythromycin—reduce initial dose of sildenafil
Antifungals: plasma concentration of sildenafil increased by itraconazole and ketoconazole—reduce initial dose of sildenafil
Antivirals: side-effects of sildenafil possibly increased by stavudine, plasma concentration of sildenafil reduced by efavirenz; plasma concentration of sildenafil possibly increased by fosamprenavir, nelfinavir and saquinavir—reduce initial dose of sildenafil; plasma concentration of sildenafil increased by indinavir—reduce initial dose of sildenafil; plasma concentration of sildenafil significantly increased by ritonavir—avoid concomitant use
Boventan: plasma concentration of sildenafil reduced by bosentan
Calcium-channel Blockers: enhanced hypotensive effect when sildenafil given with amiodipine
Grapefruit Juice: plasma concentration of sildenafil significantly enhanced by grapefruit juice
Nicorandil: sildenafil significantly enhances anticoagulant effect of nicorandil (avoid concomitant use)
Nitrates: sildenafil significantly enhances hypotensive effect of nitrates (avoid concomitant use)
Ulcer-healing Drugs: plasma concentration of sildenafil increased by cimetidine (reduce initial dose of sildenafil)

Simovalstatin see Statins
Siroliimus (continued)
Ciclosporin: plasma concentration of sirolimus increased by ciclosporin
• Grapefruit Juice: plasma concentration of sirolimus increased by grapefruit juice—avoid concomitant use

Sitaxentan
• Anticoagulants: sitaxentan enhances anticoagulant effect of coumarins
• Ciclosporin: plasma concentration of sitaxentan increased by ciclosporin—avoid concomitant use
Oestrogens: sitaxentan increases plasma concentration of oestrogens
Progestogens: sitaxentan increases plasma concentration of progestogens

Sodium Aurothiomalate see Gold
Sodium Benzoate Antiepileptics: effects of sodium benzoate possibly reduced by valproate
Antipsychotics: effects of sodium benzoate possibly reduced by haloperidol
Corticosteroids: effects of sodium benzoate possibly reduced by corticosteroids
Probendil: excretion of conjugate formed by sodium benzoate possibly reduced by probendil
Sodium Bicarbonate see Antacids
Sodium Clodranate see Bisphosphonates
Sodium Nitroprusside see Vasodilator Antihypertensives
Sodium Oxybate Analgesics: effects of sodium oxybate enhanced by opioid analgesics (avoid concomitant use)
Antidepressants: increased risk of side-effects when sodium oxybate given with tricycles
Antipsychotics: effects of sodium oxybate possibly enhanced by antipsychotics
Anxiolytics and Hypnotics: effects of sodium oxybate enhanced by benzodiazepines (avoid concomitant use)
Barbiturates: effects of sodium oxybate enhanced by barbiturates (avoid concomitant use)

Sodium Phenylbutyrate
Antiepileptics: effects of sodium phenylbutyrate possibly reduced by valproate
Antipsychotics: effects of sodium phenylbutyrate possibly reduced by haloperidol
Corticosteroids: effects of sodium phenylbutyrate possibly reduced by corticosteroids
Probendil: excretion of conjugate formed by sodium phenylbutyrate possibly reduced by probendil
Sodium Valproate see Valproate
Solifenacin see Antimuscarinics
Somatropin Corticosteroids: growth-promoting effect of somatropin may be inhibited by corticosteroids
Oestrogens: increased doses of somatropin may be needed when given with oestrogens (when used as oral replacement therapy)

Sorafenib
Antibacterials: plasma concentration of sorafenib reduced by rifampicin
Anticoagulants: sorafenib possibly enhances anticoagulant effect of coumarins
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Cytotoxics: sorafenib possibly increases plasma concentration of doxorubicin and irinotecan; sorafenib increases plasma concentration of docetaxel
Sotalol see Beta-blockers
Spirinolactone see Diuretics
Statins Anticandies: absorption of rosuvastatin reduced by antacids
Anti-arrhythmics: increased risk of myopathy when simvastatin given with amiodarone
Statins (continued)

- Antibacterials: plasma concentration of atorvastatin and pravastatin increased by erlotinib; increased risk of myopathy when simvastatin given with clarithromycin, erythromycin, or telithromycin (avoid concomitant use); plasma concentration of rosuvastatin reduced by clarithromycin; possible increased risk of myopathy when atorvastatin given with erythromycin or fusidic acid; plasma concentration of pravastatin increased by erythromycin; plasma concentration of atorvastatin and simvastatin possibly reduced by rifampicin; metabolism of fluvastatin accelerated by rifampicin (reduced effect); increased risk of myopathy when statins given with dapotimycin (preferably avoid concomitant use); increased risk of myopathy when statins given with imatinib; increased risk of myopathy when atorvastatin given with telithromycin (avoid concomitant use)

- Anticoagulants: atorvastatin may transiently reduce anticoagulant effect of warfarin; rosuvastatin possibly enhances anticoagulant effect of coumarins and phenindione; fluvastatin and simvastatin enhance anticoagulant effect of coumarins

- Antidepressants: plasma concentration of simvastatin reduced by St John’s wort

- Antidiabetics: fluvastatin possibly increases plasma concentration of glibenclamide

- Antiepileptics: combination of fluvastatin with phenytoin may increase plasma concentration of either drug (or both)

- Antifungals: increased risk of myopathy when simvastatin given withitraconazole, ketoconazole or posaconazole (avoid concomitant use); possible increased risk of myopathy when simvastatin given with itraconazole—avoid concomitant use; plasma concentration of fluvastatin increased by fluconazole; increased risk of myopathy when atorvastatin given with itraconazole or posaconazole (avoid concomitant use); possible increased risk of myopathy when atorvastatin or simvastatin given with imidazoles; possible increased risk of myopathy when atorvastatin or simvastatin given with triazoles

- Antivirals: possible increased risk of myopathy when rosuvastatin given with atazanavir, darunavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir or tipranavir—avoid concomitant use; increased risk of myopathy when simvastatin given with atazanavir, indinavir, nelfinavir, ritonavir, or saquinavir (avoid concomitant use); possible increased risk of myopathy when atorvastatin given with atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir or saquinavir; plasma concentration of pravastatin possibly reduced by darunavir; plasma concentration of atorvastatin, pravastatin and simvastatin reduced by elavirenz; plasma concentration of atorvastatin possibly reduced by etravirine; possible increased risk of myopathy when simvastatin given with fosamprenavir or lopinavir—avoid concomitant use

- Bosentan: plasma concentration of simvastatin reduced by bosentan

- Calcium-channel Blockers: plasma concentration of atorvastatin increased by diltiazem; possible increased risk of myopathy when simvastatin given with diltiazem; increased risk of myopathy when simvastatin given with verapamil

- Cardiac Glycosides: atorvastatin possibly increases plasma concentration of digoxin

- Ciclosporin: increased risk of myopathy when statins given with ciclosporin; increased risk of myopathy when rosuvastatin given with ciclosporin (avoid concomitant use)

- Colchicine: possible increased risk of myopathy when statins given with colchicine

- Cytotoxics: plasma concentration of simvastatin possibly increased by dasatinib; plasma concentration of simvastatin increased by imatinib

Statins (continued)

- Grapefruit juice: plasma concentration of atorvastatin possibly increased by grapefruit juice; plasma concentration of simvastatin increased by grapefruit juice—avoid concomitant use

- Hormone Antagonists: possible increased risk of myopathy when simvastatin given with danazol

- Lipid-regulating Drugs: increased risk of myopathy when statins given with gemfibrozil (preferably avoid concomitant use); increased risk of myopathy when statins given with fibrates; increased risk of myopathy when statins given with nicotinic acid (applies to lipid regulating doses of nicotinic acid)

- Oestrogens: atorvastatin and rosuvastatin increase plasma concentration of ethinylestradiol

- Progestogens: atorvastatin increases plasma concentration of norethisterone; rosuvastatin increases plasma concentration of norgestrel

- Retinoids: plasma concentration of simvastatin reduced by altretinoin

Stavudine

- Antivirals: increased risk of side-effects when stavudine given with didanosine; effects of stavudine possibly inhibited by abacavir; effects of stavudine possibly inhibited by efavirenz (manufacturers advise avoid concomitant use)

- Cytotoxics: effects of stavudine possibly inhibited by doxorubicin; increased risk of toxicity when stavudine given with hydroxyurea—avoid concomitant use

Streptomycin see Aminoglycosides

Strontium Ranelate

- Antibacterials: strontium ranelate reduces absorption of quinolones and tetracyclines (manufacturer of strontium ranelate advises avoid concomitant use)

Sucralfate

- Antibacterials: sucralfate reduces absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin, ofloxacin and tetracyclines

- Anticoagulants: sucralfate possibly reduces absorption of coumarins (reduced anticoagulant effect)

- Antiepileptics: sucralfate reduces absorption of phenytoin

- Antifungals: sucralfate reduces absorption of ketoconazole

- Antipsychotics: sucralfate reduces absorption of sulpiride

- Cardiac Glycosides: sucralfate possibly reduces absorption of digitoxin

- Theophylline: sucralfate possibly reduces absorption of theophylline (give at least 2 hours apart)

- Thyroid Hormones: sucralfate reduces absorption of levothyroxine (thyroxine)

- Ulcer-healing Drugs: sucralfate possibly reduces absorption of lansoprazole

Sugammadex

- Antibacterials: response to sugammadex possibly reduced by fluoroquinolones and fusidic acid

- Hormone Antagonists: response to sugammadex possibly reduced by tamoxifen

- Oestrogens: sugammadex possibly reduces plasma concentration of oestrogens

- Progestogens: sugammadex possibly reduces plasma concentration of progestogens

Sulfadiazine see Sulphonamides

Sulfadoxine see Sulphonamides

Sulfamethoxazole see Sulphonamides

Sulfasalazine see Aminosalicylates

Sulfinpyrazone Antagonists: effects of sulfinpyrazone antagonised by aspirin

- Antibacterials: sulfinpyrazone reduces excretion of nitrofurantoin (increased risk of toxicity); sulfinpyrazone reduces excretion of penicillins; effects of sulfinpyrazone antagonised by pyrazinamide

- Anticoagulants: sulfinpyrazone enhances anti-coagulant effect of coumarins

- Antidiabetics: sulfinpyrazone enhances effects of sulphonylureas
Anticoagulants: sulfipyrazone increases plasma concentration of dicumarol.

Ciclosporin: increased risk of nephrotoxicity when sulphonamides given with dicumarol.

Ciclosporin: increased risk of haematological toxicity when sulphonamides given with methotrexate; sulfadiazine.

Anticoagulants: increased risk of hypotensive effect of sympathomimetics given with dicumarol.

Anticoagulants: increased risk of arrhythmias when sulphonamides given with prilocaine.

Ciclosporin: increased risk of ventricular arrhythmias when sulphonamides (as co-trimoxazole) given with amiodarone—avoid concomitant use of co-trimoxazole.

Antibacterials: increased risk of crystalluria when sulphonamides given with methenamine.

Anticoagulants: sulfipyrazone enhances anticoagulant effect of coumarins.

Anticoagulants: sulfipyrazone increases plasma concentration of phenytoin.

Anticoagulants: increased risk of methaemoglobinemia when sulphonamides given with propranolol.

Anticoagulants: increased antifolate effect when sulphonamides given with pyrimethamine (includes Fansidar).

Anticoagulants: increased risk of hypertension when vasoconstrictor sympathomimetics given with methylphenidate possibly increases plasma concentration of primidone.

Anticoagulants: increased risk of severe hypertension and bradycardia when adrenaline (epinephrine) given with non-cardioselective beta-blockers, also response to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when dobutamine given with non-cardioselective beta-blockers; possible increased risk of severe hypertension and bradycardia when noradrenaline (norepinephrine) given with non-cardioselective beta-blockers.

Clonidine: possible risk of hypertension when adrenaline (epinephrine) or noradrenaline (norepinephrine) given with clonidine; serious adverse events reported with concomitant use of methylphenidate and clonidine (causality not established).

Corticosteroids: ephedrine accelerates metabolism of dexamethasone.

Dopaminergics: risk of toxicity when isometheptene or phenylpropanolamine given with bromocriptine; effects of adrenaline (epinephrine), dobutamine, dopamine and noradrenaline (norepinephrine) possibly enhanced by entacapone; avoid concomitant use of sympathomimetics with rasagiline; risk of hypertensive crisis when dopamine given with selegiline.

Dopaminergics: increased risk of ergotism when sympathomimetics given with ergotamine and methysergide.

Oxytocin: risk of hypertension when vasoconstrictor sympathomimetics given with oxytocin (due to enhanced vasopressor effect).

Sympathomimetics: effects of adrenaline (epinephrine) possibly enhanced by parkalol; dopamine, possibly enhances effects of noradrenaline (norepinephrine).

Sympathomimetics: adrenaline (epinephrine) possibly increased by ritonavir; possible increased risk of hyper-tensive crisis when dopamine given with selegline.

Sympathomimetics: increased risk of hypertension when sympathomimetics given with doxapram.

Sympathomimetics: increased risk of hypertensive crisis when sympathomimetics given with high doses of beta sympathomimetics.


Beta-blockers: increased risk of arrhythmias when adrenaline (epinephrine) given with volatile liquid general anaesthetics; increased risk of hypertension when methyldenamine given with volatile liquid general anaesthetics.

Anticoagulants: methylphenidate possibly enhances anticoagulant effect of coumarins.
Appendix 1: Interactions

Potassium Salts: 
- Diuretics:
- Barbiturates:
- Antidepressants:
- Antibacterials:

Barbiturates: increased risk of nephrotoxicity when tacrolimus given with phenytoin; plasma concentration of phenytoin possibly increased.

Antifungals: manufacturer of telithromycin advises avoid concomitant use with ketoconazole in severe renal and hepatic impairment.

Antimuscarinics: manufacturer of fesoterodine advises dose reduction when telithromycin given with fesoterodine—consult fesoterodine product literature.

Antipsychotics: increased risk of ventricular arrhythmias; avoid concomitant use with telithromycin given with pimozide—avoid concomitant use.

Antivirals: manufacturer of telithromycin advises avoid concomitant use with ketoconazole in severe renal and hepatic impairment.

Alpha-blockers: enhanced hypotensive effect when tadalafil given with alpha-blockers—avoid concomitant use.

Antibacterials: plasma concentration of tadalafil possibly increased by clarithromycin and erythromycin; plasma concentration of tadalafil reduced by rifampicin.

Antifungals: plasma concentration of tadalafil increased by ketoconazole; plasma concentration of tadalafil possibly increased by itraconazole.

Antivirals: plasma concentration of tadalafil possibly increased by fosamprenavir and indinavir; plasma concentration of tadalafil given with ritonavir; plasma concentration of tadalafil possibly increased by saquinavir—reduce initial dose of tadalafil.

Grapefruit Juice: plasma concentration of tadalafil possibly increased by grapefruit juice.

Nicorandil: tadalafil significantly enhances hypotensive effect of nicorandil (avoid concomitant use).

Nitricates: tadalafil significantly enhances hypotensive effect of nitricates (avoid concomitant use).

Tamoxifen: Anticoagulants: tamoxifen enhances anticoagulant effect of coumarins.

Tamsulosin: see Alpha-blockers.

Taxanes: see Docetaxel and Paclitaxel.

Tegafur with uracil: see Fluorouracil.

Teicoplanin: Antifungals: increased risk of nephrotoxicity and otoxicity when teicoplanin given with aminoglycosides or colistin.

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439).

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 879.

Telmisartan: Interferons: increased risk of peripheral neuropathy when telmisartan given with interferon alpha.

Telithromycin: Antivirals: plasma concentration of telithromycin reduced by ritonavir, nelfinavir and ritonavir; plasma concentration of telithromycin increased by saquinavir (consider reducing dose of telithromycin).

Alpha-blockers—avoid concomitant use with telithromycin given with aciclovir or ganciclovir.

Antituberculosis: increased risk of nephrotoxicity when telithromycin given with aciclovir or ganciclovir; plasma concentration of telithromycin possibly increased by atazanavir, nelfinavir and ritonavir; plasma concentration of telithromycin increased by saquinavir (consider reducing dose of telithromycin).

Barbiturates: plasma concentration of telithromycin reduced by St John’s wort—avoid concomitant use.

Antiepileptics: plasma concentration of telithromycin reduced by phenytoin, also plasma concentration of phenytoin possibly increased.

Antifungals: plasma concentration of telithromycin increased by fluconazole, itraconazole, ketoconazole and voriconazole; increased risk of nephrotoxicity when telithromycin given with amphotericin; plasma concentration of telithromycin increased by posaconazole (reduce dose of telithromycin); plasma concentration of telithromycin reduced by caspofungin; plasma concentration of telithromycin possibly increased by imidazoles and triazoles.

Antivirals: possible increased risk of nephrotoxicity when telithromycin given with aciclovir or ganciclovir; plasma concentration of telithromycin possibly increased by atazanavir, nelfinavir and ritonavir; plasma concentration of telithromycin increased by saquinavir (consider reducing dose of telithromycin).

Calcium-channel Blockers: plasma concentration of telithromycin possibly increased by felodipine, nifedipine and verapamil; plasma concentration of telithromycin increased by ediltiazem and nefedipine.

Ciclosporin: telithromycin increases plasma concentration of ciclosporin (increased risk of nephrotoxicity)—avoid concomitant use.

Diuretics: increased risk of hyperkalaemia when telithromycin given with potassium-sparing diuretics and aldosterone antagonists.

Grapefruit Juice: plasma concentration of telithromycin increased by grapefruit juice.

Hormone Antagonists: plasma concentration of telithromycin possibly increased by danazol.

Oestrogens: telithromycin possibly inhibits metabolism of oestrogens; plasma concentration of telithromycin possibly increased by ethinylestradiol.

Potassium Salts: increased risk of hyperkalaemia when telithromycin given with potassium salts.

Progestogens: telithromycin possibly inhibits metabolism of progestogens.

Sevelamer: plasma concentration of telithromycin possibly reduced by sevelamer.

Tacrolimus: Ulcer-healing Drugs: plasma concentration of tacrolimus possibly increased by omeprazole.

Tadalafil: when telithromycin given with atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir in severe renal and hepatic impairment; telithromycin possibly increases plasma concentration of tipranavir (consider reducing dose of maraviroc).

Anxiolytics and Hypnotics: telithromycin inhibits metabolism of midazolam (increased plasma concentration with increased sedation).

Aprepitant: telithromycin possibly increases plasma concentration of aprepitant.

Barbiturates: plasma concentration of telithromycin reduced by phenobarbital (avoid during and for 2 weeks after phenobarbital).
Telithromycin (continued)
Cardiac Glycosides: telithromycin possibly increases plasma concentration of digoxin
● Ciclosporin: telithromycin possibly increases plasma concentration of ciclosporin
● Cytotoxics: avoidance of telithromycin advised by manufacturer of lapatinib and nilotinib
● Diuretics: telithromycin increases plasma concentration of spironolactone—avoid concomitant use
● Ergot Alkaloids: increased risk of ergotism when telithromycin given with ergotamine and methysergide—avoid concomitant use
● Ivabradine: telithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use
● Lipid-regulating Drugs: increased risk of myopathy when telithromycin given with atorvastatin or simvastatin (avoid concomitant use)
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439) Sildenafil: telithromycin possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil
● Sirolimus: telithromycin increases plasma concentration of sirolimus—avoid concomitant use
● Tacrolimus: telithromycin possibly increases plasma concentration of tacrolimus—avoid concomitant use
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679
Telmisartan see Angiotensin-II Receptor Antagonists Temazepam see Anxiolytics and Hypnotics Temocillin see Penicillins Temoperforin
● Cytotoxics: increased skin photosensitivity when temoperforin given with topical fluourouracil
Temozolomide
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin; plasma concentration of temozolomide increased by valproate
● Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis) Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Tensirolimus
Note The main active metabolite of tensirolimus is sirolimus—see also interactions of sirolimus and consult product literature
● Antibacterials: plasma concentration of active metabolite of tensirolimus reduced by rifampicin—avoid concomitant use Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
● Antifungals: plasma concentration of active metabolite of tensirolimus increased by ketoconazole—avoid concomitant use
● Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis) Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Tenfovir
● Antivirals: manufacturer of tenofovir advises avoid concomitant use with adefovir; tenofovir reduces plasma concentration of atazanavir, also plasma concentration of tenofovir possibly increased; combination of tenofovir with cidofovir may increase plasma concentration of either drug (or both); tenofovir increases plasma concentration of didanosine (increased risk of toxicity)—avoid concomitant use; plasma concentration of tenofovir increased by lopinavir
Tenoxam see NSAIDs Terazosin see Alpha-blockers Terbinafine
Antibacterials: plasma concentration of terbinafine reduced by rifampicin Antidepressants: terbinafine possibly increases plasma concentration of imipramine and nortriptyline

Terbinafine (continued)
Oestrogens: occasional reports of breakthrough bleeding when terbinafine given with oestrogens (when used for contraception) Progestogens: occasional reports of breakthrough bleeding when terbinafine given with progestogens (when used for contraception) Ulcer-healing Drugs: plasma concentration of terbinafine increased by cimetidine
Terbutaline see Sympathomimetics, Beta-2 Agonists Terpene Mixture see Rowachol Testolactone
● Antiagoualants: testolactone enhances anticoagulant effect of ecarin and phenindione
Testosterone
● Antiagoualants: testosterone enhances anticoagulant effect of ecarin and phenindione Antidiabetics: testosterone possibly enhances hypoglycaemic effect of antidiabetics
Tetrabenazine
● Antidepressants: risk of CNS excitation and hypertension when tetrabenazine given with MAOIs Antipsychotics: increased risk of extrapyramidal side-effects when tetrabenazine given with antipsychotics Dopaminergics: increased risk of extrapyramidal side-effects when tetrabenazine given with amantadine Metoclopramide: increased risk of extrapyramidal side-effects when tetrabenazine given with metoclopramide
Tetracosactide see Corticosteroids Tetracycline see Tetracyclines Tetracyclines
ACE Inhibitors: absorption of tetracyclines reduced by quinapril tablets (quinapril tablets contain magnesium carbonate) Adsorbents: absorption of tetracyclines possibly reduced by kaolin Antacids: absorption of tetracyclines reduced by antacids
● Antiagoualants: tetracyclines possibly enhance anticoagulant effect of ecarin and phenindione Antiepileptics: metabolism of doxycycline accelerated by carbamazepine (reduced effect); metabolism of doxycycline accelerated by phenytoin and primidone (reduced plasma concentration) Atovaquone: tetracycline reduces plasma concentration of atovaquone Barbiturates: metabolism of doxycycline accelerated by barbiturates (reduced plasma concentration) Calcium Salts: absorption of tetracycline reduced by calcium salts
● Ciclosporin: doxycycline possibly increases plasma concentration of ciclosporin Cytotoxics: doxycycline or tetracycline increase risk of methotrexate toxicity Dairy Products: absorption of tetracyclines (except doxycycline and minocycline) reduced by dairy products Diuretics: manufacturer of lymecycline advises avoid concomitant use with diuretics Ergot Alkaloids: increased risk of ergotism when tetracyclines given with ergotamine and methysergide Iron: absorption of tetracyclines reduced by oral iron, also absorption of oral iron reduced by tetracyclines Lipid-regulating Drugs: absorption of tetracycline possibly reduced by colestipol and colestyramine Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 439)
● Retinoids: possible increased risk of benign intracranial hypertension when tetracyclines given with retinoids (avoid concomitant use) Strontium Ranelate: absorption of tetracyclines reduced by strontium ranelate (manufacturer of strontium ranelate advises avoid concomitant use) Ulcer-healing Drugs: absorption of tetracyclines reduced by sucralfate and tripotassium dicrato-bismuthate
Appendix 1: Interactions

**Theophylline** (continued)

**Theophylline**

- **Allopurinol**: plasma concentration of theophylline possibly increased by allopurinol
- **Anaesthetics, General**: increased risk of convulsions when theophylline given with ketamine; increased risk of arrhythmias when theophylline given with halothane

- **Antibacterials**: plasma concentration of theophylline possibly increased by azithromycin and isoniazid; metabolism of theophylline inhibited by clarithromycin (increased plasma concentration); metabolism of theophylline inhibited by erythromycin (increased plasma concentration), if erythromycin given by mouth, also decreased plasma-thymoxin concentration; plasma concentration of theophylline increased by ciprofloxacin and norfloxacin; metabolism of theophylline accelerated by rifampicin (reduced plasma concentration); possible increased risk of convulsions when theophylline given with quinolones

- **Antidepressants**: plasma concentration of theophylline increased by fluvoxamine (concomitant use should usually be avoided, but where not possible halve theophylline dose and monitor plasma-theophylline concentration); plasma concentration of theophylline reduced by St John’s wort—avoid concomitant use

- **Antiepileptics**: metabolism of theophylline accelerated by carbamazepine and primidone (reduced effect); plasma concentration of both drugs reduced when theophylline given with phenytoin

- **Antifungals**: plasma concentration of theophylline possibly increased by fluconazole and itraconazole

- **Antivirals**: metabolism of theophylline accelerated by ritonavir (reduced plasma concentration)

- **Barbiturates**: metabolism of theophylline accelerated by barbiturates (reduced effect)

- **Calcium-channel Blockers**: plasma concentration of theophylline possibly increased by calcium-channel blockers (enhanced effect); plasma concentration of theophylline increased by diltiazem; plasma concentration of theophylline increased by verapamil (enhanced effect)

- **Corticosteroids**: increased risk of hypokalaemia when theophylline given with corticosteroids

- **Cytotoxics**: plasma concentration of theophylline possibly increased by methotrexate

- **Disulfiram**: metabolism of theophylline inhibited by disulfiram (increased risk of toxicity)

- **Diuretics**: increased risk of hypokalaemia when theophylline given with acetazolamide, loop diuretics or thiazide diuretics

- **Doxapram**: increased CNS stimulation when theophylline given with doxapram

- **Interferons**: metabolism of theophylline inhibited by interferon alfa (increased plasma concentration)

- **Leukotriene Antagonists**: plasma concentration of theophylline possibly increased by zafirlukast, also plasma concentration of zafirlukast reduced

- **Lithium**: theophylline increases excretion of lithium (reduced plasma concentration)

- **Oestrogens**: excretion of theophylline reduced by oestrogens (increased plasma concentration)

- **Pentoxifylline (oxpentifylline)**: plasma concentration of theophylline increased by pentoxifylline (oxpentifylline)

- **Sulfipyrazole**: plasma concentration of theophylline reduced by sulfipyrazole

Theophylline (continued)

**Symptomimetics**: manufacturer of theophylline advises concomitant use with ephedrine in children

**Symptomimetics, Beta**: increased risk of hypokalaemia when theophylline given with high doses of beta symptomimetics—for CSM advice (hypokalaemia) see p. 153

**Tobacco**: metabolism of theophylline increased by tobacco smoking (reduced plasma concentration)

**Ulceral-Healing Drugs**: metabolism of theophylline inhibited by cinemetine (increased plasma concentration); absorption of theophylline possibly reduced by sucralfate (give at least 2 hours apart)

**Vaccines**: plasma concentration of theophylline possibly increased by influenza vaccine

**Thiazolinediones** see Anti-diabetics

**Thiopental** see Anaesthetics, General

**Thiotepa**

- **Antiepileptics**: cytotoxics possibly reduce absorption of phenytoin

- **Antipsychotics**: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

- **Cardiac Glycosides**: cytotoxics reduce absorption of digoxin tablets

- **Muscle Relaxants**: thiopental enhances effects of suxamethonium

**Thioxanthines** see Antipsychotics

**Thyroid Hormones**

**Antacids**: absorption of levothyroxine (thyroxine) possibly reduced by antacids

**Anti-arthmetics**: for concomitant use of thyroid hormones and amiodarone see p. 82

**Antibacterials**: metabolism of levothyroxine (thyroxine) accelerated by rifampicin (may increase requirements for levothyroxine (thyroxine) in hypothyroidism), also plasma concentration of phenytoin possibly increased

**Barbiturates**: metabolism of thyroid hormones accelerated by barbiturates (may increase requirements for thyroid hormones in hypothyroidism) Beta-blockers: levothyroxine (thyroxine) accelerates metabolism of propranolol

**Calcium Salts**: absorption of levothyroxine (thyroxine) reduced by calcium salts

**Cytotoxics**: plasma concentration of levothyroxine (thyroxine) possibly reduced by imatinib

**Iron**: absorption of levothyroxine (thyroxine) reduced by oral iron (give at least 2 hours apart)

**Lipid-regulating Drugs**: absorption of thyroid hormones reduced by colestipol and colestyramine Oestrogens and related drugs for thyroid hormones in hypothyroidism may be increased by oestrogens Polyestre-Sulphonate Resins: absorption of levothyroxine (thyroxine) reduced by polysytrene sulphonate resins

**Ulcer-healing Drugs**: absorption of levothyroxine (thyroxine) reduced by cimetidine and sucralfate

**Tiagabine**

**Antidepressants**: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIIs and tricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort

**Antiepileptics**: plasma concentration of tiagabine reduced by carbamazepine, phenytoin and primidone
Antivirals: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine

Barbiturates: plasma concentration of tiagabine reduced by phenobarbital

Tipranavir reduces plasma concentration of tipranavir increased by:
- Abacavir, saquinavir, and ritonavir

Tipranavir increases plasma concentration of tipranavir possibly reduced by:
- Emtricitabine; tipranavir increases plasma concentration of emtricitabine

Antidepressants: metabolism of tetroxetine possibly reduced by antacids

Anticoagulants: possible increased risk of bleeding when tipranavir given with high doses of vitamin E

Tirofiban: increased risk of bleeding when tirofiban given with iloprost

Tizanidine: see Muscle Relaxants

Tobacco: smoking increases cinacalcet metabolism (reduced plasma concentration)

Cytotoxics: possibly reduced by antiepileptics

Theophylline: possibly reduced by antiepileptics

Tipranavir possibly reduced by:
- Abacavir, saquinavir, and ritonavir

Antiepileptics: increases plasma concentration of:
- Oxcarbazepine; tipranavir increases plasma concentration of oxcarbazepine

Antibacterials: reduces plasma concentration of:
- EtBr, didanosine, fosamprenavir, lopinavir, aminoglycosides, and doxorubicin; plasma concentration of tipranavir increased by atazanavir (also plasma concentration of atazanavir reduced); tipranavir reduces plasma concentration of etravirine, also

Tipranavir increases plasma concentration of tipranavir possibly antagonised by:
- Measles

Antivirals: tipranavir increases plasma concentration of:
- Abacavir, saquinavir, and ritonavir

Antibacterials: reduces plasma concentration of:
- EtBr, didanosine, fosamprenavir, lopinavir, aminoglycosides, and doxorubicin; plasma concentration of tipranavir increased by atazanavir (also plasma concentration of atazanavir reduced); tipranavir reduces plasma concentration of etravirine, also
Appendix 1: Interactions

Antidepressants:
- Tropicamide
- Tripotassium Dicitratobismuthate

Cytotoxics:
- Ciclosporin

Anti-arrhythmics:
- Trihexyphenidyl (benzhexol)
- Trifluoperazine
- Trienterine
- see Triclofos
- see Triamterene
- see Triamcinolone
- see Tretinoin
- Trazodone
- Tranylcypromine
- see Tramadol
- Travectedin

Increased risk of haematological toxicity
Increased antifolate effect when tri-trimethoprim increases plasma concentration of trimethoprim possibly enhances hypoglycaemic effect of repaglinide—manufacturer advises avoid concomitant use; trimethoprim rarely enhances the effects of sulphonylureas

Antipsychotics:
- Trihexyphenidyl (benzhexol) see Antimuscarinics

Anticoagulants:
- Clopidogrel
- see Clozapine
- see Captopril
- see Cerebrolysin
- see Cetuximab
- see Cetirizine
- see Ceftriaxone
- see Cefixime
- see Cefpodoxime
- see Cefuroxime
- see Cefazolin
- see Cefuroxime Axetil
- see Cefepime
- see Ceftriaxone
- see Cefepime
- see Cefoperazone
- see Cefuroxime Axetil
- see Cefuroxime
- see Ceftriaxone
- see Cefazolin
- see Cefuroxime
- see Ceftriaxone
- see Cefepime
- see Cefoperazone
- see Cefuroxime Axetil
- see Cefuroxime
- see Ceftriaxone
- see Cefepime
- see Cefoperazone
- see Cefuroxime Axetil
- see Cefuroxime
- see Ceftriaxone
- see Cefepime
- see Cefoperazone
- see Cefuroxime Axetil
- see Cefuroxime
- see Ceftriaxone

Antiepileptics:
- Toremifene (continued)
- Suggest medadex: toremifene possibly reduces response to sugammadex

Trabectedin

Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Tramadol see Opioid Analgesics

Trandolapril see ACE Inhibitors

Tranylcypromine see MAOIs

Trazodone see Antidepressants, Tricyclic (related)

Tretinoin

Trazodone

Triacylcylic Acid
Antacids: absorption of bile acids possibly reduced by antacids
- Ciclosporin: ursooaclylic acid increases absorption of ciclosporin

Lipid-regulating Drugs: absorption of bile acids possibly reduced by cholestipol and colestyramine
- Oestrogens: elimination of cholesterol in bile increased when bile acids with oestrogens

Vaccines
Note For a general warning on live vaccines and high doses of corticosteroids or other immunosuppressive drugs, see p. 660; for advice on live vaccines and immunoglobulins, see under Normal Immunoglobulin, p. 681
- Abatacept: avoid concomitant use of live vaccines with abatacept (see p. 660)
- Adalimumab: avoid concomitant use of live vaccines with adalimumab (see p. 660)
- Anakinra: avoid concomitant use of live vaccines with anakinra (see p. 660)
- Antibacterials: oral typhoid vaccine inactivated by Antibacterials—see p. 679
- Anticoagulants: influenza vaccine enhances effects of anticoagulant effect of warfarin
- Antiepileptics: influenza vaccine enhances effects of phenytoin
- Antimalarials: oral typhoid vaccine inactivated by antimalarials—see p. 679

Corticosteroids: immune response to vaccines impaired by high doses of corticosteroids, avoid concomitant use with live vaccines (see p. 660)
- Eflazolumab: live or live-attenuated vaccines should be given 2 weeks before eflazolumab or withheld until 8 weeks after discontinuation
- Etanercept: avoid concomitant use of live vaccines with etanercept (see p. 660)
- Infliximab: avoid concomitant use of live vaccines with infliximab (see p. 660)
- Interferons: avoid of vaccines advised by manufacturer of interferon gamma
- Leflunomide: avoid concomitant use of live vaccines with leflunomide (see p. 660)
- Theophylline: influenza vaccine possibly increases plasma concentration of theophylline

Valaciclovir see Aciclovir

Ganciclovir see Ganciclovir

Valproate
Analgesics: effects of valproate enhanced by aspirin
Antibacterials: plasma concentration of valproate possibly reduced by doripenem and ertapenem; plasma concentration of valproate reduced by metronidazole; metabolism of valproate possibly inhibited by erythromycin (increased plasma concentration)
- Anticoagulants: valproate possibly enhances anticoagulant effect of coumarins
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold
Valproate
- Antidepressants (continued) lowered); avoid concomitant use of antiepileptics with St. John’s wort
- Antiepileptics: plasma concentration of valproate reduced by carbamazepine, also plasma concentration of active metabolite of carbamazepine increased; valproate possibly increases plasma concentration of ethosuximide; valproate increases plasma concentration of lamotrigine; valproate sometimes reduces plasma concentration of an active metabolite of oxcarbazepine; valproate increases or possibly decreases plasma concentration of phenytoin, also plasma concentration of valproate reduced; valproate possibly increases plasma concentration of primidone (plasma concentration of active metabolite of primidone increased), also plasma concentration of valproate reduced; valproate possibly increases plasma concentration of rufinamide (reduced dose of rufinamide)
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by nefluprine
- Antipsychotics: anticonvulsant effect of valproate antagonised by antipsychotics (convulsive threshold lowered); increased risk of neutropenia when valproate given with olanzapine

Antivirals: valproate possibly increases plasma concentration of zidovudine (increased risk of toxicity) Anxiolytics and Hypnotics: plasma concentration of valproate possibly increased by clobazam; increased risk of side-effects when valproate given with clonazepam; valproate possibly increases plasma concentration of diazepam and lorazepam

Barbiturates: valproate increases plasma concentration of phenobarbital (also plasma concentration of valproate reduced) Bupropion: valproate inhibits the metabolism of bupropion
Cytotoxics: valproate increases plasma concentration of temozolomide
Lipid-regulating Drugs: absorption of valproate possibly reduced by colestyramine
Sodium Benzoate: valproate possibly reduces effects of sodium benzoate
Sodium Phenylbutyrate: valproate possibly reduces effects of sodium phenylbutyrate
- Ulcer-healing Drugs: metabolism of valproate inhibited by omeprazole (increased plasma concentration) Valsartan see Angiotensin-II Receptor Antagonists

Valproate

Vancomycin (continued)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 679

Vancomycin
- Alpha-blockers: enhanced hypotensive effect when vardenafil given with alpha-blockers (excludes tamsulosin)—avoid vardenafil for 6 hours after alpha-blockers
Antibacterials: plasma concentration of vardenafil increased by erythromycin (reduce dose of vardenafil)
- Antifungals: plasma concentration of vardenafil increased by ketoconazole—avoid concomitant use; plasma concentration of vardenafil possibly increased by itraconazole—avoid concomitant use
- Antivirals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by indinavir—avoid concomitant use; plasma concentration of vardenafil possibly increased by nelfinavir—avoid concomitant use; plasma concentration of vardenafil possibly increased by saquinavir—reduce initial dose of vardenafil
Calcium-channel Blockers: enhanced hypotensive effect when vardenafil given with nifedipine
- Grapefruit juice: plasma concentration of vardenafil possibly increased by grapefruit juice—avoid concomitant use
- Nicorandil: possible increased hypotensive effect when vardenafil given with nicorandil—avoid concomitant use
- Nitrates: possible increased hypotensive effect when vardenafil given with nitrates—avoid concomitant use

Vasodilator Antihypertensives
ACE Inhibitors: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with ACE inhibitors
Adrenergic Neurone Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with adrenergic neurone blockers
Alcohol: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given after alcohol
Aldesleukin: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with aldesleukin
Alpha-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with alpha-blockers
Anasthetic, General: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with general anaesthetics
Analgesics: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by NSAIDs
Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with angiotensin-II receptor antagonists
Antidepressants: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with MAOIs; enhanced hypotensive effect when hydralazine or sodium nitroprusside given with tricyclic-related antidepressants
Antipsychotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with phenothiazines
Anxiolytics and Hypnotics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with anxiolytics and hypnotics
Beta-blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with beta-blockers
Calcium-channel Blockers: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with calcium-channel blockers
Appendix 1: Interactions

Verapamil
- see Dopaminergics: Antipsychotics; Antidepressants:
- Anticoagulants:
- Analgesics:
- Venlafaxine
- Vecuronium

Anticoagulants:
- increased risk of bleeding when venlafaxine given with warfarin

Antidepressants:
- increased risk of bleeding when high doses of vitamin E given with tizanidine

Vasodilator Antihypertensives:
- Clonidine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with clonidine
- Corticosteroids: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by corticosteroids
- Diazoxide: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with diazoxide
- Diuretics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with diuretics
- Dopaminergic:
- Antipsychotics:
- Antidepressants:
- Anticoagulants:
- Analgesics:
- Venlafaxine
- Vecuronium

Anticoagulants:
- increased risk of bleeding when venlafaxine given with warfarin

Antidepressants:
- increased risk of bleeding when venlafaxine given with MAOIs and cyclic-related antidepressants (convulsive threshold lowered); avoid concomitant use of antidepressants with St John’s wort
- Antimalarias: possible increased risk of convulsions when antidepressants given with clozapine and haloperidol
- Antipsychotics: possible increased risk of bleeding when antidepressants given with clozapine and haloperidol

Barbiturates: venlafaxine possibly reduces plasma concentration of primidone

Vilaglaptin see Antiabetic

Vinblastine
- Antibacterials: toxicity of vinblastine increased by eritromycin—avoid concomitant use
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
- Antifungals: metabolism of vinblastine possibly inhibited by posaconazole (increased risk of neurotoxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
- Calcium-channel Blockers: metabolism of vinblastine possibly inhibited by nifedipine

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Vincristine
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
- Antifungals: metabolism of vincristine possibly inhibited by itraconazole and posaconazole (increased risk of neurotoxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
- Calcium-channel Blockers: metabolism of vincristine possibly inhibited by nifedipine

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Vinorelbine
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Vitamin A see Vitamins

Vitamin D see Vitamins

Vitamin E see Vitamins

Vitamin K (Phytomenadione) see Vitamins

Vitamins
- Antibacterials: absorption of vitamin A possibly reduced by neomycin
- Anticoagulants: vitamin K antagonises anticoagulant effect of warfarin and aspirin
- Antidepressants: possibly increased serotoninergic effects when venlafaxine given with duloxetine; enhanced CNS effects and toxicity when venlafaxine given with MAOIs (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping venlafaxine); after stopping SSRI-related antidepressants do not start moclobemide for at least 1 week
- Antimalarias: avoidance of antidepressants advised by manufacturer of arteether/lumefantrine
- Antipsychotics: venlafaxine increases plasma concentration of clozapine and haloperidol
- Atorvastatin: possible increased risk of convulsions when antidepressants given with atorvastatin
- Dopaminergic: caution with venlafaxine advised by manufacturer of entacapone; increased risk of hypertension and CNS excitation when venlafaxine given with selegiline (selegiline should not be started until 1 week after stopping venlafaxine, avoid venlafaxine for 2 weeks after stopping selegiline)
- Lithium: possible increased serotonergic effects when venlafaxine given with lithium
- Sibutramine: increased risk of CNS toxicity when SSRIs-related antidepressants given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Verapamil see Calcium-channel Blockers

Vigabatrin
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and cyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and etrics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort
- Antimalearias: possible increased risk of convulsions when antidepressants given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine

Barbiturates: vigabatrin possibly reduces plasma concentration of phenobarbital

Vildagliptin see Antiabetic

Xipamide see Diuretics
Xylometazoline see Sympathomimetics
Zafirlukast see Leukotriene Antagonists
Zaleplon see Anxiolytics and Hypnotics
Zidovudine

Note Increased risk of toxicity with nephrotoxic and myelosuppressive drugs—for further details consult product literature

Analgesics: increased risk of haematological toxicity when zidovudine given with NSAIDs; plasma concentration of zidovudine possibly increased by methadone

Antibacterials: absorption of zidovudine reduced by clarithromycin tablets (give at least 2 hours apart); manufacturer of zidovudine advises avoid concomitant use with rifampicin

Antiepileptics: zidovudine increases or decreases plasma concentration of phenytoin; plasma concentration of zidovudine possibly increased by valproate (increased risk of toxicity)

● Antifungals: plasma concentration of zidovudine increased by fluconazole (increased risk of toxicity)

Antimalarials: increased antifolate effect when zidovudine given with pyrimethamine

Antivirals: profound myelosuppression when zidovudine given with ganciclovir (if possible avoid concomitant administration, particularly during initial ganciclovir therapy); increased risk of anaemia when zidovudine given with stavudine—avoid concomitant use; zidovudine possibly inhibits effects of atazanavir (manufacturers advise avoid concomitant use); plasma concentration of zidovudine reduced by tipranavir

Atovaquone: metabolism of zidovudine possibly inhibited by atovaquone (increased plasma concentration)

● Probenecid: excretion of zidovudine reduced by probenecid (increased plasma concentration and risk of toxicity)

Zinc

Antibacterials: zinc reduces absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin; zinc reduces absorption of tetracyclines, also absorption of zinc reduced by tetracyclines

Calcium Salts: absorption of zinc reduced by calcium salts

Iron: absorption of zinc reduced by oral iron, also absorption of oral iron reduced by zinc

Penicillamine: absorption of zinc reduced by penicillamine, also absorption of penicillamine reduced by zinc

Trientine: absorption of zinc reduced by trientine, also absorption of trientine reduced by zinc

Zoledronic Acid see Bisphosphonates
Zolmitriptan see 5HT Agonists
Zolpidem see Anxiolytics and Hypnotics
Zonisamide

● Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort

Antiepileptics: plasma concentration of zonisamide reduced by carbamazepine and phenytoin

● Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine

Barbiturates: plasma concentration of zonisamide reduced by phenobarbital

Zopiclone see Anxiolytics and Hypnotics
Zotepine see Antipsychotics
Zuclopenthixol see Antipsychotics
Liver disease may alter the response to drugs in several ways as indicated below, and drug prescribing should be kept to a minimum in all patients with severe liver disease. The main problems occur in patients with jaundice, ascites, or evidence of encephalopathy.

**Impaired drug metabolism** Metabolism by the liver is the main route of elimination for many drugs, but hepatic reserve is large and liver disease has to be severe before important changes in drug metabolism occur. Routine liver-function tests are a poor guide to the capacity of the liver to metabolise drugs, and in the individual patient it is not possible to predict the extent to which the metabolism of a particular drug may be impaired.

A few drugs, e.g. rifampicin and fusidic acid, are excreted in the bile unchanged and can accumulate in patients with intrahepatic or extrahepatic obstructive jaundice.

**Hypoproteinaemia** The hypoalbuminemia in severe liver disease is associated with reduced protein binding and increased toxicity of some highly protein-bound drugs such as phenytoin and prednisolone.

**Reduced clotting** Reduced hepatic synthesis of blood-clotting factors, indicated by a prolonged prothrombin time, increases the sensitivity to oral anti-coagulants such as warfarin and phenindione.

**Hepatic encephalopathy** In severe liver disease many drugs can further impair cerebral function and may precipitate hepatic encephalopathy. These include all sedative drugs, opioid analgesics, those diuretics that produce hypokalaemia, and drugs that cause constipation.

**Fluid overload** Oedema and ascites in chronic liver disease can be exacerbated by drugs that give rise to fluid retention, e.g. NSAIDs and corticosteroids.

**Hepatotoxic drugs** Hepatotoxicity is either dose-related or unpredictable (idiosyncratic). Drugs that cause dose-related toxicity may do so at lower doses in the presence of hepatic impairment than in individuals with normal liver function, and some drugs that produce reactions of the idiosyncratic kind do so more frequently in patients with liver disease. These drugs should be avoided or used very carefully in patients with liver disease.

### Table of drugs to be avoided or used with caution in liver disease

The list of drugs given below is not comprehensive and is based on current information concerning the use of prescribed drugs in therapeutic dosage. Products introduced or amended since publication of BNF No. 56 (September 2008) are underlined.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Avoid in severe liver disease—increased risk of bleeding</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Avoid</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Use of prodrugs such as cilazapril, enalapril, fosinopril, imidapril, moexipril, perindopril, quinapril, ramipril, and trandolapril requires close monitoring in patients with impaired liver function</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Acemetacin</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Acenocoumarol (nicoumalone)</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Avoid—further impairment of hepatic function may occur</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>Reduce dose in mild to moderate liver disease; avoid if severe</td>
</tr>
<tr>
<td>Alimemazine (trimipramine)</td>
<td>Avoid—may precipitate coma in severe liver disease; hepatotoxic</td>
</tr>
<tr>
<td>Alitretinoin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Manufacturer advises caution in mild to moderate liver disease; avoid in severe liver disease</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Alteplase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Amfetramine</td>
<td>see Bupropion</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>see Theophylline</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>Half-life prolonged—may need dose reduction</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Anabolic steroids</td>
<td>Preferably avoid—dose-related toxicity</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>Manufacturer advises caution in mild hepatic impairment; avoid in moderate to severe impairment</td>
</tr>
<tr>
<td>Analgesics</td>
<td>see Aspirin, NSAIDs, Opioid Analgesics and Paracetamol</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Avoid in moderate to severe liver disease</td>
</tr>
<tr>
<td>Androgens</td>
<td>Preferably avoid—dose-related toxicity with some, and produce fluid retention</td>
</tr>
</tbody>
</table>

Appendix 2: Liver disease
### Appendix 2: Liver disease

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
<th>Manufacturer advises avoid tablets in severe hepatic impairment—no information available</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine</td>
<td>Manufacturer of APO-go® advises avoid</td>
<td></td>
</tr>
<tr>
<td>Aprepitant</td>
<td>see Neurokinin Receptor Antagonists</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Manufacturer advises use with caution in severe impairment</td>
<td></td>
</tr>
<tr>
<td>Artemether [ingredient]</td>
<td>see Riamet®</td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>Avoid in severe hepatic impairment—increased risk of gastro-intestinal bleeding</td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Manufacturer advises caution in mild hepatic impairment; avoid in moderate to severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Halve dose in moderate liver disease; quarter dose in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>see Statins</td>
<td></td>
</tr>
<tr>
<td>Atosiban</td>
<td>No information available</td>
<td></td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Manufacturer advises caution—monitor more closely</td>
<td></td>
</tr>
<tr>
<td>Auranofin</td>
<td>Caution in mild to moderate liver disease; avoid in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Azapropazone</td>
<td>see NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Azathioprine</td>
<td>May need dose reduction</td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Manufacturer advises avoid in severe liver disease—no information available</td>
<td></td>
</tr>
<tr>
<td>Bambuterol</td>
<td>Avoid in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Beclometasone dipropionate</td>
<td>Manufacturer advises avoid</td>
<td></td>
</tr>
<tr>
<td>Beneporid</td>
<td>see Thiazides and Related Diuretics</td>
<td></td>
</tr>
<tr>
<td>Benfotiamide</td>
<td>Avoid; see Thiazides and Related Diuretics</td>
<td></td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Avoid in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>Increased accumulation possible in moderate to severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Bicalutamide</td>
<td>see Loop Diuretics</td>
<td></td>
</tr>
<tr>
<td>Bosantan</td>
<td>Avoid in moderate and severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Dose reduction may be necessary</td>
<td></td>
</tr>
<tr>
<td>Buclizine</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
<td></td>
</tr>
<tr>
<td>Budesonide</td>
<td>Plasma-budesonide concentration may increase on oral administration</td>
<td></td>
</tr>
<tr>
<td>Bumetanide</td>
<td>see Loop Diuretics</td>
<td></td>
</tr>
<tr>
<td>Bupiravacaine</td>
<td>Manufacturer advises caution in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Bupropion</td>
<td>see Opioid Analgesics</td>
<td></td>
</tr>
<tr>
<td>Buspirone</td>
<td>Reduce dose in mild to moderate liver disease; avoid in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Busulfan</td>
<td>Manufacturer advises monitor liver function—no information available</td>
<td></td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Reduce dose in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Manufacturer of topical calcitriol advises avoid—no information available</td>
<td></td>
</tr>
<tr>
<td>Candesartan</td>
<td>For hypertension, initially 2 mg once daily in mild or moderate hepatic impairment (no initial dose adjustment necessary in heart failure); avoid in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Manufacturer advises avoid in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Metabolism impaired in advanced liver disease</td>
<td></td>
</tr>
<tr>
<td>Carboprost</td>
<td>Manufacturer advises avoid</td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Avoid</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70 mg on first day then 35 mg once daily in moderate hepatic impairment; no information available for severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment</td>
<td></td>
</tr>
<tr>
<td>Celecoxib</td>
<td>see NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Cetorelix</td>
<td>Manufacturer advises avoid in moderate or severe liver impairment</td>
<td></td>
</tr>
<tr>
<td>Chlormethiazole</td>
<td>see Antidepressants, Tricyclic (and related)</td>
<td></td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Manufacturer advises consider dose reduction in severe hepatic impairment—limited information available</td>
<td></td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Avoid if possible—increased risk of bone-marrow depression; reduce dose and monitor plasma-chloramphenicol concentration</td>
<td></td>
</tr>
<tr>
<td>Chloridiazepoxide</td>
<td>see Anxiolytics and Hypnotics</td>
<td></td>
</tr>
<tr>
<td>Chlorphenamine</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
<td></td>
</tr>
<tr>
<td>Chlorphthiramine</td>
<td>see Chlorphenamine</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>see Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>see Sulphonylureas</td>
<td></td>
</tr>
<tr>
<td>Chlortalidone</td>
<td>see Thiazides and Related Diuretics</td>
<td></td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>May need dose adjustment</td>
<td></td>
</tr>
<tr>
<td>Clazapril</td>
<td>see ACE Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>Avoid in moderate or severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Cimetiadine</td>
<td>Increased risk of confusion; reduce dose</td>
<td></td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Manufacturer advises caution in moderate to severe hepatic impairment—monitor closely especially when increasing dose</td>
<td></td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
<td></td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>Avoid in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Citalopram</td>
<td>Use doses at lower end of range</td>
<td></td>
</tr>
<tr>
<td>Cladribine</td>
<td>Regular monitoring recommended</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Hepatic dysfunction including jaundice reported</td>
<td></td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>see Co-amoxiclav, below and Timentin®, p. 799</td>
<td></td>
</tr>
<tr>
<td>Clemastine</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Reduce dose in mild to moderate impairment; avoid in severe liver impairment; see also Anxiolytics and Hypnotics</td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Manufacturer advises caution (risk of bleeding); avoid in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Clozapine</td>
<td>Monitor hepatic function regularly; avoid in symptomatic or progressive liver disease or hepatic failure</td>
<td></td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>Monitor liver function in liver disease. Cholestatic jaundice, see p. 295</td>
<td></td>
</tr>
<tr>
<td>Codeine</td>
<td>see Opioid Analgesics</td>
<td></td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Manufacturer advises caution</td>
<td></td>
</tr>
<tr>
<td>Contraceptives, oral</td>
<td>Avoid in active liver disease and if history of pruritus or cholestasis during pregnancy</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Reduce dose</td>
<td></td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>see Ciclosporin</td>
<td></td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
<td></td>
</tr>
<tr>
<td>Cyproterone acetate</td>
<td>Dose-related toxicity; see also side-effects of cyproterone, section 8.3.4.2</td>
<td></td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Reduce dose</td>
<td></td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>see Anticoagulants, Oral</td>
<td></td>
</tr>
<tr>
<td>Dacarabazine</td>
<td>Dose reduction may be required in mild to moderate liver disease; avoid if severe—see Synercid®</td>
<td></td>
</tr>
<tr>
<td>Dalipristin [ingredi-</td>
<td>Use with caution in moderate hepatic impairment (increased risk of bleeding); avoid in severe hepatic impairment unless patient has heparin-induced thrombocytopenia and no alternative</td>
<td></td>
</tr>
<tr>
<td>Darteparin</td>
<td>Avoid oral use—may cause severe liver damage; injection may be used in emergency for malignant hyperthermia</td>
<td></td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
<td></td>
</tr>
<tr>
<td>Dantrone</td>
<td>Avoid oral use—may cause severe liver damage; injection may be used in emergency for malignant hyperthermia</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
<td></td>
</tr>
<tr>
<td>Darbeopetin</td>
<td>Manufacturer advises caution Max. 7.5 mg daily in moderate hepatic impairment; avoid in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Darifenacin</td>
<td>Manufacturer advises caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment—no information available</td>
<td></td>
</tr>
<tr>
<td>Darunavir</td>
<td>Manufacturer advises caution in moderate to severe hepatic impairment—no information available</td>
<td></td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Manufacturer advises caution in moderate to severe hepatic impairment—no information available</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
<td>Drug</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------------------------------</td>
<td>---------------------------</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Reduce dose</td>
<td>Efavirenz</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>Manufacturer advises caution—no information available; avoid in severe hepatic impairment</td>
<td>Eletroptan</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Manufacturer advises monitor liver function—interrupt treatment if persistent elevation in serum alanine aminotransferase</td>
<td>Enalapril</td>
</tr>
<tr>
<td>Demeclocycline</td>
<td>see Tetracyclines</td>
<td>Enfuvirtide</td>
</tr>
<tr>
<td>Desflurane</td>
<td>Reduce dose</td>
<td>Enoxaparin</td>
</tr>
<tr>
<td>Desogenestrel</td>
<td>Avoid; see also Contraceptives, Oral</td>
<td>Entacapone</td>
</tr>
<tr>
<td>Dextibuprofen</td>
<td>see NSAIDs</td>
<td>Epirubicin</td>
</tr>
<tr>
<td>Dextketoprofen</td>
<td>see NSAIDs</td>
<td>Eplerenone</td>
</tr>
<tr>
<td>Dextoxazone</td>
<td>Monitor liver function in patients with liver disease</td>
<td>Epoetin</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>see Opioid Analgesics</td>
<td>Eprosartan</td>
</tr>
<tr>
<td>Diamorphine</td>
<td>see Opioid Analgesics</td>
<td>Eptifibatide</td>
</tr>
<tr>
<td>Diazepam</td>
<td>see Antiepileptics and Hypnotics</td>
<td>Ergorectine</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>see NSAIDs</td>
<td>Ergotamine</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Insufficient information but monitor for toxicity</td>
<td>Ertotinib</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>Avoid; see also Contraceptives, Oral</td>
<td>Erythromycin</td>
</tr>
<tr>
<td>Dihydropyramid</td>
<td>Half-life prolonged—may need dose reduction</td>
<td>Escitalopram</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Monitor liver function—reduce dose according to liver enzymes; avoid in severe hepatic impairment</td>
<td>Esomeprazole</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Avoid</td>
<td>Estradiol</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Manufacturer advises caution in mild to moderate hepatic impairment</td>
<td>Estramustine</td>
</tr>
<tr>
<td>Doxetepin (dothiepin)</td>
<td>see Antidepressants, Tricyclic (and related)</td>
<td>Estril</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
<td>Estriol</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>No information—manufacturer advises caution</td>
<td>Estropipate</td>
</tr>
<tr>
<td>Doxepin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
<td>Ethynylestradiol</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Reduce dose according to bilirubin concentration</td>
<td>Etodolac</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>see Tetracyclines</td>
<td>Etopimidate</td>
</tr>
<tr>
<td>Drotrecogin alfa (activated)</td>
<td>Avoid in chronic severe liver disease</td>
<td>Etoposide</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
<td></td>
</tr>
<tr>
<td>Etravirine</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe hepatic impairment—no information available</td>
<td></td>
</tr>
<tr>
<td>Etynodiol diacetate</td>
<td>Avoid; see also Contraceptives, Oral</td>
<td></td>
</tr>
<tr>
<td>Exemestane</td>
<td>Manufacturer advises caution</td>
<td></td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Avoid in moderate and severe hepatic impairment—may accumulate</td>
<td></td>
</tr>
<tr>
<td>Famiclovir</td>
<td>Usual dose in well compensated liver disease (information not available on decompensated)</td>
<td></td>
</tr>
<tr>
<td>Felodipine</td>
<td>Reduce dose</td>
<td></td>
</tr>
<tr>
<td>Fenbufen</td>
<td>see NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>Avoid in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>see NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Fentanyl</td>
<td>see Opioid Analgesics</td>
<td></td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>Use with caution; avoid in conditions where iron overload increases risk of impairment</td>
<td></td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Manufacturer advises increase dose cautiously; max. 4 mg daily in moderate hepatic impairment; avoid in severe hepatic impairment; consult product literature before concomitant use of cytochrome P450 enzyme inhibitors</td>
<td></td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>Avoid in severe hepatic impairment—increased risk of bleeding</td>
<td></td>
</tr>
<tr>
<td>Flecaainide</td>
<td>Avoid (or reduce dose) in severe liver disease</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>Caution in hepatic impairment (risk of cholestatic jaundice and hepatitis, see p. 292)</td>
<td></td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>Toxicity with related drugs</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Carefully titrate dose</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Manufacturer advises caution</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>see Antidepressants, SSRI</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>see Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>see Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Flurazepam</td>
<td>see Anxiolytics and Hypnotics</td>
<td></td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>see NSAIDs</td>
<td></td>
</tr>
<tr>
<td>Flutamide</td>
<td>Use with caution (hepatotoxic)</td>
<td></td>
</tr>
<tr>
<td>Fluvalastin</td>
<td>see Statins</td>
<td></td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>see Antidepressants, SSRI</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux sodium</td>
<td>Caution in severe hepatic impairment (increased risk of bleeding)</td>
<td></td>
</tr>
<tr>
<td>Formoterol (eflomoterol)</td>
<td>Metabolism possibly reduced in severe cirrhosis</td>
<td></td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Manufacturer advises caution in mild hepatic impairment; reduce dose to 450 mg twice daily in moderate hepatic impairment; avoid in severe hepatic impairment</td>
<td></td>
</tr>
<tr>
<td>Fosaprepitant</td>
<td>see Neurokinin Receptor Antagonists</td>
<td></td>
</tr>
<tr>
<td>Fosinopril</td>
<td>see ACE Inhibitors</td>
<td></td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>Consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frovatriptan</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Furosemide</td>
<td>see Loop Diuretics</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Manufacturer advises caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Furosemide (furosemide)</td>
<td>see Loop Diuretics</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>Reduce dose in moderate hepatic impairment; avoid in severe impairment</td>
</tr>
<tr>
<td>Ganirelix</td>
<td>Manufacturer advises caution in moderate or severe hepatic impairment</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>Avoid in liver disease</td>
</tr>
<tr>
<td>Gestodene</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Gestrone</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Glidencamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Manufacturer advises caution in severe hepatic impairment</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>see Nitrates</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Halothane</td>
<td>Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane</td>
</tr>
<tr>
<td>Heparin</td>
<td>Reduce dose in severe liver disease</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Avoid</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Elimination reduced in hepatic impairment—initially 2.5 micrograms no more frequently than every 3 hours (max. 6 times daily), adjusted according to response (consult product literature)</td>
</tr>
<tr>
<td>Imatinib</td>
<td>Max. 400 mg daily; reduce dose further if not tolerated</td>
</tr>
<tr>
<td>Imidapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Imipramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Indapamide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>------</td>
<td>---------</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Increased risk of nephrolithiasis; reduce dose to 600 mg every 8 hours in mild to moderate hepatic impairment; not studied in severe impairment</td>
</tr>
<tr>
<td>Indometacin</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Indoramin</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Interferon alfa</td>
<td>Close monitoring in mild to moderate hepatic impairment; avoid if severe</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>Avoid in decompensated liver disease</td>
</tr>
<tr>
<td>Interferon gamma-1b</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Monitor closely for neutropenia if plasma-bilirubin concentration 1.5–3 times upper limit of normal range; avoid if plasma-bilirubin concentration greater than 3 times upper limit of normal range</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>Use with caution; avoid in conditions where iron overload increases risk of impairment</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>see Antidepressants, MAOI see Mirtind®</td>
</tr>
<tr>
<td>Isome-thepene [ingredient]</td>
<td>Use with caution; monitor liver function regularly and particularly frequently in first 2 months; see also p. 319</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>see Nitrates</td>
</tr>
<tr>
<td>Isoosorbide dinitrate</td>
<td>see Nitrates</td>
</tr>
<tr>
<td>Isoosorbide mono-nitrate</td>
<td></td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Avoid—further impairment of liver function may occur</td>
</tr>
<tr>
<td>Isradipine</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Use only if potential benefit outweighs risk of hepatotoxicity (see p. 331); dose reduction may be necessary</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Avoid oral solution because of propylene glycol content; manufacturer advises avoid capsules and tablets in severe hepatic impairment</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Avoid; see also p. 332</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>Sedation inappropriate in severe liver disease—avoid</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Avoid—severe hepatocellular injury reported</td>
</tr>
<tr>
<td>Lacidipine</td>
<td>Antihypertensive effect possibly increased</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Manufacturer advises caution in severe hepatic impairment — no information available</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Halve dose in moderate hepatic impairment; quarter dose in severe hepatic impairment</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>In severe liver disease dose should not exceed 30 mg daily</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Manufacturer advises caution in moderate to severe hepatic impairment—metabolism reduced</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Avoid—active metabolite may accumulate</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>No information—manufacturer advises that cirrhosis may affect renal excretion</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Halve dose in severe hepatic impairment if creatinine clearance less than 70 mL/minute</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>Manufacturer advises caution in liver disease</td>
</tr>
<tr>
<td>Levomepromazine (methotrimeprazine)</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Avoid (however levonorgestrel emergency contraception can be used); see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Lidocaine (lignocaine)</td>
<td>Manufacturer advises caution—increased risk of side-effects</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>see Lido-caine</td>
</tr>
<tr>
<td>Linezolid</td>
<td>In severe hepatic impairment manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis see Kaletra®</td>
</tr>
<tr>
<td>Lopinavir [ingredient]</td>
<td>see Antihistamines and Antipruritics</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>see Antihistamines and Antipruritics</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>see Antihistamines and Antipruritics</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>see Antihistamines and Antipruritics</td>
</tr>
<tr>
<td>Losartan</td>
<td>Consider lower dose see Riamet®</td>
</tr>
<tr>
<td>Lume-fantrine [ingredient]</td>
<td>see Antipyretics</td>
</tr>
<tr>
<td>Lymecycline</td>
<td>Magnesium salts</td>
</tr>
<tr>
<td>Magnesium salts</td>
<td>Avoid in hepatic coma if risk of renal failure</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Mefloquine</td>
<td>Avoid for prophylaxis in severe liver disease</td>
</tr>
<tr>
<td>Megestrol</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Melatonin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>see Antihistamines and Antipruritics</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Meptazinol</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>May need dose reduction</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Monitor transaminase and bilirubin concentrations</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Avoid in severe hepatic impairment see Androgens</td>
</tr>
<tr>
<td>Mesterolone</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Mestranol</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Metformin</td>
<td>Withdraw if tissue hypoxia likely</td>
</tr>
<tr>
<td>Methadone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Methenamine</td>
<td>Avoid</td>
</tr>
<tr>
<td>Methionine</td>
<td>May precipitate coma</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>Manufacturer advises caution; half-life may be prolonged</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Dose-related toxicity—avoid in non-malignant conditions (e.g. psoriasis); avoid for all indications in severe hepatic impairment</td>
</tr>
<tr>
<td>Methotrimoprazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Methoxy polyethylene glycol-epoetin beta</td>
<td></td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Manufacturer advises caution in history of liver disease; avoid in active liver disease</td>
</tr>
<tr>
<td>Methylaltrexone</td>
<td>Manufacturer advises avoid in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Avoid</td>
</tr>
<tr>
<td>Metclopramide</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Metolazone</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Reduce dose in severe hepatic impairment</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>In severe liver disease reduce total daily dose to one-third, and give once daily</td>
</tr>
<tr>
<td>Mianserin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Mifafungin</td>
<td>Use with caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Avoid</td>
</tr>
<tr>
<td>Midazolam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Midrid®</td>
<td>Avoid in severe liver disease; see also Paracetamol</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Miglustat</td>
<td>No information available—manufacturer advises caution</td>
</tr>
<tr>
<td>Minocycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Manufacturer advises caution in mild to moderate impairment—monitoring of plasma-mitotane concentration recommended; avoid in severe impairment</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Manufacturer advises caution in mild to moderate impairment—monitoring of plasma-mitotane concentration recommended; avoid in severe impairment</td>
</tr>
<tr>
<td>Mitoxantrone</td>
<td>Manufacturer advises caution in severe hepatic impairment</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>Reduce dose in severe liver impairment</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>Manufacturer recommends avoid in significant hepatic impairment</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Reduce dose in severe liver disease</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Halve dose in severe liver disease</td>
</tr>
<tr>
<td>Moexipril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Morphine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Manufacturer advises avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Manufacturer advises caution in liver disease</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Manufacturer advises caution in acute hepatitis or hepatic failure</td>
</tr>
<tr>
<td>Nandrolone</td>
<td>see Anabolic Steroids</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Max. 2.5 mg in 24 hours in moderate hepatic impairment; avoid if severe</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment—no information available</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>No information available—manufacturer advises caution</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>No information available—manufacturer advises caution</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Absorbed from gastrointestinal tract in liver disease—increased risk of ototoxicity</td>
</tr>
<tr>
<td>Neurokinin receptor antagonists</td>
<td>Manufacturer advises caution in moderate to severe hepatic impairment</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe hepatic impairment; see also p. 342</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Half-life prolonged in severe hepatic impairment—may need dose reduction</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Manufacturers advise caution in moderate to severe hepatic impairment</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Manufacturer advises monitor liver function in mild to moderate hepatic impairment and avoid in severe impairment; discontinue if severe abnormalities in liver function tests</td>
</tr>
<tr>
<td>Nicomunalone</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Dose reduction may be required in severe liver disease</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Elimination reduced in cirrhosis—monitor blood pressure</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Caution in severe hepatic impairment</td>
</tr>
<tr>
<td>Nitazepam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Cholestatic jaundice and chronic active hepatitis reported</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>see Sodium Nitroprusside</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Increased risk of gastro-intestinal bleeding and can cause fluid retention; avoid in severe liver disease; celecoxib, halve initial dose in moderate liver disease; dexketoprofen, reduce initial dose to max. 50 mg daily in mild to moderate hepatic impairment; parecoxib, halve dose in moderate hepatic impairment (max. 40 mg daily); tiaprofenic acid, reduce dose in mild or moderate hepatic impairment; see also Etoricoxib</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Elimination may be reduced in severe hepatic impairment</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Consider initial dose of 5 mg daily</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Dose should not exceed 20 mg daily in moderate impairment; manufacturer advises avoid in severe impairment—no information available</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Omega-3-acid ethyl esters</td>
<td>Monitor liver function</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>In liver disease not more than 20 mg daily should be needed</td>
</tr>
<tr>
<td>Ondanatetron</td>
<td>Max. 8 mg daily in moderate or severe hepatic impairment</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Avoid or reduce dose—may precipitate coma</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Oxycodeone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Possibly slower onset, higher dose requirement and prolonged recovery time</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Max. 20 mg daily in severe hepatic impairment and cirrhosis—monitor liver function (discontinue if deterioration)</td>
</tr>
<tr>
<td>Papaveretum</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Dose-related toxicity—avoid large doses</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Avoid; see NSAIDs</td>
</tr>
<tr>
<td>Parecoxib</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Peginterferon alfa</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pericyazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Perindopril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pethidine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>see Antidepressants, MAOI</td>
</tr>
<tr>
<td>Phenindione</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>May precipitate coma</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Reduce dose to avoid toxicity</td>
</tr>
<tr>
<td>Pholcodine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Reduce initial oral dose in moderate or severe cirrhosis—see Antipsychotics</td>
</tr>
<tr>
<td>Pimozide</td>
<td>Avoid; see Antipsychotics</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Avoid; see Opioid Analgesics</td>
</tr>
<tr>
<td>Piperazine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Pipotiazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Piracetam</td>
<td>Avoid; see NSAIDs</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Monitor liver function; use with caution in severe hepatic impairment</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Initially 500 micrograms daily; increased with caution</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>Side-effects more common</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Primidone</td>
<td>Reduce dose; may precipitate coma</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Progestogens</td>
<td>Avoid; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Promazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Avoid—may precipitate coma</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Propiverine</td>
<td>Avoid in moderate to severe hepatic impairment</td>
</tr>
<tr>
<td>Propofol</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Reduce oral dose</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Prothrombin Complex, Dried</td>
<td>Increased risk of thromboembolic events—manufacturer advises use with caution</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Monitor hepatic function—idiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment; see also p. 319</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>For immediate-release tablets, initially 25 mg daily, increased daily in steps of 25–50 mg; for modified-release tablets, initially 50 mg daily, increased daily in steps of 50 mg</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>see Synercid®</td>
</tr>
<tr>
<td>Quinagolide</td>
<td>Manufacturer advises avoid; no information available</td>
</tr>
<tr>
<td>Quinapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Quinupristin [ingredient]</td>
<td>Rabeprazole</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Manufacturer advises caution in severe hepatic dysfunction</td>
</tr>
<tr>
<td>Rabeprazol</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Ralitrexed</td>
<td>Caution in mild or moderate disease; avoid if severe</td>
</tr>
<tr>
<td>Ramipril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Rasagline</td>
<td>Manufacturer advises caution in mild hepatic impairment; avoid in moderate to severe impairment</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Initial dose 2 mg twice daily, increased according to tolerance</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Replaglinide</td>
<td>Manufacturer advises avoid in severe liver disease</td>
</tr>
<tr>
<td>Reteplase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Ribaavirin</td>
<td>No dosage adjustment required; avoid oral administration in severe hepatic dysfunction or decompensated cirrhosis</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Reduce dose in severe hepatic impairment</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg/daily; see also p. 320</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Manufacturer advises initial oral dose of 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily; if an oral dose of at least 2 mg daily tolerated, 25 mg as a depot injection can be given every 2 weeks</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Avoid in decompensated liver disease; in severe hepatic impairment without decompensation, use ‘booster’ doses with caution (avoid treatment doses)</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Manufacturer advises caution in cirrhotic patients with moderate hepatic impairment; avoid in liver disease with coagulopathy</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>No information available—manufacturer advises avoid in severe liver disease</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Reduce dose to 5 mg in mild to moderate liver disease; avoid in severe liver disease</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Manufacturer advises caution in severe liver disease</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Avoid</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Manufacturer advises caution and careful dose titration in mild to moderate hepatic impairment; avoid in severe impairment</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Slower titration and lower maintenance dose in mild to moderate hepatic impairment; avoid in severe hepatic impairment; see also Antipsychotics</td>
</tr>
<tr>
<td>Sertraline</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Increased plasma-sibutramine concentration; manufacturer advises caution in mild to moderate hepatic impairment; avoid if severe impairment</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>For erectile dysfunction, initial dose 25 mg; for pulmonary hypertension reduce to 20 mg twice daily if usual dose not tolerated; manufacturer advises avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Sirolium</td>
<td>Monitor blood-sirolium trough concentration</td>
</tr>
<tr>
<td>Sitaxentan sodium</td>
<td>Caution in mild to moderate liver disease; avoid in severe liver disease</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Impaired biliary excretion; possibly increased risk of hepatotoxicity; avoid or reduce dose</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>Halve initial dose</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Max. 5 mg daily in moderate liver disease; avoid if severe</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Statins</td>
<td>Avoid in active liver disease or unexplained persistent elevations in serum transaminases</td>
</tr>
<tr>
<td>Stilboestrol (diethylstilbestrol)</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Sulindac</td>
<td>see NSAIDs</td>
</tr>
</tbody>
</table>

798 Appendix 2: Liver disease
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulphonylureas</td>
<td>Increased risk of hypoglycaemia in severe liver disease; avoid or use small dose; can produce jaundice; see also Glimepiride</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Manufacturer advises 50 mg oral dose in hepatic impairment; avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>Prolonged apnoea may occur in severe liver disease because of reduced hepatic synthesis of pseudocholinesterase</td>
</tr>
<tr>
<td><em>Synercid</em>®</td>
<td>Consider reducing dose to 5 mg/kg every 8 hours in moderate hepatic impairment, adjusted according to clinical response; avoid in severe hepatic impairment or if plasma-bilirubin concentration greater than 3 times upper limit of reference range</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>Dose reduction may be necessary in severe hepatic impairment</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Max. dose 10 mg; manufacturer advises monitor patient in severe hepatic impairment</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Tegafur with uracil</td>
<td>see <em>Uftoral</em>®</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Manufacturer advises caution; see also p. 309</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>20–40 mg once daily in mild or moderate impairment; avoid in severe hepatic impairment or biliary obstruction</td>
</tr>
<tr>
<td>Temazepam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Manufacturer advises caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Manufacturer advises avoid—elimination reduced</td>
</tr>
<tr>
<td>Testosterone and esters</td>
<td>see Androgens</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Avoid (or use with caution); tetracycline and demeclocycline max. 1 g daily in divided doses; see also Tigecycline</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Manufacturer advises caution in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Thiadizones and related diuretics</td>
<td>Use with caution in mild to moderate impairment; avoid in severe liver disease; hypokalaemia may precipitate coma (potassium-sparing diuretic can prevent); increased risk of hypomagnesaemia in alcoholic cirrhosis</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Reduce dose for induction in severe liver disease</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Maintenance dose 5–10 mg 1–2 times daily initially in mild to moderate hepatic impairment; avoid in severe impairment</td>
</tr>
<tr>
<td>Tiaprofenic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Tibolone</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Ticarcillin [ingredient]</td>
<td>see <em>Timentin</em>®</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>Initially 100 mg then 25 mg every 12 hours in severe hepatic impairment—no information available</td>
</tr>
<tr>
<td><em>Timentin</em>®</td>
<td>Cholestatic jaundice, see under Co-amoxiclav p. 295</td>
</tr>
<tr>
<td>Timolol</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>see Heparin</td>
</tr>
<tr>
<td>Tioguanine</td>
<td>Reduce dose in hepatic impairment</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Manufacturer advises monitor liver function in mild hepatic impairment (see p. 341); avoid in moderate or severe hepatic impairment—no information available</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Caution in mild to moderate liver disease; avoid in severe liver disease—increased risk of bleeding</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Avoid in severe liver disease</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Avoid</td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Reduce dose to 1 mg twice daily</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Use with caution in hepatic impairment—clearance may be decreased</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Torasemide</td>
<td>see Loop Diuretics</td>
</tr>
<tr>
<td>Toremifene</td>
<td>Elimination decreased in hepatic impairment—avoid if severe</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Manufacturer advises caution in liver impairment—consider dose reduction; avoid in patients with raised bilirubin</td>
</tr>
<tr>
<td>Tramadol</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Tranylcypromine</td>
<td>see Antidepressants, MAOI</td>
</tr>
<tr>
<td>Trazodone</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Tretinoin (oral)</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Tribavirin</td>
<td>see Ribavirin</td>
</tr>
<tr>
<td>Triclofos</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Trimeprazine</td>
<td>see Alimemazine</td>
</tr>
<tr>
<td>Trimipramide</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Triprolidate</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Trisoprodil</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Trimepolis</td>
<td>Manufacturer advises monitor liver function in mild to moderate hepatic impairment and avoid in severe impairment</td>
</tr>
<tr>
<td>Urikase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>Avoid in chronic liver disease (but used in primary biliary cirrhosis)</td>
</tr>
<tr>
<td>Uftoral®</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>Manufacturer advises caution with high doses used for preventing cytomegalovirus disease—no information available</td>
</tr>
<tr>
<td>Valproate</td>
<td>Avoid if possible—hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months); see also p. 258</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Halve dose in mild to moderate hepatic impairment; avoid if severe</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>Initial dose 5 mg in mild to moderate hepatic impairment, increased subsequently according to response (max. 10 mg in moderate hepatic impairment); manufacturer advises avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Halve dose in moderate hepatic impairment; avoid if severe</td>
</tr>
<tr>
<td>Verapamil</td>
<td>Reduce oral dose</td>
</tr>
<tr>
<td>Verteporfin</td>
<td>Avoid in severe hepatic impairment</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Dose reduction may be necessary</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Dose reduction may be required in significant hepatic impairment</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>In mild to moderate hepatic cirrhosis use usual initial dose then halve subsequent doses; no information available for severe hepatic cirrhosis—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Accumulation may occur</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Manufacturer advises caution in severe hepatic impairment—limited information available</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Max. 5 mg in 24 hours in moderate or severe hepatic impairment</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Initially, increase dose at 2-week intervals if mild or moderate hepatic impairment; avoid in severe impairment</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Zotepine</td>
<td>Initial dose 25 mg twice daily, increased gradually according to response (max. 75 mg twice daily); monitor liver function at weekly intervals for first 3 months</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>see Antipsychotics</td>
</tr>
</tbody>
</table>
Renal impairment

The use of drugs in patients with reduced renal function can give rise to problems for several reasons:

- reduced renal excretion of a drug or its metabolites may cause toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by patients with renal impairment;
- some drugs are not effective when renal function is reduced.

Many of these problems can be avoided by reducing the dose or by using alternative drugs.

Principles of dose adjustment in renal impairment

The level of renal function below which the dose of a drug must be reduced depends on the proportion of the drug eliminated by renal excretion and its toxicity.

For many drugs with only minor or no dose-related side-effects very precise modification of the dose regimen is unnecessary and a simple scheme for dose reduction is sufficient.

For more toxic drugs with a small safety margin or patients at extremes of weight, dose regimens based on creatinine clearance (see Use of Dosage Table for details) should be used. When both efficacy and toxicity are closely related to plasma-drug concentration, recommended regimens should be regarded only as a guide to initial treatment; subsequent doses must be adjusted according to clinical response and plasma-drug concentration.

Renal function declines with age; many elderly patients have renal impairment but, because of reduced muscle mass, this may not be indicated by a raised serum creatinine. It is wise to assume at least mild impairment of renal function when prescribing for the elderly.

The total daily maintenance dose of a drug can be reduced either by reducing the size of the individual doses or by increasing the interval between doses. For some drugs, although the size of the maintenance dose is reduced it is important to give a loading dose if an immediate effect is required. This is because it takes about five times the half-life of the drug to achieve steady-state plasma concentrations. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment it can take many doses for the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same size as the initial dose for a patient with normal renal function.

Nephrotoxic drugs should, if possible, be avoided in patients with renal disease because the consequences of nephrotoxicity are likely to be more serious when renal reserve is already reduced.

Use of dosage table

Dose recommendations are based on the severity of renal impairment.

Renal function is measured either in terms of estimated glomerular filtration rate (eGFR) calculated from a formula derived from the Modification of Diet in Renal Disease study (‘MDRD formula’ that uses serum creatinine, age, sex, and race (for Afro-Caribbean patients)) or it can be expressed as creatinine clearance (best derived from a 24-hour urine collection but often calculated from the Cockcroft and Gault formula (CG) or a nomogram that uses serum creatinine, weight, sex, and age).

Cockcroft and Gault formula

Estimated Creatinine Clearance in mL/minute = \frac{(140 – Age) \times Weight \times Constant}{Serum creatinine}\n
Age in years  
Weight in kilograms; use ideal body-weight  
Serum creatinine in micromol/litre  
Constant = 1.23 for men; 1.04 for women

The serum-creatinine concentration is sometimes used instead as a measure of renal function but it is only a rough guide to drug dosing.

Important

The information on dosage adjustment in the BNF is based on creatinine clearance. This is because published information on the effects of renal impairment on drug elimination is usually given in terms of creatinine clearance as a surrogate for glomerular filtration rate (GFR).

Special care is required when interpreting advice on dosage adjustment based on creatinine clearance (e.g. calculated from the Cockcroft and Gault formula) because renal function in adults is increasingly being reported on the basis of estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73 m and derived from the MDRD (Modification of Diet in Renal Disease) formula. Although, the two measures of renal function are not interchangeable, in practice, for most drugs and for most patients (over 18 years) of average build and height, eGFR (MDRD) can be used to determine dosage adjustments in place of creatinine clearance. An individual’s absolute glomerular filtration rate can be calculated from the eGFR as follows:

\[ \text{GFR} = \text{eGFR} \times \left( \frac{\text{individual’s body surface area}}{1.73} \right) \]

Toxic drugs For potentially toxic drugs with a small safety margin, creatinine clearance (calculated from the Cockcroft and Gault formula or a nomogram) should be used to adjust drug dosages in addition to plasma-drug concentration and clinical response.

Patients at extremes of weight In patients at both extremes of weight (BMI of less than 18.5 kg/m or greater than 30 kg/m) the absolute glomerular filtration rate or creatinine clearance (calculated from the Cockcroft and Gault formula or a nomogram) should be used to adjust drug dosages.
In the BNF, values for creatinine clearance or another measure of renal function are included where possible. However, where such values are not available, the BNF reflects the terms used in the published information. 

Chronic kidney disease in adults: UK guidelines for identification, management and referral (March 2006) define renal function as follows:

<table>
<thead>
<tr>
<th>Degree of impairment</th>
<th>eGFR mL/minute/1.73 m</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal - Stage 1</td>
<td>More than 90 (with other evidence of kidney damage)</td>
</tr>
<tr>
<td>Mild - Stage 2</td>
<td>60–89 (with other evidence of kidney damage)</td>
</tr>
<tr>
<td>Moderate - Stage 3</td>
<td>30–59</td>
</tr>
<tr>
<td>Severe - Stage 4</td>
<td>15–29</td>
</tr>
<tr>
<td>Established renal failure - Stage 5</td>
<td>Less than 15</td>
</tr>
</tbody>
</table>

1. NICE clinical guideline 73 (September 2008)—Chronic kidney disease: Stage 3A eGFR 45–59, Stage 3B eGFR 30–44

Dialysis

For prescribing in patients on continuous ambulatory peritoneal dialysis (CAPD) or haemodialysis, consult specialist literature.

The following table can be used as a guide to drugs which require a reduction in dose in renal impairment, and to those which are potentially harmful or are ineffective. Drug prescribing should be kept to the minimum in all patients with severe renal disease.

If even mild renal impairment is considered likely on clinical grounds, renal function should be checked before prescribing any drug which requires dose modification.

Absence of a drug from the table does not imply safety. For adjusting drug doses in renal impairment, see Important on p. 801.

Table of drugs to be avoided or used with caution in renal impairment

The list of drugs given below may not be comprehensive and is based on current information concerning the use of prescribed drugs in therapeutic dosage.

Products introduced or amended since publication of BNF No. 56 (September 2008) are underlined.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Manufacturer advises avoid in end-stage renal disease</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Use with caution in severe renal impairment—increased risk of bleeding</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Avoid if serum-creatinine greater than 120 micromol/litre</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Manufacturer advises avoid if creatinine clearance less than 25 mL/minute</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Use with caution and monitor response (see also p. 101); hyperkalaemia and other side-effects more common; see also individual drugs</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>Avoid; metabolic acidosis</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>Risk of neurological reactions increased; use normal intravenous dose every 12 hours if creatinine clearance 25–50 mL/minute (every 24 hours if creatinine clearance 10–25 mL/minute); consult product literature for intravenous dose if creatinine clearance less than 10 mL/minute; for herpes zoster, use normal oral dose every 8 hours if creatinine clearance 10–25 mL/minute (every 12 hours if creatinine clearance less than 10 mL/minute); for herpes simplex, use normal oral dose every 12 hours if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Acipimox</td>
<td>Reduce dose if creatinine clearance 30–60 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Avoid; increased risk of toxicity</td>
</tr>
<tr>
<td>Alendronic acid</td>
<td>Manufacturer advises avoid if glomerular filtration rate less than 35 mL/minute</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Alfuzosin</td>
<td>Start at 2.5 mg twice daily and adjust according to response</td>
</tr>
<tr>
<td>Alimemazine (trimiprazine)</td>
<td>Avoid</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Manufacturer advises caution if estimated glomerular filtration rate less than 30 mL/minute—no information available</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Manufacturer advises avoid in severe renal impairment—no information available</td>
</tr>
<tr>
<td>Max. 100 mg daily, increased only if response inadequate; if creatinine clearance less than 10 mL/minute, reduce daily dose below 100 mg, or increase dose interval; if facilities available, adjust dose to maintain plasma-oxipurinol concentration below 100 micromol/litre</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Max. 12.5 mg in 24 hours if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Aluminium salts</td>
<td>Risk of accumulation and aluminium toxicity Note Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics)</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Reduce dose; avoid if creatinine clearance less than 15 mL/minute</td>
</tr>
<tr>
<td>Ambrisenan</td>
<td>Use with caution if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Amfebutamone</td>
<td>see Bupropion</td>
</tr>
<tr>
<td>Amikacin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Amiloride</td>
<td>see Potassium-sparing Diuretics</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Reduce dose; monitor serum concentrations; see also Neomycin and section 5.1.4</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Halve dose if creatinine clearance 30–60 mL/minute; use one-third dose if creatinine clearance 10–30 mL/minute; manufacturers advise intermittent treatment with a reduced dose if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>Risk of crystalluria with high doses (particularly during parenteral therapy). Reduce dose if creatinine clearance less than 10 mL/minute; rashes more common</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>Use only if no alternative; nephrotoxicity may be reduced with use of lipid formulations</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>Reduce dose if creatinine clearance less than 10 mL/minute; rashes more common</td>
</tr>
<tr>
<td>Amsacrine</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>Manufacturer advises avoid if creatinine clearance less than 50 mL/minute but usual doses have been used</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Manufacturer advises caution if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Analgesics</td>
<td>see Opioid Analgesics and NSAIDs</td>
</tr>
<tr>
<td>Anastrozole</td>
<td>Avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Angeliq</td>
<td>Manufacturer advises avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Anticoagulants, oral</td>
<td>Avoid if creatinine clearance less than 10 mL/minute; see also Dabigatran Exetilate and Rivaroxaban</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Start with small doses in severe impairment; increased cerebral sensitivity; see also Amisulpride, Clozapine, Flupentixol, Fluphenazine, Haloperidol, Olanzapine, Paliperdone, Pericyazine, Quetiapine, Risperidone, Sulpiride, and Zoftepine</td>
</tr>
<tr>
<td>Anxiolytics and hypnotics</td>
<td>Start with small doses in severe impairment; increased cerebral sensitivity; see also Buspirone, Chloral Hydrate, Melatonin, and Sodium Oxybate</td>
</tr>
<tr>
<td>Arsenic trioxide</td>
<td>Manufacturer advises caution see Riomet®</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>Avoid if creatinine clearance less than 10 mL/minute; sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding</td>
</tr>
<tr>
<td>Atosiban</td>
<td>No information available</td>
</tr>
<tr>
<td>Atovoquone</td>
<td>Manufacturer advises caution—monitor more closely</td>
</tr>
<tr>
<td>Atripla®</td>
<td>Manufacturer advises avoid if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Auranofin</td>
<td>see Sodium Aurothiomalate</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>Reduce dose (max. 600 mg daily) in rheumatoid arthritis and ankylosing spondylitis; avoid in severe impairment (avoid in gout if creatinine clearance less than 60 mL/minute)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Reduce dose and monitor full blood count</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>If creatinine clearance 10–30 mL/minute, usual initial dose, then half normal dose; if creatinine clearance less than 10 mL/minute usual initial dose, then one-quarter normal dose</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Use smaller doses (e.g. 5 mg daily by mouth); excreted by kidney</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Bambuterol</td>
<td>Reduce initial dose by half if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Barbitaltates</td>
<td>Reduce dose if creatinine clearance less than 10 mL/minute; see also Phenobarbital</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Bemiparin</td>
<td>Risk of bleeding may be increased—use with caution; use of unfractionated heparin may be preferable</td>
</tr>
<tr>
<td>Bendrofluazide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Bendroflumethiazide</td>
<td>(bendrofluazide)</td>
</tr>
<tr>
<td>Benperidol</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Ben佐xazepines</td>
<td>Use with caution; reduce dose</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>Reduce dose—consult product literature; high doses may cause cerebral irritation, convulsions, or coma</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>see under individual drugs</td>
</tr>
<tr>
<td>Bezaflurex</td>
<td>Reduce dose to 400 mg daily if creatinine clearance 40–60 mL/minute; reduce dose to 200 mg every 1–2 days if creatinine clearance 15–40 mL/minute; avoid if creatinine clearance less than 15 mL/minute; avoid modified-release preparations in renal impairment</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>Reduce dose if creatinine clearance less than 20 mL/minute (max. 10 mg daily)</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Reduce dose of infusion to 1.4 mg/kg/hour if creatinine clearance 30–60 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Reduce dose by half if serum-creatinine 177–354 micromol/litre; reduce dose further if serum-creatinine greater than 354 micromol/litre</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>No information available for creatinine clearance less than 20 mL/minute/1.73 m</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>Manufacturer advises avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Manufacturer recommends 150 mg daily</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Reduce dose; avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Manufacturer of topical calcitriol advises avoid—no information available</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Initially 4 mg daily</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Reduce starting dose of 1250 mg/m to 75% if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Reduce dose—consult product literature; nephrotoxic; otoxic</td>
</tr>
</tbody>
</table>

For adjusting drug doses in renal impairment, see Important on p. 801.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captopril</td>
<td>see ACE inhibitors; reduce dose; max. initial dose 25 mg daily (do not exceed 100 mg daily) if creatinine clearance 20–40 mL/minute; max. initial dose 12.5 mg daily (do not exceed 70 mg daily) if creatinine clearance 10–20 mL/minute; max. initial dose 6.25 mg daily (do not exceed 37.5 mg daily) if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Carbetrocin</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Reduce dose and monitor haematological parameters and renal function; avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Carboprost</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>No dose adjustment required—manufacturer advises caution</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Reduce dose if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>Max. 3 g daily if creatinine clearance 40–50 mL/minute; max. 1.5 g daily if creatinine clearance 10–40 mL/minute; max. 750 mg daily if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Reduce dose if creatinine clearance less than 40 mL/minute</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>If creatinine clearance less than 5 mL/minute, initial dose of 1 g then use half normal dose</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Reduce dose if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Ceftarline</td>
<td>Use half normal dose if creatinine clearance 5–20 mL/minute; use one-quarter normal dose if creatinine clearance less than 5 mL/minute</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Reduce dose if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Ceftibuten</td>
<td>Reduce dose if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Ceftoxime</td>
<td>Use parenteral dose of 750 mg twice daily if creatinine clearance 10–20 mL/minute; use parenteral dose of 750 mg once daily if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------------------------</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>see NSAIDs; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Cefprozil</td>
<td>Reduce dose by half if creatinine clearance 15–40 mL/minute; avoid if creatinine clearance less than 15 mL/minute</td>
</tr>
<tr>
<td>Citazapril</td>
<td>see ACE inhibitors; reduce dose; max. initial dose 500 micrograms once daily (do not exceed 2.5 mg once daily) if creatinine clearance 10–40 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Reduce dose; 200 mg 4 times daily if creatinine clearance 30–50 mL/minute; 200 mg 3 times daily if creatinine clearance 15–30 mL/minute; 200 mg twice daily if creatinine clearance less than 15 mL/minute; occasional risk of confusion</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>100 mg on alternate days if creatinine clearance 10–20 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Use half normal dose if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Avoid if possible; nephrotoxic</td>
</tr>
<tr>
<td>Citralazine</td>
<td>No information available for creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>CitraFleet®</td>
<td>Avoid if creatinine clearance less than 30 mL/minute—risk of hypermagnesaemia</td>
</tr>
</tbody>
</table>

### Appendix 3: Renal impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Citramag®</td>
<td>Risk of hypermagnesaemia; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Citrates</td>
<td>Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations (such as effervescent analgesics)</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Use half normal dose if creatinine clearance less than 30 mL/minute; avoid Klaricid XL® if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Regular monitoring recommended</td>
</tr>
<tr>
<td>Clavulanic acid</td>
<td>see Co-amoxiclav and Time-tran®</td>
</tr>
<tr>
<td>Clofazimine</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>see Sodium Clofibrate</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>300 mg 2 times daily if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Clodeine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Reduce dose up to 50% if creatinine clearance less than 50 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Reduce dose and monitor plasma-colistin concentration during parenteral or nebulised treatment—consult product literature</td>
</tr>
<tr>
<td>Clofibrate</td>
<td>Use half normal dose if creatinine clearance 15–30 mL/minute; avoid if creatinine clearance less than 15 mL/minute and if plasma-sulphamethoxazole concentration cannot be monitored</td>
</tr>
<tr>
<td>Cyclopentazine</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Reduce dose (see also p. 318); avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>see Ciclosporin</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Reduce initial dose to 75 mg and subsequent doses to 150 mg once daily if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Dose reduction may be required in combined renal and hepatic impairment; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
</tbody>
</table>
## Appendix 3: Renal impairment

### Drug | Comment
---|---
Dalteparin | Risk of bleeding may be increased—dose reduction, and monitoring of anti-Factor Xa, may be required; use of unfractionated heparin may be preferable
Danaparoid | Caution if creatinine clearance 10–20 mL/minute; increased risk of bleeding (monitor anti-Factor Xa activity); avoid if creatinine clearance less than 10 mL/minute unless patient has heparin-induced thrombocytopenia and no alternative
Daptomycin | Monitor renal function if creatinine clearance less than 80 mL/minute; for complicated skin and soft-tissue infections without bacteremia use 4 mg/kg every 48 hours if creatinine clearance less than 30 mL/minute; for other indications, consult product literature if creatinine clearance less than 50 mL/minute
Daunorubicin | Reduce dose by 25% if serum creatinine 105–265 micromol/litre and by 50% if serum creatinine greater than 265 micromol/litre
Deferasirox | Reduce dose by 10 mg/kg if creatinine clearance 60–90 mL/minute and if serum creatinine increased by more than 33% of baseline measurement on 2 consecutive occasions—interrupt treatment if deterioration in renal function persists after dose reduction; avoid if creatinine clearance less than 60 mL/minute
Deferiprone | Manufacturer advises caution—no information available
Demeclocycline | Avoid
Desflurane | Reduce dose if creatinine clearance less than 20 mL/minute
Desloratadine | Manufacturer advises caution in severe renal insufficiency
Desmopressin | Antidiuretic effect may be reduced
Dexibuprofen | see NSAIDs; reduce initial dose; avoid if glomerular filtration rate less than 30 mL/minute
Dexketoprofen | see NSAIDs; reduce initial dose to 50 mg daily if creatinine clearance 20–50 mL/minute; avoid if creatinine clearance less than 20 mL/minute
Dexrazoxane | Manufacturer of Cardioxane® advises reduce dose by 50% if creatinine clearance less than 40 mL/minute
Dextromethorphan | see Opioid Analgesics
Diamorphine | see Opioid Analgesics
 Diazepam | see Anxiolytics and Hypnotics
 Diazoxide | Dose reduction may be required
 Diclofenac | see NSAIDs; avoid if creatinine clearance less than 10 mL/minute; avoid Dyloject® if creatinine clearance less than 30 mL/minute
 Didanosine | Reduce dose if creatinine clearance less than 60 mL/minute; consult product literature
 Digoxin | Reduce dose; toxicity increased by electrolyte disturbances
 Dihydrocodeine | see Opioid Analgesics
 Diltilazem | Start with smaller dose
 Dinoprostone | Manufacturers advise avoid
 Diphenoxylate | see Opioid Analgesics
 Dipipanone | see Opioid Analgesics
 Disodium etidronate | Reduce dose if creatinine clearance 20–50 mL/minute; avoid if creatinine clearance less than 20 mL/minute
 Disodium pamidronate | Max. infusion rate 20 mg/hour; except in life-threatening hypercalcaemia, manufacturer advises avoid if creatinine clearance less than 30 mL/minute; if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value
 Doripenem | 250 mg every 8 hours if creatinine clearance 30–50 mL/minute; 250 mg every 12 hours if creatinine clearance less than 30 mL/minute
 Dorzolamide | Manufacturer advises avoid if creatinine clearance less than 30 mL/minute
 Doxycycline | Use with caution (avoid excessive doses)
 Drospirenone | see Angelique®, Yasmin®, and Yaz®
 Duloxetine | Avoid if creatinine clearance less than 30 mL/minute
 Efavirenz | Manufacturer advises caution in severe renal failure—no information available; see also Atripla®
 Eletriptan | Reduce initial dose to 20 mg; max. 40 mg in 24 hours; avoid if creatinine clearance less than 30 mL/minute
 Emtricitabine | Reduce dose if creatinine clearance less than 50 mL/minute; consult product literature; see also Atripla® and Truvada®

For adjusting drug doses in renal impairment, see Important on p. 801.
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>see ACE inhibitors; max. initial dose 2.5 mg daily if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td><strong>Enoxaparin</strong></td>
<td>Risk of bleeding increased; reduce dose if creatinine clearance less than 30 mL/minute; monitoring of anti-factor Xa may be required; use of unfractionated heparin may be preferable</td>
</tr>
<tr>
<td>Enoximone</td>
<td>Consider dose reduction</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Reduce dose if creatinine clearance less than 50 mL/minute; consult product literature</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Increased risk of hyperkalaemia—close monitoring required; avoid if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>Halve initial dose if creatinine clearance less than 60 mL/minute</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Reduce infusion to 1 microgram/kg/minute if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Erdostine</td>
<td>Manufacturer advises avoid if creatinine clearance less than 25 mL/minute—no information available</td>
</tr>
<tr>
<td>Ergometrine</td>
<td>Manufacturer advises caution in mild or moderate renal impairment and avoid in severe renal impairment</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>Avoid; risk of renal vasoconstriction</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Manufacturer advises avoid if creatinine clearance less than 15 mL/minute—no information available</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Risk of seizures; max. 500 mg daily if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Max. 1.5 g daily in severe renal impairment (ototoxicity)</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>Manufacturer advises caution if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Esmolol</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Manufacturer advises caution in severe renal insufficiency</td>
</tr>
<tr>
<td>Estramustine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Reduce dose; if creatinine clearance less than 30 mL/minute monitor plasma-ethambutol concentration; optic nerve damage</td>
</tr>
<tr>
<td>Etidronate disodium</td>
<td>see Disodium Etidronate</td>
</tr>
<tr>
<td>Etodolac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Consider dose reduction</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>Avoid if creatinine clearance less than 30 mL/minute; see also NSAIDs</td>
</tr>
<tr>
<td>Exemestane</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td><strong>Exenatide</strong></td>
<td>Manufacturer advises caution if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Famciclovir</td>
<td>Reduce dose; consult product literature</td>
</tr>
<tr>
<td>Famotidine</td>
<td>Use normal dose every 36–48 hours or use half normal dose if creatinine clearance less than 50 mL/minute; seizures reported very rarely</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>Reduce to 134 mg daily if creatinine clearance less than 60 mL/minute; reduce dose to 67 mg daily if creatinine clearance less than 20 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Fenofibrate</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>Manufacturer advises increase dose cautiously; max. 4 mg daily if creatinine clearance less than 30 mL/minute; consult product literature before concomitant use of cytochrome P450 enzyme inhibitors</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>Reduce initial oral dose to max. 100 mg daily or reduce intravenous dose by 50% if creatinine clearance less than 35 mL/minute</td>
</tr>
<tr>
<td><strong>Fleet Phospho-soda</strong></td>
<td>Manufacturer advises avoid in severe renal impairment</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>Reduce dose if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Usual initial dose then halve subsequent doses if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Reduce dose and monitor plasma-flucytosine concentration—consult product literature</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Reduce dose by up to 50% if creatinine clearance 30–70 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>see Antipsychotics; manufacturer advises caution; avoid in renal failure</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>see Antipsychotics; manufacturer advises caution; avoid in renal failure</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>see Anxiolytics and Hypnotics; see NSAIDs</td>
</tr>
<tr>
<td>Fluoribprofen</td>
<td>see Antipsychotics; manufacturer advises caution; avoid in renal failure</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Start with smaller dose</td>
</tr>
</tbody>
</table>
Drug Comment
Fondaparinux Increased risk of bleeding; for treatment of acute coronary syndromes avoid if creatinine clearance less than 20 mL/minute; for treatment of venous thromboembolism use with caution if creatinine clearance 30–50 mL/minute, avoid if creatinine clearance less than 30 mL/minute; for prophylaxis of venous thromboembolism reduce dose to 1.5 mg daily if creatinine clearance 20–50 mL/minute, avoid if less than 20 mL/minute
Foscarnet Reduce dose; consult product literature
Fosinopril see ACE inhibitors
Fosphenytoin Consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

For adjusting drug doses in renal impairment, see Important on p. 801.

Frusemide see Furosemide
Furosemide (frusemide) May need high doses; deafness may follow rapid i/v injection
Fydogel Mebeverine® Contains 2.5 mmol potassium per sachet
Gabapentin Reduce dose if creatinine clearance less than 80 mL/minute; consult product literature
Galantamine Avoid if creatinine clearance less than 9 mL/minute
Ganciclovir Reduce dose if creatinine clearance less than 70 mL/minute; consult product literature
Ganirelix Avoid if creatinine clearance less than 20 mL/minute
Gemcitabine Manufacturer advises caution
Gemeprost Manufacturer advises avoid
Gemfibrozil Initially 900 mg daily if creatinine clearance 30–80 mL/minute; avoid if creatinine clearance less than 30 mL/minute
Gentamicin see Aminoglycosides
Gestrinone Avoid if creatinine clearance less than 10 mL/minute
Glatiramer No information available—manufacturer advises caution
Glibenclamide Avoid if creatinine clearance less than 10 mL/minute
Gliclazide Reduce initial dose and monitor closely; avoid if creatinine clearance less than 10 mL/minute
Glimepiride Avoid if creatinine clearance less than 10 mL/minute
Glipizide Increased risk of hypoglycaemia; avoid if creatinine clearance less than 10 mL/minute or if hepatic impairment also present
Glyceryl trinitrate see Nitrates

Drug Comment
Guanethidine Reduce dose if creatinine clearance less than 65 mL/minute, avoid if creatinine clearance less than 40 mL/minute
Haloperidol see Antipsychotics; manufacturer advises caution in renal impairment
Heparin Risk of bleeding increased if creatinine clearance less than 10 mL/minute—dose may need to be reduced
Hctastarch Avoid if creatinine clearance less than 10 mL/minute; excreted by kidney
Hydralazine Reduce dose if creatinine clearance less than 30 mL/minute
Hydrochlorothiazide see Thiazides and Related Diuretics
Hydroflumethiazide see Thiazides and Related Diuretics
Hydromorphone see Opioid Analgesics
Hydroxyzine Use half normal dose
Hyoscine hydrobromide Manufacturer advises caution
Hypnotics see Anxiolytics and Hypnotics
Ibandronic acid For repeated doses, if creatinine clearance less than 30 mL/minute, reduce intravenous dose to 2 mg every 3–4 weeks and in bone metastasis, change oral dose to 50 mg once weekly
Ibuprofen see NSAIDs
Iferon Reduce dose; avoid if creatinine clearance less than 10 mL/minute
Ifofamide Avoid if serum creatinine concentration greater than 120 micromol/litre
Imatinib Max. starting dose 400 mg daily if creatinine clearance less than 60 mL/minute
Imidapril see ACE inhibitors; max. initial dose 2.5 mg daily if creatinine clearance 30–80 mL/minute; avoid if creatinine clearance less than 30 mL/minute
Imipenem [ingredient] see Primaxin®
Indapamide see Thiazides and Related Diuretics
Indometacin see NSAIDs; avoid if creatinine clearance less than 10 mL/minute
Indoramin Manufacturer advises caution
Inosine pranobex Manufacturer advises caution; metabolised to uric acid
Insulin May need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon alfa</td>
<td>Close monitoring required; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>Manufacturers advise caution and close monitoring in severe renal impairment</td>
</tr>
<tr>
<td>Interferon gamma-1b</td>
<td>Manufacturer advises caution if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>Manufacturer advises avoid— no information available</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>Avoid in acute renal failure</td>
</tr>
<tr>
<td>Isometheptene [ingredient]</td>
<td>see Midri®</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Max. 200 mg daily if creatinine clearance less than 10 mL/minute; peripheral neuropathy</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>see Nitrates</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>see Nitrates</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Reduce initial dose (e.g. 10 mg daily) and increase gradually up to 1 mg/kg daily as tolerated</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Risk of congestive heart failure; bioavailability of oral formulations possibly reduced; use intravenous infusion with caution if creatinine clearance 30–50 mL/minute (monitor renal function); avoid intravenous infusion if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Manufacturer advises caution if creatinine clearance less than 15 mL/minute</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Avoid oral solution due to propylene glycol content; use capsules and tablets with caution if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Ketoprotien</td>
<td>see NSAIDs; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>see NSAIDs; use lowest effective dose (max. 60 mg daily when given by intramuscular or intravenous injection); avoid if serum creatinine more than 160 micromol/litre</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Dose reduction may be required</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Manufacturer advises caution; max. 250 mg/daily if creatinine clearance is less than 30 mL/minute</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Reduce dose if creatinine clearance less than 50 mL/minute; consult product literature</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Manufacturer advises caution in renal failure; metabolite may accumulate</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Manufacturer advises caution in severe renal impairment—no information available</td>
</tr>
<tr>
<td>Leflunomide</td>
<td>Manufacturer advises avoid in moderate or severe impairment—no information available</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Starting dose 10 mg once daily if creatinine clearance 30–50 mL/minute; starting dose 15 mg on alternate days if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Reduce initial intravenous injection dose to 200 micrograms/kg and reduce subsequent infusion dose by 50–85% if creatinine clearance less than 60 mL/minute; but avoid or stop infusion if creatinine clearance less than 15 mL/minute (consult product literature)</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>Avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Manufacturer advises caution if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Max. 2 g daily if creatinine clearance 50–80 mL/minute; max. 1.5 g daily if creatinine clearance 30–50 mL/minute; max. 1 g daily if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>5 mg on alternate days if creatinine clearance 30–50 mL/minute; 5 mg every 3 days if creatinine clearance 10–30 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Usual initial dose then reduce subsequent doses (consult product literature) if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Levomepromazine (methotrimeprazine)</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Lidocaine</td>
<td>Caution if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Manufacturer advises metabolites may accumulate if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>see ACE inhibitors; max. initial doses 5–10 mg daily if creatinine clearance 30–80 mL/minute (max. 40 mg daily); 2.5–5 mg daily if creatinine clearance 10–30 mL/minute (max. 40 mg daily); 2.5 mg daily if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Lithium salts</td>
<td>Avoid if possible or reduce dose and monitor serum-lithium concentration carefully</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>Manufacturer advises avoid in severe impairment</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>Manufacturer advises caution in chronic renal impairment see Kaletra®</td>
</tr>
<tr>
<td>Lopinavir [ingredient]</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Losartan</td>
<td>Start with 25 mg once daily if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lomefamtrine [ingre-</td>
<td>see Riamet®</td>
</tr>
<tr>
<td>dient]</td>
<td></td>
</tr>
<tr>
<td>Lysemcycline</td>
<td>Avoid</td>
</tr>
<tr>
<td>Magnesium salts</td>
<td>Avoid or reduce dose; increased risk of toxicity; magnesium carbonate mixture and magnesium trisilicate mixture also have high sodium content</td>
</tr>
<tr>
<td>Malarone*</td>
<td>Avoid for malaria prophylaxis (and if possible for malaria treatment) if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>If creatinine clearance less than 80 mL/min, consult product literature</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>see NSAIDs; avoid if creatinine clearance less than 10 mL/min</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Midazolam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Midrin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Miglustat</td>
<td>Use with caution; renal function may deteriorate</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Meptazoln</td>
<td>Use with caution (avoid excessive doses)</td>
</tr>
<tr>
<td>Mephenamine</td>
<td>Avoid if creatinine clearance less than 10 mL/min—risk of hippurate crystalluria</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Meprapunine</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Increase dose interval to every 12 hours if creatinine clearance 26–50 mL/min; use half normal dose every 12 hours if creatinine clearance 10–25 mL/min; use half normal dose every 24 hours if creatinine clearance less than 10 mL/min</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Use with caution; avoid if creatinine clearance less than 20 mL/min</td>
</tr>
<tr>
<td>Metformin</td>
<td>see Metformin, p. 378</td>
</tr>
<tr>
<td>Methadone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Methenamine</td>
<td>Avoid if creatinine clearance less than 10 mL/min—risk of hippurate crystalluria</td>
</tr>
<tr>
<td>Methocarbamol</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Reduce dose; nephrotoxic and accumulates; avoid if creatinine clearance less than 20 mL/min</td>
</tr>
<tr>
<td>Methotrimeneprazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Methyldopa</td>
<td>Start with small dose; increased sensitivity to hypotensive and sedative effect</td>
</tr>
</tbody>
</table>

For adjusting drug doses in renal impairment, see Important on p. 801.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylaltrexone</td>
<td>If creatinine clearance less than 30 mL/min, reduce dose as follows: body-weight under 62 kg, 75 micrograms/kg on alternate days; body-weight 62–114 kg, 8 mg on alternate days; body-weight over 114 kg, 75 micrograms/kg on alternate days</td>
</tr>
<tr>
<td>Methyrsedide</td>
<td>Avoid</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Avoid or use small dose if creatinine clearance less than 10 mL/min; increased risk of extrapyramidal reactions</td>
</tr>
<tr>
<td>Metolazone</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Micafungin</td>
<td>Use with caution; consult product literature for details</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Minocycline</td>
<td>Use with caution (avoid excessive doses)</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>Clinical effect prolonged in end-stage renal failure—reduce dose according to response</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Use half normal dose if creatinine clearance less than 10 mL/min</td>
</tr>
<tr>
<td>Moexipril</td>
<td>see ACE inhibitors; initial dose 3.75 mg once daily if creatinine clearance less than 40 mL/min</td>
</tr>
<tr>
<td>Morphine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Moviprep®</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Max. single dose 200 micrograms and max. daily dose 400 micrograms if creatinine clearance 30–60 mL/min; avoid if creatinine clearance less than 30 mL/min</td>
</tr>
<tr>
<td>Nalbuphine</td>
<td>see NSAIDs; avoid if creatinine clearance less than 30 mL/min</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Increase dosage interval if creatinine clearance less than 50 mL/min</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Use with caution; avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Manufacturers advise caution</td>
</tr>
<tr>
<td>Naproxen</td>
<td>see NSAIDs; avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Max. 2.5 mg in 24 hours; avoid if creatinine clearance less than 15 mL/minute</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>For hypertension, initially 2.5 mg once daily, increased to 5 mg once daily if required; for heart failure, manufacturer advises avoid if serum creatinine greater than 250 micro mol/litre</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>No information available—manufacturer advises caution</td>
</tr>
<tr>
<td>Neomycin</td>
<td>Avoid; ototoxic; nephrotoxic</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>May need dose reduction</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Start with small dose</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Manufacturers advise caution in severe renal impairment</td>
</tr>
<tr>
<td>Nicoumalone</td>
<td>see Atenocoumarol</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Manufacturer advises caution with intravenous administration</td>
</tr>
<tr>
<td>Nitrates</td>
<td>Use with caution if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>see Anxiolitics and Hypnotics</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Avoid if creatinine clearance less than 60 mL/minute; ineffective because of inadequate urine concentrations</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>see Sodium Nitroprusside</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Use half normal dose if creatinine clearance 20–50 mL/minute; use one-quarter normal dose if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>Use half normal dose if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure; deterioration also reported after topical use; avoid if possible creatinine clearance less than 20 mL/minute; see also individual drugs</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>Usual initial dose, then use half normal dose if creatinine clearance 20–50 mL/minute; 100 mg every 24 hours if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Consider lower initial dose of 5 mg daily</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Max. 20 mg daily if creatinine clearance 20–60 mL/minute; avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olsalazine</td>
<td>Use with caution; manufacturer advises avoid if significant renal impairment</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Reduce doses or avoid; increased and prolonged effect; increased cerebral sensitivity</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Reduce dose if creatinine clearance 10–30 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Manufacturer advises avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Oxoanalogic</td>
<td>see Anxiolitics and Hypnotics</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Use half initial dose if creatinine clearance less than 30 mL/minute; increase according to response at intervals of at least 1 week see Pentoxifylline</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Manufacturer advises caution see Opioid Analgesics</td>
</tr>
<tr>
<td>Oxytetraycline</td>
<td>Avoid</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Initially 3 mg daily if creatinine clearance 30–80 mL/minute; initially 3 mg on alternate days if creatinine clearance 10–30 mL/minute; manufacturer advises avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Pamidronate disodium</td>
<td>see Disodium Pamidronate</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Manufacturer advises caution; prolonged duration of block</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Max oral dose 40 mg daily see Opioid Analgesics</td>
</tr>
<tr>
<td>Papaveretum</td>
<td>Increase infusion dose interval to every 6 hours if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Close monitoring required—reduce dose if necessary</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Parecoxib</td>
<td>see NSAIDs; manufacturer advises caution</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Reduce dose if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Peginterferon alfa</td>
<td>Close monitoring required—reduce dose if necessary</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Manufacturer advises avoid if creatinine clearance less than 45 mL/minute</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Reduce dose and monitor renal function or avoid (consult product literature)</td>
</tr>
<tr>
<td>Pentamidine</td>
<td>Reduce dose for pneumocystis pneumonia if creatinine clearance less than 10 mL/minute—consult product literature see Opioid Analgesics</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Pentoxifylline (oxpentifylline)</td>
<td>Reduce dose by 30–50% if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Pericyazine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Perindopril arginine</td>
<td>see ACE inhibitors; max. initial doses 2.5 mg daily if creatinine clearance 30–60 mL/minute; 2.5 mg on alternate days if creatinine clearance 15–30 mL/minute</td>
</tr>
<tr>
<td>Perindopril erbumine</td>
<td>see ACE inhibitors; max. initial doses 2 mg daily if creatinine clearance 30–60 mL/minute; 2 mg on alternate days if creatinine clearance 15–30 mL/minute</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pethidine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phenindione</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pholcodine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Picrocine [ingredient]</td>
<td>Avoid if creatinine clearance less than 30 mL/minute—risk of hypermagnesaemia</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Manufacturer advises caution with tablets</td>
</tr>
<tr>
<td>Pimozide</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pindolol</td>
<td>May adversely affect renal function in severe impairment—manufacturer advises avoid</td>
</tr>
<tr>
<td>Piperacillin [ingredient]</td>
<td>see Tazocin</td>
</tr>
<tr>
<td>Piperazine</td>
<td>Use with caution; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Pipotiazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Piracetam</td>
<td>Use two-thirds of normal dose if creatinine clearance 50–80 mL/minute; use one-third of normal dose in 2 divided doses if creatinine clearance 30–50 mL/minute; use one-sixth normal dose as a single dose if creatinine clearance 20–30 mL/minute; avoid if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Potassium salts</td>
<td>Close monitoring required—high risk of hyperkalaemia; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Potassium-sparing diuretics</td>
<td>Monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment); manufacturers advise avoid in severe renal impairment; see also Eplerenone</td>
</tr>
<tr>
<td>Povidone–iodine</td>
<td>Avoid regular application to inflamed or broken mucosa</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>In Parkinson’s disease, initially 88 micrograms twice daily if creatinine clearance 20–50 mL/minute (88 micrograms once daily if creatinine clearance less than 20 mL/minute); if renal function declines during treatment, reduce dose by the same percentage as the decline in creatinine clearance; in restless legs syndrome, reduce dose if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Start at lower end of dosage range if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Initially 500 micrograms daily in moderate to severe renal impairment; increased with caution</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Primaclin®</td>
<td>Reduce dose if creatinine clearance less than 70 mL/minute—consult product literature</td>
</tr>
<tr>
<td>Primidone</td>
<td>see Phenobarbital</td>
</tr>
<tr>
<td>Probenecid</td>
<td>Avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Use with caution; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Proguanil</td>
<td>100 mg once daily if creatinine clearance 20–60 mL/minute; 50 mg on alternate days if creatinine clearance 10–20 mL/minute; 50 mg once weekly if creatinine clearance less than 10 mL/minute (increased risk of hematological toxicity)</td>
</tr>
<tr>
<td>Promazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Propiverine</td>
<td>Doses above 30 mg daily should be used with caution if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Propofol</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Propranolol</td>
<td>Manufacturer advises caution—dose reduction may be required</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Use three-quarters normal dose if creatinine clearance 10–50 mL/minute; use half normal dose if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------</td>
<td>---------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Manufacturer advises caution in moderate to severe renal impairment</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Reduce dose; excreted by kidney</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>For immediate-release tablets, initially 25 mg daily, increased daily in steps of 25–50 mg; for modified-release tablets, initially 50 mg daily, increased daily in steps of 50 mg</td>
</tr>
<tr>
<td>Quinagolide</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Quinapril</td>
<td>see ACE inhibitors; max. initial dose 2.5 mg once daily if creatinine clearance less than 40 mL/minute</td>
</tr>
<tr>
<td>Quinine</td>
<td>For treatment of falciparum malaria, reduce parenteral maintenance dose to 5–7 mg/kg of salt</td>
</tr>
<tr>
<td>Raloxifene</td>
<td>Manufacturer advises caution in mild to moderate renal impairment; avoid in severe renal impairment</td>
</tr>
<tr>
<td>Ralitrexed</td>
<td>Reduce dose and increase dosing interval if creatinine clearance less than 65 mL/minute (consult product literature); avoid if creatinine clearance less than 25 mL/minute</td>
</tr>
<tr>
<td>Ramipril</td>
<td>see ACE inhibitors; max. initial dose 1.25 mg once daily (do not exceed 5 mg once daily) if creatinine clearance less than 30 mL/minute; max. initial dose 1.25 mg once daily (do not exceed 2.5 mg once daily) if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Use half normal dose if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Initial dose 2 mg twice daily, increased according to tolerance</td>
</tr>
<tr>
<td>Riamet®</td>
<td>Manufacturer advises caution in severe renal impairment—monitor ECG and plasma potassium concentration</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Plasma-ribavirin concentration increased; manufacturer advises avoid oral ribavirin unless essential if creatinine clearance less than 50 mL/minute—monitor haemoglobin concentration closely</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Use half normal dose if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Riluzole</td>
<td>No information available—manufacturer advises avoid</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Manufacturer advises avoid in severe impairment—no information available</td>
</tr>
<tr>
<td>Risedronate sodium</td>
<td>Manufacturer advises avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Manufacturer advises initial oral dose of 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily; if an oral dose of at least 2 mg daily tolerated, 25 mg as a depot injection can be given every 2 weeks</td>
</tr>
<tr>
<td>Ritonavir [ingredient]</td>
<td>see Kaletra®</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td></td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>Reduce dose to 5 mg if creatinine clearance 10–60 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Reduce maintenance dose; prolonged paralysis</td>
</tr>
<tr>
<td>Roxivorenone</td>
<td>Manufacturers advise avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Manufacturer advises caution in severe renal impairment</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Initially 5 mg once daily and avoid dose of 40 mg daily if creatinine clearance less than 60 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>For erectile dysfunction initial dose 25 mg if creatinine clearance less than 30 mL/minute; for pulmonary hypertension reduce to 20 mg twice daily if usual dose not tolerated</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Doses above 10 mg daily should be used with caution if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Manufacturer advises avoid if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Sodium aurothiomalate</td>
<td>Caution in mild to moderate renal impairment; avoid in severe renal impairment</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Sodium bicarbonate</td>
<td>Avoid; specialised role in some forms of renal disease, see section 9.2.1.3</td>
</tr>
<tr>
<td>Sodium citrate</td>
<td>Use with caution, see also Citrates</td>
</tr>
<tr>
<td>Sodium clodronate</td>
<td>Use half normal oral dose if creatinine clearance 10–30 mL/minute; use three quarters of normal injection dose if creatinine clearance 50–80 mL/minute, use half if creatinine clearance 10–50 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Metabolite may accumulate; avoid prolonged use</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>Caution—Xyrem® oral solution contains 2.98 mmol Na+ /mL</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Max. 5 mg daily if creatinine clearance less than 30 mL/minute</td>
</tr>
</tbody>
</table>

For adjusting drug doses in renal impairment, see Important on p. 801.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solpadol®</td>
<td>Avoid effervescent tablets; contains 16.9 mmol sodium per tablet; see also Opioid Analgesics</td>
</tr>
<tr>
<td>Sotalol</td>
<td>Use half normal dose if creatinine clearance 30–60 mL/minute; use one-quarter normal dose if creatinine clearance 10–30 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>see Potassium-sparing Diuretics</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Use half normal dose every 12 hours if creatinine clearance 25–50 mL/minute; use half normal dose every 24 hours if creatinine clearance less than 25 mL/minute</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Manufacturer advises no dose adjustment required if creatinine clearance 30–70 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Sucralfate</td>
<td>Use with caution; aluminium is absorbed and may accumulate</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>Avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>Use with caution; avoid if creatinine clearance less than 10 mL/minute; high risk of crystalluria</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Risk of toxicity including crystalluria—ensure high fluid intake; avoid if creatinine clearance less than 15 mL/minute</td>
</tr>
<tr>
<td>Sulfapyrazine</td>
<td>Reduce dose; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Sulindac</td>
<td>see NSAIDs; reduce dose; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Ensure high fluid intake; rashes and blood disorders; crystalluria a risk; see also individual drugs</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>see under individual drugs</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Reduce dose; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Tacalcitol</td>
<td>Monitor serum calcium concentration</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>Max. dose 10 mg if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Tamsulosin</td>
<td>Manufacturer advises caution if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Tazobactam [ingredi-ent]</td>
<td>Max. 4.5 g every 8 hours if creatinine clearance 20–80 mL/minute; max. 4.5 g every 12 hours if creatinine clearance less than 20 mL/minute; child under 12 years: Consult product literature</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>On day 4 use half normal dose if creatinine clearance is 40–60 mL/minute and use one-third normal dose if creatinine clearance is less than 40 mL/minute</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Use normal dose every 48 hours if creatinine clearance 30–49 mL/minute; use normal dose every 72 hours if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Manufacturer advises avoid if possible if creatinine clearance less than 30 mL/minute—if no alternative, use alternating daily doses of 800 mg and 400 mg, starting with 800 mg dose</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Initially 20 mg once daily if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Temazepam</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Temocillin</td>
<td>Use normal dose every 24 hours if creatinine clearance 10–30 mL/minute; use normal dose every 48 hours if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>Manufacturer advises caution in severe renal impairment—no information available</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Monitor renal function interrupt treatment if further deterioration; 245 mg every 2 days if creatinine clearance 30–50 mL/minute; 245 mg every 3–4 days if creatinine clearance 10–30 mL/minute; see also Atripla® and Truvada®</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Use half normal dose if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Avoid tetracyclines except doxycycline or minocycline which may be used cautiously (avoid excessive doses)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Manufacturer advises caution in severe renal impairment—no information available</td>
</tr>
<tr>
<td>Thiazides and related diuretics</td>
<td>Avoid if creatinine clearance less than 30 mL/minute—ineffective (metolazone remains effective but risk of excessive diuresis)</td>
</tr>
<tr>
<td>Tiaprofenic acid</td>
<td>see NSAIDs; reduce dose; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Ticarcillin [ingredient]</td>
<td>see <em>Timentin</em>®</td>
</tr>
<tr>
<td>Tiludronic acid</td>
<td>Manufacturer advises caution if creatinine clearance 30–90 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td><em>Timentin</em>®</td>
<td>Reduce dose to 3.2 g every eight hours if creatinine clearance 30–60 mL/minute; 1.6 g every eight hours if creatinine clearance 10–30 mL/minute; 1.6 g every twelve hours if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Timolol</td>
<td>Manufacturer advises caution—dose reduction may be required</td>
</tr>
<tr>
<td><em>Tinzaparin</em></td>
<td>Risk of bleeding may be increased—dose reduction, and monitoring of anti-Factor Xa may be required; use with caution in elderly and avoid if age over 90 years; unfractionated heparin may be preferable</td>
</tr>
<tr>
<td>Tioguanine</td>
<td>Reduce dose</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Plasma-tiotropium concentration raised; manufacturer advises caution if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Use half normal dose if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Initially 2 mg once daily if creatinine clearance less than 25 mL/minute; increase once-daily dose gradually according to response before increasing frequency</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Avoid if possible; if no alternative reduce dose and monitor closely</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Caution if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Reduce dose to 1 mg twice daily if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Longer time to steady-state plasma concentrations</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Reduce dose; avoid infusion if creatinine clearance less than 20 mL/minute; avoid oral route if creatinine clearance less than 60 mL/minute</td>
</tr>
<tr>
<td>Torasemide</td>
<td>May need high doses</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>see ACE Inhibitors; max. 2 mg daily if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>Reduce dose—consult product literature for details</td>
</tr>
<tr>
<td>Tretinoin (oral)</td>
<td>Reduce dose to 25 mg/m</td>
</tr>
<tr>
<td>Triamterene</td>
<td>see Potassium-sparing Diuretics</td>
</tr>
<tr>
<td>Tribavirin</td>
<td>see Ribavirin</td>
</tr>
<tr>
<td>Tricloside</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Triluoperazine</td>
<td>see Alimemazine</td>
</tr>
<tr>
<td>Trimetoprim</td>
<td>Use half normal dose after 3 days if creatinine clearance 15–30 mL/minute; use half normal dose if creatinine clearance less than 15 mL/minute (monitor plasma-trimetoprim concentration if creatinine clearance less than 10 mL/minute)</td>
</tr>
<tr>
<td>Tripotassium dicitratobismuthate</td>
<td>Avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Tropium</td>
<td>Reduce dose to 20 mg once daily or 20 mg on alternate days if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td><em>Truvada</em>®</td>
<td>Monitor renal function; use normal dose every 48 hours if creatinine clearance 30–50 mL/minute; avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Tylox*</td>
<td>Manufacturer advises caution in severe impairment; effervescent tablets contain 13.6 mmol sodium per tablet; see also <em>Opioid Analgesics</em></td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>For herpes zoster, 1 g every 12 hours if creatinine clearance 15–30 mL/minute (every 24 hours if creatinine clearance less than 15 mL/minute); for treatment of herpes simplex, 500 mg every 24 hours if creatinine clearance less than 15 mL/minute; for suppression of herpes simplex, 250 mg (500 mg in immunocompromised) every 24 hours if creatinine clearance less than 15 mL/minute; for reduction of genital herpes transmission, 250 mg every 24 hours if creatinine clearance less than 15 mL/minute; reduce dose according to creatinine clearance for cytomegalovirus prophylaxis following renal transplantation (consult product literature)</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>Reduce dose; consult product literature</td>
</tr>
<tr>
<td>Valproate</td>
<td>Reduce dose; adjust dosage according to free serum valproic acid concentration</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Initially 40 mg once daily if creatinine clearance less than 20 mL/minute</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Reduce dose—monitor plasma-vancomycin concentration and renal function regularly</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>Initial dose 5 mg if creatinine clearance less than 30 mL/minute; avoid in endstage renal disease requiring dialysis</td>
</tr>
<tr>
<td>Varenicline</td>
<td>If creatinine clearance less than 30 mL/minute initial dose 500 micrograms once daily, increased after 3 days to 1 mg once daily</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Use half normal dose if creatinine clearance 10–30 mL/minute; avoid if creatinine clearance less than 10 mL/minute</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Manufacturer advises caution if creatinine clearance less than 60 mL/minute: consider dose reduction; monitor for sedation or confusion</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Manufacturer advises avoid if creatinine clearance less than 50 mL/minute</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Intravenous vehicle may accumulate if creatinine clearance less than 50 mL/minute—manufacturer advises use intravenous infusion only if potential benefit outweighs risk, and monitor renal function; alternatively, use tablets or oral suspension (no dose adjustment required)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td><em>Yasmin</em>®</td>
<td>Manufacturer advises avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td><em>Yaz</em>®</td>
<td>Manufacturer advises avoid if creatinine clearance less than 30 mL/minute</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises caution in moderate to severe impairment</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Reduce oral dose to 300–400 mg daily in divided doses or intravenous dose to 1 mg/kg 3–4 times daily if creatinine clearance less than 10 mL/minute</td>
</tr>
</tbody>
</table>

For adjusting drug doses in renal impairment, see Important on p. 801.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zoledronic acid</td>
<td>Avoid if serum creatinine above 400 micromol/litre in tumour-induced hypercalcaemia; in cancer and bone metastases, if creatinine clearance 50–60 mL/minute reduce dose to 3.5 mg every 3–4 weeks, if creatinine clearance 40–50 mL/minute reduce dose to 3.3 mg every 3–4 weeks, if creatinine clearance 30–40 mL/minute reduce dose to 3 mg every 3–4 weeks, and avoid if creatinine clearance less than 30 mL/minute (or if serum creatinine greater than 265 micromol/litre); if renal function deteriorates in patients with bone metastases, withhold dose until serum creatinine returns to within 10% of baseline value; avoid in Paget’s disease, treatment of postmenopausal osteoporosis and osteoporosis in men if creatinine clearance less than 35 mL/minute</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Initially increase dose at 2-week intervals; discontinue if renal function deteriorates</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>see Anxiolytics and Hypnotics</td>
</tr>
<tr>
<td>Zotepine</td>
<td>Initial dose 25 mg twice daily, increased gradually according to response (max. 75 mg twice daily)</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>see Antipsychotics</td>
</tr>
</tbody>
</table>
Drugs can have harmful effects on the embryo or fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a woman of childbearing age or for men trying to father a child.

During the first trimester drugs can produce congenital malformations (teratogenesis), and the period of greatest risk is from the third to the eleventh week of pregnancy.

During the second and third trimesters drugs can affect the growth or functional development of the fetus, or they can have toxic effects on fetal tissues.

Drugs given shortly before term or during labour can have adverse effects on labour or on the neonate after delivery.

Not all the damaging effects of intrauterine exposure to drugs are obvious at birth, some may only manifest later in life. Such late-onset effects include malignancy, e.g. adenocarcinoma of the vagina after puberty in females exposed to diethylstilbestrol in the womb, and adverse effects on intellectual, social, and functional development.

The following list includes drugs which:

- may have harmful effects in pregnancy and indicates the trimester of risk
- are not known to be harmful in pregnancy

The list is based on human data, but information from animal studies has been included for some drugs when its omission might be misleading.

Drugs should be prescribed in pregnancy only if the expected benefit to the mother is thought to be greater than the risk to the fetus, and all drugs should be avoided if possible during the first trimester. Drugs which have been extensively used in pregnancy and appear to be usually safe should be prescribed in preference to new or untried drugs; and the smallest effective dose should be used.

Few drugs have been shown conclusively to be teratogenic in man, but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available when there is a known risk of certain defects.

Absence of a drug from the list does not imply safety.

It should be noted that the BNF provides independent advice and may not always agree with the product literature.

Information on drugs and pregnancy is also available from the National Teratology Information Service Telephone: (0191) 232 1525 (0191) 282 5944 (out of hours emergency only) www.nyrdc.nhs.uk/Services/teratology/teratology.html

### Table of drugs to be avoided or used with caution in pregnancy

Products introduced or amended since publication of BNF No. 56 (September 2008) are underlined.

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Manufacturer advises avoid (toxicity in animal studies); see also p. 334</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Manufacturer advises avoid unless essential—no information available; effective contraception required during treatment and for 14 weeks after last dose</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>ACE inhibitors (1, 2, 3)</td>
<td>Avoid; may adversely affect fetal and neonatal blood pressure control and renal function; also possible skull defects and oligohydramnios; toxicity in animal studies</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Acemetacin</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Acenocoumarol (nicoumalone)</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Acetazolamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>Not known to be harmful—manufacturers advise use only when potential benefit outweighs risk; limited absorption from topical aciclovir preparations</td>
</tr>
<tr>
<td>Acipimox</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Acitretin (1, 2, 3)</td>
<td>Teratogenic; effective contraception must be used for at least 1 month before treatment, during treatment, and for at least 3 years after stopping (oral progestogen-only contraceptives not considered effective)</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Avoid; manufacturer advises adequate contraception during and for at least 5 months after last dose</td>
</tr>
<tr>
<td>Adapalene</td>
<td>Manufacturer advises teratogenicity in animal studies and recommends effective contraception during treatment</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk; effective contraception required during treatment</td>
</tr>
<tr>
<td>Agalsidase</td>
<td>Use with caution</td>
</tr>
<tr>
<td>Alcohol (1, 2)</td>
<td>Regular daily drinking is teratogenic (fetal alcohol syndrome) and may cause growth restriction; occasional single drinks are probably safe</td>
</tr>
<tr>
<td>Alpha-blockers, post-synaptic (3)</td>
<td>Withdrawal syndrome may occur in babies of alcoholic mothers</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Avoid; manufacturer advises effective contraception during and for 6 months after treatment in men or women</td>
</tr>
<tr>
<td>Alendronic acid</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Alfacalcidol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Alglucosidase alfa</td>
<td>Manufacturer advises avoid unless essential—no information available</td>
</tr>
<tr>
<td>Alimemazine (trimethazine)</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Manufacturer advises avoid—no information available; other drugs acting on the renin-angiotensin system have been associated with fetal malformations and neonatal death</td>
</tr>
<tr>
<td>Alitretinoin (1, 2, 3)</td>
<td>Teratogenic; effective contraception must be used for at least 1 month before treatment, during treatment, and for 1 month after stopping; see also Pregnancy Prevention, p. 630</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Toxicity not reported; manufacturer advises use only if no safer alternative and disease carries risk for mother or child</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>see 5HT Agonists</td>
</tr>
<tr>
<td>Alpha-blockers, post-synaptic</td>
<td>No evidence of teratogenicity; manufacturers advise use only when potential benefit outweighs risk</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Alprostadil (urethral application only)</td>
<td>Manufacturer advises barrier contraception if partner pregnant</td>
</tr>
<tr>
<td>Alteplase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Avoid; toxicity in animal studies</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Avoid (teratogenic in animal studies); exclude pregnancy before treatment and ensure effective contraception during treatment; monthly pregnancy tests advised</td>
</tr>
<tr>
<td>Amfebutamone</td>
<td>see Bupropion</td>
</tr>
<tr>
<td>Amikacin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Amiloride</td>
<td>see Diuretics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (2, 3)</td>
<td>Auditory or vestibular nerve damage: risk greatest with streptomycin; probably very small with gentamicin and tobramycin, but avoid unless essential (if given, serum-aminoglycoside concentration monitoring essential)</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>see Theophylline</td>
</tr>
<tr>
<td>Amiodarone (2, 3)</td>
<td>Possible risk of neonatal goitre; use only if no alternative</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Amlopidine</td>
<td>No information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension</td>
</tr>
<tr>
<td>Amobarbital</td>
<td>see Barbiturates</td>
</tr>
<tr>
<td>Amorolfine</td>
<td>Systemic absorption very low, but manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>Not known to be harmful but manufacturers advise avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Anapplestics, general (3)</td>
<td>Avoid (teratogenic and toxic in animal studies); may reduce fertility; see also section 8.1</td>
</tr>
<tr>
<td>Anaesthetic, local (3)</td>
<td>Masculinisation of female fetus</td>
</tr>
<tr>
<td>Analgesics</td>
<td>Depress neonatal respiration; for maintenance of anaesthesia, doses of propofol should not exceed 6 mg/kg/hour; dose of thiopental should not exceed 250 mg</td>
</tr>
<tr>
<td>Anabolic steroids (1, 2, 3)</td>
<td>With large doses, neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block; neonatal methaemoglobinemia with prilocaine and procaine; use lower doses of bupivacaine for intrathecal use during late pregnancy; see also Levobupivacaine and Ropivacaine</td>
</tr>
<tr>
<td>Anagrelide</td>
<td>Manufacturer advises avoid (toxicity in animal studies)</td>
</tr>
<tr>
<td>Anakinra</td>
<td>Manufacturer advises avoid; effective contraception must be used during treatment</td>
</tr>
<tr>
<td>Analgesics</td>
<td>see Opioid Analgesics, Nefopam, NSAIDs, and Paracetamol</td>
</tr>
<tr>
<td>Androgens (1, 2, 3)</td>
<td>Masculinisation of female fetus</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Anticoagulants, oral (1, 2, 3)</td>
<td>Congenital malformations; fetal and neonatal haemorrhage; see also section 2.8.2; see also Dabigatran Etxelilate and Rivaroxaban</td>
</tr>
<tr>
<td>Antidepressants, MAOI (1, 2, 3)</td>
<td>No evidence of harm but manufacturers advise avoid unless compelling reasons</td>
</tr>
<tr>
<td>Antidepressants, SSRI</td>
<td>Manufacturers advise use only if potential benefit outweighs risk; risk of neonatal withdrawal, particularly with fluoxetine and paroxetine; toxicity in animal studies with escitalopram and paroxetine</td>
</tr>
<tr>
<td>Antidepressants, tricyclic (and related) (3)</td>
<td>Tachycardia, irritability, and muscle spasms in neonate reported with imipramine</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Benefit of treatment outweighs risk to fetus; risk of teratogenicity greater if more than one drug used; important: see also Carbamazepine, Ethosuximide, Gabapentin, Lamotrigine, Levetiracetam, Oxcarbazepine, Phenobarbital, Phenytoin, Pregabalin, Primidone, Rufinamide, Topiramate, Valproate, Vigabatrin, Zonisamide, and p. 250</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>No evidence of teratogenicity; embryotoxicity in animal studies; see also individual drugs and p. 353 and p. 355</td>
</tr>
<tr>
<td>Antimalarials (1, 3)</td>
<td>Benefit of prophylaxis and treatment in malaria outweighs risk; important: see also individual drugs and p. 353 and p. 355</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>See also Amisulpride, Clozapine, Fluoxetine, Olanzapine, Paliperidone, Quetiapine, Risperidone, Sertindole, Sulpiride, Zotepine</td>
</tr>
<tr>
<td>Antithymocyte immunoglobulin</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Apomorphine (3)</td>
<td>Extrapyramidal effects in neonate occasionally reported</td>
</tr>
<tr>
<td>Azathiopepin</td>
<td>Caution</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>see Neurokinin Receptor Antagonists</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>see p. 486</td>
</tr>
<tr>
<td>Azatropine</td>
<td>Manufacturer advises use only if adequate alternatives not available</td>
</tr>
<tr>
<td>Azelastine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies)</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Manufacturer advises use—no information available</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Bambuterol</td>
<td>see section 3.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic trioxide</td>
<td>Avoid (teratogenic and embryotoxic in animal studies); manufacturer advises effective contraception during treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Artemether</td>
<td>see Riamet®</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>Impaired platelet function and risk of haemorrhage; delayed onset and increased duration of labour with increased blood loss; avoid analgesic doses if possible in last few weeks (low doses probably not harmful); with high doses, closure of fetal ductus arteriosus in utero and possibly persistent pulmonary hypertension of newborn; kernicterus in jaundiced neonates</td>
</tr>
<tr>
<td>Atenolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>For use in premature labour see section 7.1.3</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Atracurium</td>
<td>Does not cross placenta in significant amounts but manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Atrazine</td>
<td>Not known to be harmful; manufacturer advises caution</td>
</tr>
<tr>
<td>Auranofin</td>
<td>Manufacturer advises avoid (effective contraception should be used during and for at least 6 months after treatment) but limited data suggests usually not necessary to withdraw if condition well controlled—consider reducing dose and frequency</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>see NSAIIDs</td>
</tr>
<tr>
<td>Azuthiopepin</td>
<td>see p. 250</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Manufacturer advises avoid (toxicity in animal studies)</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>see also p. 250</td>
</tr>
<tr>
<td>Baclofen</td>
<td>see section 3.1</td>
</tr>
<tr>
<td>Bambuterol</td>
<td>see section 3.1</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Barbiturates (1, 2, 3)</td>
<td>Fetal abnormalities reported Withdrawal effects in neonate; respiratory depression in neonate if used during labour; see also Phenobarbital</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Avoid; adequate contraception must be used during treatment and for 8 weeks after last dose</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Beniparil</td>
<td>Manufacturer advises avoid unless essential—no information available</td>
</tr>
<tr>
<td>Bendrofluazide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Bendrofluamide (bendrofluazide)</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Benperidol</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Avoid regular use (risk of neonatal withdrawal symptoms); use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothermia, hypotonia and respiratory depression)</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>May cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension; see also section 2.5</td>
</tr>
<tr>
<td>Betaine</td>
<td>Manufacturer advises avoid unless essential—limited information available</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Bethanechol</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Manufacturer advises avoid—toxicity in animal studies; effective contraception required during and for at least 6 months after treatment in women (see also section 8.1)</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>Avoid; manufacturer advises effective contraception during and for at least 1 month after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Bezafibrate</td>
<td>see Fibrates</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Manufacturers advise avoid</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>Avoid (teratogenic and carcinogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Manufacturer advises effective contraception required during and for 3 months after treatment in men or women— toxicity in animal studies; see also section 8.1</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Avoid (teratogenic in animal studies); effective contraception required during and for at least 3 months after administration (hormonal contraception not considered effective); monthly pregnancy tests advised</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Manufacturers advise avoid unless essential—toxicity in animal studies</td>
</tr>
<tr>
<td>Brinzolamide</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Buclizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Budesonide</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Bupicavaine</td>
<td>see Anaesthetics, Local</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Buserelin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Buspirone</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Busulfan</td>
<td>Avoid (teratogenic in animals); manufacturers advise effective contraception during and for 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>No evidence of harm; manufacturer advises discontinuation one month before intended conception and avoidance during pregnancy; see also section 8.7.1</td>
</tr>
<tr>
<td>Calcipotriol</td>
<td>Manufacturer advises avoid if possible; see also Vitamin D</td>
</tr>
<tr>
<td>Calcitonin (salmon) (salcatonin)</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies)</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Calcium folinate</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Calcium levofolinate</td>
<td>see Calcium Folinate</td>
</tr>
<tr>
<td>Candesartan</td>
<td>As for ACE Inhibitors</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Avoid (teratogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Capremycin</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—teratogenic in animal studies</td>
</tr>
<tr>
<td>Captopril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Risk of teratogenesis including increased risk of neural tube defects; see also Antiepileptics</td>
</tr>
<tr>
<td>Carbimazole</td>
<td>Neonatal goitre and hypothyroidism; has been associated with congenital defects including aplasia cutis of the neonate</td>
</tr>
<tr>
<td>Carbocisteine (1)</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>Avoid (teratogenic and embryotoxic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Carglumic acid</td>
<td>Manufacturer advises avoid unless essential—no information available</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Carmustine</td>
<td>Avoid (teratogenic and embryotoxic in animals); manufacturer advises effective contraception during treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Carnitine</td>
<td>Appropriate to use; no evidence of teratogenicity in animal studies</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Manufacturer advises avoid unless essential—toxicity in animal studies</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefradine</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Manufacturer advises avoid (teratogenic in animal studies); see also NSAIDs</td>
</tr>
<tr>
<td>Celiprolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Cetorelix</td>
<td>Manufacturer advises avoid in confirmed pregnancy</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Avoid</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Avoid; manufacturer advises effective contraception during treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Chloramphenicol (3)</td>
<td>Neonatal ‘grey’ syndrome</td>
</tr>
<tr>
<td>Chlor Diazepoxide</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>see Antimalarials</td>
</tr>
<tr>
<td>Chlorphenamine (chlorpheniramine)</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Chlorpheniramine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Chloralidone</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Ciclofenide</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>see p. 486</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Avoid (toxicity in animal studies); effective contraception required during and for 1 month after treatment; also men should avoid fathering a child during and for 3 months after treatment</td>
</tr>
<tr>
<td>Cilastatin [ingredient]</td>
<td>see Primaxin®</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Cilostavol</td>
<td>Avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Cinnarizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>see Fibrates</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>see Quinolones</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>Avoid (teratogenic and toxic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Citalopram</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Cladribine</td>
<td>Avoid (teratogenic in animal studies); manufacturer advises that men should not father children during and for 6 months after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Clavulanic acid [ingredient]</td>
<td>see Co-amoxiclav, Timentin®</td>
</tr>
<tr>
<td>Clemastine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Clofazimide</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Clofazimide</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Clodronate sodium</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Cloraphine</td>
<td>Manufacturer advises avoid (teratogenic in animal studies); see also NSAIDs</td>
</tr>
<tr>
<td>Clomethiazole</td>
<td>Avoid if possible—especially during first and third trimesters</td>
</tr>
<tr>
<td>Clomifene</td>
<td>Possible effects on fetal development</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Clozaril</td>
<td>May lower fetal heart rate, but risk should be balanced against risk of uncontrolled maternal hypertension; avoid intravenous injection</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Clotrimazole</td>
<td>Minimal absorption from skin and vagina; not known to be harmful; see also section 7.2.2</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Codeine</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Co-beneldopa</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Co-careldopa</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Co-cyprindol (1, 2, 3)</td>
<td>Feminisation of male fetus (due to cyproterone)</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Colchithromazine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Use with caution—drug not absorbed but may cause fat-soluble vitamin deficiency on prolonged use</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Use with caution—drug not absorbed but may cause fat-soluble vitamin deficiency on prolonged use</td>
</tr>
<tr>
<td>Colestyramine</td>
<td>Use with caution—drug not absorbed but may cause fat-soluble vitamin deficiency on prolonged use</td>
</tr>
<tr>
<td>Colistin (2, 3)</td>
<td>Avoid—possible risk of fetal toxicity</td>
</tr>
<tr>
<td>Contraceptives, oral</td>
<td>Epidemiological evidence suggests no harmful effects on fetus</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Benefit of treatment, e.g. in asthma, outweighs risk (see also CSM advice, section 6.3.2); risk of intra-uterine growth restriction on prolonged or repeated systemic treatment; corticosteroid cover required by mother during labour; monitor closely if fluid retention</td>
</tr>
<tr>
<td>Co-trimoxazole (1)</td>
<td>Teratogenic risk (trimethoprim a folate antagonist)</td>
</tr>
<tr>
<td>(3)</td>
<td>Neonatal haemolysis and methaemoglobinemia; fear of increased risk of kernicterus in neonates appears to be unfounded</td>
</tr>
<tr>
<td>Crisantaspase</td>
<td>Avoid; see also section 8.1</td>
</tr>
<tr>
<td>Cromoglicate</td>
<td>see Sodium Cromoglicate</td>
</tr>
<tr>
<td>Cyclizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Cyclopenthiazide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Avoid (manufacturer advises effective contraception during and for at least 3 months after treatment in men or women); see also section 8.1</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—crosses the placenta</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>see p. 486</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Cyproterone [ingredient]</td>
<td>see Co-cyprindiol</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Avoid (teratogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Dabigatran etexilate</td>
<td>Manufacturer advises avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>Avoid (carcinogenic and teratogenic in animal studies); ensure effective contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Daclomycine</td>
<td>Avoid (teratogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Dalfopristin [ingredient]</td>
<td>see Synercid®</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Danaparoid</td>
<td>Limited information available but not known to be harmful—manufacturer advises avoid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danazol (1, 2, 3)</td>
<td>Avoid; has weak androgenic effects and virilisation of female fetus reported</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Use only for malignant hyperthermia if potential benefit outweighs risk; avoid use in chronic spasticity—embryotoxic in animal studies</td>
</tr>
<tr>
<td>Dantron (danthron)</td>
<td>see Co-danthramer, Co-danthrusate</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Folic acid 5 mg daily should be given to mother throughout pregnancy</td>
</tr>
<tr>
<td>(3)</td>
<td>Neonatal haemolysis and methaemoglobinemia reported</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>No evidence of harm in animal studies—manufacturer advises caution</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>Manufacturer advises avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies; effective contraception required during treatment</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>Avoid (teratogenic and carcinogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Manufacturer advises avoid before intended conception and during pregnancy—teratogenic and embryotoxic in animal studies; contraception advised in women of child-bearing potential</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Denclohexycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Desferrioxamine (3)</td>
<td>Teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Desflurane</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Desloratadine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Desmopressin (3)</td>
<td>Small oxytocic effect in third trimester; increased risk of pre-eclampsia</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Manufacturer advises avoid (retrospective evidence of uncertain significance suggesting possible embryotoxicity)</td>
</tr>
<tr>
<td>Danazol</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Danibuprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Dexrazoxane</td>
<td>Manufacturer advises avoid unless essential; ensure effective contraception during and for 3 months after treatment in men and women</td>
</tr>
<tr>
<td>Dextran</td>
<td>Avoid—reports of anaphylaxis in mother causing fetal anoxia, neurological damage and death</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Diazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Diazoxide (2, 3)</td>
<td>Prolonged use may produce alopecia and impaired glucose tolerance in neonate; inhibits uterine activity during labour</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Diethylstilbestrol (1)</td>
<td>High doses associated with vaginal carcinoma, urogenital abnormalities, and reduced fertility in female offspring; increased risk of hypospadias in male offspring</td>
</tr>
<tr>
<td>Diflucortolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Digoxin</td>
<td>May need dosage adjustment</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Dihydractylosdrol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Diloxanide</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Diltiazem</td>
<td>Avoid</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Diphenoxylate</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Dipipanone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Disodium etidronate</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Disodium pamidronate</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Disopyramide (3)</td>
<td>May induce labour</td>
</tr>
<tr>
<td>Distigmine</td>
<td>Manufacturer advises avoid (may stimulate uterine contractions)</td>
</tr>
<tr>
<td>Disulfiram (1)</td>
<td>High concentrations of acetaldehyde which occur in presence of alcohol may be teratogenic</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Not used to treat gestational hypertension; see also Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Dobutamine</td>
<td>No information available</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Avoid (toxicity and reduced fertility in animal studies); manufacturer advises effective contraception during and for at least 3 months after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>Not known to be harmful—manufacturer advises caution</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolasetron</td>
<td>Not known to be harmful but manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Dopexamine</td>
<td>No information available</td>
</tr>
<tr>
<td>Doripenem</td>
<td>Manufacturer advises avoid unless essential—no information available</td>
</tr>
<tr>
<td>Domase alfa</td>
<td>No evidence of teratogenicity; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Dosulepin (dothiepin)</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Dothiepin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Doxazosin</td>
<td>see Alpha-blockers, Post-synaptic</td>
</tr>
<tr>
<td>Doxepin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Avoid (teratogenic and toxic in animal studies); manufacturer of liposomal product advises effective contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Drotrecogin alfa (activated)</td>
<td>Manufacturer advises avoid unless benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Duloxetine</td>
<td>Toxicity in animal studies—manufacturer advises avoid in patients with stress urinary incontinence and use only if potential benefit outweighs risk in depression; risk of neonatal withdrawal symptoms if used near term</td>
</tr>
<tr>
<td>Dutasteride (1, 2, 3)</td>
<td>Avoid unprotected intercourse (see section 6.4.2). May cause feminisation of male fetus</td>
</tr>
<tr>
<td>Dydrogesterone</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Econazole</td>
<td>Minimal absorption from skin and vagina; not known to be harmful; see also section 7.2.2</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>No information available—use only if potential benefit outweighs risk; human IgG antibodies known to cross placenta; manufacturer advises effective contraception during and for 5 months after treatment</td>
</tr>
<tr>
<td>Edrophonium</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Efalizumab</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Manufacturer advises avoid unless no alternative available</td>
</tr>
<tr>
<td>Efomithine</td>
<td>Toxicity in animal studies—manufacturer advises avoid see SHT Agonists</td>
</tr>
<tr>
<td>Eileptiutan</td>
<td>No information available—manufacturer advises use only if essential</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Enalapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Enoximone</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Entacapone</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk; effective contraception required during treatment</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Increased fetal heart rate reported with parenteral ephedrine</td>
</tr>
<tr>
<td>Epinastine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Epilubricin</td>
<td>Avoid (carcinogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Epoetin</td>
<td>No evidence of harm; benefits probably outweigh risk of anaemia and of transfusion in pregnancy</td>
</tr>
<tr>
<td>Epoprostenol</td>
<td>Manufacturer advises use with caution—no information available</td>
</tr>
<tr>
<td>Eprosartan</td>
<td>As for ACE Inhibitors</td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Erdosteine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Ergocalciferol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Ergotamine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>(1, 2, 3)</td>
<td>Avoid; oxytocic effect on the uterus</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>Manufacturer advises avoid—toxicity in animal studies; effective contraception required during and for at least 2 weeks after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Esomolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Etanercept</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Not known to be harmful; see also p. 316</td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>May possibly be teratogenic; see also Antiepileptics (1)</td>
</tr>
<tr>
<td>EtiRonate disodium</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Etodolac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Etomivate</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Avoid (teratogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Etravirine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Etynodiol</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Exenatide</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Manufacturer advises avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Famiclovia</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Famotidine</td>
<td>see Aciclovir</td>
</tr>
<tr>
<td>Fandisar*</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Felodipine</td>
<td>Possible teratogenic risk (pyrimethamine a folate antagonist) (1)</td>
</tr>
<tr>
<td>Fenbufen</td>
<td>Neonatal haemolyis and methaemoglobinemia; fear of increased risk of kernicterus in neonates appears to be unfounded see also Antimalarials (3)</td>
</tr>
<tr>
<td>FenoBiflrate</td>
<td>Avoid; toxicity in animal studies; may inhibit labour see NSAIDs</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>see section 3.1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Ferric carboxymal-</td>
<td>Avoid in first trimester; crosses the placenta in animal studies; may influence skeletal development</td>
</tr>
<tr>
<td>tose</td>
<td>Manufacturers advises avoid toxicity in animal studies</td>
</tr>
<tr>
<td>Fesoterodine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>Embryotoxicity in animal studies—manufacturers advise avoid</td>
</tr>
<tr>
<td>Fibrates</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Fibrinolytics</td>
<td>Possibility of premature separation of placenta in first 18 weeks; risk of maternal haemorrhage throughout pregnancy and on post-partum; theoretical risk of fetal haemorrhage throughout pregnancy (1, 2, 3)</td>
</tr>
<tr>
<td>Fligastim</td>
<td>Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Finasteride</td>
<td>Avoid unprotected intercourse (see section 6.4.2). May cause feminisation of male fetus (1, 2, 3)</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>Manufacturer advises avoid unless no safer alternative</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>Used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in animal studies; infant hyperbilirubinemia also reported</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>Teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Avoid (embryotoxic and teratogenic in animal studies); manufacturer advises effective contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Fludrocortisone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fludroxy cortide (flurandrenolone)</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>May cross placenta in small amounts—manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fluconolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Flucononide</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fluocortolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fluorometholone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>Avoid (teratogenic); see also section 8.1</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Flurandrenolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fluvalastin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Follitropin alfa and beta</td>
<td>Avoid</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Manufacturer advises avoid unless potential benefit outweighs possible risk—no information available</td>
</tr>
<tr>
<td>Formoterol (efomotecrol)</td>
<td>Manufacturers advise use only if potential benefit outweighs risk; see also section 3.1</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Fosaprepitant</td>
<td>see Neurokinin Receptor Antagonists</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>see Phenytoin</td>
</tr>
<tr>
<td>Framycetin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>see 5HT Agonists</td>
</tr>
<tr>
<td>Frusemide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Manufacturer advises avoid—increased incidence of fetal abnormalities and death in animal studies</td>
</tr>
<tr>
<td>Furosemide (frusemide)</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>see Sodium Fusidate</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Toxicity in animal studies; see also Antiepileptics</td>
</tr>
<tr>
<td>Galsulfase</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Ganciclovir</td>
<td>Avoid—teratogenic risk; see also p. 346</td>
</tr>
<tr>
<td>Gani relix</td>
<td>Manufacturer advises avoid in confirmed pregnancy—toxicity in animal studies</td>
</tr>
<tr>
<td>Gelatin</td>
<td>Manufacturer of Geloplasma® advises avoid at the end of pregnancy</td>
</tr>
<tr>
<td>Gemcitabine</td>
<td>Avoid (teratogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Gemfibrozil</td>
<td>see Fibrates</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Gestrone</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Gestrone (1, 2, 3)</td>
<td>Avoid</td>
</tr>
<tr>
<td>Glatiramer</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Gliclazide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Glimepiride</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Glipizide</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Glucosamine</td>
<td>Not known to be harmful but most manufacturers advise avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>see individual entries</td>
</tr>
<tr>
<td>Gonadorelin analogues</td>
<td>Manufacturer advises avoid in pregnancy—exclude pregnancy before treatment and use non-hormonal contraceptives during treatment</td>
</tr>
<tr>
<td>Gosere lin</td>
<td>Manufacturer advises use only when compelling reasons—no information available</td>
</tr>
<tr>
<td>Granisetron</td>
<td>Avoid (fetotoxicity and teratogenicity in animals); effective contraception required during and for at least 1 month after administration (important: effectiveness of oral contraceptives reduced, see p. 439); also men should avoid fathering a child during and for at least 6 months after administration</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Guanethidine (3)</td>
<td>Postural hypotension and reduced uteroplacental perfusion; should not be used to treat hypertension in pregnancy</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Haem arginate</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Halothane</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Heparin (1, 2, 3)</td>
<td>Does not cross the placenta; maternal osteoporosis reported after prolonged use; multidose vials may contain benzyl alcohol—some manufacturers advise avoid; see also Bemiparin, Dalteparin, Enoxaparin, and Tinzaparin</td>
</tr>
<tr>
<td>5HT agonists</td>
<td>Limited experience—manufacturers advise avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Human menopausal gonadotrophins</td>
<td>Avoid</td>
</tr>
<tr>
<td>Hydralazine (1, 2)</td>
<td>Manufacturer advises avoid before third trimester; no reports of serious harm following use in third trimester</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Hydroflumethiazide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Hydroxybutyramide (hydroxyurea)</td>
<td>Avoid (teratogenic in animal studies); manufacturer advises effective contraception before and during treatment see also section 8.1</td>
</tr>
<tr>
<td>Hydroxychloroquine</td>
<td>Manufacturer advises avoid but see p. 565</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>see Hydroxyurea</td>
</tr>
<tr>
<td>Hydroxyzine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Hyoscine butylbromide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Hyoscine hydrobromide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk; injection may depress neonatal respiration</td>
</tr>
<tr>
<td>Ibandronic acid</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Icatibant</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Idarubicin</td>
<td>Avoid (teratogenic and toxic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Idoxuridine</td>
<td>Teratogenic in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Idursulfase</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>Avoid (teratogenic and carcinogenic in animals); manufacturer advises adequate contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Manufacturer advises avoid (toxicity in animal studies); effective contraception must be used during treatment</td>
</tr>
<tr>
<td>Imitinib</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk; see also section 8.1</td>
</tr>
<tr>
<td>Imidapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Imiglucerase</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available see Primaxin®</td>
</tr>
<tr>
<td>Imipenem [ingredi-</td>
<td></td>
</tr>
<tr>
<td>ent]</td>
<td></td>
</tr>
<tr>
<td>Imipramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>No evidence of teratogenicity or toxicity in animal studies; manufacturer advises caution</td>
</tr>
<tr>
<td>Indapamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia and renal stones in neonate if used at term</td>
</tr>
<tr>
<td>Indometacin</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Avoid; manufacturer advises adequate contraception during and for at least 6 months after last dose</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Inosine pranobex</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Inositol nicotinate</td>
<td>No information available—manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin requirements should be assessed frequently by an experienced diabetes physician; safety of long-acting insulin analogues not established; short-acting insulin analogues, insulin aspart and insulin lispro, not known to be harmful; see also p. 369</td>
</tr>
<tr>
<td>Interferon beta</td>
<td>Manufacturers advise avoid—increased risk of spontaneous abortion; effective contraception required during treatment</td>
</tr>
<tr>
<td>Interferons</td>
<td>Manufacturers recommend avoid unless compelling reasons; effective contraception to be used by men and women receiving treatment; see also Interferon Beta</td>
</tr>
<tr>
<td>Iodine and iodides (2, 3)</td>
<td>Neonatal goitre and hypothyroidism; see also Iodine, Radioactive and Povidone–iodine</td>
</tr>
<tr>
<td>Iodine, radioactive (1, 2, 3)</td>
<td>Permanent hypothyroidism—avoid see Povidone–iodine</td>
</tr>
<tr>
<td>Iodoform</td>
<td>Not known to be harmful; see section 3.1</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>As for ACE Inhibitors</td>
</tr>
<tr>
<td>Irbesartan</td>
<td></td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Iretinocan</td>
<td>Avoid (teratogenic and toxic in <em>animal</em> studies); manufacturer advises effective contraception during and for at least 3 months after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Iron (parenteral)</td>
<td>Avoid in first trimester; see also Ferrie Carboxymaltose</td>
</tr>
<tr>
<td>Iron dextran</td>
<td>see Iron (parenteral)</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>see Iron (parenteral)</td>
</tr>
<tr>
<td>Isocarboxazid</td>
<td>see Antidepressants, MAOI</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>May cross placenta—manufacturers advise avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Isosorbide mono-nitrate</td>
<td>Manufacturers advise avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Isotretinoin (1, 2, 3)</td>
<td>Teratogenic; effective contraception must be used for at least 1 month before oral treatment, during treatment and for at least 1 month after stopping (oral progestogen-only contraceptives not considered effective); also avoid topical treatment</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Manufacturer advises use only in life-threatening situations (toxicity at high doses in <em>animal</em> studies); ensure effective contraception during treatment and until the next menstrual period following end of treatment</td>
</tr>
<tr>
<td>Isradipine</td>
<td>May inhibit labour; risk to fetus should be balanced against risk of uncontrolled maternal hypertension</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Manufacturer advises use only in life-threatening situations (toxicity at high doses in <em>animal</em> studies); ensure effective contraception during treatment and until the next menstrual period following end of treatment</td>
</tr>
<tr>
<td>Ivermectine</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Avoid oral solution due to high propylene glycol content; manufacturer advises use capsules and tablets only if potential benefit outweighs risk (toxicity in <em>animal</em> studies)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Lidoconazole</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk (teratogenicity in <em>animal</em> studies)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Labelatal</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Lacinoprost</td>
<td>Manufacturer advises avoid; may inhibit labour</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Lactulose</td>
<td>Not known to be harmful</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine (1)</td>
<td>Manufacturer advises avoid during first trimester; see also p. 334</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Risk of teratogenesis; see also Antiepileptics</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Lanthanum</td>
<td>Manufacturer advises avoid—activity in <em>animal</em> studies; effective contraception essential during treatment and for at least 2 years after treatment in women and at least 3 months after treatment in men (see also Leflunomide section 10.1.3)</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Manufacturer advises avoid under essential—no information available</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>Manufacturer advises avoid—activity metabolite teratogenic in <em>animal</em> studies; effective contraception essential during treatment and for at least 1 month after treatment (oral combined hormonal contraceptives and copper-releasing intrauterine devices not recommended); men should use condoms during treatment and for at least 1 week after stopping</td>
</tr>
<tr>
<td>Lenzolidide</td>
<td>Teratogenic risk; effective contraception must be used for at least 1 month before, during, and for at least 1 month after treatment (oral combined hormonal contraceptives and copper-releasing intrauterine devices not recommended); men should use condoms during treatment and for at least 1 week after stopping</td>
</tr>
<tr>
<td>Lenorelin</td>
<td>Avoid—teratogenic in <em>animal</em> studies</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Letrosal</td>
<td>Avoid (toxicity in <em>animal</em> studies); manufacturer advises effective contraception required until postmenopausal status fully established</td>
</tr>
<tr>
<td>Levobupivacaine (1)</td>
<td>Manufacturer advises avoid if possible—activity in <em>animal</em> studies; see also Anaesthetics, Local</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Manufacturers advise toxicity in <em>animal</em> studies</td>
</tr>
<tr>
<td>Levomepromazine (methotrimpeprazine)</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Levotyroxine (thry-oxine)</td>
<td>Monitor maternal serum-thyrotrophin concentration—levotyroxine may cross the placenta and excessive maternal concentration can be detrimental to fetus</td>
</tr>
<tr>
<td>Lidocaine (ligno-caine)</td>
<td>see Anaesthetics, Local</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>see Anaesthetics, Local</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Liothyronine</td>
<td>Does not cross the placenta in significant amounts; monitor maternal thyroid function tests—dosage adjustment may be necessary</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Lithium salts</td>
<td>Avoid if possible (risk of teratogenicity, including cardiac abnormalities)</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>Manufacturer advises use only if benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Lonustine</td>
<td>Avoid (manufacturer advises effective contraception during and for at least 6 months after treatment in men or women); see also section 8.1</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Manufacturers advise avoid—no information available</td>
</tr>
<tr>
<td>Lonipinavir [ingredient]</td>
<td>see Kaletra®</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Loratadine</td>
<td>Embryotoxic in animal studies; see also Antihistamines</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Losantan</td>
<td>As for ACE Inhibitors see Riomet®</td>
</tr>
<tr>
<td>Lumefantrine [ingredient]</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Macrogols (oral)</td>
<td>Manufacturers advise use only if essential—no information available</td>
</tr>
<tr>
<td>Magnesium sulphate</td>
<td>Not known to be harmful for short-term intravenous administration in eclampsia but excessive doses cause neonatal respiratory depression</td>
</tr>
<tr>
<td>Malenine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Mebeverine</td>
<td>Not known to be harmful; manufacturers advise caution</td>
</tr>
<tr>
<td>Mecasermin</td>
<td>Manufacturer advises avoid unless essential; contraception advised in women of child-bearing potential</td>
</tr>
<tr>
<td>Mecysteine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Avoid—genital malformations and cardiac defects reported with high doses; no evidence of adverse effect with depot injection for contraception see NSAIIds</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Melatonin</td>
<td>No information available—manufacturer advises avoid see NSAIIds</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>Avoid (manufacturer advises adequate contraception during treatment in men or women); see also section 8.1</td>
</tr>
<tr>
<td>Memantine</td>
<td>Manufacturer advises avoid unless essential—intra-uterine growth restriction in animal studies</td>
</tr>
<tr>
<td>Menadiol</td>
<td>Neonatal haemolytic anaemia, hyperbilirubinaemia and increased risk of kernicterus in jaundiced infants</td>
</tr>
<tr>
<td>Menotrophin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Meptazinol</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Mercaptothamine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>Avoid (teratogenic); see also section 8.1</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Manufacturer advises avoid only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>Negligible quantities cross placenta</td>
</tr>
<tr>
<td>Mesna</td>
<td>Not known to be harmful; see also section 8.1</td>
</tr>
<tr>
<td>Mesterolone</td>
<td>see Androgens</td>
</tr>
<tr>
<td>Mestranol</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>May reduce placental perfusion—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Metformin</td>
<td>Used in pregnancy for both pre-existing and gestational diabetes—see also p. 375; manufacturer advises avoid see Opioid Analgesics</td>
</tr>
<tr>
<td>Methadone</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
</tbody>
</table>
| Methocarbamol | }
<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Avoid (teratogenic; fertility may be reduced during therapy but this may be reversible); manufacturer advises effective contraception during and for at least 3 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Methotrimeneprazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Methoxy polyethylene glycol-epoetin bio- (beta)</td>
<td>No evidence of harm in animal studies—manufacturer advises caution</td>
</tr>
<tr>
<td>Methylidopa</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Methylaminotrexone</td>
<td>Toxicity at high doses in animal studies—manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Methylenephidate</td>
<td>Limited experience—manufacturer advises avoid unless potential benefit outweighs risk; toxicity in animals</td>
</tr>
<tr>
<td>Methylprednisolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Methysergide</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Not known to be harmful but manufacturer advises use only when compelling reasons</td>
</tr>
<tr>
<td>Metolazone</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>Manufacturer advises avoidance of high-dose regimens</td>
</tr>
<tr>
<td>Metyrapone</td>
<td>Avoid (may impair biosynthesis of fetal-placental steroids)</td>
</tr>
<tr>
<td>Mianserin</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Micafungin</td>
<td>Manufacturer advises avoid unless essential—toxicity in animal studies</td>
</tr>
<tr>
<td>Miconazole</td>
<td>Manufacturer advises avoid if possible—toxicity at high doses in animal studies; small amount absorbed from vagina—not known to be harmful (see also section 7.2.2)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Midirex®</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Mifepristone</td>
<td>Manufacturer advises that if treatment fails, essential that pregnancy be terminated by another method</td>
</tr>
<tr>
<td>Miglustat</td>
<td>Manufacturer advises avoid (toxicity in animal studies)—effective contraception must be used during treatment; also men should avoid fathering a child during and for 3 months after treatment</td>
</tr>
<tr>
<td>Milrinone</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Minoxycycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Minoxidil</td>
<td>(3) Neonatal hirsutism reported</td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Manufacturers advise avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>(1, 2, 3) Avoid—potent uterine stimulant (has been used to induce abortion) and may be teratogenic</td>
</tr>
<tr>
<td>Mitomycin</td>
<td>Avoid (teratogenic in animal studies); see also animal studies</td>
</tr>
<tr>
<td>Mitotane</td>
<td>Manufacturer advises avoid—women of childbearing age should use effective contraception during and after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Mitoxantrone (mito- zantrone)</td>
<td>Avoid; manufacturer advises effective contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Mitozantrone</td>
<td>see Mitoxantrone</td>
</tr>
<tr>
<td>Mivacurium</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>Manufacturer advises avoid; see also Antihistamines</td>
</tr>
<tr>
<td>MMIR vaccine, live</td>
<td>Avoid vaccination during pregnancy; avoid pregnancy for at least 1 month after vaccination</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>see Antidepressants, MAOI</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Moexipril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Morphine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>see Quinolones</td>
</tr>
<tr>
<td>Moxisylyte (thymox- amine)</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Manufacturer advises avoid—congenital malformations reported; effective contraception required before treatment, during treatment, and for 6 weeks after discontinuation of treatment</td>
</tr>
<tr>
<td>Mefotil</td>
<td>see Mycophenolate mofetil</td>
</tr>
<tr>
<td>Nabilonone</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Nadolol</td>
<td>Avoid</td>
</tr>
<tr>
<td>Nafarelin</td>
<td>see Quinolones</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Naloxone</td>
<td>see Mycophenolate mofetil</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Manufacturers advise use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Nandrolone</td>
<td>see Anabolic Steroids</td>
</tr>
<tr>
<td>Naproxen</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>see 5HT Agonists</td>
</tr>
<tr>
<td>Narcotic analgesics</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Manufacturer advises avoid unless essential—toxicity in animal studies</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Manufacturer advises avoid— toxicity in animal studies</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>see section 3.1</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Nefopam</td>
<td>No information available—manufacturer advises avoid unless no safer treatment</td>
</tr>
<tr>
<td>Nelarabine</td>
<td>Avoid (toxicity in animal studies); manufacturer advises effective contraception during and for at least 3 months after treatment in men and women; see also Section 8.1</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>No information available—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Neomycin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Neurokinin receptor antagonists</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Although manufacturers advise avoid, may be appropriate to use if clearly indicated; see also p. 334</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>May inhibit labour; manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>No information available—manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Nicoumalone</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>May inhibit labour; manufacturer advises avoid before week 20; risk to fetus should be balanced against risk of uncontrolled maternal hypertension; use only if other treatment options are not indicated or have failed</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies; effective contraception required during treatment; see also section 8.1</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Nitisinone</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Nitazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Nitofurantoin (3)</td>
<td>May produce neonatal haemolytic crisis if used at term</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>see Sodium Nitroprusside</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrous oxide</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Noradrenaline (norepinephrine) (1, 2, 3)</td>
<td>Avoid—may reduce placental perfusion</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>Masculinisation of female fetuses and other defects reported; see also Contraceptives, Oral</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>see Quinolones</td>
</tr>
<tr>
<td>Norgestimate</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Most manufacturers advise avoid (or avoid unless potential benefit outweighs risk); ketorolac contra-indicated during pregnancy, labour and delivery</td>
</tr>
<tr>
<td>Octreotide (1, 2, 3)</td>
<td>Possible effect on fetal growth; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>see Quinolones</td>
</tr>
<tr>
<td>Olanzapine (3)</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Manufacturer advises avoid unless essential; no evidence of teratogenicity in animal studies</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>As for ACE inhibitors</td>
</tr>
<tr>
<td>Omega-3-acid ethyl esters</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>No information available; manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Manufacturer advises avoid—toxicity in animal studies; effective contraception required during and for 4 months after treatment in women and 6 months after treatment in men; see also section 8.1</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Risk of teratogenesis including increased risk of neural tube defects; see also Antiepileptics</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Oxybuprocaine</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Avoid (toxicity in animal studies); ensure effective contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Palifermin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies; if discontinuation during pregnancy is necessary, paliperidone should be withdrawn gradually</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Pamidronate disodium</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Pancracetin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Avoid (toxicity in animal studies); manufacturer advises effective contraception during and for 6 months after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—fetotoxic in animal studies</td>
</tr>
<tr>
<td>Papaveretum</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>Manufacturer advises avoid unless essential—crosses the placenta</td>
</tr>
<tr>
<td>Paezcoxiib</td>
<td>see NSAIDS</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>Toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk; see also Vitamin D</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Pegaptinib</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Avoid (toxicity in animal studies); manufacturer advises effective contraception during treatment; men must avoid fathering a child during and for at least 6 months after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Fetal abnormalities reported rarely; avoid if possible</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Pentamidine isetionate</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>Avoid (teratogenic in animal studies); manufacturer advises that men should not father children during and for 6 months after treatment; see also section 8.1</td>
</tr>
<tr>
<td>Pergolide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Pericyzine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Perindopril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pethidine</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phenelzine</td>
<td>see Antidepressants, MAOI</td>
</tr>
<tr>
<td>Phenindione</td>
<td>see Anti-convulsants, Oral</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>Hypotension may occur in newborn</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Congenital malformations; see also Antiepileptics</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Use with caution—may cause marked decrease in maternal blood pressure with resulting fetal anoxia</td>
</tr>
<tr>
<td>Phenylephrine (1)</td>
<td>Malformations reported</td>
</tr>
<tr>
<td>Phenylephrine (3)</td>
<td>Avoid if possible—fetal hypoxia and bradycardia reported in late pregnancy and labour</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Use with caution—may cause marked decrease in maternal blood pressure with resulting fetal anoxia</td>
</tr>
<tr>
<td>Photocidone</td>
<td>see Opioid Analgesics</td>
</tr>
<tr>
<td>Phytomenadione</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no specific information available</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Avoid—smooth muscle stimulant; toxicity in animal studies</td>
</tr>
<tr>
<td>Pimozide</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Pindolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Manufacturer advises avoid— toxicity in animal studies</td>
</tr>
<tr>
<td>Piperacillin [ingredient]</td>
<td>see Tazocin®</td>
</tr>
<tr>
<td>Piperazine</td>
<td>Not known to be harmful but manufacturer advises avoid in first trimester</td>
</tr>
<tr>
<td>Pipotiazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Piracetam</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Podophyllum</td>
<td>Avoid—neonatal death and teratogenesis have been reported</td>
</tr>
<tr>
<td>Polystyrene sulphonate resins</td>
<td>Manufacturers advise use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Porfirmer</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk and recommends effective contraception during treatment; toxicity in animal studies</td>
</tr>
<tr>
<td>Povidone–iodine (2, 3)</td>
<td>Sufficient iodine may be absorbed to affect the fetal thyroid</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Prazosin</td>
<td>see Alpha-blockers, Post-synaptic</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Toxicity in animal studies— manufacturer advises use only if potential benefit outweighs risk; see also Antiepileptics</td>
</tr>
<tr>
<td>Prilocaine (3)</td>
<td>Neonatal methaemoglobinemia reported after paracervical block or pudendal block; see also Anaesthetics, Local</td>
</tr>
<tr>
<td>Primaquine (3)</td>
<td>Neonatal haemolysis and methaemoglobinemia; see also Antimalarials</td>
</tr>
<tr>
<td>Primaxin®</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies)</td>
</tr>
<tr>
<td>Primidone</td>
<td>see Phenobarbital</td>
</tr>
<tr>
<td>Procaine (3)</td>
<td>Neonatal methaemoglobinemia; see also Anaesthetics, Local</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>Avoid (teratogenic in animal studies and isolated reports in humans); see also section 8.1</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>see Antipsychotics</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procyclidine</td>
<td>Manufacturers advise use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Progynonal</td>
<td>Adequate folate supplements should be given to mother; see also Antimalarials</td>
</tr>
<tr>
<td>Promazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Promethazine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Manufacturer advises avoid— no information available</td>
</tr>
<tr>
<td>Propantheline</td>
<td>Manufacturer advises avoid— no information available</td>
</tr>
<tr>
<td>Propiverine</td>
<td>Manufacturer advises avoid (restriction of skeletal development in animals)</td>
</tr>
<tr>
<td>Propofol</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Propylthiouracil (2, 3)</td>
<td>Neonatal goitre and hypothyroidism</td>
</tr>
<tr>
<td>Prontionamide</td>
<td>May be teratogenic</td>
</tr>
<tr>
<td>Pseudoephedrine (1)</td>
<td>Defective closure of the abdominal wall (gastroschisis) reported very rarely in newborns after first trimester exposure</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Manufacturer advises use only if potential benefit outweighs risk; see also p. 316</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Pyrimethamine (1)</td>
<td>Theoretical teratogenic risk (folic acid antagonist); adequate folate supplements should be given to mother; see also Antimalarials</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Quinagolide</td>
<td>Manufacturer advises discontinue when pregnancy confirmed unless medical reason for continuing</td>
</tr>
<tr>
<td>Quinapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Quinine (1)</td>
<td>High doses are teratogenic; but in malaria benefit of treatment outweighs risk</td>
</tr>
<tr>
<td>Quinolones (1, 2, 3)</td>
<td>Avoid—arthropathy in animal studies; safer alternatives available</td>
</tr>
<tr>
<td>Quinupristin [ingredient]</td>
<td>see Synercid®</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Manufacturer advises avoid— no information available</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Manufacturer advises avoid— toxicity in animal studies</td>
</tr>
<tr>
<td>Raltitrexed</td>
<td>Pregnancy must be excluded before treatment; ensure effective contraception during and for at least 6 months after treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Ramipril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk and recommends effective contraception during treatment</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Manufacturer advises avoid unless essential, but not known to be harmful</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—limited information available</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>No information available; see also Opioid Analgesics</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Reteplase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Riamet®</td>
<td>Toxicity in animal studies with arteriome; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Avoid; teratogenicity in animal studies; ensure effective contraception during oral administration and for 4 months after treatment in women and for 7 months after treatment in men; see also Ribavirin section 5.3.5</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Manufacturers advise very high doses teratogenic in animal studies; see also p. 316</td>
</tr>
<tr>
<td></td>
<td>(1) Risk of neonatal bleeding may be increased</td>
</tr>
<tr>
<td></td>
<td>(3) For use in premature labour see section 7.1.3</td>
</tr>
<tr>
<td>Riluzole</td>
<td>No information available; manufacturer advises avoid</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Manufacturer advises avoid—see Bisphosphonates</td>
</tr>
<tr>
<td>Risedronate sodium</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Extrapyramidal effects reported in neonates</td>
</tr>
<tr>
<td></td>
<td>(3) Extrapyramidal effects reported in neonates</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus—effective contraception required during and for 12 months after treatment</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Rizatriptan</td>
<td>see 5HT Agonists</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Manufacturer advises caution</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Safety not established but not known to be harmful</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Manufacturer advises avoid—toxicity in animal studies see Statins</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—fetotoxic in animal studies; effective contraception must be used during treatment; see also Antiepileptics</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>For use in asthma see section 3.1</td>
</tr>
<tr>
<td>Salgoterinol</td>
<td>see section 3.1</td>
</tr>
<tr>
<td>Salcatonin</td>
<td>Manufacturer advises avoid only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Manufacturer advises avoid—see Antidepressants, SSRI</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Manufacturer advises avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Manufacturer advises avoid only if potential benefit outweighs risk—</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>see Sulphonamides</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>see Statins</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Manufacturer advises avoid—(toxicity in animal studies); effective contraception must be used during treatment and for 12 weeks after stopping</td>
</tr>
<tr>
<td>Simeprevir</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>Avoid unless essential—toxicity in animal studies; manufacturer advises effective contraception during treatment</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>避</td>
</tr>
<tr>
<td>Sodium aurothiomalate</td>
<td>Manufacturer advises avoid but limited data suggests usually not necessary to withdraw if condition well controlled—consider reducing dose and frequency</td>
</tr>
<tr>
<td>Sodium aurothioglycollate</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Sodium furoxide</td>
<td>Not known to be harmful; see also section 3.1</td>
</tr>
<tr>
<td>Sodium furoxide</td>
<td>Not known to be harmful; manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>Potential for accumulation of cyanide in fetus—avoid prolonged use</td>
</tr>
<tr>
<td>Sodium oxamate</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>Avoid (toxicity in animal studies); manufacturer advises adequate contraception during administration</td>
</tr>
<tr>
<td>Sodium stibogluconate</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Discontinue if pregnancy occurs—no information available but theoretical risk</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Manufacturer advises avoid unless essential—toxicity in animal studies; see also section 8.1</td>
</tr>
<tr>
<td>Sotalol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Manufacturers advise toxicity in animal studies</td>
</tr>
<tr>
<td>Statins</td>
<td>Avoid—congenital anomalies reported; decreased synthesis of cholesterol possibly affects fetal development</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>see Fibrinolytics</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Sugammadex</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>see Sulphonamides</td>
</tr>
<tr>
<td>Sulfadoxine</td>
<td>see Sulphonamides</td>
</tr>
<tr>
<td>Sulfasalazine (3)</td>
<td>Theoretical risk of neonatal haemolysis; adequate folate supplements should be given to mother</td>
</tr>
<tr>
<td>Sulindac</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Sulphonamides (3)</td>
<td>Neonatal haemolysis and methaemoglobinemia; fear of increased risk of kernicterus in neonates appears to be unfounded</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>Avoid; possible neonatal hypoglycaemia</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>Limited experience but no evidence of harm in animal studies</td>
</tr>
<tr>
<td>Sumatriptan</td>
<td>see 5HT Agonists</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies; see also section 8.1</td>
</tr>
<tr>
<td>Suxamethonium</td>
<td>Mildly prolonged maternal paralysis may occur</td>
</tr>
<tr>
<td><strong>Synercid</strong></td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
</tbody>
</table>

### Drug (trimester of risk) | Comment

| Tacalcitol               | Manufacturer advises avoid unless no safer alternative—no information available; see also Vitamin D |
| Tacrolimus               | Avoid; manufacturer advises toxicity in animal studies following systemic administration |
| Tamoxifen                | Avoid—possible effects on fetal development; effective contraception must be used during treatment and for 2 months after stopping |
| Tazarotene               | Avoid; effective contraception required (oral progesterone-only contraceptives not considered effective) |
| Tazobactam [ingredient]  | see Tazocin® |
| **Tazocin**<sup>®</sup>  | Manufacturer advises use only if potential benefit outweighs risk |
| Tegafur with uracil      | see Uftoral® |
| Teicoplanin              | Manufacturer advises use only if potential benefit outweighs risk |
| Telbivudine              | Manufacturer advises use only if potential benefit outweighs risk |
| Telithromycin            | Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk |
| Telmisartan              | As for ACE Inhibitors |
| Temazepam                | see Benzodiazepines |
| Temocillin               | Temocillin see Penicillins |
| Temoporfin               | Toxicity in animal studies—manufacturer advises avoid pregnancy for at least 3 months after treatment |
| Temozolomide             | Avoid (teratogenic and embryotoxic in animal studies); manufacturer advises adequate contraception during treatment; see also section 8.1; also men should avoid fathering a child during and for at least 6 months after treatment |
| Temsirolimus             | Manufacturer advises avoid (toxicity in animal studies); ensure effective contraception during treatment in men and women; see also section 8.1 see Fibrinolytics |
| Tenecteplase             | see Fibrinolytics |
| Tenofovir                | No information available—manufacturer advises use only if potential benefit outweighs risk |
| Tenoxicam                | see NSAIDs |
| Terazosin                | see Alpha-blockers, Post-synaptic |
| Terbinafine              | Manufacturer advises use only if potential benefit outweighs risk—no information available |
| Terbutaline              | For use in asthma see section 3.1 |
| Testosterone             | For use in premature labour see section 7.1.3 |

**Androgens**
<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tetrabenazine</td>
<td>Inadequate information but no evidence of harm</td>
</tr>
<tr>
<td>Tetracyclines (1)</td>
<td>Effects on skeletal development in animal studies</td>
</tr>
<tr>
<td>(2, 3)</td>
<td>Dental discoloration; maternal hepatotoxicity with large par enteral doses</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Teratogenic risk; effective contraception must be used for at least 1 month before, during, and for at least 1 month after treatment (oral combined hormonal contraceptives and copper-releasing intrauterine devices not recommended); men should use condoms during treatment and for at least 1 week after stopping</td>
</tr>
<tr>
<td>Theophylline (3)</td>
<td>Neonatal irritability and apnoea have been reported</td>
</tr>
<tr>
<td>Thiazides and related diuretics</td>
<td>Not used to treat gestational hypertension; may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may also be reduced; stimulation of labour, uterine inertia, and meconium staining also reported</td>
</tr>
<tr>
<td>Thiopental</td>
<td>see Anaesthetics, General</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Avoid (teratogenic and embryotoxic in animals); see also section 8.1</td>
</tr>
<tr>
<td>Thymoxamine</td>
<td>see Moxisylyte</td>
</tr>
<tr>
<td>Thyroxine</td>
<td>see Levothyroxine</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk; see also Antiepileptics</td>
</tr>
<tr>
<td>Tiaprofenic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Ticarcillin [ingredient]</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Tiludronic acid</td>
<td>see Bisphosphonates</td>
</tr>
<tr>
<td>Timentin®</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Timolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Manufacturer advises avoid in first trimester</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Ticlofenol</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Tioguanine</td>
<td>Avoid (teratogenicity reported when men receiving tioguanine have fathered children); ensure effective contraception during treatment in men or women; see also section 8.1</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug (trimester of risk)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tizanidine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>see Aminoglycosides</td>
</tr>
<tr>
<td>Tocopheryl acetate (1, 2, 3)</td>
<td>No evidence of safety of high doses</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Toxicity in animal studies—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>see NSAIDs</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Manufacturer advises avoid— toxicity in animal studies</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk— toxicity in animal studies; see also Antiepileptics</td>
</tr>
<tr>
<td>Topotecan</td>
<td>Avoid (teratogenicity and fetal loss in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Torasemide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Effective contraception recommended during and for at least 3 months after treatment in women and at least 5 months after treatment in men; see also section 8.1</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Embryotoxic in animal studies—manufacturers advise avoid; see also Opioid Analgesics</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>see ACE Inhibitors</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>No evidence of teratogenicity in animal studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta</td>
</tr>
<tr>
<td>Tranlycypromine</td>
<td>see Antidepressants, MAOI</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Travoprost</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Trazodon</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Treosulfan</td>
<td>Avoid; see also section 8.1</td>
</tr>
<tr>
<td>Tretinoin (1, 2, 3)</td>
<td>Teratogenic; effective contraception must be used for at least 1 month before oral treatment, during treatment and for at least 1 month after stopping (oral progestogen-only contraceptives not considered effective); also avoid topical treatment</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Triamterene</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Tribavirin</td>
<td>see Ribavirin</td>
</tr>
<tr>
<td>Triclosa</td>
<td>Avoid</td>
</tr>
<tr>
<td>Tientine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk; monitor maternal and neonatal serum-copper concentration; teratogenic in animal studies</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Trihexyphenidyl</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Triostane (1, 2, 3)</td>
<td>Interferes with placental sex hormone production</td>
</tr>
<tr>
<td>Trimethoprim (1)</td>
<td>Teratogenic risk (folate antagonist); manufacturers advise avoid</td>
</tr>
<tr>
<td>Trimeprazine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>Ursodeoxycholic acid</td>
</tr>
<tr>
<td>Ursodiol</td>
<td>No evidence of harm but manufacturer advises avoid</td>
</tr>
<tr>
<td>Vaccines (live)</td>
<td>Theoretical risk of fetal infection, but need for vaccination may outweigh possible risk to fetus (see also p. 680); see also MMR vaccine, live; avoid varicella-zoster vaccine, see p. 680</td>
</tr>
<tr>
<td>Valaclovir</td>
<td>see Aciclovir</td>
</tr>
<tr>
<td>Valganciclovir</td>
<td>see Ganciclovir</td>
</tr>
<tr>
<td>Valproate (1, 3)</td>
<td>Increased risk of congenital malformations and developmental delay (counselling and screening advised—important: see also Antiepileptics and p. 250); neonatal bleeding (related to hypofibrinemia) and neonatal hepatotoxicity also reported</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Valsartan</td>
<td>As for ACE Inhibitors</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Manufacturer advises avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Varicella-zoster vaccine</td>
<td>see Vaccines (live)</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Oxytocic effect in third trimester</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk; risk of withdrawal effects in neonate</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Limited information available; manufacturer advises use only if clearly indicated; see also p. 334</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Verapamil</td>
<td>May reduce uterine blood flow with fetal hypoxia; manufacturer advises avoid in first trimester unless absolutely necessary; may inhibit labour</td>
</tr>
<tr>
<td>Verteporfin</td>
<td>Manufacturer advises use only if potential benefit outweighs risk (teratogenic in animal studies)</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Congenital anomalies reported—manufacturer advises avoid unless potential benefit outweighs risk; see also Antiepileptics</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Manufacturer advises avoid— toxicity in animal studies</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>Avoid (limited experience suggests fetal harm; teratogenic in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Vincristine</td>
<td>Avoid (teratogenicity and fetal loss in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>Avoid (teratogenicity and fetal loss in animal studies); see also section 8.1</td>
</tr>
<tr>
<td>Vitamin A (1)</td>
<td>Excessive doses may be teratogenic; see also p. 538</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>High systemic doses teratogenic in animals but therapeutic doses unlikely to be harmful; avoid topical calcitriol—use in restricted amounts if clearly necessary (significant systemic absorption; monitor urine and plasma-calcium concentration); see also Calcipotriol, Paricalcitol, and Tacalcitol</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk; effective contraception required during treatment</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamide</td>
<td>see Diuretics</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Use only if necessary and restrict to occasional short-term use; risk of withdrawal symptoms in neonate if used in late pregnancy</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Drug (trimester of risk)</td>
<td>Comment</td>
</tr>
<tr>
<td>-------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Zinc sulphate</td>
<td>Safety not established—crosses placenta</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Manufacturer advises avoid—toxicity in animal studies</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>see 5HT Agonists</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk—effective contraception required during and for 4 weeks after treatment; see also Antiepileptics</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Zotepine</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>see Antipsychotics</td>
</tr>
</tbody>
</table>
Breast-feeding is beneficial; the immunological and nutritional value of breast milk to the infant is greater than that of formula feeds.

Although there is concern that drugs taken by the mother might affect the infant, there is very little information on this. In the absence of evidence of an effect, the potential for harm to the infant can be inferred from:

- the amount of drug or active metabolite of the drug delivered to the infant (dependent on the pharmacokinetic characteristics of the drug in the mother);
- the efficiency of absorption, distribution and elimination of the drug by the infant (infant pharmacokinetics);
- the nature of the effect of the drug on the infant (pharmacodynamic properties of the drug in the infant).

The amount of drug transferred in breast milk is rarely sufficient to produce a discernible effect on the infant. This applies particularly to drugs that are poorly absorbed and need to be given parenterally. However, there is a theoretical possibility that the small amount of drug present in breast milk can induce a hypersensitivity reaction.

A clinical effect can occur in the infant if a pharmacologically significant quantity of the drug is present in milk. For some drugs (e.g. fluvastatin), the ratio between the concentration in milk and that in maternal plasma may be high enough to expose the infant to adverse effects. Some infants, such as those born prematurely or who have jaundice, are at a slightly higher risk of toxicity.

Some drugs inhibit the infant’s sucking reflex (e.g. phenobarbital) while others can affect lactation (e.g. bromocriptine).

The following table identifies drugs:

- that should be used with caution or are contraindicated in breast-feeding;
- which can be given to the mother during breast-feeding because they are present in milk in amounts which are too small to be harmful to the infant;
- which might be present in milk in significant amount but are not known to be harmful.

For many drugs insufficient evidence is available to provide guidance and it is advisable to use only essential drugs to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast-feeding, absence from the table does not imply safety.

### Table of drugs present in breast milk

Products introduced or amended since publication of BNF No. 56 (September 2008) are underlined.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abacavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Abatacept</td>
<td>Present in milk in animal studies—manufacturer advises avoid breast-feeding during treatment and for 14 weeks after last dose</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Acamprosate</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Acebutolol</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>Significant amount in milk after systemic administration—not known to be harmful but manufacturer advises caution</td>
</tr>
<tr>
<td>Acipimox</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Acitretin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Adalimumab</td>
<td>Avoid; manufacturer advises avoid for at least 5 months after last dose</td>
</tr>
<tr>
<td>Adalpine</td>
<td>Manufacturer advises avoid (if used, avoid application to chest)—no information available</td>
</tr>
<tr>
<td>Adefovir dipivoxil</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Agalsidase</td>
<td>Use with caution—no information available</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Large amounts may affect infant and reduce milk consumption</td>
</tr>
<tr>
<td>Alemtuzumab</td>
<td>Avoid; manufacturer advises avoid breast-feeding for at least 4 weeks after administration</td>
</tr>
<tr>
<td>Alendronic acid</td>
<td>No information available</td>
</tr>
<tr>
<td>Alfalcacidol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Alfentanil</td>
<td>Present in milk—manufacturer advises withhold breast-feeding for 24 hours</td>
</tr>
<tr>
<td>Alglucosidase alfa</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Alimemazine (trimethazine)</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Alitretinoin</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>---------------------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Allopurinol</td>
<td>Present in milk—not known to be harmful</td>
</tr>
<tr>
<td>Almotriptan</td>
<td>Present in milk in animal studies—withdraw breast-feeding for 24 hours</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Alverine</td>
<td>Manufacturer advises avoid—little information available</td>
</tr>
<tr>
<td>Amantadine</td>
<td>Avoid; present in milk; toxicity in infant reported</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Amfetubamone</td>
<td>see Bupropion</td>
</tr>
<tr>
<td>Amiloride</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Aminophylline</td>
<td>see Theophylline</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>Avoid; present in milk in significant amounts; theoretical risk from release of iodine; see also Iodine</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>see Antidepressants. Tricyclic (and related)</td>
</tr>
<tr>
<td>Amiodolone</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Aminefetamine</td>
<td>Significant amount in milk. Avoid</td>
</tr>
<tr>
<td>Amikacin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>Significant amount in milk. Avoid</td>
</tr>
<tr>
<td>Amphotericin</td>
<td>No information available</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Antimetabolite</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Apomorphine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Aprepitant</td>
<td>see Neurokinin Receptor Antagonists</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Atovaquone</td>
<td>see Neurokinin Receptor Antagonists</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Atropine</td>
<td>Small amount present in milk—manufacturer advises caution</td>
</tr>
<tr>
<td>Auranofin</td>
<td>Present in milk; manufacturer advises avoid</td>
</tr>
<tr>
<td>Azapropazone</td>
<td>Small amount present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>Teratogenic metabolite present in milk in low concentration but no evidence of harm in small studies—consider if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Present in milk; use only if no suitable alternative</td>
</tr>
<tr>
<td>Aztrenonam</td>
<td>Amount probably too small to be harmful—manufacturer advises avoid</td>
</tr>
<tr>
<td>Baclofen</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Balsalazide</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>Avoid if possible (see also Phenobarbital); large doses may produce drowsiness</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Avoid</td>
</tr>
<tr>
<td>Beclometasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Beniparin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Bendrofluzide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Bendrofluozide</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Benperidol</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Present in milk—avoid if possible; see also Midazolam</td>
</tr>
<tr>
<td>Benzylpenicillin</td>
<td>Monitor infant; possible toxicity due to beta-blockade but amount of most beta-blockers may be too small to affect infant; acebutolol, atenolol, nadolol, and sotalol are present in greater amounts than other beta-blockers; manufacturers advise avoid cerelrolo and nebivalol</td>
</tr>
<tr>
<td>Betafibre</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Bithanechol</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Manufacturer advises avoid breast-feeding during and for at least 6 months after treatment</td>
</tr>
<tr>
<td>Bexarotene</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Bezaflibrate</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Bivalirudin</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Bosentan</td>
<td>Manufacturer advises avoid (or avoid unless essential)—no information available</td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>Manufacturers advise avoid (or avoid unless essential)—no information available</td>
</tr>
<tr>
<td>Bromocriptine</td>
<td>Suppresses lactation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buclizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Budesonide</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Bumetanide</td>
<td>Manufacturer advises avoid if possible—no information available</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Avoid unless essential—may inhibit lactation; manufacturer advises contra-indicated in the treatment of opioid dependence</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Buserelin</td>
<td>Small amount present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Buspironide</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Busulfan</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Butobarbital</td>
<td>see Barbiturates</td>
</tr>
<tr>
<td>Cabergoline</td>
<td>Suppresses lactation</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Regular intake of large amounts can affect infant—see Vitamin D</td>
</tr>
<tr>
<td>Calcifotoler</td>
<td>No information available</td>
</tr>
<tr>
<td>Calcitriol</td>
<td>Avoid, inhibits lactation in animals—see Vitamin D</td>
</tr>
<tr>
<td>Calcium folinate</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Calcium levofolinate</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Candesartan</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>Discontinue breast-feeding</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Captopril</td>
<td>Present in milk—manufacturers advise avoid</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Carbimazole</td>
<td>Amounts in milk may be sufficient to affect neonatal thyroid function therefore lowest effective dose should be used (see also section 6.2.2)</td>
</tr>
<tr>
<td>Carboxicline</td>
<td>No information available</td>
</tr>
<tr>
<td>Carboplatin</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Carglamic acid</td>
<td>Manufacturer advises—present in milk in animal studies</td>
</tr>
<tr>
<td>Carisoprodol</td>
<td>Concentrated in milk; no adverse effects reported but best avoided</td>
</tr>
<tr>
<td>Carmustine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Cefadroxil</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Cefalexin</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Cefixime</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Cefradine</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>Present in milk in low concentration</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Celiaprolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Celitizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Cetrorelax</td>
<td>Manufacturer advises avoid breast-feeding during and for 2 months after treatment—no information available</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Use another antibiotic; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey syndrome'</td>
</tr>
<tr>
<td>Chloral hydrate</td>
<td>Sedation in infant—manufacturer advises avoid</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Use another antibiotic; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause 'grey syndrome'</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>Amount probably too small to be harmful when used for malaria prophylaxis; inadequate for reliable protection against malaria, see section 5.4.1; avoid breast-feeding when used for rheumatic diseases</td>
</tr>
<tr>
<td>Chlorphenamine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Drowsiness in infant reported; see Antipsychotics</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Chlortalidone</td>
<td>see Thiazides and Related Diuretics</td>
</tr>
<tr>
<td>Ciclosporine</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Cilastatin [ingredient]</td>
<td>see Primaxin®</td>
</tr>
<tr>
<td>Cilazapril</td>
<td>No information available—manufacturer advises avoid</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Cimetidine</td>
<td>Significant amount—not known to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Cinacalcet</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Cinnarazine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Ciprofibrate</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Amount probably too small to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>No information available</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Cladribine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—present in milk</td>
</tr>
<tr>
<td>Clavulanic acid [ingredient]</td>
<td>see Co-amoxiclav, Timentin®</td>
</tr>
<tr>
<td>Clenamidine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Amount probably too small to be harmful but bloody diarrhoea reported in 1 infant</td>
</tr>
<tr>
<td>Clofazamine</td>
<td>May alter colour of milk; skin discoloration of infant</td>
</tr>
<tr>
<td>Clomethiazole</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Clomifene</td>
<td>May inhibit lactation</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Clonidine</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Co-beneldopa</td>
<td>see Levodopa</td>
</tr>
<tr>
<td>Co-careldopa</td>
<td>see Levodopa</td>
</tr>
<tr>
<td>Co-danthramer</td>
<td>Manufacturer advises avoid—limited information available</td>
</tr>
<tr>
<td>Co-danthrusate</td>
<td>Manufacturer advises avoid—limited information available</td>
</tr>
<tr>
<td>Codeine</td>
<td>Amount usually too small to be harmful; however mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant</td>
</tr>
<tr>
<td>Co-fluampicil</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Colchicine</td>
<td>Present in milk but no adverse effects reported; manufacturers advise avoid because of risk of cytotoxicity</td>
</tr>
<tr>
<td>Colecalciferol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Use with caution—drug not absorbed but may cause fatsoluble vitamin deficiency on prolonged use</td>
</tr>
<tr>
<td>Colestipol</td>
<td>Use with caution—drug not absorbed but may cause fatsoluble vitamin deficiency on prolonged use</td>
</tr>
<tr>
<td>Colestyramine</td>
<td>Use with caution—drug not absorbed but may cause fatsoluble vitamin deficiency on prolonged use</td>
</tr>
<tr>
<td>Colistin</td>
<td>Present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk)</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Contraceptives, oral</td>
<td>Avoid combined oral contraceptives until weaning or for 6 months after birth (adverse effects on lactation); progestogen-only contraceptives do not affect lactation (start 3 weeks after birth or later)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Systemic effects in infant unlikely with maternal dose of prednisolone up to 40 mg daily; monitor infant’s adrenal function with higher doses—the amount of inhaled drugs in breast milk is probably too small to be harmful</td>
</tr>
<tr>
<td>Cortisone acetate</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>Small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole)</td>
</tr>
<tr>
<td>Crisantaspase</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Cromoglicate</td>
<td>see Sodium Cromoglicate</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Discontinue breast-feeding during and for 36 hours after stopping treatment</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>see Ciclosporin</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Cyproterone</td>
<td>Caution; possibility of antiandrogen effects in neonate</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Cytotoxic drugs</td>
<td>Discontinue breast-feeding; see also Azathioprine, Naltuzumab, Nilotinib, Panitumumab, Rituximab, and Trabecedit</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Dalteparin</td>
<td>No information available</td>
</tr>
<tr>
<td>Danazol</td>
<td>Amount probably too small to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Dantrolene</td>
<td>Present in milk—manufacturer advises avoid use in chronic spasticity; use only for malignant hyperthermia if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Dantron (danthron)</td>
<td>see Co-danthramer, Co-danthrurate</td>
</tr>
<tr>
<td>Dapsone</td>
<td>Haemolytic anaemia; although significant amount in milk, risk to infant very small unless infant is G6PD deficient</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Darbepoetin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Darifenacin</td>
<td>Present in milk in animal studies—manufacturer advises caution</td>
</tr>
<tr>
<td>Darunavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Daunorubicin</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Deferiprone</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Deflacozart</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Demeclocycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Desferrioxamine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Desloratidine</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Desmopressin</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Dexametamine</td>
<td>see Amphetamines</td>
</tr>
<tr>
<td>Dexibuprofen</td>
<td>Present in milk—but risk to infant minimal</td>
</tr>
<tr>
<td>Dextroketoprofen</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Dexamfetamine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring see Benzodiazepines</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Avoid—present in milk; apnoea reported in infant</td>
</tr>
<tr>
<td>Didanosine</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Dihydrotachysterol</td>
<td>see Vitamin D</td>
</tr>
<tr>
<td>Diloxanide</td>
<td>Manufacturer advises avoid—significant amount present in milk—no evidence of harm but avoid unless no safer alternative</td>
</tr>
<tr>
<td>Diluziam</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Dimenhydrinate</td>
<td>Small amount present in milk—manufacturer advises caution</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>No information available</td>
</tr>
<tr>
<td>Disodium etidronate</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Disodium pamidronate</td>
<td>No information available</td>
</tr>
<tr>
<td>Disopyramide</td>
<td>Present in milk—use only if essential and monitor infant for antimuscarinic effects</td>
</tr>
<tr>
<td>Distigmine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Disulfiram</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Docusate sodium</td>
<td>Present in milk following oral administration—manufacturer advises caution; rectal administration not known to be harmful</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Dolasetron</td>
<td>Not known to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Domperidone</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Donepezil</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Doripenem</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies</td>
</tr>
<tr>
<td>Domase alfa</td>
<td>Amount probably too small to be harmful—manufacturer advises caution</td>
</tr>
<tr>
<td>Eplerenone</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td></td>
</tr>
<tr>
<td>Epinastine</td>
<td></td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Irritability and disturbed sleep reported</td>
</tr>
<tr>
<td>Epinephrine</td>
<td></td>
</tr>
<tr>
<td>Entecavir</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Present in milk—no adverse effects reported</td>
</tr>
<tr>
<td>Eclizumab</td>
<td>No information available—manufacturer advises avoid breast-feeding during and for 5 months after treatment</td>
</tr>
<tr>
<td>Enzaluzumab</td>
<td></td>
</tr>
<tr>
<td>Efizolubine</td>
<td>May be present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Efornithine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Etoriptan</td>
<td>Present in milk—avoid breast-feeding for 24 hours</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Emtricitabine</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Enfuvirtide</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Enoximone</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Entacapone</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Ephedrine</td>
<td>Irritability and disturbed sleep reported</td>
</tr>
<tr>
<td>Epinastine</td>
<td>Present in milk in animal studies—manufacturer advises caution</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>see Cytoxic Drugs</td>
</tr>
<tr>
<td>Eplerenone</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Fenoprofen</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Fosoterodine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Fexofenadine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Filgrastim</td>
<td>No information available—manufacturer advises avoid</td>
</tr>
<tr>
<td>Flavoxate</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Flecaïnide</td>
<td>Significant amount present in milk but not known to be harmful</td>
</tr>
<tr>
<td>Flucloxacillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Present in milk but amount probably too small to be harmful</td>
</tr>
<tr>
<td>Fluycytosine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Fluticasone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Follitropin alfa and beta</td>
<td>Avoid</td>
</tr>
<tr>
<td>Fomepizole</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Formoterol (efomoro- terol)</td>
<td>Amount in milk probably too small to be harmful but manufacturers advise avoid</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Fosaprepitant</td>
<td>see Neurokinin Receptor Antagonists</td>
</tr>
<tr>
<td>Foscarnet</td>
<td>Avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Fenofurate</td>
<td>see Phenytoin</td>
</tr>
<tr>
<td>Fosphenytoin</td>
<td>see Phenytoin</td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>Present in milk in animal studies— withheld breast-feeding for 24 hours</td>
</tr>
<tr>
<td>Frusenide</td>
<td>see Furosemide</td>
</tr>
<tr>
<td>Fulvestrant</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Furosemide (fruse- mide)</td>
<td>Amount too small to be harmful; may inhibit lactation</td>
</tr>
<tr>
<td>Fusidic acid</td>
<td>see Sodium Fusidate</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Present in milk—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Galantamine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Galsulfase</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Glucose</td>
<td>see Sulphurylureas</td>
</tr>
<tr>
<td>Glutathione</td>
<td>see Cysteamine</td>
</tr>
<tr>
<td>Glucocorticoids</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Glyceryl trinitrate</td>
<td>No information available—manufacturers advise use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Iloprost</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Imatinib</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Imidapril</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Imiglucerase</td>
<td>see Primazin*</td>
</tr>
<tr>
<td>Imipramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Imiquimod</td>
<td>Manufacturer advises no information available</td>
</tr>
<tr>
<td>Indapamid</td>
<td>No information available—</td>
</tr>
<tr>
<td>Indinavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Indometacin</td>
<td>Amount probably too small to be harmful but convulsions reported in one infant—manufacturer advises avoid</td>
</tr>
<tr>
<td>Infliximab</td>
<td>Avoid; manufacturer advises avoid for at least 6 months after last dose</td>
</tr>
<tr>
<td>Influenza vaccine</td>
<td>Not known to be harmful—</td>
</tr>
<tr>
<td>Interferons</td>
<td>Manufacturers advise avoid—</td>
</tr>
<tr>
<td>Iodine and iodides</td>
<td>Stop breast-feeding; danger of neonatal hypothyroidism or goitre; appears to be concentrated in milk; see also Povidone–iodine</td>
</tr>
<tr>
<td>Iodine, radioactive</td>
<td>Breast-feeding contra-indicated after therapeutic doses. With diagnostic doses withhold breast-feeding for at least 24 hours</td>
</tr>
<tr>
<td>Ipratropium</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Irbesartan</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Isonicotan</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant</td>
</tr>
<tr>
<td>Isosorbide dinitrate</td>
<td>No information available— manufacturers advise use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Isosorbide mononitrate</td>
<td>No information available— manufacturers advise use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Irsapipine</td>
<td>Manufacturer advises avoid— present in milk in animal studies</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>Small amounts present in milk—may accumulate; manufacturer advises avoid</td>
</tr>
<tr>
<td>Ivabradine</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Kaletra®</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>Amount probably too small to be harmful but manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>Amount too small to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Ketotifen</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Labetalol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Lacidipine</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Manufacturer advises avoid— present in milk in animal studies</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>Present in milk—manufacturer advises avoid; breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Present in milk but limited data suggest no harmful effects on infants</td>
</tr>
<tr>
<td>Lanreotide</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>Manufacturer advises avoid unless essential—present in milk in animal studies</td>
</tr>
<tr>
<td>Lanthanum</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Laronibib</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Latanoprost</td>
<td>May be present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Lefunomide</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>Manufacturer advises discontinue breast-feeding—no information available</td>
</tr>
<tr>
<td>Lenograstim</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Lepirudin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Lercanidipine</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Letrozole</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Leuprorelin</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Levobupivacaine</td>
<td>Likely to be present in milk but risk to infant minimal</td>
</tr>
<tr>
<td>Levocetirizine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Levodopa</td>
<td>May suppress lactation; present in milk—manufacturers advise avoid</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Levomepromazine (methotrexate)</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Levothryoxine (thyroxine)</td>
<td>Amount too small to affect tests for neonatal hypothyroidism</td>
</tr>
<tr>
<td>Lidocaine (lignocaine)</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Lignocaine</td>
<td>see Lidothine</td>
</tr>
<tr>
<td>Linezolid</td>
<td>Manufacturer advises avoid— present in milk in animal studies</td>
</tr>
<tr>
<td>Lithoynorine</td>
<td>Amount too small to affect tests for neonatal hypothyroidism</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>No information available—manufacturer advises avoid</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Lithium salts</td>
<td>Present in milk and risk of toxicity in infant—manufacturers advise avoid</td>
</tr>
<tr>
<td>Lofepramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Lofexidine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Loperamide</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Lopinavir [ingredient]</td>
<td>see Kaletra®</td>
</tr>
<tr>
<td>Loprazolam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Loratadine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Losartan</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Macrogols</td>
<td>Use only if no suitable alternative available; see also p. 355</td>
</tr>
<tr>
<td>Malarone®</td>
<td>see Riamet®</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Mebendazole</td>
<td>Amount too small to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Mecysteine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Medroxyprogesterone</td>
<td>Present in milk—no adverse effects reported</td>
</tr>
<tr>
<td>Mefenamic acid</td>
<td>Amount too small to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Melphalan</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Memantine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Menotrophin</td>
<td>No information available</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Avoid</td>
</tr>
<tr>
<td>Melphalan</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Avoid; concentration in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in infant</td>
</tr>
<tr>
<td>Meprobamate</td>
<td>Avoid; concentration in milk may exceed maternal plasma concentrations fourfold and may cause drowsiness in infant</td>
</tr>
<tr>
<td>Mercaptamine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Mercaptopurine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Meropenem</td>
<td>Unlikely to be absorbed (however, manufacturer advises avoid unless potential benefit justifies potential risk)</td>
</tr>
<tr>
<td>Mesalamine</td>
<td>Diarrhoea reported but manufacturers advise negligible amounts detected in breast milk</td>
</tr>
<tr>
<td>Mesterolone</td>
<td>see Androgens</td>
</tr>
<tr>
<td>Mestranol</td>
<td>see Oestrogens</td>
</tr>
<tr>
<td>Metaraminol</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Appendix 5: Breast-feeding

BNF 57
<table>
<thead>
<tr>
<th>Drug</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mitozantrone</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Mizolastine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Amount too small to be harm-</td>
</tr>
<tr>
<td></td>
<td>ful, but patient leaflet adv</td>
</tr>
<tr>
<td>Modafinil</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td></td>
<td>present in milk in animal s-</td>
</tr>
<tr>
<td>Moexipril</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Montelukast</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Morphine</td>
<td>Therapeutic doses unlikely to</td>
</tr>
<tr>
<td></td>
<td>affect infant; withdrawal</td>
</tr>
<tr>
<td></td>
<td>symptoms in infants of depen-</td>
</tr>
<tr>
<td></td>
<td>dent mothers; breast-feeding</td>
</tr>
<tr>
<td></td>
<td>not best method of treating</td>
</tr>
<tr>
<td></td>
<td>dependence in offspring</td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Moxonidine</td>
<td>Present in milk—manufacturer</td>
</tr>
<tr>
<td>Mupirocin</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Mofetil</td>
<td>present in milk in animal s-</td>
</tr>
<tr>
<td>Nabilone</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>No information available—</td>
</tr>
<tr>
<td>Nadolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Nafarelin</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Risk to infant very small bu-</td>
</tr>
<tr>
<td></td>
<td>t one case of haemolytic ana-</td>
</tr>
<tr>
<td></td>
<td>emia reported</td>
</tr>
<tr>
<td>Naloxone</td>
<td>No information available—</td>
</tr>
<tr>
<td>Naltrexone</td>
<td>Manufacturers advise avoid—</td>
</tr>
<tr>
<td>Naproxen</td>
<td>Amount too small to be harm-</td>
</tr>
<tr>
<td>Naratriptan</td>
<td>Manufacturer advises caution-</td>
</tr>
<tr>
<td>Natalizumab</td>
<td>Present in milk in animal s-</td>
</tr>
<tr>
<td>Nateglinide</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td></td>
<td>present in milk in animal s-</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Nedocromil</td>
<td>Unlikely to be present in</td>
</tr>
<tr>
<td>Nelorabine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Breast-feeding not advised</td>
</tr>
<tr>
<td>Neostigmine</td>
<td>Amount probably too small to</td>
</tr>
<tr>
<td></td>
<td>be harmful; monitor infant</td>
</tr>
<tr>
<td>Neurokinin receptor</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>antagonists</td>
<td>present in milk in animal s-</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>Breast-feeding not advised</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Nicorandil</td>
<td>No information available—</td>
</tr>
<tr>
<td></td>
<td>manufacturer advises avoid</td>
</tr>
<tr>
<td>Nicotine</td>
<td>Present in milk; intermittent</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Present in milk—avoid</td>
</tr>
<tr>
<td>Nicoumalone</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Amount too small to be harm-</td>
</tr>
<tr>
<td>Nilotinib</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Nimodipine</td>
<td>No information available—</td>
</tr>
<tr>
<td>Nitinsone</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Only small amounts in milk</td>
</tr>
<tr>
<td></td>
<td>could be enough to produce</td>
</tr>
<tr>
<td></td>
<td>haemolysis in G6PD-deficient</td>
</tr>
<tr>
<td>Nitroprusside</td>
<td>see Sodium Nitroprusside</td>
</tr>
<tr>
<td>Nizatidine</td>
<td>Amount too small to be harm-</td>
</tr>
<tr>
<td>Nonoxinol 9</td>
<td>Present in milk in animal s-</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>Higher doses may suppress</td>
</tr>
<tr>
<td></td>
<td>lactation and alter milk co-</td>
</tr>
<tr>
<td></td>
<td>mposition—use lowest effect-</td>
</tr>
<tr>
<td></td>
<td>ve dose; see also Contracept-</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>No information available—</td>
</tr>
<tr>
<td>Norgestimete</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Norgestrel</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>see Antidepressants, Tricyc-</td>
</tr>
<tr>
<td></td>
<td>(and related)</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>see individual entries</td>
</tr>
<tr>
<td>Nystatin</td>
<td>No information available, b-</td>
</tr>
<tr>
<td></td>
<td>ut absorption from gastro-in-</td>
</tr>
<tr>
<td></td>
<td>tesinal tract negligible</td>
</tr>
<tr>
<td>Octreotide</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>Avoid; adverse effects on</td>
</tr>
<tr>
<td></td>
<td>lactation; see also Contra-</td>
</tr>
<tr>
<td>Olfoxacin</td>
<td>Amount probably too small to</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td></td>
<td>present in milk</td>
</tr>
<tr>
<td>Olsalazine</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>Omalizumab</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td></td>
<td>present in milk in animal s-</td>
</tr>
<tr>
<td>Omega-3-acid ethyl</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td>esters</td>
<td>no information available—</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Present in milk but not kno-</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Not known to be harmful but</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>see individual entries</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>see Contraceptives, Oral</td>
</tr>
<tr>
<td>Orlistat</td>
<td>Manufacturer advises avoid—</td>
</tr>
<tr>
<td></td>
<td>no information available</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Orphenadrine</td>
<td>Manufacturers advise caution</td>
</tr>
<tr>
<td>Osetamivir</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Oxazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Oxicarbazepine</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Oxenolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Oxybutynin</td>
<td>Present in milk—manufacturers advise avoid</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Oxytetracycline</td>
<td>see Tetracyclines</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Palifermin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>Manufacturer advises avoid—present in milk</td>
</tr>
<tr>
<td>Palonosetron</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Pamidronate disodium</td>
<td>see Disodium Pamidronate</td>
</tr>
<tr>
<td>Pancuronium</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Manufacturer advises avoid breast-feeding during and for 3 months after treatment</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—small amount present in milk in animal studies</td>
</tr>
<tr>
<td>Papaveretum</td>
<td>see Morphine</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Paraldehyde</td>
<td>Manufacturer advises avoid unless essential—present in milk</td>
</tr>
<tr>
<td>Parecoxib</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Paricalcitol</td>
<td>Manufacturer advises caution—no information available; see also Vitamin D</td>
</tr>
<tr>
<td>Paroxetine</td>
<td>Present in milk but amount too small to be harmful</td>
</tr>
<tr>
<td>Pegaptinib</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Pegfilgrastim</td>
<td>No information available—manufacturer advises avoid</td>
</tr>
<tr>
<td>Peginterferon alfa</td>
<td>see Interferons</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Penicillamine</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Penicillins</td>
<td>Trace amounts in milk</td>
</tr>
<tr>
<td>Pentamidine isetionate</td>
<td>Manufacturer advises avoid unless essential</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>Small amount present in milk—manufacturer advises caution</td>
</tr>
<tr>
<td>Pentostatin</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Pergolide</td>
<td>May suppress lactation</td>
</tr>
<tr>
<td>Pericyazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Perindopril</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pethidine</td>
<td>Present in milk but not known to be harmful</td>
</tr>
<tr>
<td>Phenindione</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Avoid when possible; drowsiness may occur but risk probably small; one report of methaemoglobinemia with phenobarbital and phenytoin</td>
</tr>
<tr>
<td>Phenoxybenzamine</td>
<td>May be present in milk</td>
</tr>
<tr>
<td>Phenoxymethylpenicilllin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Small amount present in milk; manufacturer advises avoid—see section 4.8.1</td>
</tr>
<tr>
<td>Phytomenadione</td>
<td>Present in milk</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Pimozide</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Pindolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Piperacillic [ingredient]</td>
<td>see Tazocin®</td>
</tr>
<tr>
<td>Piperazine</td>
<td>Present in milk—manufacturer advises avoid breast-feeding for 8 hours after dose (express and discard milk during this time)</td>
</tr>
<tr>
<td>Piracetam</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Pivmecillinam</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Pizotifen</td>
<td>Amount probably too small to be harmful, but manufacturer advises avoid</td>
</tr>
<tr>
<td>Podophyllium</td>
<td>No information available—manufacturer advises avoid</td>
</tr>
<tr>
<td>Porfiner</td>
<td>No information available—manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Povidone–iodine</td>
<td>Avoid; iodine absorbed from vaginal preparations is concentrated in milk</td>
</tr>
<tr>
<td>Pramipexole</td>
<td>May suppress lactation; manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>Small amount present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Prazosin</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Present in milk in animal studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Prilocaine</td>
<td>Present in milk but not known to be harmful</td>
</tr>
<tr>
<td>Primaxin®</td>
<td>Present in milk but unlikely to be absorbed (however, manufacturer advises avoid)</td>
</tr>
<tr>
<td>Primidone</td>
<td>see Phenobarbital</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>----------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Probenecid</td>
<td>No information available</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Prochlorperazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Procyclidine</td>
<td>No information available</td>
</tr>
<tr>
<td>Progesterone</td>
<td>Manufacturers advise avoid—present in milk</td>
</tr>
<tr>
<td>Proguanil</td>
<td>Amount probably too small to be harmful when used for malaria prophylaxis; inadequate for reliable protection against malaria in breast-fed infant, see p. 355; for Proguanil with Atovaquone see Malarone®</td>
</tr>
<tr>
<td>Promazine</td>
<td>see Antipsychotics</td>
</tr>
<tr>
<td>Primethazine</td>
<td>see Antihistamines</td>
</tr>
<tr>
<td>Propafenone</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Propanephone</td>
<td>May suppress lactation</td>
</tr>
<tr>
<td>Proparphenone</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Propofol</td>
<td>Present in milk but amount probably too small to be harmful</td>
</tr>
<tr>
<td>Propranolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Propylthiouracil</td>
<td>Monitor infant’s thyroid status but amounts in milk probably too small to affect infant; high doses might affect neonatal thyroid function</td>
</tr>
<tr>
<td>Protirelin</td>
<td>Breast enlargement and leaking of milk reported</td>
</tr>
<tr>
<td>Pseudoephedrine</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Praziquantinel</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Pyridostigmine</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Pyrimethamine</td>
<td>Significant amount—avoid administration of other folic acid antagonists to infant; avoid breast-feeding during toxoplasmosis treatment</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Quinagolide</td>
<td>Suppresses lactation</td>
</tr>
<tr>
<td>Quinapril</td>
<td>Present in milk—manufacturers advise avoid</td>
</tr>
<tr>
<td>Quinupristin [ingredi-ent]</td>
<td>see Synercid®</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Ralitrexed</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Ramipril</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>Significant amount but not known to be harmful</td>
</tr>
<tr>
<td>Rasagiline</td>
<td>Manufacturer advises caution—may suppress lactation</td>
</tr>
<tr>
<td>Rasburicase</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Reboxetine</td>
<td>Small amount present in milk—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Manufacturer advises caution—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Repaglinide</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Retaploise</td>
<td>Manufacturer advises avoid breast-feeding for 24 hours after dose (express and discard milk during this time)</td>
</tr>
<tr>
<td>Ripamet®</td>
<td>Manufacturer advises avoid breast-feeding for at least 1 week after last dose; present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>Avoid—no information available</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Riluzole</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Rimonabant</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Risedronate sodium</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Avoid breast-feeding during and for 12 months after treatment</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Rivastigmine</td>
<td>Present in milk in <em>animal</em> studies—manufacturer advises avoid</td>
</tr>
<tr>
<td>Rizatrapir</td>
<td>Present in milk in <em>animal</em> studies—withhold breast-feeding for 24 hours</td>
</tr>
<tr>
<td>Rocuronium</td>
<td>Manufacturer advises avoid unless potential benefit outweighs risk—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Ropinirole</td>
<td>May suppress lactation—manufacturer advises avoid</td>
</tr>
<tr>
<td>Ropivacaine</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Rotigotine</td>
<td>May suppress lactation—manufacturer advises avoid</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>Probably present in milk; manufacturer advises avoid—unless potential benefit outweighs risk—the amount of inhaled drugs in breast milk is probably too small to be harmful</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Probably present in milk; manufacturer advises avoid</td>
</tr>
<tr>
<td>Calcitonin (salmon)</td>
<td>see Calcitonin (salmon)</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>------------------------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Secobarbital</td>
<td>see Barbiturates</td>
</tr>
<tr>
<td>Selegiline</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Senna</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Sertindole</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Sertraline</td>
<td>Present in milk but not known to be harmful in short-term use</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>Manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Sibutramine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>No information available</td>
</tr>
<tr>
<td>Silver sulfadiazine</td>
<td>see Sulphonamides</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>see Statins</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Discontinue breast-feeding</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Sitaxentan sodium</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Sodium aurothiomolate</td>
<td>Caution—present in milk; theoretical possibility of rashes and idiosyncratic reactions</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>No information available</td>
</tr>
<tr>
<td>Sodium cromoglicate</td>
<td>Unlikely to be present in milk</td>
</tr>
<tr>
<td>Sodium fusidate</td>
<td>Present in milk—manufacturer advises caution</td>
</tr>
<tr>
<td>Sodium nitroprusside</td>
<td>No information available; caution advised due to cyanide metabolite</td>
</tr>
<tr>
<td>Sodium oxybate</td>
<td>No information available</td>
</tr>
<tr>
<td>Sodium phenylbutyrate</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Sodium picosulfate</td>
<td>Not known to be present in milk but manufacturer advises avoid</td>
</tr>
<tr>
<td>Sodium stibogluconate</td>
<td>Amount probably too small to be harmful</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Somatropin</td>
<td>No information available</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>see Cytoxic Drugs</td>
</tr>
<tr>
<td>Sotalol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Amount probably too small to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Statins</td>
<td>Manufacturers of atorvastatin, fluvastatin, rosuvastatin and simvastatin advise avoid—no information available; see also pravastatin</td>
</tr>
<tr>
<td>Stavudine</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>Avoid</td>
</tr>
<tr>
<td>Sulfadiazine</td>
<td>see Sulphonamides</td>
</tr>
<tr>
<td>Sulfasalazine</td>
<td>Small amounts in milk (1 report of bloody diarrhoea and rashes); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>No information available</td>
</tr>
<tr>
<td>Tabelenazine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Tacaridil</td>
<td>No information available</td>
</tr>
<tr>
<td>Tacalcitrol</td>
<td>Manufacturer advises avoid application to breast area—no information available; see also Vitamin D</td>
</tr>
<tr>
<td>Tacuridil</td>
<td>Avoid—present in milk following systemic administration</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Supresses lactation; manufacturer advises avoid unless potential benefit outweighs risk</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Tazobactam [ingredient]</td>
<td>see Tazocin®</td>
</tr>
<tr>
<td>Tazocin®</td>
<td>Present in milk—manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>tegafur with uracil</td>
<td>see Cytoxic Drugs</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>No information available</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Telithromycin</td>
<td>Manufacturer advises avoid—present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Telmisartan</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Temazepam</td>
<td>see Benzodiazepines</td>
</tr>
<tr>
<td>Temocillin</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Temoparin</td>
<td>Manufacturer advises avoid breast-feeding for at least 1 month after treatment—no information available</td>
</tr>
<tr>
<td>Temozolomide</td>
<td>see Cytoxic Drugs</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>see Cytoxic Drugs</td>
</tr>
<tr>
<td>Tenecteplase</td>
<td>Manufacturer advises avoid breast-feeding for 24 hours (express and discard milk during this time)</td>
</tr>
<tr>
<td>Tenoforv</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>Present in milk in <em>animal</em> studies</td>
</tr>
<tr>
<td>Teratosin</td>
<td>No information available</td>
</tr>
<tr>
<td>Terbinafine</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Terlipressin</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Testosterone</td>
<td>see Androgens</td>
</tr>
<tr>
<td>Tetrobenazine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>No information available</td>
</tr>
<tr>
<td>Tetracycline cyclohexylamide</td>
<td>No information available</td>
</tr>
<tr>
<td>Tetracycline lactate</td>
<td>No information available</td>
</tr>
<tr>
<td>Tetracycline succinylamide</td>
<td>No information available</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>------------------------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Avoid (although absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk); see also tigecycline</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Theophylline</td>
<td>Present in milk—irritability in infant reported; modified-release preparations preferable</td>
</tr>
<tr>
<td>Thiamine</td>
<td>Severely thiamine-deficient mothers should avoid breast-feeding as toxic methyl-glyoxal present in milk</td>
</tr>
<tr>
<td>Thiazides and related diuretics</td>
<td>Amount too small to be harmful; large doses may suppress lactation</td>
</tr>
<tr>
<td>Thiopental</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Thiopental</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Timolol</td>
<td>see Beta-blockers</td>
</tr>
<tr>
<td>Tinidazole</td>
<td>Present in milk—manufacturer advises avoid during and for 3 days after stopping treatment</td>
</tr>
<tr>
<td>Tinzaparin</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Tioguanine</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Tiotropium</td>
<td>Amount in milk probably too small to be harmful (present in milk in animal studies) — manufacturer advises use only if potential benefit outweighs risk</td>
</tr>
<tr>
<td>Tipranavir</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Tizanidine</td>
<td>Manufacturer advises use only if potential benefit outweighs risk—no information available</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>see Sulphonylureas</td>
</tr>
<tr>
<td>Tolcapone</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Tolfenamic acid</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Tolterodine</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Manufacturer advises avoid—present in milk</td>
</tr>
<tr>
<td>Topotecan</td>
<td>see Penicillins</td>
</tr>
<tr>
<td>Torasemide</td>
<td>No information available</td>
</tr>
<tr>
<td>Trabectedin</td>
<td>Manufacturer advises avoid breast-feeding during and for 3 months after treatment</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Amount probably too small to be harmful, but manufacturer advises avoid</td>
</tr>
<tr>
<td>Trandolapril</td>
<td>Manufacturers advise avoid</td>
</tr>
<tr>
<td>Tranexamic acid</td>
<td>Small amount present in milk—antifibrinolytic effect in infant unlikely</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Avoid breast-feeding during treatment and for six months after</td>
</tr>
<tr>
<td>Travoprost</td>
<td>Present in milk in animal studies; manufacturer advises avoid</td>
</tr>
<tr>
<td>Trazodone</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Treosulfan</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Avoid</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>see Corticosteroids</td>
</tr>
<tr>
<td>Triamterene</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Trimipramine</td>
<td>see Antidepressants, Tricyclic (and related)</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>Present in milk—short-term use not known to be harmful</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>No information available</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>Manufacturers advise avoid</td>
</tr>
<tr>
<td>Tropolium</td>
<td>Manufacturer advises caution—no information available</td>
</tr>
<tr>
<td>Tryptophan</td>
<td>No information available</td>
</tr>
<tr>
<td>Urokinase</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Ursodeoxycholic acid</td>
<td>Not known to be harmful but manufacturer advises avoid</td>
</tr>
<tr>
<td>Valaciclovir</td>
<td>No information available; see also Aciclovir</td>
</tr>
<tr>
<td>Valganclovir</td>
<td>see Ganciclovir</td>
</tr>
<tr>
<td>Valproate</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>see Valproate</td>
</tr>
<tr>
<td>Valsartan</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>Present in milk—significant absorption following oral administration unlikely</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Present in milk in animal studies</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Not known to be harmful</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>No information available</td>
</tr>
<tr>
<td>Vecuronium</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Amount too small to be harmful</td>
</tr>
<tr>
<td>Verteporfin</td>
<td>No information available</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Vindesine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Vincristine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Drug</td>
<td>Comment</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>see Cytotoxic Drugs</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Theoretical risk of toxicity in infants of mothers taking large doses</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Caution with high systemic doses; may cause hypercalcaemia in infant—monitor serum-calcium concentration; manufacturer of topical calcitriol advises avoid; see also Calcipotriol, Paricalcitol, and Tacalcitol</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Warfarin</td>
<td>see Anticoagulants, Oral</td>
</tr>
<tr>
<td>Xipamidine</td>
<td>No information available</td>
</tr>
<tr>
<td>Zafirlukast</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Zaleplon</td>
<td>Present in milk but amount probably too small to be harmful</td>
</tr>
<tr>
<td>Zanamivir</td>
<td>Manufacturer advises avoid—present in milk in animal studies</td>
</tr>
<tr>
<td>Zidovudine</td>
<td>Breast-feeding not advised in HIV infection</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>Manufacturer advises avoid—no information available</td>
</tr>
<tr>
<td>Zolmitriptan</td>
<td>Manufacturer advises caution—present in milk in animal studies</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Small amounts present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Avoid; manufacturer advises avoid breast-feeding for 4 weeks after administration</td>
</tr>
<tr>
<td>Zopiclone</td>
<td>Present in milk—manufacturer advises avoid</td>
</tr>
<tr>
<td>Zotepine</td>
<td>Manufacturer advises avoid</td>
</tr>
<tr>
<td>Zuclopenthixol</td>
<td>see Antipsychotics</td>
</tr>
</tbody>
</table>
Intravenous additives policies

A local policy on the addition of drugs to intravenous fluids should be drawn up by a multi-disciplinary team in each Strategic Health Authority (or equivalent) and issued as a document to the members of staff concerned.

Centralised additive services are provided in a number of hospital pharmacy departments and should be used in preference to making additions on wards.

The information that follows should be read in conjunction with local policy documents.

Guidelines

1. Drugs should only be added to infusion containers when constant plasma concentrations are needed or when the administration of a more concentrated solution would be harmful.

2. In general, only one drug should be added to any infusion container and the components should be compatible. Ready-prepared solutions should be used whenever possible. Drugs should not normally be added to blood products, mannitol, or sodium bicarbonate. Only specially formulated additives should be used with fat emulsions or amino-acid solutions (section 9.3).

3. Solutions should be thoroughly mixed by shaking and checked for absence of particulate matter before use.

4. Strict asepsis should be maintained throughout and in general the giving set should not be used for more than 24 hours (for drug admixtures).

5. The infusion container should be labelled with the patient’s name, the name and quantity of additives, and the date and time of addition (and the new expiry date or time). Such additional labelling should not interfere with information on the manufacturer’s label that is still valid. When possible, containers should be retained for a period after use in case they are needed for investigation.

6. It is good practice to examine intravenous infusions from time to time while they are running. If cloudiness, crystallisation, change of colour, or any other sign of interaction or contamination is observed the infusion should be discontinued.

Problems

Microbial contamination

The accidental entry and subsequent growth of micro-organisms converts the infusion fluid pathway into a potential vehicle for infection with micro-organisms, particularly species of Candida, Enterobacter, and Klebsiella. Ready-prepared infusions containing the additional drugs, or infusions prepared by an additive service (when available) should therefore be used in preference to making extemporaneous additions to infusion containers on wards etc.

However, when this is necessary strict aseptic procedure should be followed.

Incompatibility

Physical and chemical incompatibilities may occur with loss of potency, increase in toxicity, or other adverse effect. The solutions may become opalescent or precipitation may occur, but in many instances there is no visual indication of incompatibility. Interaction may take place at any point in the infusion fluid pathway, and the potential for incompatibility is increased when more than one substance is added to the infusion fluid.

Common incompatibilities

Precipitation reactions are numerous and varied and may occur as a result of pH, concentration changes, ‘salting-out’ effects, complexation or other chemical changes. Precipitation or other particle formation must be avoided since, apart from lack of control of dosage on administration, it may initiate or exacerbate adverse effects. This is particularly important in the case of drugs which have been implicated in either thrombophlebitis (e.g. diazepam) or in skin sloughing or necrosis caused by extravasation (e.g. sodium bicarbonate and certain cytotoxic drugs). It is also especially important to effect solution of colloidal drugs and to prevent their subsequent precipitation in order to avoid a pyrogenic reaction (e.g. amphotericin).

It is considered undesirable to mix beta-lactam antibiotics, such as semi-synthetic penicillins and cephalosporins, with proteinaceous materials on the grounds that immunogenic and allergenic conjugates could be formed.

A number of preparations undergo significant loss of potency when added singly or in combination to large volume infusions. Examples include ampicillin in infusions that contain glucose or lactates. The breakdown products of dacarbazine have been implicated in adverse effects.

Blood

Because of the large number of incompatibilities, drugs should not normally be added to blood and blood products for infusion purposes. Examples of incompatibility with blood include hypertonic mannitol solutions (irreversible crenation of red cells), dextrans (rouleaux formation and interference with cross-matching), glucose (clumping of red cells), and oxytocin (inactivated).

If the giving set is not changed after the administration of blood, but used for other infusion fluids, a fibrin clot may form which, apart from blocking the set, increases the likelihood of microbial growth.

Intravenous fat emulsions

These may break down with coalescence of fat globules and separation of phases when additions such as antibacterials or electrolytes are made, thus increasing the possibility of embolism. Only specially formulated products such as Vitlipid N® (section 9.3) may be added to appropriate intravenous fat emulsions.

Other infusions

Infusions that frequently give rise to incompatibility include amino acids, mannitol, and sodium bicarbonate.
Appendix 6: Intravenous additives

**Potassium chloride** are present in some injection solutions. The total volume of such solutions added to a container for infusion on one occasion should not exceed 15 mL.

**Method**

Ready-prepared infusions should be used whenever available. **Potassium chloride** is usually available in concentrations of 20, 27, and 40 mmol/litre in sodium chloride intravenous infusion (0.9%), glucose intravenous infusion (5%) or sodium chloride and glucose intravenous infusion. **Lidocaine hydrochloride** (lignocaine hydrochloride) is usually available in concentrations of 0.1 or 0.2% in glucose intravenous infusion (5%).

When addition is required to be made extemporaneously, any product reconstitution instructions such as those relating to concentration, vehicle, mixing, and handling precautions should be strictly followed using an aseptic technique throughout. Once the product has been reconstituted, addition to the infusion fluid should be made immediately in order to minimise microbial contamination and, with certain products, to prevent degradation or other formulation change which may occur; e.g. reconstituted ampicillin injection degrades rapidly on standing, and also may form polymers which could cause sensitivity reactions.

It is also important in certain instances that an infusion fluid of specific pH be used (e.g. furosemide (frusemide) injection requires dilution in infusions of pH greater than 5.5).

When drug additions are made it is important to mix thoroughly; additions should not be made to an infusion container that has been connected to a giving set, as mixing is hampered. If the solutions are not thoroughly mixed a concentrated layer of the additive may form owing to differences in density. **Potassium chloride** is particularly prone to this ‘layering’ effect when added without adequate mixing to infusions packed in non-rigid infusion containers; if such a mixture is administered it may have a serious effect on the heart.

A time limit between addition and completion of administration must be imposed for certain admixtures to guarantee satisfactory drug potency and compatibility. For admixtures in which degradation occurs without the formation of toxic substances, an acceptable limit is the time taken for 10% decomposition of the drug. When toxic substances are produced stricter limits may be imposed. Because of the risk of microbial contamination a maximum time limit of 24 hours may be appropriate for additions made elsewhere than in hospital pharmacies offering central additive service.

Certain injections must be protected from light during continuous infusion to minimise oxidation, e.g. amphotericin, dacarbazine, and sodium nitroprusside.

Dilution with a small volume of an appropriate vehicle and administration using a motorised infusion pump is advocated for preparations such as heparin where strict control over administration is required. In this case the appropriate dose may be dissolved in a convenient volume (e.g. 24 to 48 mL) of sodium chloride intravenous infusion (0.9%).

**Use of table**

The table lists preparations given by three methods: continuous infusion, intermittent infusion, and addition via the drip tubing.

**Drugs for continuous infusion** must be diluted in a large volume infusion. Penicillins and cephalosporins are not usually given by continuous infusion because of stability problems and because adequate plasma and tissue concentrations are best obtained by intermittent infusion. Where it is necessary to administer them by continuous infusion, detailed literature should be consulted.

Drugs that are both compatible and clinically suitable may be given by intermittent infusion in a relatively small volume of infusion over a short period of time, e.g. 100 mL in 30 minutes. The method is used if the product is incompatible or unstable over the period necessary for continuous infusion; the limited stability of ampicillin or amoxicillin in large volume glucose or lactate infusions may be overcome in this way.

Intermittent infusion is also used if adequate plasma and tissue concentrations are not produced by continuous infusion as in the case of drugs such as dacarbazine, gentamicin, and tetracyclines.

An in-line burette may be used for intermittent infusion techniques in order to achieve strict control over the time and rate of administration, especially for infants and children and in intensive care units. Intermittent infusion may also make use of the ‘piggy-back’ technique provided that no additions are made to the primary infusion. In this method the drug is added to a small secondary container connected to a Y-type injection site on the primary infusion giving set; the secondary solution is usually infused within 30 minutes.

Addition via the drip tubing is indicated for a number of cytotoxic drugs in order to minimise extravasation. The preparation is added aseptically via the rubber septum of the injection site of a fast-running infusion. In general, drug preparations intended for a bolus effect should be given directly into a separate vein where possible. Failing this, administration may be made via the drip tubing provided that the preparation is compatible with the infusion fluid when given in this manner.

**Table of drugs given by intravenous infusion**

Covers addition to Glucose intravenous infusion 5 and 10%, Sodium chloride intravenous infusion 0.9%, Compound sodium chloride intravenous infusion (Ringer’s solution), and Compound sodium lactate intravenous infusion (Hartmann’s solution). Compatibility with glucose 5% and with sodium chloride 0.9% indicates compatibility with Sodium chloride and glucose intravenous infusion. Infusion of a large volume of hypotonic solution should be avoided therefore care should be taken if water for injections is used. The information in the Table relates to the proprietary preparations indicated; for other preparations suitability should be checked with the manufacturer.
**Appendix 6: Intravenous additives**

**Abatacept (Orencia®)**
Intermittent in Sodium chloride 0.9%
Reconstitute each vial with 10 mL water for injections using the silicone-free syringe provided. Dilute requisite dose in infusion fluid to 100 mL, (using the same silicone-free syringe), give over 30 minutes through a low protein-binding filter ( pore size 0.2–1.2 micron).

**Abciximab (ReoPro®)**
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute requisite dose in infusion fluid and give via infusion pump; filter upon dilution with infusion fluid through a low-protein binding 0.2, 0.22, or 5 micron filter or upon administration through an in-line non-proteinogenic low protein-binding 0.2 or 0.22 micron filter.

**Acetylcysteine (Parvolex®)**
Continuous in Glucose 5% or Sodium chloride 0.9%
Glucose 5% is preferable—see Emergency Treatment of Poisoning.

**Aciclovir (as sodium salt) (Zovirax IV®, Aciclovir IV, Hospira; Aciclovir IV, Genus; Aciclovir Sodium, Zurich)**
Intermittent in Sodium chloride 0.9% or Sodium chloride and glucose or Compound sodium lactate For Zovirax IV®, Aciclovir IV (Genus) initially reconstitute to 25 mg/mL in water for injections or sodium chloride 0.9% then dilute to not more than 5 mg/mL with the infusion fluid, to be given over 1 hour, alternatively, may be administered in a concentration of 25 mg/mL with a suitable infusion pump and given over 1 hour; for Aciclovir IV (Hospira) dilute to not more than 5 mg/mL with infusion fluid, give over 1 hour.

**Agalsidase alfa (Replagel®)**
Intermittent in Sodium chloride 0.9%
Dilute requisite dose with 100 mL infusion fluid and give over 40 minutes using an in-line filter; use within 3 hours of dilution.

**Agalsidase beta (Fabrazyme®)**
Intermittent in Sodium chloride 0.9%
Reconstitute with water for injections (35 mg in 7.2 mL, 5 mg in 1.1 mL) to produce a solution containing 5 mg/mL, dilute with infusion fluid (for doses less than 35 mg dilute with at least 50 mL, doses 35–70 mg dilute with at least 100 mL, doses 70–100 mg dilute with at least 250 mL, doses greater than 100 mg dilute with 500 mL) and give through an in-line low protein-binding 0.2 micron filter at an initial rate of no more than 15 mg/hour; for subsequent infusions, infusion rate may be increased gradually once tolerance has been established.

**Alemutzumab (MabCampath®)**
Intermittent in Glucose 5% or Sodium chloride 0.9%
Add requisite dose to 100 mL infusion fluid; infuse over 2 hours.

**Alfentanil (as hydrochloride) (Rapifen®)**
Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

**Algglucosidase alfa (Myozyme®)**
Intermittent in Sodium chloride 0.9%
Reconstitute 50 mg with 10.3 mL water for injections to produce 5 mg/mL solution, gently rotate vial without shaking; dilute requisite dose with infusion fluid to give a final concentration of 0.5–4 mg/mL, give through a low protein-binding in-line filter (0.2 micron) at an initial rate of 1 mg/kg/hour increased by 1 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour.

**Alprostadil (Prostin VR®)**
Continuous in Glucose 5% or Sodium chloride 0.9%
Add directly to the infusion solution avoiding contact with the walls of plastic containers.

**Alteplase (Actilyse®)**
Continuous or intermittent in Sodium chloride 0.9%
Dissolve in water for injections to a concentration of 1 mg/mL or 2 mg/mL and infuse intravenously, alternatively dilute the solution further in the infusion fluid to a concentration of not less than 200 micrograms/mL; not to be infused in glucose solution

**Amikacin sulphate (Amikin®)**
Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate
To be given over 30 minutes.

**Aminophylline**
Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

**Amiodarone hydrochloride (Cordarone®)**
Continuous or intermittent in Glucose 5%
Suggested initial infusion volume 250 mL given over 20–120 minutes; for repeat infusions up to 1.2 g in max. 500 mL; infusion in extreme emergency see section 2.7.3, should not be diluted to less than 600 micrograms/mL, incompatible with sodium chloride infusion, avoid equipment containing the plasticizer di-2-ethylhexylphthalate (DEHP).

**Amoxicillin (as sodium salt) (Amoxil®)**
Intermittent in Glucose 5% or Sodium chloride 0.9%
Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes via drip tubing in Glucose 5% or Sodium chloride 0.9%
Continuous infusion not usually recommended

**Amphotericin (colloidal) (Amphocil®)**
Intermittent in Glucose 5%
Initially reconstitute with water for injections (30 mg in 10 mL, 100 mg in 20 mL) shaking gently to dissolve (fluid may be opalescent) to produce a colloidal concentration of 1 mg/mL (1 volume of reconstituted solution with 7 volumes of infusion fluid); give at a rate of 1–2 mg/kg/hour or slower if not tolerated (initial test dose 2 mg of a 100 microgram/mL solution over 10 minutes), incompatible with sodium chloride or other electrolyte solutions, flush existing intravenous line with glucose 5% or use separate line

**Amphotericin (lipid complex) (Abelcet®)**
Intermittent in Glucose 5%
Allow suspension to reach room temperature, shake gently to ensure no yellow settlement, withdraw requisite dose (using 17–19 gauge needle) into one or more 20 mL syringes; replace needle on syringe with a 5-micron filter needle provided (fresh needle for each syringe) and dilute to a concentration of 1 mg/mL (2 mg/mL can be used in fluid restriction and in children); preferably give via an infusion pump at a rate of 2.5 mg/kg/hour (initial test dose of 1 mg given over 15 minutes); an in-line filter (pore size no less than 15 micron) may be used, do not use sodium chloride or other electrolyte solutions, flush existing intravenous line with glucose 5% or use separate line

**Amphotericin (as deoxycholate complex) (Fungizone®)**
Intermittent in Glucose 5%
Reconstitute each vial with 12 mL water for injections and shake vigorously to produce a preparation containing 4 mg/mL, withdraw requisite dose from vial and introduce into infusion fluid through the 5 micron filter provided to produce a final concentration of 0.2–2 mg/mL, infuse over 30–60 minutes (initial test dose 1 mg over 10 minutes); incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or use separate line.

**Amphotericin (as sodium deoxycholate complex) (AmBisome®)**
Intermittent in Glucose 5%
Reconstitute each vial with 10 mL water for injections and shake immediately to produce a 5 mg/mL colloidal solution, dilute further in infusion fluid to a concentration of 100 micrograms/mL, pH of the glucose must not be below 4.2 (check each container—consult product literature for details of buffer), infuse over 2–4 hours, or longer if not tolerated (initial test dose 1 mg over 20–30 minutes), begin infusion on a preferably after dilution and protect from light; incompatible with sodium chloride solutions, flush existing intravenous line with glucose 5% or use separate line; an in-line filter (pore size no less than 1 micron) may be used

**Ampicillin sodium (Penbritin®)**
Intermittent in Glucose 5% or Sodium chloride 0.9%
Reconstituted solutions diluted and given without delay, suggested volume 100 mL given over 30–60 minutes via drip tubing in Glucose 5% or Sodium chloride 0.9% or Ringer's solution or Compound sodium lactate
Continuous infusion not usually recommended.
Appendix 6: Intravenous additives

Amsacrine (Arsidine®)
Intermittent in Glucose 5%
Reconstitute with diluent provided and dilute to suggested volume 500 mL; give over 60–90 minutes; use glass syringes; incompatible with sodium chloride infusion

Anidulafungin (Ecalta®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Reconstitute each 100 mg with solvent provided, allow up to 5 minutes for reconstitution; dilute dose in infusion fluid to a concentration of 360 micrograms/mL; give at a rate not exceeding 1.1 mg/minute

Antithymocyte immunoglobulin (Thymoglobulin®)
Continuous in Glucose 5% or Sodium chloride 0.9%
Reconstitute each vial with 5 mL water for injections to produce a solution of 5 mg/mL; gently rotate to dissolve. Dilute requisite dose with infusion fluid to a total volume of 50–500 mL (usually 50 mL/vial); begin infusion immediately after dilution, give through an in-line filter (pore size 0.22 micron); not to be given with heparin and hydrocortisone in glucose infusion as precipitation reported

Arsenic trioxide (Trisenox®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute requisite dose with 100–250 mL infusion fluid, infuse over 1–2 hours (up to 4 hours if vasomotor reactions observed)

Atenolol (Tenormin®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Suggested infusion time 20 minutes

Atosiban (Tractocile® concentrate for intravenous infusion)
Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate
Withdraw 10 mL infusion fluid from 100-mL bag and replace with 10 mL atosiban concentrate (7.5 mg/mL) to produce a final concentration of 750 micrograms/mL

Atracurium besilate (Atracurium injection/infusion)
Continuous in Glucose 5% or Sodium chloride 0.9%
Intermittent in Sodium chloride 0.9%
Reconstitute each 250-mg vial with 5 mL water for injections; then dilute requisite dose in 250 mL infusion fluid (35- or 50-mg doses may be diluted in 100 mL infusion fluid if necessary); give over 60 minutes; incompatible with sodium solutions

Azathioprine (as sodium salt) (Imuran®)
Intermittent in Sodium chloride 0.9% or Sodium chloride and glucose
Reconstitute 50 mg with 5–15 mL water for injections; dilute with 20–200 mL infusion fluid

Aztreonam (Azactam®)
Intermittent in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate
Dissolve initially in water for injections (1 g per 3 mL) then dilute to a concentration of less than 20 mg/mL; to be given over 20–60 minutes

Basiliximab (Simulect®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Reconstitute 10 mg with 5 mL water for injections then dilute to at least 25 mL with infusion fluid, reconstitute 20 mg with 10 mL water for injections then dilute to at least 50 mL with infusion fluid, give over 20–30 minutes

Benzydamine (Crystapen®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Suggested volume 100 mL given over 30–60 minutes

Betamethasone (as sodium phosphate) (Betnesol®)
Continuous or intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%

Bevacizumab (Avastin®)
Intermittent in Sodium chloride 0.9%
Dilute requisite dose in infusion fluid to 100 mL and give over 90 minutes, if initial dose well tolerated give second dose over 60 minutes; if second dose well tolerated give subsequent doses over 30 minutes, incompatible with glucose solutions

Bivalirudin (Angiox®)
Continuous in Glucose 5% or Sodium chloride 0.9%
Reconstitute each 250-mg vial with 5 mL water for injections then withdraw 5 mL and dilute to 50 mL with infusion fluid

Bleomycin sulphate
Intermittent in Sodium chloride 0.9%
To be given slowly, suggested volume 200 mL

Bumetanide (Burinex®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Suggested volume 500 mL given over 30–60 minutes

Busulfan (Busilve®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute to a concentration of 500 micrograms/mL; give through a central venous catheter over 2 hours

Calcitonin (salmon)/Salgotatin (Miacalcic®)
Intermittent in Sodium chloride 0.9%
Diluted solution given without delay; dilute in 500 mL and give over at least 6 hours, glass or hard plastic containers should not be used; some loss of potency on dilution and administration

Calcium folinate (Calcium Leucovorin®, Refolin®)
Intermittent in Sodium chloride 0.9%
Calcium Leucovorin can also be infused in Glucose 5 and 10% or Compound sodium lactate
Protect from light

Calcium gluconate
Continuous in Glucose 5% or Sodium chloride 0.9%
Avoid bicarbonates, phosphates, or sulphates

Calcium levofolinate (Isovorin®)
Intermittent in Glucose 5 and 10% or Sodium chloride 0.9% or Compound sodium lactate
Final concentration as low as 500 micrograms/mL; give over 15–60 minutes

Caspofungin (Cancidas®)
Intermittent in Sodium chloride 0.9% or Compound sodium lactate
Allow vial to reach room temperature, initially reconstitute each vial with 10.5 mL water for injections, mixing gently to dissolve then dilute requisite dose in 250 mL infusion fluid (35- or 50-mg doses may be diluted in 100 mL infusion fluid if necessary); give over 60 minutes; incompatible with sodium solutions

Cefotaxime (as sodium salt)
Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate or Water for injections
Suggested volume 40–100 mL given over 20–60 minutes; incompatible with sodium solutions

Cefadoline (Velocef®)
Continuous or intermittent in Glucose 5% and 10% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate
Reconstitute 500 mg with 5 mL water for injections or glucose 5% or sodium chloride 0.9% then dilute with infusion fluid

Ceftazidime (as pentahydrate) (Fortum®, Kefadim®)
Intermittent or via drip tubing in Glucose 5 and 10% or Sodium chloride 0.9% or Compound sodium lactate
Dissolve 2 g initially in 10 mL (3 g in 15 mL) infusion fluid, for Fortum dilute further to a concentration of 40 mg/mL; for Kefadim dilute further to a concentration of 20 mg/mL, give over up to 30 minutes
Ceftriaxone (as sodium salt) (Rocephin<sup>®</sup>; Ceftriaxone Injection, Genus)  
**Intermittent or via drip tubing in Glucose 5% and 10% or Sodium chloride 0.9%**  
Reconstitute 2-g vial with 40 mL infusion fluid; give intermittent infusion over at least 30 minutes (60 minutes in neonates); not to be given with total parenteral nutrition or infusion fluids containing calcium, even by different infusion lines

Cefuroxime (as sodium salt) (Zinacef<sup>®</sup>)  
**Intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate**  
Dissolve initially in water for injections (at least 2 mL for each 250 mg, 15 mL for 1.5 g); suggested volume 50–100 mL given over 30 minutes

Chloramphenicol (as sodium succinate) (Kemicetine<sup>®</sup>)  
**Intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%**

Ciclosporin (Sandimmun<sup>®</sup>)  
**Intermittent or continuous in Glucose 5% or Sodium chloride 0.9%**  
Dilute to a concentration of 0.1–2 mg/mL; give intermittent infusion over 2–6 hours; not to be used with PVC equipment

Cidofovir (Vistide<sup>®</sup>)  
**Intermittent in Sodium chloride 0.9%**  
Dilute requisite dose with 100 mL infusion fluid; infuse over 1 hour

Cisatracurium (Nimbex<sup>®</sup>, Nimbex Forte<sup>®</sup>)  
**Continuous in Glucose 5% or Sodium chloride 0.9%**  
Solutions of 2 mg/mL and 5 mg/mL may be infused undiluted; alternatively dilute with infusion fluid to a concentration of 10–30 mg/L

Cisplatin (Cisplatin, Pharmacia; Cisplatin injection solution, Hospira)  
**Intermittent in Sodium chloride 0.9% or Sodium chloride and glucose**  
Reconstitute initially with water for injections to produce 1 mg/mL then dilute in 2 litres infusion fluid; give over 6–8 hours

Cladribine (Leustar<sup>®</sup>)  
**Continuous in Sodium chloride 0.9%**  
Dilute with 100–500 mL; glucose solutions are unsuitable

Clarithromycin (Klacid<sup>®</sup> I.V.)  
**Intermittent in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate**  
Dissolve initially in water for injections (500 mg in 10 mL) then dilute to a concentration of 2 mg/mL; give over 60 minutes

Clindamycin (as phosphate) (Dalacin<sup>®</sup> C Phosphate)  
**Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%**  
Dilute to not more than 18 mg/mL and give over 10–60 minutes at a rate not exceeding 30 mg/minute (1.2 g over at least 60 minutes; higher doses by continuous infusion)

Clolarabine (Evoltra<sup>®</sup>)  
**Intermittent in Sodium chloride 0.9%**  
Filter requisite dose through a 0.2 micron filter and dilute with infusion fluid; give over 2 hours

Clonazepam (Rivotril<sup>®</sup>)  
**Intermittent in Glucose 5% and 10% or Sodium chloride 0.9%**  
Suggested volume 250 mL

Co-amoxiclav (Augmentin<sup>®</sup>; Co-amoxiclav Injection, Wockhardt)  
**Intermittent in Sodium chloride 0.9% or Water for injections; see also package leaflet**  
Suggested volume 50–100 mL given over 30–40 minutes and completed within 4 hours of reconstitution  
**via drip tubing in Glucose 5% or Sodium chloride 0.9%**

Co-fluampicil (as sodium salts) (Magnapen<sup>®</sup>)  
**Intermittent in Glucose 5% or Sodium chloride 0.9%**  
Reconstituted solutions diluted and given without delay; suggested volume 100 mL given over 30–60 minutes  
**via drip tubing in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate**

Colistimethate sodium (Colomycin<sup>®</sup>)  
**Intermittent in Sodium chloride 0.9% or Water for injections**  
Dilute with 50 mL infusion fluid and give over 30 minutes

Co-trimoxazole (Septrin<sup>®</sup> for infusion)  
**Intermittent in Glucose 5% and 10% or Sodium chloride 0.9% or Ringer’s solution**  
Dilute contents of 1 ampoule (5 mL) to 125 mL; 2 ampoules (10 mL) to 250 mL or 3 ampoules (15 mL) to 500 mL; suggested duration of infusion 60–90 minutes (but may be adjusted according to fluid requirements); if fluid restriction necessary, 1 ampoule (5 mL) may be diluted with 75 mL glucose 5% and infused over max. 60 minutes

Cyclophosphamide (Endoxana<sup>®</sup>)  
**via drip tubing in Glucose 5% or Sodium chloride 0.9%**  
Reconstitute with sodium chloride 0.9%

Cytarabine (Cytarabine injection solution, Pharmacia, Hospira)  
**Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%**  
For Cytarabine injection solution 100 mg/mL (Pharmacia) before use, vials should be warmed to 55 °C for 30 minutes, with adequate shaking, and allowed to cool to room temperature

Dacarbazine (Dacarbazine, Medac)  
**Intermittent in Glucose 5% or Sodium chloride 0.9%**  
Reconstitute initially with water for injections then dilute in 200–300 mL infusion fluid; give over 15–30 minutes; protect infusion from light

Dactinomycin (Cosmegen Lyovac<sup>®</sup>)  
**Intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%**  
Reconstitute with water for injections

Danaparoid sodium (Orgaran<sup>®</sup>)  
**Continuous in Glucose 5% or Sodium chloride 0.9%**

Daptomycin (Cubicin<sup>®</sup>)  
**Intermittent in Sodium chloride 0.9%**  
Reconstitute with water for injections

Daunorubicin (as hydrochloride) (Cerubidin<sup>®</sup>)  
**via drip tubing in Sodium chloride 0.9%**  
Reconstitute vial with 4 mL water for injections to give 5 mg/mL solution; dilute requisite dose with infusion fluid to a concentration of 1 mg/mL; give over 20 minutes

Daunorubicin (liposomal) (Daunoxome<sup>®</sup>)  
**Intermittent in Glucose 5%**  
Dilute to a concentration of 0.2–1 mg/mL; give over 30–60 minutes; incompatible with sodium chloride solutions; in-line filter not recommended (if used, pore size should be no less than 5 micron)

Desferrioxamine mesilate (Desferal<sup>®</sup>)  
**Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%**  
Reconstitute with water for injections to a concentration of 100 mg/mL; dilute with infusion fluid

Desmopressin (DDAVP<sup>®</sup>, Octim<sup>®</sup>)  
**Intermittent in Sodium chloride 0.9%**  
Dilute with 50 mL and give over 20 minutes
Appendix 6: Intravenous additives

### Disopyramide (as phosphate) (*Rythmodan*)
Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate
Max. rate by continuous infusion 20–30 mg/hour (or 400 micrograms/kg/hour)

### Dobutamine (as hydrochloride)
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilate to a concentration of 0.5–1 mg/mL and give via a controlled infusion device; give higher concentration (max. 5 mg/mL) with infusion pump, incompatible with bicarbonate

### Docetaxel (*Taxotere*)
Continuous in Glucose 5% or Sodium chloride 0.9%
Stand docetaxel vials and diluent at room temperature for 5 minutes; add diluent to produce a concentrate containing 10 mg/mL and allow to stand for a further 5 minutes; dilute the requisite dose with at least 250 mL infusion fluid to a final concentration not exceeding 740 micrograms/mL; infuse over 1 hour

### Dolasetron mesilate (*Anzemet*)
Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate
Suggested volume 50 mL given over 30 seconds–15 minutes

### Dopamine hydrochloride
Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate
Dilute to max concentration of 3.2 mg/mL, incompatible with bicarbonate

### Dopexamine hydrochloride (*Dopacard*)
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute to a concentration of 400 or 800 micrograms/mL; max. concentration via large peripheral vein 1 mg/mL, concentrations up to 4 mg/mL may be infused via central vein; give via infusion pump or other device which provides accurate control of rate; contact with metal should be minimised; incompatible with bicarbonate

### Doripenem (*Doribax*)
Continuous in Glucose 5% or Sodium chloride 0.9%
Reconstitute 500 mg with 10 mL water for injections or sodium chloride 0.9% then dilute with 100 mL infusion fluid; give over 1 hour (for severe hospital-acquired pneumonia or hospital-acquired pneumonia caused by less sensitive organisms, may extend infusion time to 4 hours using sodium chloride 0.6% as the infusion fluid)

### Doxorubicin hydrochloride
Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9%
Reconstitute with water for injections or sodium chloride 0.9% (10 mg in 5 mL, 50 mg in 25 mL); give over 3–5 minutes; for continuous infusion over 24 hours (Doxorubicin, Medac and Dorubicin, Teva UK only), consult local protocol

### Doxorubicin hydrochloride (liposomal) (*Caelyx*)
via drip tubing in Glucose 5%
Dilute up to 90 mg in 250 mL infusion fluid and over 90 mg in 500 mL infusion fluid

### Eculizumab (*Soliris*)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute requisite dose to a concentration of 5 mg/mL and mix gently; give over 25–45 minutes (infusion time may be increased to 2 hours if infusion-related reactions occur)

### Enoximone (*Perfar*)
Continuous or intermittent in Sodium chloride 0.9% or Water for injections
Dilute to a concentration of 2.5 mg/mL, incompatible with glucose solutions; use only plastic containers or syringes

### Appendix 6: Intravenous additives

- **Dexamethasone sodium phosphate** (*Dexamethasone, Hospira; Dexamethasone, Organon*)
  Continuous or intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%
  Dexamethasone (Organon) can also be infused in Ringer’s solution or Compound sodium lactate

- **Deroxazole** (*Savene*®)
  Intermittent *in Savene*® diluent
  Reconstitute 500 mg with 25 mL of Water for Injections then dilute in 500 mL Savene® diluent; give over 1–2 hours into a large vein in an area other than the one affected

- **Diamorphine hydrochloride** (*Diamorphine Injection, Wockhardt*)
  Continuous in Glucose 5% or Sodium chloride 0.9%
  Glucose is preferred as infusion fluid

- **Diazepam** *(solution)* (*Diazepam, Wockhardt*)
  Continuous in Glucose 5% or Sodium chloride 0.9%
  Dilute to a concentration of not more than 10 mg in 200 mL; adsorbed to some extent by the plastics of bags and infusion sets

- **Diazepam (emulsion)** (*Diazemuls*®)
  Continuous in Glucose 5% and 10%
  May be diluted to a max. concentration of 200 mg in 500 mL, max. 6 hours between addition and completion of administration; adsorbed to some extent by the plastics of the infusion set via drip tubing in Glucose 5% and 10% or Sodium chloride 0.9%
  Adsorbed to some extent by the plastics of the infusion set

- **Diclofenac sodium** (*Voltarol*®)
  Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%
  Dilute 75 mg with 100–500 mL infusion fluid (previously buffered with 0.5 mL sodium bicarbonate 8.4% solution or with 1 mL sodium bicarbonate 4.2% solution); for intermittent infusion give 25–50 mg over 15–60 minutes or 75 mg over 30–120 minutes; for continuous infusion give at a rate of 5 mg/hour

- **Digoxin** (*Lanoxin*®)
  Intermittent in Glucose 5% or Sodium chloride 0.9%
  Dilute to a concentration of not more than 62.5 micrograms/mL.
  To be given over at least 2 hours. Protect from light

- **Digoxin-specific antibody fragments** (*Digibind*®)
  Intermittent in Sodium chloride 0.9%
  Dissolve initially in water for injections (4 mL/vial) then dilute with the sodium chloride 0.9% and give through a 0.22 micron sterile, disposable filter over 30 minutes

- **Dinoprostone** (*Prostin E2*®)
  Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%
  Protect from light
  Avoid bicarbonate containing infusions

- **Disodium folinate** (*Sodiofolin*®)
  Intermittent in Sodium chloride 0.9%
  Protect from light
  Avoid bicarbonate containing infusions

- **Disodium pamidronate** (*Aredia*®; *Disodium pamidronate, Britannia, Hospira, Medac*)
  Intermittent in Glucose 5% or Sodium chloride 0.9%
  For *Aredia* and *Pamidronate disodium* (Britannia), reconstitute initially with water for injections (15 mg in 5 mL, 30 mg or 90 mg in 10 mL); for *Aredia*, *Pamidronate disodium* (Britannia), *Disodium pamidronate* (Hospira), dilute with infusion fluid to a concentration of not more than 80 mg in 250 mL; for *Disodium pamidronate* (Medac) dilute with infusion fluid to a concentration of not more than 90 mg in 250 mL; give at a rate not exceeding 1 mg/minute; not to be given with infusion fluids containing calcium

- **Disopyramide (as phosphate)** (*Rythmodan*)
  Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate
  Max. rate by continuous infusion 20–30 mg/hour (or 400 micrograms/kg/hour)

- **Dobutamine (as hydrochloride)**
  Continuous in Glucose 5% or Sodium chloride 0.9%
  Dilute to a concentration of 0.5–1 mg/mL and give via a controlled infusion device; give higher concentration (max. 5 mg/mL) with infusion pump, incompatible with bicarbonate

- **Docetaxel** (*Taxotere*)
  Continuous in Glucose 5% or Sodium chloride 0.9%
  Stand docetaxel vials and diluent at room temperature for 5 minutes; add diluent to produce a concentrate containing 10 mg/mL and allow to stand for a further 5 minutes; dilute the requisite dose with at least 250 mL infusion fluid to a final concentration not exceeding 740 micrograms/mL; infuse over 1 hour

- **Dolasetron mesilate** (*Anzemet*)
  Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate
  Suggested volume 50 mL given over 30 seconds–15 minutes

- **Dopamine hydrochloride**
  Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate
  Dilute to max concentration of 3.2 mg/mL, incompatible with bicarbonate

- **Dopexamine hydrochloride** (*Dopacard*)
  Continuous in Glucose 5% or Sodium chloride 0.9%
  Dilute to a concentration of 400 or 800 micrograms/mL; max. concentration via large peripheral vein 1 mg/mL, concentrations up to 4 mg/mL may be infused via central vein; give via infusion pump or other device which provides accurate control of rate; contact with metal should be minimised, incompatible with bicarbonate

- **Doripenem** (*Doribax*)
  Continuous in Glucose 5% or Sodium chloride 0.9%
  Reconstitute 500 mg with 10 mL water for injections or sodium chloride 0.9% then dilute with 100 mL infusion fluid; give over 1 hour (for severe hospital-acquired pneumonia or hospital-acquired pneumonia caused by less sensitive organisms, may extend infusion time to 4 hours using sodium chloride 0.6% as the infusion fluid)

- **Doxorubicin hydrochloride**
  Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9%
  Reconstitute with water for injections or sodium chloride 0.9% (10 mg in 5 mL, 50 mg in 25 mL); give over 3–5 minutes; for continuous infusion over 24 hours (Doxorubicin, Medac and Dorubicin, Teva UK only), consult local protocol

- **Doxorubicin hydrochloride (liposomal)** (*Caelyx*)
  via drip tubing in Glucose 5%
  Dilute up to 90 mg in 250 mL infusion fluid and over 90 mg in 500 mL infusion fluid

- **Eculizumab** (*Soliris*)
  Intermittent in Glucose 5% or Sodium chloride 0.9%
  Dilute requisite dose to a concentration of 5 mg/mL and mix gently; give over 25–45 minutes (infusion time may be increased to 2 hours if infusion-related reactions occur)

- **Enoximone** (*Perfar*)
  Continuous or intermittent in Sodium chloride 0.9% or Water for injections
  Dilute to a concentration of 2.5 mg/mL, incompatible with glucose solutions; use only plastic containers or syringes
Fentanyl

Etoposide

Esomeprazole (as sodium salt)

Erythromycin (as lactobionate)

Ertapenem (Invanza®)

Epirubicin hydrochloride (Pharmorubicin® Rapid Dissolution, Pharmorubicin® Solution)

via drip tubing in Sodium chloride 0.9%

Reconstitute Pharmorubicin Rapid Dissolution with sodium chloride 0.9% or with water for injections (10 mg in 5 mL, 20 mg in 10 mL, 50 mg in 25 mL), give over 3–5 minutes

Epoprostenol (Flolan®)

Continuous in Sodium chloride 0.9% (but see also below)

Reconstitute using the filter and solvent (glycine buffer dihydant) provided to make a concentrate, may be diluted further (consult product literature), for pulmonary hypertension dilute further with glycine buffer dihydant only, for renal dialysis may be diluted further with sodium chloride 0.9%

Ertapenem (Invanza®)

Intermittent in Sodium chloride 0.9%

Reconstitute 1 g with 10 mL water for injections or sodium chloride 0.9%; dilute requisite dose in infusion fluid to a final concentration not exceeding 20 mg/mL; give over 30 minutes; incompatible with glucose solutions

Erythromycin (as lactobionate)

Continuous or intermittent in Glucose 5% (neutralised with sodium bicarbonate) or Sodium chloride 0.9%

Dissolve initially in water for injections (1 g in 20 mL) then dilute to a concentration of 1 mg/mL for continuous infusion and 1–5 mg/mL for intermittent infusion, give intermittent infusion over 20–60 minutes

Esmolol hydrochloride (Brevisloc®)

Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute to a concentration of 10 mg/mL, for continuous infusion use a suitable infusion control device, incompatible with bicarbonate

Esomeprazole (as sodium salt) (Nexium®)

Intermittent in Sodium chloride 0.9%

Reconstitute 40 mg with 5 mL sodium chloride 0.9% then dilute with up to 100 mL infusion fluid, give requisite dose over 10–30 minutes

Ethanol

Continuous in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate

Dilute to a concentration of 5–10%

Etoposide (Eposin®, Etoposide, TEVA UK and Hospira)

Intermittent in Sodium chloride 0.9%

For Etoposide (TEVA UK) dilute with either sodium chloride 0.9% or glucose 5% to a concentration of 200 micrograms/mL and give over 30–60 minutes; for Etoposide (Hospira) dilute with either sodium chloride 0.9% or glucose 5% to a concentration not more than 250 micrograms/mL and give over not less than 30 minutes; for Etoposide in either sodium chloride 0.9% or glucose 5% to a concentration of 200–400 micrograms/mL and give over at least 30 minutes; check container for haze or precipitate during infusion

Etoposide (as phosphate) (Etopophos®)

Intermittent in Glucose 5% or Sodium chloride 0.9%

Reconstitute with 5–10 mL of either water for injections or with infusion fluid then dilute further with infusion fluid to a concentration as low as 100 micrograms/mL and give over 5 minutes to 3.5 hours

Fentanyl (Sublimaze®)

Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%

Ferric carboxymaltose (Ferinject®)

Intermittent in Sodium chloride 0.9%

Dilute 200–500 mg in up to 100 mL infusion fluid and give over at least 6 minutes; dilute 0.5–1 g in up to 250 mL infusion fluid and give over at least 15 minutes

Filgrastim (Neupogen®, Ratiogranstim®)

Continuous or intermittent in Glucose 5%

For a filgrastim concentration of less than 1 500 000 units/mL (15 micrograms/mL) albumin solution (human serum albumin) is added to produce a final albumin concentration of 2 mg/mL; should not be diluted to a filgrastim concentration of less than 200 000 units/mL (2 micrograms/mL) and should not be diluted with sodium chloride solution

Flecainide acetate (Tambocor®)

Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

Minimum volume in infusion fluids containing chlorides 500 mL

Flucloxacillin (as sodium salt) (Flxin®)

Intermittent in Glucose 5% or Sodium chloride 0.9%

Suggested volume 100 mL given over 30–60 minutes via drip tubing in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate

Continuous infusion not usually recommended

Fludarabine phosphate (Fludara®)

Intermittent in Sodium chloride 0.9%

Reconstitute each 50 mg with 2 mL water for injections and dilute requisite dose in 100 mL, give over 30 minutes

Flumazenil (Anexate®)

Continuous in Glucose 5% or Sodium chloride 0.9%

Fluorouracil (as sodium salt)

Continuous or intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%

Give intermittent infusion over 30–60 minutes or over 4 hours

Fondaparinux (Arixtra®)

Intermittent in Sodium chloride 0.9%

For ST-segment elevation myocardial infarction, add requisite dose to 25–50 mL infusion fluid and give over 1–2 minutes

Fosaprepitant (Ivend®)

Intermittent in Sodium chloride 0.9%

Reconstitute each 115-mg vial with 5 mL sodium chloride 0.9% gently without shaking to avoid foaming, then dilute in 110 mL infusion fluid, give over 15 minutes

Foscarnet sodium (Foscavir®)

Intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute to a concentration of 12 mg/mL for infusion into peripheral vein (undiluted solution via central venous line only); infuse over at least 1 hour

Fosphenytoin Sodium (Pro-Epanutin®)

Intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute to a concentration of 1.5–25 mg (phenytoin sodium equivalent)/mL

Furosemide (Lasix®)

Continuous in Sodium chloride 0.9% or Ringer’s solution

Infusion pH must be above 5.5 and rate should not exceed 4 mg/minute, glucose solutions are unsuitable

Fusidic acid (as sodium salt)

Continuous in Glucose 5% (but see below) or Sodium chloride 0.9%

Reconstitute with the buffer solution provided and dilute to 500 mL, give through central venous line over 2 hours (or over 6 hours if superficial vein used), incompatible in solution of pH less than 7.4

Galsulfase (Naglazyme®)

Intermittent in Sodium chloride 0.9%

Dilute requisite dose with infusion fluid to final volume of 250 mL and mix gently, infuse through a 0.2 micron in-line filter, give approx. 2.5% of the total volume over 1 hour, then infuse remaining volume over next 3 hours, if body-weight under 20 kg and at risk of fluid overload, dilute requisite dose in 100 mL infusion fluid and give over at least 4 hours
Appendix 6: Intravenous additives

Ganciclovir (as sodium salt) (Cymevene®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
or Ringer’s solution or Compound sodium lactate
Reconstitute initially in water for injections (500 mg/10 mL) then
dilute to not more than 10 mg/mL with infusion fluid (usually
100 mL), give over 1 hour

Gemcitabine (Gemzar®)
Intermittent in Sodium chloride 0.9%
Reconstitute initially with sodium chloride 0.9% (200 mg in at
least 5 mL, 1 g in at least 25 mL); may be diluted further with
infusion fluid; give over 30 minutes

Gentamicin (as sulphate) (Cidomycin®, Gentamicin
Paediatric Injection, Beacon; Gentamicin Injection,
Hospira)
Intermittent or via drip tubing in Glucose 5% or Sodium
chloride 0.9%
Suggested volume for intermittent infusion 50–100 mL given over
20–30 minutes

Glyceryl trinitrate (Nitrocin®, Nitronal®)
Continuous in Glucose 5% or Sodium chloride 0.9%
For Nitrocin suggested infusion concentration 100 micrograms/
ml incompatible with polyvinyl chloride infusion containers such
as Viaflex or Sterifeed; use glass or polyethylene containers or
give via a syringe pump

Granisetron (as hydrochloride) (Kytril®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
or Compound sodium lactate
Dilute 3 mL in 20–50 mL infusion fluid (up to 3 mL in 10–30 mL for
children); give over 5 minutes

Haem arginate (Normosang®)
Intermittent in Sodium chloride 0.9%
Dilute requisite dose in 100 mL infusion fluid in glass bottle and
give over at least 30 minutes via large antebellial vein, admin-
sters within 1 hour after dilution

Heparin sodium
Continuous in Glucose 5% or Sodium chloride 0.9%
Administration with a motorised pump advisable

Hydralazine hydrochloride (Apresoline®)
Continuous in Sodium chloride 0.9% or Ringer’s solution
Suggested infusion volume 500 mL

Hydrocortisone (as sodium phosphate) (Efcorbeso®)
Continuous or intermittent or via drip tubing in Glu-
cose 5% or Sodium chloride 0.9%

Hydrocortisone (as sodium succinate) (SoluCortef®)
Continuous or intermittent or via drip tubing in Glu-
cose 5% or Sodium chloride 0.9%

Ibandronic acid (Bondronat®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute requisite dose in 500 mL infusion fluid and give over 1–2
hours

Idarubicin hydrochloride (Zavedos®)
via drip tubing in Sodium chloride 0.9%
Reconstitute with water for injections; give over 5–10 minutes

Idursulfase (Elaprase®)
Intermittent in Sodium chloride 0.9%
Dilute requisite dose in 100 mL infusion fluid and mix gently (do
not shake); give over 3 hours (gradually reduced to 1 hour if no
infusion-related reactions)

Ifosfamide (Mitoxana®)
Continuous or intermittent or via drip tubing in Glu-
cose 5% or Sodium chloride 0.9%
For continuous infusion, suggested volume 3 litres given over 24
hours; for intermittent infusion, give over 30–120 minutes

Imiglucerase (Cerezyme®)
Intermittent in Sodium chloride 0.9%
Initially reconstitute with water for injections (200 units in 5.1 mL,
400 units in 10.2 mL) to give 40 units/mL solution, dilute requisite
dose with infusion fluid to a final volume of 100–200 mL and give
over 1–2 hours or at a rate not exceeding 1 unit/kg/minute;
administer within 3 hours after reconstitution

Imipenem with cilastatin (as sodium salt) (Primaxin®)
Intermittent in Sodium chloride 0.9% or Sodium
chloride and Glucose
Dilute to a concentration of 5 mg (as imipenem)/mL, infuse 250–
500 mg (as imipenem) over 20–30 minutes, 1 g over 40–60 min-
utes
Continuous infusion not usually recommended

Infliximab (Remicade®)
Intermittent in Sodium chloride 0.9%
Reconstitute each 100-mg vial with 10 mL water for injections
using a 21-gauge or smaller needle; gently swirl vial without
shaking to dissolve, allow to stand for 5 minutes; dilute requisite
dose with infusion fluid to a final volume of 250 mL and give
through a low protein-binding filter (1.2 micron or less) over at
least 2 hours (patients being treated for rheumatoid arthritis who
have tolerated 3 initial 2-hour infusions may be given subsequent
infusions of up to 6 mg/kg over at least 1 hour); start infusion
within 3 hours of reconstitution

Insulin (soluble)
Continuous in Sodium chloride 0.9% or Compound sodium
lactate
Adsorbed to some extent by plastics of infusion set; see also
section 6.1.3, ensure insulin is not injected into ‘dead space’ of
injection port of the infusion bag

Insulin aspart
Continuous in Sodium chloride 0.9% or Glucose 5%
Dilute to 0.05–1 unit/mL with infusion fluid; adsorbed to some
extent by plastics of infusion set

Insulin lispro
Continuous in Sodium chloride 0.9% or Glucose 5%

Interferon alfa-2b (IntronA®)
Intermittent in Sodium chloride 0.9%
For IntronA solution, dilute requisite dose in 50 mL infusion fluid
and administer over 20 minutes; not to be diluted to less than
300 000 units/mL.
For IntronA powder, reconstitute with 1 mL water for injections;
dilute requisite dose in 100 mL infusion fluid and administer over
20 minutes; not to be diluted to less than 100 000 units/mL.

Irinotecan hydrochloride (Campto®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute requisite dose in 250 mL infusion fluid; give over 30–90
minutes

Iron dextran (Cosmofe®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute 100–200 mg in 100 mL infusion fluid, give 25 mg over 15
minutes as a test dose initially, then give at a rate not exceeding
6.67 mg/minute; total dose infusion diluted in 500 mL infusion fluid
and given over 4–6 hours (initial test dose 25 mg over 15 minutes)

Iron sucrose (Venofe®)
Intermittent in Sodium chloride 0.9%
Dilute 100 mg in up to 100 mL infusion fluid; give 25 mg over 15
minutes as a test dose initially, then give at a rate not exceeding
3.33 mg/minute
Appendix 6: Intravenous additives

Isosorbide dinitrate (Isoket 0.05%, Isoket 0.1%) Continuous in Glucose 5% or Sodium chloride 0.9% Adsorbed to some extent by polyvinyl chloride infusion containers; preferably use glass or polyethylene containers or give via a syringe pump. Isoket 0.05% can alternatively be administered undiluted using a syringe pump with a glass or rigid plastic syringe.

Itraconazole (Sporanox®) Intermittent in Sodium chloride 0.9% Dilute 250 mg in 50 mL infusion fluid and infuse only 60 mL through an in-line filter (0.2 micron) over 60 minutes.

Ketamine (as hydrochloride) (Ketalar®) Continuous in Glucose 5% or Sodium chloride 0.9% Dilute to 1 mg/mL; microdroop infusion for maintenance of anaesthesia.

Labetalol hydrochloride (Trandate®) Intermittent in Glucose 5% or Sodium chloride and glucose Dilute to a concentration of 1 mg/mL; suggested volume 200 mL; adjust rate with in-line burette.

Lacosamide (Vimpat®) Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate solution. May be administered undiluted.

Laronidase (Aldurazyme®) Intermittent in Sodium chloride 0.9% Body-weight under 20 kg, use 100 mL infusion fluid; body-weight over 20 kg use 250 mL infusion fluid; withdraw volume of infusion fluid equivalent to volume of laronidase concentrate being added; give through an in-line filter (0.22 micron) at an initial rate of 2 units/kg/hour then increasing gradually every 15 minutes to max. 43 units/kg/hour.

Lenograstim (Granocyte®) Intermittent in Sodium chloride 0.9% Initially reconstitute with 1 mL water for injection provided (do not shake vigorously) then dilute with up to 50 mL infusion fluid for each vial of Granocyte-13 or up to 100 mL infusion fluid for Granocyte-34, give over 30 minutes.

Lepirudin (Refudan®) Continuous in Glucose 5% or Sodium chloride 0.9% Reconstitute initially with water for injections or sodium chloride 0.9% then dilute to a concentration of 2 mg/mL with infusion fluid.

Levetiracetam (Keppra®) Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate DILUTE the requisite dose with at least 100 mL of infusion fluid; give over 15 minutes.

Magnesium sulphate Continuous in Glucose 5% or Sodium chloride 0.9% Suggested concentration up to 200 mg/mL; max. rate 150 mg/minute.

Melphalan (Alkeran®) Intermittent or via drip tubing in Sodium chloride 0.9% Reconstitute with the solvent provided then dilute with infusion fluid; max. 90 minutes between addition and completion of administration; incompatible with glucose infusion.

Meropenem (Meropen®) Intermittent in Glucose 5 and 10% or Sodium chloride 0.9% Dilute in 50–200 mL infusion fluid and give over 15–30 minutes.

Mesna (Uromitexan®) Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9%

Metaraminol (as tartrate) (Aramine®) Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9% Suggested volume 500 mL.

Methotrexate (as sodium salt) (Methotrexate, Leaderle) Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate or Ringer’s solution Dilute in a large-volume infusion; max. 24 hours between addition and completion of administration.

Methylprednisolone (as sodium succinate) (Solu-Medrone®) Continuous or intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9% Reconstitute initially with water for injections; doses up to 250 mg should be given over at least 5 minutes, high doses over at least 30 minutes.

Metoclopramide hydrochloride (Maxolon High Dose®) Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate Continuous infusion recommended; loading dose, dilute with 50–100 mL and give over 15–20 minutes; maintenance dose, dilute with 500 mL and give over 8–12 hours; for intermittent infusion dilute with at least 50 mL and give over at least 15 minutes.

Mepacurin (Mycamine®) Intermittent in Glucose 5% or Sodium chloride 0.9% Reconstitute each vial with 5 mL infusion fluid, gently rotate vial, without shaking, to dissolve; dilute requisite dose with infusion fluid to 100 mL (final concentration 0.5–2 mg/mL); protect from light; give over 60 minutes.

Midazolam (Hypnovel®) Continuous in Glucose 5% or Sodium chloride 0.9% For neonates and children under 15 kg dilute to a max. concentration of 1 mg/mL.

Milrinone (Primacor®) Continuous in Glucose 5% or Sodium chloride 0.9% Dilute to a suggested concentration of 200 micrograms/mL.

Mitoxantrone/Mitozantrone (as hydrochloride) (Ontkarene®) Intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9% For administration via drip tubing suggested volume at least 50 mL; give over at least 3–5 minutes, for intermittent infusion, dilute with 50–100 mL and give over 15–30 minutes.

Mivacurium (as chloride) (Mivacron®) Continuous in Glucose 5% or Sodium chloride 0.9% Dilute to a concentration of 500 micrograms/mL; may also be given undiluted.

Mycophenolate mofetil (as hydrochloride) (CellCept®) Intermittent in Glucose 5% Reconstitute each 500-mg vial with 14 mL glucose 5% and dilute the contents of 2 vials in 140 mL infusion fluid, give over 2 hours.

Naloxone (Min-I-Jet® Naloxone Hydrochloride) Continuous in Glucose 5% or Sodium chloride 0.9% Reversal of opioid-induced respiratory depression, dilute to a concentration of 4 micrograms/mL; opioid overdose only; dilute 10 mg in 50 mL glucose 5%, see Emergency Treatment of Poisoning.
Appendix 6: Intravenous additives

**Natalizumab** *(Tysabri®)*

Intermittent in Sodium chloride 0.9%

Dilute 300 mg in 100 mL infusion fluid; gently invert to mix, do not shake. Use within 8 hours of dilution and give over 1 hour

**Nimodipine** *( Nimotop®)*

via drip tubing in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

Not to be added to infusion container; administer via an infusion pump through a Y-piece into a central catheter; incompatible with polyvinyl chloride giving sets or containers; protect infusion from light

**Nizatidine** *( Axid®)*

Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

For continuous infusion, dilute 300 mg in 150 mL and give at a rate of 10 mg/hour; for intermittent infusion, dilute 100 mg in 50 mL and give over 15 minutes

**Noradrenaline acid tartrate/Norepinephrine bitartrate**

Continuous in Glucose 5% or Sodium chloride and glucose

Give via controlled infusion device; for administration via syringe pump, dilute 4 mg noradrenaline acid tartrate (2 mL solution) with 48 mL; for administration via drip counter dilute 40 mg (20 mL solution) with 480 mL; give through a central venous catheter; incompatible with alkaline solution

**Omeprazole (as sodium salt)** *(Losec®)*

Intermittent or continuous in Glucose 5% or Sodium chloride 0.9%

Reconstitute each 40 mg vial with infusion fluid and dilute to 100 mL; give intermittent infusion over 20–30 minutes; stable for 3 hours in glucose 5% or 12 hours in sodium chloride 0.9%

**Ondansetron (as hydrochloride)** *(Zofran®)*

Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution

For intermittent infusion, dilute 32 mg in 50–100 mL and give over at least 15 minutes

**Oxaliplatin** *( Eloxatin®)*

Continuous in Glucose 5%

Dilute requisite dose to a concentration of 220–700 micrograms/mL and give over 2–6 hours; incompatible with alkaline or chloride-containing fluids; avoid equipment containing aluminium

**Oxycodone hydrochloride** *(OxyNorm®)*

Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute to a concentration of 1 mg/mL

**Oxytocin** *( Syntocinon®)*

Continuous in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate or Ringer’s solution

Preferably given via a variable-speed infusion pump in a concentration appropriate to the pump; if given by drip infusion for induction or enhancement of labour: dilute 5 units in 500 mL infusion fluid or for higher doses, 10 units in 500 mL for treatment of postpartum uterine haemorrhage dilute 5–30 units in 500 mL, if high doses given for prolonged period (e.g. for inevitable or missed abortion or for postpartum haemorrhage), use low volume of an electrolyte-containing infusion fluid (not Glucose 5%) given at higher concentration than for induction or enhancement of labour; close attention to patient’s fluid and electrolyte status essential

**Paclitaxel** *( Taxo®)*

Continuous in Glucose 5% or Sodium chloride 0.9%

Dilute to a concentration of 0.3–1.2 mg/mL and give through an in-line filter (0.22 micron or less) over 3 hours; not to be used with PVC equipment (short PVC inlet or outlet on filter may be acceptable)

**Panitumumab** *( Vectibix®)*

Intermittent in Sodium chloride 0.9%

Flush intravascular line with Sodium chloride 0.9% before and after infusion, dilute requisite dose with infusion fluid to 100 mL (final concentration not to exceed 10 mg/mL), gently invert to mix, do not shake; give via infusion pump through a low protein-binding in-line filter (0.2 or 0.22 micron) over 60 minutes, for doses higher than 1 g, dilute requisite dose with infusion fluid to 150 mL and give over 90 minutes

**Pantoprazole (as sodium sesquihydrate)** *(Protonix®)*

Intermittent in Glucose 5 and 10% or Sodium chloride 0.9%

Reconstitute 40 mg with 10 mL sodium chloride 0.9% and dilute to 100 mL with infusion fluid

**Paracetamol** *(Perfalgan®)*

Intermittent in Sodium chloride 0.9% or Glucose 5%

Dilute to a concentration of 1 mg/mL and use within 1 hour; may also be given undiluted

**Pemetrexed** *(Alimta®)*

Intermittent in Sodium chloride 0.9%

Reconstitute 500–mL vial with 20 mL sodium chloride 0.9% to produce a 25 mg/mL solution; dilute requisite dose with infusion fluid to 100 mL; give over 10 minutes

**Pentamidine isethionate** *(Pentacarinat®)*

Intermittent in Glucose 5% or Sodium chloride 0.9%

Dissolve initially in water for injections (300 mg in 3–5 mL) then dilute in 50–250 mL; give over at least 60 minutes

**Pentostatin** *(Nipen®)*

Intermittent in Glucose 5% or Sodium chloride 0.9%

Reconstitute initially with 5 mL water for infusions to produce a 2 mg/mL solution; dilute requisite dose in 25–50 mL infusion fluid (final concentration 180–330 micrograms/mL) and give over 20–30 minutes

**Phenoxymenzamine hydrochloride**

Intermittent in Sodium chloride 0.9%

Dilute in 200–500 mL infusion fluid, give over at least 2 hours, max. 4 hours between dilution and completion of administration

**Phenylephrine hydrochloride**

Intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute 10 mg in 500 mL infusion fluid

**Phenytin sodium** *(Epanutin®)*

Intermittent in Sodium chloride 0.9%

Flush intravascular line with Sodium chloride 0.9% before and after infusion, dilute in 50–100 mL infusion fluid (final concentration not to exceed 10 mg/mL) and give through an in-line filter (0.22–0.50 micron) at a rate not exceeding 50 mg/minute (neonates, give at a rate of 1–3 mg/kg/minute); complete administration within 1 hour of preparation

**Phytomenadione (in mixed micelles vehicle)** *(Konakion® MM)*

Intermittent in Glucose 5%

Dilute with 55 mL, may be injected into lower part of infusion apparatus

**Piperacillin with tazobactam (as sodium salts)** *(Tazocin®)*

Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate or Water for infusions

Reconstitute initially with water for injections or sodium chloride 0.9% (2.25 g in 10 mL, 4.5 g in 20 mL), then dilute to 50–150 mL with infusion fluid (to max. 50 mL with water for injections); give over 20–30 minutes

Important Generic preparations of piperacillin with tazobactam may have different compatibilities to Tazocin — consult product literature
Potassium chloride
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute in a large-volume infusion; mix thoroughly to avoid 'layering', especially in non-rod infusion containers; use ready-prepared solutions when possible

Propofol (emulsion) (Diprivan®, Abbott; Baxter; Propofol-Lipuro®, Propofen®, Braun; Hospira; Fresenius Kabi; Zurich)
1% or 2% emulsion
via drip tubing in Glucose 5% or Sodium chloride 0.9%
To be administered via a Y-piece close to injection site; microbiological filter not recommended
1% emulsion only
Continuous in Glucose 5% (or Sodium chloride 0.9% for Propofol-Lipuro®, Propofen®, Braun, Fresenius Kabi, and Zurich brands only)
Dilute to a concentration not less than 2 mg/mL; microbiological filter not recommended; administer using suitable device to control infusion rate; use glass or PVC containers (if PVC bag used it should be full—withdraw volume of infusion fluid equal to that of propofol to be added); give within 6 hours of preparation; propofol may alternatively be infused undiluted using a suitable infusion pump.

Quinine dihydrochloride
Continuous in Glucose 5% or Sodium chloride 0.9%
To be given over 4 hours; see also section 5.4.1

Quinupristin with dalfopristin (Synercid®)
Intermittent in Glucose 5%
Reconstitute 500 mg with 5 mL water for injections or glucose 5%; gently swirl vial without shaking to dissolve; allow to stand for at least 2 minutes until foam disappears; dilute requisite dose in 100 mL infusion fluid and give over 60 minutes via central venous catheter (in an emergency, first dose may be diluted in 250 mL infusion fluid and given over 60 minutes via peripheral line); flush line with glucose 5% before and after infusion; incompatible with sodium chloride solutions

Raltitrexed (TomudeX®)
Intermittent in Glucose 5%
Reconstitute with water for injections; dilute requisite dose in 50–250 mL infusion fluid and give over 15 minutes

Ranitidine (as hydrochloride) (Zantac®)
Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

Rasburicase (Fasturect®)
Intermittent in Sodium chloride 0.9%
Reconstitute with solvent provided; gently swirl vial without shaking to dissolve; dilute requisite dose to 50 mL with infusion fluid and give over 30 minutes

Remifentanil (Ultiva®)
Continuous in Glucose 5% or Sodium chloride 0.9% or Water for injections
Reconstitute with infusion fluid to a concentration of 1 mg/mL; then dilute further to a concentration of 20–250 micrograms/mL. (50 micrograms/mL recommended for general anaesthesia, 20–25 micrograms/mL recommended for children 1–12 years; 20–50 micrograms/mL recommended when used with target controlled infusion (TCI) device)

Rifampicin (Rifadin®)
Intermittent in Glucose 5 and 10% or Sodium chloride 0.9% or Ringer’s solution
Reconstitute with solvent provided then dilute with 500 mL infusion fluid; give over 2–3 hours

Ritodrine hydrochloride (Yutopar®)
Continuous in Glucose 5%
Give via controlled infusion device, preferably a syringe pump; if syringe pump available dilute to a concentration of 3 mg/mL, if syringe pump not available dilute to a concentration of 300 micrograms/mL; close attention to patient’s fluid and electrolyte status essential

Rituximab (MabThera®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute to 1–4 mg/mL and gently invert bag to avoid foaming

Rocuronium bromide (Esmeron®)
Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9%

Salbutamol (as sulphate) (Ventolin® For Intravenous Infusion)
Continuous in Glucose 5%
For bronchodilatation dilute to a concentration of 200 micrograms/mL with glucose 5%, sodium chloride 0.9%, or water for injections; for premature labour dilute with glucose 5% to a concentration of 200 micrograms/mL for use in a syringe pump or for other infusion methods (preferably via controlled infusion device), dilute to a concentration of 20 micrograms/mL, close attention to patient’s fluid and electrolyte status essential

Sodium calcium edetate (Ledclair®)
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute to a concentration of not more than 3%; suggested volume 250–500 mL given over at least 1 hour

Sodium clonidine (Bonefa® Concentrate)
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute 100 mg in 500 mL and give over at least 2 hours or 1.5 g in 500 mL and give over at least 4 hours

Sodium valproate (Epilim®, Episenta®)
Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%
Reconstitute Epilim with solvent provided then dilute with infusion fluid

Sotalol hydrochloride (Sotacor®)
Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%
Dilute to a concentration of between 0.01–2 mg/mL

Streptokinase (Streptase®, Streptokinase, Braun)
Continuous or intermittent in Glucose 5% or Sodium chloride 0.9%
Reconstitute Streptase with sodium chloride 0.9%, and Streptokinase (Braun) with either water for injections or sodium chloride 0.9% then dilute further with infusion fluid

Sulfadiazine sodium
Continuous in Sodium chloride 0.9%
Suggested volume 500 mL; ampoule solution has a pH of over 10

Suxamethonium chloride (Anectine®)
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute 300 mg in 500 mL and give over at least 2 hours or 1.5 g in 500 mL and give over at least 4 hours

Tacrolimus (Prograf®)
Continuous in Glucose 5% or Sodium chloride 0.9%
Dilute concentration in infusion fluid to a final concentration of 4–100 micrograms/mL; give over 24 hours; incompatible with PVC

Teicoplanin (Targocid®)
Intermittent in Glucose 5% or Sodium chloride 0.9%
Or Compound sodium lactate
Reconstitute initially with water for injections provided; infuse over 30 minutes

Teicoplanin (Targocid®)
Continuous infusion not usually recommended

Temocillin
Continuous in Sodium chloride 0.9%
Dilute further to a concentration of 20–250 micrograms/mL; give over 30 minutes; compatible with PVC

Temsirolimus (Torisel®)
Intermittent in Sodium chloride 0.9%
Add 1.8 mL of the supplied diluent to the vial of concentrate to produce a concentration of 10 mg/mL; dilute requisite dose with 250 mL of sodium chloride 0.9%, give (preferably via infusion pump) through an in-line filter with a maximum pore size of 5 microns; avoid PVC equipment; protect from light and administer within 6 hours of dilution
Appendix 6: Intravenous additives

**Terbutaline sulphate** *(Bricanyl®)*
Continuous in Glucose 5%

For bronchodilatation dilute 1.5–2.5 mg with 500 mL glucose 5% or sodium chloride 0.9% and give over 8–10 hours; for premature labour dilute in glucose 5% and give via controlled infusion device preferably a syringe pump, if syringe pump available dilute to a concentration of 10 micrograms/mL; if syringe pump not available dilute to a concentration of 10 micrograms/mL, close attention to patient's fluid and electrolyte status essential.

**Ticarcillin sodium with clavulanic acid** *(Timentin®)*
Intermittent in Glucose 5% or Water for injections

Suggested volume (depending on dose) glucose 5% 100–150 mL or water for injections 50–100 mL, given over 30–40 minutes.

**Tigecycline** *(Tygaci®)*
Intermittent in Glucose 5% or Sodium chloride 0.9%

Reconstitute each vial with 5.3 mL infusion fluid to produce a 10 mg/mL solution; dilute requisite dose in 100 mL infusion fluid; give over 30–60 minutes

**Tirofiban** *(Aggrastat®)*
Continuous in Glucose 5% or Sodium chloride 0.9%

Withdraw 50 mL infusion fluid from 250-mL bag and replace with 50 mL tirofiban concentrate (250 micrograms/mL) to give a final concentration of 50 micrograms/mL.

**Tobramycin (as sulphate)** *(Tygacil®)*
Intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%

For adult intermittent infusion suggested volume 50–100 mL (children proportionately smaller volume) given over 20–60 minutes.

**Topotecan (as hydrochloride)** *(Hycamit®)*
Intermittent in Glucose 5% or Sodium chloride 0.9%

Reconstitute 4 mg with 4 mL water for injections then dilute to a final concentration of 25–50 micrograms/mL, give over 30 minutes

**Tramadol hydrochloride** *(Zydo®)*
Continuous or intermittent in Glucose 5% or Sodium chloride 0.9% or Ringer's solution or Compound sodium lactate

**Tranexamic acid** *(Cyklokapron®)*
Continuous in Glucose 5% or Sodium chloride 0.9% or Ringer's solution

**Trastuzumab** *(Herceptin®)*
Intermittent in Sodium chloride 0.9%

Reconstitute each 150-mg vial with 7.2 mL water for injections to produce a 21 mg/mL solution, swirl vial gently to avoid excessive foaming and allow to stand for approximately 5 minutes; dilute requisite dose in 250 mL infusion fluid

**Tresolufan** *(Treosulfan®)*
Intermittent in Water for injections

Infusion suggested for doses above 5 g, dilute to a concentration of 5 g in 100 mL

**Urokinase** *(Syner-KINASE®)*
Continuous or intermittent in Sodium chloride 0.9%

**Vancomycin (as hydrochloride)** *(Vancocin®)*
Intermittent in Glucose 5% or Sodium chloride 0.9%

Reconstitute each 500 mg with 10 mL water for injections and dilute with infusion fluid to a concentration of up to 5 mg/mL (10 mg/mL in fluid restriction but increased risk of infusion-related effects), give over at least 60 minutes (rate not to exceed 10 mg/minute for doses over 500 mg); use continuous infusion only if intermittent not feasible

**Vasopressin, synthetic** *(Pitressin®)*
Intermittent in Glucose 5%

Suggested concentration 20 units/100 mL given over 15 minutes

**Vecuronium bromide** *(Norcuron®)*
Continuous or via drip tubing in Glucose 5% or Sodium chloride 0.9% or Ringer's solution

Reconstitute each vial with 5 mL water for injections to give 2 mg/mL solution, alternatively reconstitute with up to 10 mL glucose 5% or sodium chloride 0.9% or water for injections—unsuitable for further dilution if not reconstituted with water for injections. For continuous intravenous infusion, dilute to a concentration of not less than 40 micrograms/mL

**Verteporfin** *(Visudyne®)*
Intermittent in Glucose 5%

Reconstitute each 15 mg with 7 mL water for injections to produce a 2 mg/mL solution then dilute requisite dose with infusion fluid to a final volume of 30 mL and give over 10 minutes; protect from light and administer within 4 hours of reconstitution. Incompatible with sodium chloride infusion

**Vinblastine sulphate** *(Velbe®)*
via drip tubing in Sodium chloride 0.9%

Reconstitute with sodium chloride 0.9%; give over approx. 1 minute

**Vincristine sulphate** *(Oncovin®)*
via drip tubing in Glucose 5% or Sodium chloride 0.9%

**Vindesine sulphate** *(Elldisine®)*
via drip tubing in Glucose 5% or Sodium chloride 0.9%

Reconstitute with sodium chloride 0.9%; give over 1–3 minutes

**Vinorelbine** *(Navelbine®)*
Intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute in 125 mL infusion fluid, give over 20–30 minutes

**Vitamins B & C** *(Pabrinex® 1/1 High potency)*
Intermittent or via drip tubing in Glucose 5% or Sodium chloride 0.9%

Amploue contents should be mixed, diluted, and administered without delay; give over 30 minutes (see MHRA/CHM advice, section 9.6.2)

**Vitamins, multiple** *(Cernovit®)*
Intermittent in Glucose 5% or Sodium chloride 0.9%

Dissolve initially in 5 mL water for injections (or infusion fluid) *(Solivito N®)*

Intermittent in Glucose 5 and 10%

Suggested volume 500–1000 mL given over 2–3 hours; see also section 9.3

**Voriconazole** *(Vfend®)*
Intermittent in Glucose 5% or Sodium chloride 0.9% or Compound sodium lactate

Reconstitute each 200 mg with 19 mL water for injections to produce a 10 mg/mL solution, dilute dose in infusion fluid to concentration of 0.5–5 mg/mL, give at a rate not exceeding 3 mg/kg/hour

**Zidovudine** *(Retrovir®)*
Intermittent in Glucose 5%

Dilute to a concentration of 2 mg/mL or 4 mg/mL and give over 1 hour

**Zoledronic acid** *(Zometa®)*
Intermittent in Glucose 5% or Sodium chloride 0.9%

Dilute requisite dose with 100 mL infusion fluid, infuse over at least 15 minutes; administer as a single intravenous solution in a separate infusion line, do not mix with calcium or other divalent cation-containing infusion solutions such as lactated Ringer's solution.
Borderline substances

In certain conditions some foods (and toilet preparations) have characteristics of drugs and the Advisory Committee on Borderline Substances advises as to the circumstances in which such substances may be regarded as drugs. Prescriptions issued in accordance with the Committee’s advice and endorsed ‘ACBS’ will normally not be investigated.

General Practitioners are reminded that the ACBS recommends products on the basis that they may be regarded as drugs for the management of specified conditions. Doctors should satisfy themselves that the products can safely be prescribed, that patients are adequately monitored and that, where necessary, expert hospital supervision is available.

Foods which may be prescribed on FP10, GP10 (Scotland), or when available WP10 (Wales)

Note These are food products which the ACBS has approved. The clinical condition for which the product has approval follows each entry.

Foods included in this Appendix may contain carogenic sugars and patients should be advised to take appropriate oral hygiene measures.

Note Feeds containing more than 6 g/100 mL protein or 2 g/100 mL fibre should be avoided in children unless recommended by an appropriate specialist or dietician.

Enteral foods and supplements

Standard ACBS indications: short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, proven inflammatory bowel disease, following total gastrectomy, bowel fistulas, or disease-related malnutrition.

Alicalm (SHS)

Powder, protein (cows’ milk) 15 g, carbohydrate 58 g, fat 17.5 g, energy 1889 kJ (450 kcal)/100 g with vitamins, minerals and trace elements; standard dilution (30%) provides protein 4.5 g, carbohydrate 17.4 g, fat 5.3 g, energy 567 kJ (135 kcal)/100 mL. Residual lactose. Vanilla flavour. Net price 400 g = £16.20

A sole source of nutrition or nutritional supplement for dietary management of Crohn’s disease in adults and children over 5 years.

Calogen (Nutricia Clinical)

Emulsion, fat 50 g, energy 1850 kJ (450 kcal)/100 mL. Flavours: neutral, banana, and strawberry (banana- and strawberry-flavour contain sucrose approx. 4 g/100 mL), net price 200 mL = £3.80; 500 mL = £9.32.

A nutritional supplement for disease-related malnutrition, malabsorption states or other conditions requiring fortification with a high-fat supplement with or without fluid and electrolyte restrictions. Use with caution in children under 5 years; strawberry and banana flavours not suitable for children under 3 years.

Caloreen (Nestlé)

Powder, water-soluble dextrins, 390 g/100 g, with less than 1.8 mmol of Na+ and 0.3 mmol of K+/100 g. Gluten-, lactose-, and fructose-free. Net price 500 g = £3.42.

For disease-related malnutrition, malabsorption states or other conditions requiring fortification with a high or readily available carbohydrate supplement.

Calshake (Fresenius Kabi)

Powder, protein 4.9 g, carbohydrate 58 g, fat 20.4 g, energy 1809 kJ (432 kcal)/87 g. Gluten-free. Strawberry, vanilla, neutral, and banana flavours, net price 87-g sachet = £1.87; also available chocolate flavour (protein 4 g, carbohydrate 58 g, fat 20.4 g, fibre 1.6 g, energy 1809 kJ (432 kcal)/90 g = £1.87.

For disease-related malnutrition, malabsorption states or other conditions requiring fortification with a fat/carbohydrate supplement.

Clinutren 1.5 (Nestlé)

Liquid, protein 11 g, carbohydrate 42 g, fat 10 g, energy 1260 kJ (300 kcal)/200 mL with vitamins and minerals. Gluten-free; clinically lactose-free. Flavours: apricot, banana, chocolate, coffee, strawberry-raspberry or vanilla, net price 4 × 200-mL bottle = £9.59

For indications see Clinutren Fruit

Clinutren 1.5 Fibre (Nestlé)

Liquid, protein 5.7 g, carbohydrate 19 g, fat 5.9 g, fibre 2.6 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Flavours: vanilla or plum, net price 4 × 200-mL pot = £6.59.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see above) and dysphagia. Not suitable for children under 3 years; not suitable as a sole source of nutrition for children 3–6 years.

Clinutren Dessert (Nestlé)

Semi-solid, protein 12 g, carbohydrate 19 g, fat 3.3 g, energy 650 kJ (150 kcal)/125 g with vitamins and minerals. Gluten-free. Flavours: caramel, chocolate, peach or vanilla, net price 4 × 125-g pot = £5.56.

Nutritional supplement for standard ACBS indications (see above) and dysphagia, continuous ambulatory peritoneal dialysis (CAPD), or haemodialysis. Not suitable for children under 3 years; maximum of 3 units daily for children 3–6 years.

Clinutren Fruit (Nestlé)

Liquid, protein 8 g, carbohydrate 54 g, fat less than 0.4 g, energy 1040 kJ (250 kcal)/200 mL with vitamins and minerals. Gluten-free. Low-lactose. Flavours: grapefruit, orange, pear-cherry, or raspberry-blackcurrant, net price 4 × 200-mL cup = £6.63.

Nutritional supplement for standard ACBS indications (see above) and dysphagia. Not suitable for children under 3 years; maximum of 3 units daily for children 3–6 years.

Clinutren Junior (Nestlé)

Powder, protein (whey) 13.9 g, carbohydrate 62.2 g, fat 18.3 g (of which MCT 20%), energy 1950 kJ (467 kcal)/100 g with vitamins, minerals and trace elements; standard dilution (22%) provides protein 2.9 g, carbohydrate 13.3 g, fat 3.9 g, energy 420 kJ (100 kcal)/100 mL. Gluten-free; residual lactose. Flavour: vanilla, net price 400 g = £9.72.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see above), growth failure, and dysphagia in children 1–10 years.

Complan Shake (Complan Foods)

Powder, protein (cows’ milk) 8.8 g, carbohydrate 34.9 g, fat 8.4 g, fibre 200 mg, energy 1055 kJ (251 kcal)/57 g; when reconstituted with whole milk, provides protein 15.6 g, carbohydrate 44.2 g, fat 16.4 g, fibre 200 mg, energy 1619 kJ (387 kcal)/servings with vitamins, minerals and trace elements. Contains lactose; gluten-free. Flavours: banana, vanilla, chocolate, strawberry, milk, net price 4 × 57-g sachet = £3.26.

Nutritional supplement for standard ACBS indications (see above) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years.

Duobar (SHS)

Bar, carbohydrate 22.5 g, fat 22.5 g, energy 1211 kJ (292 kcal)/45 g. Milk protein-, gluten-, and lactose-free.
Appendix 7: Borderline substances

Strawberry, toffee, or neutral flavours. Net price 45-g bar = £1.87.

A nutritional supplement for disease-related malnutrition, malabsorption states or other conditions requiring fortification with fat/carbohydrate supplement

Duocal (SHS)  
**Liquid** (emulsion providing carbohydrate 23.4 g, fat 7.1 g (of which MCT 30%), energy 661 kJ (158 kcal)/100 mL; low- 
electrolyte, gluten-, lactose-, and protein-free. Net price 250 mL = £3.14; 1 litre = £10.37

**MCT Powder** (carbohydrate 74.6 g, fat 23.2 g (of which MCT 85%), energy 2042 kJ (486 kcal)/100 g; low electrolyte, 
gluten-, protein- and lactose-free. Net price 400 g = £16.84

**Super Soluble Powder** (carbohydrate 72.7 g, fat 22.3 g (of which MCT 35%), energy 2061 kJ (492 kcal)/100 g; low 
electrolyte, gluten-, and protein-lactose-free. Net price 400 g = £14.16

Nutritional supplements for disease-related malnutrition, malabsorption states or other conditions requiring fortification with fat/carbohydrate supplement

Elemental 028 Extra (SHS)  
**Liquid** (protein equivalent (essential and non-essential amino acids) 2.5 g, carbohydrate 11.3 g, fat 3.5 g (of which MCT 35%), energy 358 kJ (86 kcal)/100 mL, with vitamins, minerals, and trace elements. Flavours: grapefruit, orange and pineapple, summer fruits. Net price 250-mL carton = £2.88

**Powder** (protein equivalent (essential and non-essential amino acids) 12.5 g, carbohydrate 59.5 g, fat 17.4 g (of which MCT 35%), energy 1871 kJ (443 kcal)/100 g (unflavoured) with vitamins, minerals, and trace elements. Net price 100 g unflavoured (see also Modul FLavour System, p. 878) = £5.80; also available in banana, citrus, or orange flavour (carbohydrate 55 g, energy 1792 kJ (427 kcal)/100 g), 100 g = £5.60

A sole source of nutrition or nutritional supplement for: short-bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistulas. Not suitable for children under 1 year; use with caution in children 1–5 years

Emsogen (SHS)  
**Powder** (protein equivalent (essential and non-essential amino acids) 12.5 g, carbohydrate 60 g, fat 104 g (of which MCT 83%), energy 1839 kJ (438 kcal)/100 g, with vitamins, minerals, and trace elements; **standard dilution** (20%) unflavoured, provides protein 2.5 g, carbohydrate 12.5 g, fat 3.3 g, energy 368 kJ (86 kcal)/100 mL (see also Modul FLavour System, p. 878). Net price 100 g = £5.76; also available in orange-flavoured (carbohydrate 55 g, energy 1754 kJ (418 kcal)/100 g), 100 g = £5.76

A sole source of nutrition (when supplemented with alpha-linolenic acid) or nutritional supplement for short-bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistulas. Not suitable for children under 1 year; use with caution in children 1–5 years

 Emmix Plus Commence (Abbott)  
**Starte pack**, contains: *Ensure Plus milkshake-style* (4 flavours), yoghurt-style (2 flavours); *Ensure Plus Juce* (4 flavours) – see *Ensure Plus and Ensure Plus Juce* for product information, net price 1 pack (10 × 220 mL) = £17.14

Intended as an initial 5–10 day supply to establish patient preferences.

Ensure Plus Fibre (Abbott)  
**Liquid** protein 6.25 g, carbohydrate 20.2 g, fat 4.92 g, fibre 2.5 g, energy 623 kJ (152 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free, residual lactose. Vanilla, chocolate, fruits of the forest, raspberry, strawberry and banana flavours. Net price 200-mL bottle = £1.74

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia, continuous ambulatory peritoneal dialysis (CAPD), or haemodialysis. Not suitable for children under 1 year; use with caution in children 1–5 years

Ensure Plus Juce (Abbott)  
**Liquid** protein 4.8 g, carbohydrate 32.7 g, energy 638 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Fat- and gluten-free; residual lactose. Flavours: apple, fruit punch, grapefruit, lemon and lime, orange, peach, pineapple, strawberry, or mushroom. Net price 220-mL bottle = £1.69

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia or continuous ambulatory peritoneal dialysis (CAPD). Not suitable for children under 1 year; use with caution in children 1–5 years

Ensure Twocal (Abbott)  
**Liquid** protein 8.4 g, carbohydrate 21 g, fat 8.9 g, fibre 1 g, energy 838kJ (200 kcal)/100 mL with vitamins, minerals, and trace elements. Residual lactose; gluten-free. Flavours: banana, chocolate, strawberry, or vanilla. Net price 200-mL carton = £2.03

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865), haemodialysis, continuous ambulatory peritoneal dialysis (CAPD), and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years

Foodlink Complete (Foodlink)  
**Powder** protein 12.5 g, carbohydrate 32.7 g, fat 7.6 g, energy 1048 kJ (249 kcal)/57-g serving (serving = 3 heaped des- sertspoonfuls recomposed with approximately half a pint water), with vitamins and minerals. Flavours: banana, chocolate,
natural, or strawberry; net price 450-g carton = £3.29; also available in blackcurrant, forest fruits, lemon, orange, strawberry, tropical, and chocolate flavour (protein 5 g, carbohydrate 19.3 g, fat 5 g, energy 670 kJ (160 kcal)/100 g with vitamins and minerals. Gluten-free. Vanilla, chocolate, banana, and forest fruit flavours, net price 4 × 125-g pot = £6.09. Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years.

Forticare (Nutricia Clinical)

Forticare liquid, protein 9.5 g, carbohydrate 19.1 g, fat 5.3 g, fibre 2.1 g, energy 675 kJ (160 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free. Flavours: cappuccino, orange and lemon, or peach and ginger. Net price 125-mL carton = £1.92. As a nutritional supplement for patients with lung cancer undergoing chemotherapy, or with pancreatic cancer.

FortiCreme Complete (Nutricia Clinical)

FortiCreme Complete liquid, protein 9.5 g, carbohydrate 19.3 g, fat 5 g, energy 670 kJ (160 kcal)/100 g with vitamins and minerals. Gluten-free. Vanilla, chocolate, banana, and forest fruit flavours, net price 4 × 125-g pot = £6.09. Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia, continuous ambulatory peritoneal dialysis (CAPD), and haemodialysis. Not suitable for children under 3 years; use with caution in children 3–5 years.

Fortijuice (Nutricia Clinical)

Fortijuice liquid, protein 4 g, carbohydrate 33.5 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Fat-free. Flavours: apple, apricot, blackcurrant, forest fruits, lemon, orange, strawberry, tropical, net price 200-mL carton = £1.80; 4 × 200 mL starter pack = £7.00. Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 3 years; use with caution in children 3–5 years.

Fortimel (Nutricia Clinical)

Fortimel liquid, protein 3.4 g, carbohydrate 18.8 g, fat 6.8 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free. Flavours: strawberry or vanilla, net price 200-mL = £2.52. A sole source of nutrition or nutritional supplement for disease-related malnutrition, and growth failure. For children 1–6 years, or body-weight 8–30 kg.

Fortini (Nutricia Clinical)

Fortini liquid, protein 3.4 g, carbohydrate 18.8 g, fat 6.8 g, fibre 1.5 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free. Flavours: strawberry or vanilla, net price 200-mL = £2.52. A sole source of nutrition or nutritional supplement for disease-related malnutrition, and growth failure. For children 1–6 years (8–20 kg body-weight).

Fortini Multifibre (Nutricia Clinical)

Fortini Multifibre liquid, protein 3.4 g, carbohydrate 18.8 g, fat 6.8 g, fibre 1.5 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free. Flavours: banana, chocolate, strawberry, and vanilla, net price 200-mL = £2.65.

For indications see Fortini

Fortisip Bottle (Nutricia Clinical)

Fortisip Bottle liquid, protein 6 g, carbohydrate 18.4 g, fat 5.8 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free; clinically lactose-free. Vanilla, banana, chocolate, orange, strawberry, tomato, tomato, vanilla flavour; also available chocolate flavour (protein 5 g, carbohydrate 18.4 g, fat 6.5 g, fibre 2.2 g, energy 625 kJ (150 kcal)/100 mL, net price 200-mL = £1.85. As a sole source of nutrition or as a nutritional supplement prescribed on medical grounds for: short-bowel syndrome, intractable malabsorption, pre-operative preparation of under-nourished patients, proven inflammatory bowel disease, following total gastrectomy, dysphagia, disease-related malnutrition. Not suitable for children under 3 years; use with caution in children aged 3–5 years.

Fortisip Multi Fibre (Nutricia Clinical)

Fortisip Multi Fibre liquid, protein 6 g, carbohydrate 18.4 g, fat 5.8 g, fibre 2.3 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free, clinically lactose-free. Bananas, chocolate, orange, strawberry, tomato, vanilla flavour; also available chocolate flavour (protein 5 g, carbohydrate 18.4 g, fat 6.5 g, fibre 2.2 g, energy 625 kJ (150 kcal)/100 mL, net price 200-mL = £1.85. As a sole source of nutrition or as a nutritional supplement prescribed on medical grounds for: short-bowel syndrome, intractable malabsorption, pre-operative preparation of under-nourished patients, proven inflammatory bowel disease, following total gastrectomy, dysphagia, disease-related malnutrition. Not suitable for children under 3 years; use with caution in children aged 3–5 years.

Fortisip Range (Nutricia Clinical)

Fortisip Range Starter pack contains 4 × Fortisip Bottle, 4 × Fortijuce, 2 × Fortisip Yogurt Style, see separate entries for details, net price 1 pack (10 × 200 mL) = £17.46.

Fortisip Yogurt Style (Nutricia Clinical)

Fortisip Yogurt Style yoghurt, protein 6 g, carbohydrate 18.7 g, fat 5.8 g, fibre 0.2 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals, and trace elements. Gluten-free. Peach and orange, raspberry, vanilla and lemon flavours, net price 200-mL bottle = £1.80. A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 3 years; not suitable as a sole source of nutrition for children 3–6 years.

Frebini Energy (Fresenius Kabi)

Frebini Energy Sip feed, protein 3.75 g, carbohydrate 18.8 g, fat 6.65 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free; residual lactose. Flavours: banana or strawberry. Net price 200-mL bottle = £2.25. Tube feed, protein 3.75 g, carbohydrate 18.75 g, fat 6.7 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Flavour: neutral, net price 500-mL EasyBag = £5.93. As a sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia in children 1–10 years, or body-weight 8–30 kg. Not suitable for children under 1 year.

Frebini Energy Fibre (Fresenius Kabi)

Frebini Energy Fibre Sip feed, protein 3.75 g, carbohydrate 18.8 g, fat 6.65 g, fibre 1.1 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free; residual lactose. Chocolate or vanilla flavour, net price 200-mL bottle = £2.30. Tube feed, protein 3.75 g, carbohydrate 18.75 g, fat 6.7 g, fibre 1.13 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free, clinically lactose-free. Flavour: neutral, net price 500-mL EasyBag = £6.34. For indications see Frebini Energy

Frebini Original (Fresenius Kabi)

Frebini Original tube feed, protein 2.5 g, carbohydrate 13.5 g, fat 4 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free; residual lactose. Flavour: neutral, net price 500-mL EasyBag = £4.73. For indications see Frebini Energy

Frebini Original Fibre (Fresenius Kabi)

Frebini Original Fibre tube feed, protein 2.5 g, carbohydrate 12.5 g, fat 4.4 g, fibre 750 mg, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free, residual lactose. Neutral flavour, net price 500-mL EasyBag = £5.25. For indications see Frebini Energy

Fresubin 1000 Complete (Fresenius Kabi)

Fresubin 1000 Complete tube feed, protein 5.5 g, carbohydrate 12.5 g, fat 3.1 g, fibre 2 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free, clinically lactose-free, net price 1-litre EasyBag = £8.20. For indications see Fresubin Energy
Appendix 7: Borderline substances

Fresubin 1200 Complete (Fresenius Kabi)

**Liquid**, tube feed, protein 6 g, carbohydrate 15 g, fat 4.1 g, fibre 2 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free, clinically lactose-free. Net price 1-litre EasyBag = £10.61.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865). Not suitable for children under 2 years; use with caution in children 2–5 years.

Fresubin 2250 Complete (Fresenius Kabi)

**Tube feed**, protein 5.6 g, carbohydrate 18.8 g, fat 5.8 g, fibre 2 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Fruits of the forest or vanilla flavour, net price 200 mL = £1.69.

Nutritional supplement for standard ACBS indications (see p. 865), dysphagia, continuous ambulatory peritoneal dialysis (CAPD), and haemodialysis. Not suitable for children under 1 year; use with caution in children 1–5 years.

Fresubin 2kcal Drink (Fresenius Kabi)

**Liquid**, protein 10 g, carbohydrate 22.5 g, fat 7.8 g, energy 840 kJ (200 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Chocolate flavour, net price 200 mL = £1.69.

Nutritional supplement for standard ACBS indications (see p. 865), dysphagia, continuous ambulatory peritoneal dialysis (CAPD), and haemodialysis. Not suitable for children under 1 year; use with caution in children 1–5 years.

Fresubin Energy (Fresenius Kabi)

**Liquid**, protein 5.65 g, carbohydrate 18.8 g, fat 5.83 g, energy 630 kJ (150 kcal)/100 mL, with vitamins and minerals. Flavours: vanilla, strawberry, blackcurrant, banana, cappuccino, tropical fruits, chocolate, lemon, and neutral, net price 200 mL bottle = £1.66, unflavoured, 500 mL EasyBag = £3.91; 1-litre EasyBag = £7.70; 1.5-litre EasyBag = £10.32.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years.

Fresubin Fibre (Fresenius Kabi)

**Sip feed**, protein 5.65 g, carbohydrate 18.8 g, fat 5.83 g, fibre 2.5 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Flavours: banana, caramel, chocolate, cherry, strawberry, vanilla. Net price 200-mL bottle = £1.74.

For indications see **Fresubin Energy**

Fresubin Energy Fibre (Fresenius Kabi)

**Tube feed**, protein 5.6 g, carbohydrate 18.8 g, fat 5.8 g, fibre 2 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Unflavoured, net price 500-mL EasyBag = £4.30; 1-litre EasyBag = £8.20.

For indications see **Fresubin Energy**

Fresubin HP Energy (Fresenius Kabi)

**Liquid**, protein 7.5 g, carbohydrate 17 g, fat 6 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free and low lactose. Vanilla flavour. Net price 500 mL Flexible Pouch = £3.96; 1-litre flexible pouch = £6.36. Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia, continuous ambulatory peritoneal dialysis (CAPD), haemodialysis. Not suitable for children under 1 year; use with caution in children 1–5 years.

Fresubin Original (Fresenius Kabi)

**Liquid**, protein 3.8 g, carbohydrate 13.8 g, fat 3.4 g, fibre 2 g, energy 420 kJ (100 kcal)/100 mL, with vitamins and minerals. Flavour: neutral. Net price 500-mL EasyBag = £3.63; 1-litre EasyBag = £7.24; 1.5-litre EasyBag = £10.20.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 2 years; use with caution in children 2–5 years.

Fresubin Protein Energy Drink (Fresenius Kabi)

**Liquid**, protein 10 g, carbohydrate 12.4 g, fat 6.7 g, energy 630 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Cappuccino, chocolate, strawberry, tropical fruits, and vanilla flavours, net price 200 mL bottle = £1.69.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia, continuous ambulatory peritoneal dialysis (CAPD), or haemodialysis. Not suitable for children under 1 year; use with caution in children 1–5 years.

Infatini (Nutricia Clinical)

**Liquid**, tube feed, protein 10.3 g, fat 5.4 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free. Net price 100-mL bottle = 96p, 200-mL carton = £1.91.

A sole source of nutrition or nutritional supplement for failure to thrive, disease-related malnutrition and malabsorption. Manufactured, advises suitable for infants up to 8 kg body-weight (0–12 months of age).

Isosource Energy (Nestlé)

**Liquid**, protein 5.7 g, carbohydrate 20 g, fat 6.2 g, energy 660 kJ (160 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Net price 500-mL flexible pouch = £3.66, 1-litre flexible pouch = £7.31.

For indications see **Isosource Standard**

Isosource Energy Fibre (Nestlé)

**Liquid**, tube feed, protein 4.9 g, carbohydrate 20.2 g, fat 5.5 g, fibre 1.5 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Net price 500-mL flexible pouch = £3.96, 1-litre flexible pouch = £7.93.

For indications see **Isosource Standard**

Isosource Fibre (Nestlé)

**Liquid**, protein 3.8 g, carbohydrate 13.6 g, fat 3.4 g, fibre 1.4 g, energy 422 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Net price 500-mL flexible pouch = £3.39, 1-litre flexible pouch = £6.77.

For indications see **Isosource Standard**

Isosource Junior (Nestlé)

**Liquid**, protein 2.7 g, carbohydrate 17 g, fat 4.7 g, energy 513 kJ (123 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Net price 500-mL flexible pouch = £3.96, 1-litre flexible pouch = £7.95.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865), dysphagia and growth failure in children 1 to 6 years or body-weight 8 to 20 kg.

Isosource Standard (Nestlé)

**Liquid**, protein 4 g, carbohydrate 13.6 g, fat 3.3 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; clinically lactose-free. Net price 500-mL flexible pouch = £3.96, 1-litre flexible pouch = £7.95.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years.

Jevity (Abbott)

**Liquid**, protein 4 g, fat 3.5 g, carbohydrate 14.1 g, fibre 1.8 g, energy 441 kJ (106 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-, lactose-, and sucrose-free. Net price 500-mL ready-to-hang = £3.85, 1-litre ready-to-hang = £7.23, 1.5-litre ready-to-hang = £10.89.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 2 years; use with caution in children 2–5 years.

Jevity 1.5 kcal (Abbott)

**Liquid**, tube feed, protein 6.38 g, carbohydrate 20.1 g, fat 4.9 g, fibre 2.2 g, energy 640 kJ (152 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Flavour: neutral. Net price 500-mL EasyBag = £3.63; 1-litre EasyBag = £7.24; 1.5-litre EasyBag = £10.20. Not suitable for children under 2 years; use with caution in children 2–5 years.
free. Net price 500-mL ready-to-hang = £4.69, 1-litre ready-to-hang = £8.70, 1.5-litre ready-to-hang = £13.58.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 2 years, use with caution in children 2–10 years

**Jevity Plus** (Abbott)

**Liquid**, protein 5.6 g, carbohydrate 15.1 g, fat 3.9 g, dietary fibre 2.2 g, energy 504 kJ (120 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free. Net price 500-mL ready-to-hang = £4.24, 1-litre ready-to-hang = £8.68, 1.5-litre ready-to-hang = £13.05.

For indications see under **Jevity**

**Jevity Promote** (Abbott)

**Liquid**, protein 5.55 g, carbohydrate 11.98 g, fat 3.32 g, fibre 1.7 g, energy 427 kJ (101 kcal)/100 mL, with vitamins, minerals, and trace elements. Gluten-free, clinically lactose-free. Net price 1-litre ready-to-hang = £8.49.

For indications see **Jevity** 1.5 kkal

**Maxi-Juila** (SHS)

**Liquid**, carbohydrate 50 g, sodium less than 23 mg, phosphorus less than 5 mg, potassium less than 4 mg, energy 859 kJ (200 kcal)/100 mL. Gluten-, lactose-, and fructose-free. Flavours: orange, and natural. Net price 200 mL = £1.28

**Super Soluble Powder**, carbohydrate (as glucose polymer) 95 g, sodium less than 20 mg, phosphorous less than 5 mg, potassium less than 5 mg, energy 1615 kJ (380 kcal)/100 g. Gluten- and lactose-, and fructose-free. Unflavoured. Net price 4 × 132-g sachet pack = £5.04, 200 g = £1.96, 2.5 kg = £17.94, 25 kg = £121.85

All for disease-related malnutrition; malabsorption states or other conditions requiring fortification with high or readily available carbohydrate supplement

**Modulen IBD** (Nestlé)

**Powder**, protein (casein) 18 g, carbohydrate 54 g, fat 23 g, energy 2040 kJ (500 kcal)/100 g with vitamins, minerals, and trace elements. Gluten-free; clinically lactose-free. Net price 500-mL drink bottle = £4.39, 500-mL flexible pouch = £4.52.

For indications see **Modulen IBD**

**Novasource GI Control** (Nestlé)

**Liquid**, protein 4.1 g, carbohydrate 14.2 g, fat 3.5 g, fibre 2.2 g, energy 440 kJ (100 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free; clinically lactose-free, net price 500-mL bottle = £4.39, 500-mL flexible pouch = £4.52.

For indications see **Novasource GI Control**

**Novasource GI Forte** (Nestlé)

**Liquid**, protein 6 g, carbohydrate 18.3 g, fat 5.9 g, fibre 2.2 g, energy 631 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free; low-lactose, net price 500-mL flexible pouch = £4.49, 1-litre flexible pouch = £8.98.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years

**Nutrini** (Nestlé)

**Liquid**, protein 2.75 g, carbohydrate 12.3 g, fat 4.4 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free; clinically lactose-free. Net price 200-mL bottle = £2.12, 500-mL = £5.28.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia in children 1–6 years or 8–20 kg body-weight

**Nutrini Energy** (Nutricia Clinical)

**Liquid**, tube feed, protein 4.1 g, carbohydrate 18.5 g, fat 6.7 g, fibre 0.75 g, energy 830 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free, net price 200-mL bottle = £2.74, 500-mL pack = £6.82.

For short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, total gastroctomy, dysphagia, disease-related malnutrition, and growth failure. For children 1–6 years or 8–20 kg body-weight

**Nutrini Low Energy Multi Fibre** (Nutricia Clinical)

**Liquid**, tube feed, protein 2.06 g, carbohydrate 9.3 g, fat 3.3 g, fibre 0.75 g, energy 315 kJ (75 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and lactose-free, net price 200-mL bottle = £2.05, 500-mL pack = £5.18

For indications see **Nutrini Energy Multi Fibre**

**Nutrini Multi Fibre** (Nutricia Clinical)

**Liquid**, protein 2.75 g, carbohydrate 12.3 g, fat 4.4 g, fibre 750 mg, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free, clinically lactose-free. Net price 200-mL bottle = £2.35, 500-mL pack = £5.87

A sole source of nutrition or nutritional supplement for short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, total gastroctomy, dysphagia, disease-related malnutrition and growth failure. For children 1–6 years or 8–20 kg body-weight

**Nutrini Peptisorb** (Nutricia Clinical)

**Liquid**, (formerly Nutrisorb), protein 2.9 g, carbohydrate 13.7 g, fat 3.9 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free. Net price 500-mL = £8.15

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865), growth failure, and dysphagia in children 1–6 years or 8–20 kg body-weight

**Nutriprem 2** (Cow & Gate)

**Liquid**, protein (cows’ milk) 2 g, carbohydrate 7.5 g, fat 4.1 g, fibre 0.4 g, energy 801 kJ (190 kcal)/100 mL (75 kcal)/100 g, with vitamins, minerals, and trace elements. Contains lactose. Net price 200-mL carton = £1.54. Also available to hospitals-only as a sterilised prepared feed in 100-mL bottles

**Powder**, protein (cows’ milk) 1.9 g, carbohydrate 48.3 g, fat 26.7 g, fibre 5.2 g, energy 2030 kJ (485 kcal)/100 g with vitamins, minerals, and trace elements. Standard dilution (15.4%) provides protein 2 g, carbohydrate 7.4 g, fat 4.1 g, energy 310 kJ (75 kcal)/100 mL. Contains lactose. Net price 900 g = £10.28.

For catch-up growth in pre-term infants (less than 35 weeks at birth), and small-for-gestational-age infants, until 6 months corrected age

**Nutrison Energy** (Nutricia Clinical)

**Liquid**, protein 6 g, carbohydrate 18.5 g, fat 5.8 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and sucrose-free; clinically lactose-free. Net price 500-mL bottle = £4.25; 500-mL pack = £4.72; 1-litre pack = £8.50; 1.5-litre pack = £12.80.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrison Energy Multi Fibre** (Nutricia Clinical)

**Liquid**, protein 4.1 g, carbohydrate 18.5 g, fat 6.7 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and fructose-free. Net price 200-mL bottle = £3.99, 500-mL pack = £5.23; 1-litre pack = £9.49; 1.5-litre pack = £15.20.

A sole source of nutrition or nutritional supplement for short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, proven inflammatory bowel disease, following total gastroctomy, dysphagia, disease-related malnutrition. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrison MCT** (Nutricia Clinical)

**Liquid**, protein 5 g, carbohydrate 12.6 g, fat 3.3 g (of which MCT 61%), energy 420 kJ (100 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and fructose-free. Net price 1-litre pack = £7.73.

For indications see **Nutrition Energy**

**Nutrison Multi Fibre** (Nutricia Clinical)

**Liquid**, protein 4.1 g, carbohydrate 18.5 g, fat 6.7 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten- and sucrose-free, clinically lactose-
Appendix 7: Borderline substances

**Nutrition Protein Plus** (Nutricia Clinical)
- Liquid, protein 6.3 g, carbohydrate 14.2 g, fat 4.9 g, energy 525 kJ (125 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Net price 1-litre pack = £7.95.

For use in the dietary management of disease-related malnutrition. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrition ProPlus Multi Fibre** (Nutricia Clinical)
- Liquid, protein 6.3 g, carbohydrate 14.2 g, fat 4.9 g, fibre 1.5 g, energy 525 kJ (125 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Net price 1-litre pack = £8.85.

For use in the dietary management of disease-related malnutrition. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrition Soya Multi Fibre** (Nutricia Clinical)
- Liquid, protein 4 g, carbohydrate 12.3 g, fat 3.9 g, energy 420 kJ (100 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and sucrose-free; clinically lactose-free. Net price 500-mL bottle = £4.12; 1-litre pack = £8.24.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 885) and cow's milk protein and lactose intolerance. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrition Soya** (Nutricia Clinical)
- Liquid, protein 4 g, carbohydrate 12.3 g, fat 3.9 g, energy 425 kJ (100 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Net price 1-litre pack = £13.25.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 885), dysphagia, and cow's milk protein and lactose intolerance. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrition Standard** (Nutricia Clinical)
- Liquid, protein 4 g, carbohydrate 12.3 g, fat 3.9 g, energy 425 kJ (100 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and lactose-free. Net price 1-litre pack = £10.65.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 885) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrition 1000 Complete Multi Fibre** (Nutricia Clinical)
- Liquid, protein 5.5 g, carbohydrate 11.3 g, fat 3.7 g, fibre 2 g, energy 420 kJ (100 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and clinically lactose-free, net price 500-mL bottle = £8.75.

A sole source of nutrition or nutritional supplement for the dietary management of disease-related malnutrition in patients with low-energy and/or low fluid requirements. Not suitable for children under 1 year; use with caution in children 1–6 years

**Nutrition 1200 Complete Multi Fibre** (Nutricia Clinical)
- Liquid, protein 5.5 g, carbohydrate 15 g, fat 4.3 g, fibre 2 g, energy 505 kJ (120 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten- and clinically lactose-free, net price 500-mL bottle = £4.55; 1-litre pack = £9.10; 1.5-litre pack = £13.66.

A sole source of nutrition or nutritional supplement for short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, proven inflammatory bowel disease, following total gastrectomy, dysphagia, disease-related malnutrition. Not suitable for children under 1 year; use with caution in children 1–6 years

**Osmolite Plus** (Abbott)
- Liquid, protein 5.6 g, carbohydrate 15.8 g, fat 3.9 g, energy 508 kJ (121 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free and clinically lactose-free. Net price 500-mL ready-to-hang = £3.96, 1-litre ready-to-hang = £7.64, 1.5-litre ready-to-hang = £11.44.

For indications see Osmolite

**Paediasure Fibre** (Abbott)
- Liquid, protein 2.8 g, carbohydrate 11 g, fat 5 g, energy 422 kJ (101 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free, residual lactose. Flavours: vanilla (can, ready-to-hang and carton), strawberry, chocolate and banana (carton). Net price 250-mL can = £2.48, 500-mL ready-to-hang = £4.97, 200-mL carton = £1.99.

A sole source of nutrition or nutritional supplement for children aged 1–10 years, body-weight 8–30 kg, for short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, dysphagia, bowel fistulas, and disease-related malnutrition and/or growth failure. Not suitable for children under 1 year

**Peptamen Plus Fibre** (Abbott)
- Liquid, protein 4.2 g, carbohydrate 16.7 g, fat 7.5 g, energy 623 kJ (151 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free, residual lactose, net price 1-litre pack = £2.64, 200-mL carton = £2.19.

Flavours: vanilla (ready-to-hang and carton), banana (carton), strawberry (carton). Net price 500-mL ready-to-hang = £5.52, 200-mL carton = £2.19.

For indications see Peediaure

**Peptamen Plus** (Abbott)
- Liquid, protein 4.2 g, carbohydrate 16.4 g, fat 7.4 g, fibre 1.1 g, energy 626 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free, residual lactose, net price 200-mL carton = £2.43, 500-mL ready-to-hang = £6.23.

For indications see Peediaure

**Peptamen Junior** (Nestlé)
- Powder, 4.2 g, carbohydrate 12.7 g, fat 3.7 g (of which MCT 70%), energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free, residual lactose; dual lactose; gluten-free. Net price 500 mL = £5.97.

For indications see Peediaure

**Peptamen** (Nestlé)
- Powder, 4.2 g, carbohydrate 16.6 g, fat 7.4 g, fibre 1.1 g, energy 626 kJ (150 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free, residual lactose, net price 200 mL = £2.64, 200-mL carton = £2.19.


For indications see Peediaure

**Nestlé Nutrition Flavour Mix**
- For use with Peptamen Liquid 200-mL cup and Modulen IBD. Flavours: banana, chocolate, coffee, lemon and lime, strawberry. Net price 60 g = £6.48

**Nestlé Pediatric Liquid**
- For indications see Peptamen Liquid

**Osmolite** (Abbott)
- Liquid, protein 4 g, carbohydrate 13.5 g, fat 3.4 g, energy 424 kJ (100 kcal)/100 mL, with vitamins and minerals. Gluten- and lactose-free. Net price 250-mL can = £1.79, 500-mL bottle = £3.39, 1-litre bottle = £6.46, 1.5-litre bottle = £9.69.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years
hydrate 13.8 g, fat 3.85 g, energy 420 kJ (100 kcal)/100 mL. Residual lactose; gluten-free. Vanilla flavour, net price 400-g can = £14.52.

A sole source of nutrition or nutritional supplement for short-bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistulas, in children 1–10 years

Peptisorb (Nutricia Clinical)

Liquid, protein 4 g, carbohydrate 17.6 g, fat 1.7 g, energy 425 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free. Net price 500-mL bottle = £5.50; 500-mL pack = £6.04; 1-litre pack = £10.92.

A sole source of nutrition or nutritional supplement prescribed on medical grounds for short-bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistulas. Not suitable for children under 1 year; use with caution in children 1–5 years

Pevital (Abbott)

Powder, glucose, maltose, and polysaccharides, providing 1630 kJ (384 kcal)/100 g. Net price 400 g = £3.55.

Liquid, glucose polymers providing carbohydrate 61.9 g/100 mL. Low-electrolyte, protein-free. Flavours: orange or neutral. Net price 200 mL = £1.42.

Nutritional supplement for disease-related malnutrition, malabsorption states or other conditions requiring fortification with a high or readily available carbohydrate supplement

Polycal (Nutricia Clinical)

Powder, carbohydrate 17.7 g, fat 3.7 g, energy 552 kJ (131 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free, unflavoured. Net price 500-mL ready-to-hang = £5.52; 1-litre ready-to-hang = £11.04.

Nutritional supplement for standard ACBS indications (see p. 865). Not suitable for children under 5 years

Polarcal (Nutricia Clinical)

Powder, protein 6.7 g, carbohydrate 17.7 g, fat 3.7 g, energy 552 kJ (131 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free. Vanilla or banana flavour, net price, 240-mL carton = £4.17.

Nutritional supplement for catch-up growth in pre-term infants (less than 35 weeks at birth), and small-for-gestational-age infants, until 6 months post-natal age

Pro-Cal (Vitalfa)

Powder, protein 13.5 g, carbohydrate 26.8 g, fat 56.2 g, energy 2788 kJ (687 kcal)/100 g. Net price 25 × 15-g sachets = £12.83; 510 g = £24.21; 12.5 kg = £172.13; 25 kg = £265.25.

Nutritional supplement for disease-related malnutrition, malabsorption states or other conditions requiring fortification with a fat/carbohydrate supplement. Not suitable for children under 1 year, use with caution in children 1–5 years

Pro-Cal Shot (Vitalfa)

Liquid, protein 6.7 g, carbohydrate 13.4 g, fat 28.2 g, energy 1586 kJ (374 kcal)/100 mL, neutral or strawberry flavour; net price 6 × 250-mL bottle = £25.80.

Nutritional supplement for disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a fat/carbohydrate supplement. Not suitable for children under 1 year, use with caution in children 1–5 years

ProSure (Abbott)

Liquid, protein 6.65 g, carbohydrate 19.4 g, fat 2.56 g, fibre 97 mg. Gluten-free. Net price 500 mL (125 kcal)/100 mL, with vitamins, minerals, and trace elements. Gluten-free, clinically lactose-free. Vanilla or banana flavour, net price, 240-mL carton = £2.70.

Nutritional supplement for patients with pancreatic cancer and patients with lung cancer undergoing chemotherapy. Not suitable for children under 1 year; use with caution in children 1–4 years

Provide Xtra (Fresenius Kabi)

Liquid, protein 3.75 g, carbohydrate 27.5 g, energy 525 kJ (125 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free. Apple, blackcurrant, carrot-apple, cherry, citrus cola, lemon & lime, melon, orange & pineapple, or tomato flavour. Net price 200-mL carton = £1.63.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years

QuickCal (Vitalfa)

Powder, protein (cows' milk) 600 mg, carbohydrate (lactose) 2.2 g, fat 10 g, Na+ 13 mg (0.6 mmol), energy 418 kJ (100 kcal)/13 g, net price 25 × 13-g sachets = £11.54.

For disease-related malnutrition, malabsorption states or other conditions requiring fortification with a fat/carbohydrate supplement. Not suitable for children under 1 year, use with caution in children 1–5 years

Renilin 7.5 (Nutricia Clinical)

Liquid, protein 7.5 g, carbohydrate 20 g, fat 10 g, energy 840 kJ (200 kcal)/100 mL, with vitamins, minerals and trace elements. Gluten-free. Apricot or caramel flavour, net price 125-mL carton = £1.79.

Nutritional supplement for standard ACBS indications (see p. 865). Not suitable for children under 3 years, use with caution in children 3–4 years

Resource Benefiber (Nestlé)

Powder, fibre (hydrolysed guar gum, soluble) 78 g, carbohydrate 19 g, energy 323 kJ (76 kcal)/100 g with vitamins, minerals and trace elements. Gluten-free, low lactose. Flavours: caramel, chocolate, or vanilla, net price 125-g cup = £1.39.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia, continuous ambulatory peritoneal dialysis (CAPD), or haemodialysis. Not suitable for children under 1 year, use with caution in children 1–5 years

Resource Dessert Energy (Nestlé)

Semi-solid, protein 4.8 g, carbohydrate 21.2 g, fat 6.24 g, energy 671 kJ (160 kcal)/100 g with vitamins, minerals, and trace elements. Gluten-free; low lactose. Flavours: caramel, chocolate, or vanilla, net price 125-g cup = £1.39.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia and conditions requiring a high energy and low volume diet. Not suitable for children under 6 years, use with caution in children 6–10 years

Resource Fruit Flavour Drink (Nestlé)

Liquid, protein 4 g, carbohydrate 33.5 g, energy 638 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Fat- and gluten-free; low lactose. Flavours: apple, orange, or pineapple, net price 200-mL carton = £1.53.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 3 years, use with caution in children 3–5 years

Resource Junior (Nestlé)

Liquid, protein 2.8 g, carbohydrate 20.6 g, fat 6.2 g, energy 631 kJ (150 kcal)/100 mL with vitamins, minerals, and trace elements. Gluten-free; clinically lactose-free. Flavours: chocolate, strawberry, or vanilla, net price 200-mL carton = £1.74.

A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year

Resource Protein (Nestlé)

Liquid, protein 9 g, carbohydrate 21.4 g, fat 8.7 g, fibre 2.5 g, energy 836 kJ (200 kcal)/100 mL, with vitamins, minerals, and trace elements. Gluten-free; low lactose. Flavours: summer fruits, strawberry, vanilla, coffee, apricot, or neutral. Net price 200 mL carton = £1.70.

Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia and conditions requiring a high energy and low volume diet. Not suitable for children under 6 years, use with caution in children 6–10 years

Appendix 7: Borderline substances
Appendix 7: Borderline substances

colate, forest fruits, strawberry, or vanilla. Net price 200-mL bottle = £1.37.

For indications see Resource: Fruit Flavour Drink.

Resource Shade (Nestlé)

| Liquid | protein 5.1 g, carbohydrate 22.6 g, fat 7 g, energy 731 kJ (174 kcal)/100 mL with vitamins, minerals and trace elements. Gluten-free; low lactose. Flavours: banana, chocolate, lemon, strawberry, summer fruits, toffee, or vanilla. Net price 175-mL carton = £1.50. Nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 1 year; use with caution in children 1–5 years |

Scandishake Mix (Nutricia Clinical)

| Powder | protein 11.7 g, carbohydrate 66.8 g, fat 30.4 g, energy 2457 kJ (588 kcal)/unflavoured serving (serving = 1 sachet reconstituted with 240 mL whole milk; protein, carbohydrate and energy values vary with flavour). Flavours: banana, caramel, chocolate, strawberry, vanilla, and unflavoured. Net price 85-g sachet = £2.02. Nutritional support for disease-related malnutrition, malabsorption states or other conditions requiring fortification with a fat/carbohydrate supplement |

SMA High Energy (SMA Nutrition)

| Liquid, Powder | protein 4.5 g, carbohydrate 15.6 g, fat 2.6 g, energy 420 kJ (100 kcal)/100 mL, with vitamins, minerals, and trace elements. Gluten-free, and low lactose. Net price 500-mL EasyBag = £5.34. A sole source of nutrition or nutritional supplement for disease-related malnutrition, malabsorption, and growth failure in children up to 18 months |

Surived OPD (Fresenius Kabi)

| Liquid, Powder | protein 3.3 g, carbohydrate 12.3 g, fat 4.2 g, energy 420 kJ (100 kcal)/100 mL with vitamins, minerals and trace elements. Residual lactose; gluten-free. Unflavoured, net price 500-mL bottle or pack = £4.66. A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865), dysphagia, and growth failure. Not suitable for children under 1 year; use with caution in children 1–6 years, body-weight under 21 kg. Suitable for children 7–12 years, body-weight 21–45 kg |

Tentri (Nutricia Clinical)

| Liquid, Tube Feed | protein 3.3 g, carbohydrate 12.3 g, fat 4.2 g, energy 420 kJ (100 kcal)/100 mL, with vitamins, minerals and trace elements. Residual lactose; gluten-free. Unflavoured, net price 500-mL bottle or pack = £5.76. For indications see Tentri |

Tentri Energy Multi Fibre (Nutricia Clinical)

| Liquid, Tube Feed | protein 4.9 g, carbohydrate 18.5 g, fat 6.3 g, energy 630 kJ (150 kcal)/100 mL with vitamins, minerals and trace elements. Residual lactose; gluten-free. Unflavoured, net price 500-mL bottle or pack = £6.35. For indications see Tentri |

Tentri Multi Fibre (Nutricia Clinical)

| Liquid, Tube Feed | protein 3.3 g, carbohydrate 12.3 g, fat 4.2 g, fibre 1.12 g, energy 420 kJ (100 kcal)/100 mL, with vitamins, minerals and trace elements. Residual lactose; gluten-free. Unflavoured, net price 500-mL bottle or pack = £5.12. A sole source of nutrition for short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, inflammatory bowel disease, total gastrectomy, dysphagia, disease-related malnutrition, and growth failure. Not suitable for children under 1 year; use with caution in children 1–6 years or body-weight less than 21 kg. Suitable for children 7–12 years, body-weight 21–45 kg |

TwoCal HN (Abbott)

| Liquid | protein 8.4 g, carbohydrate 21.6 g, fat 8.0 g, fibre 840 mg, energy 850 kJ (202 kcal)/100 mL, with vitamins, minerals, and trace elements. Gluten- and lactose-free. Vanilla flavour, net price 237-mL can = £2.40. A sole source of nutrition or nutritional supplement for standard ACBS indications (see p. 865) and dysphagia. Not suitable for children under 6 years; use with caution in children 6–10 years |

Vegenat -med (Vegenat)

| Powder-high protein varieties, average nutritional content: protein 24.6 g, carbohydrate 59.2 g, fat 16.3 g, fibre 6 g, energy 2020 kJ (480 kcal)/110 g, with vitamins, minerals, and trace elements. Gluten-free, low lactose. Flavours: chicken, fish, veal, ham, winter vegetables, fish and vegetable, lentil, vegetable, and chickpea, net price 12 × 110-g sachets = £47.44; curry chicken, 12 × 110-g sachets = £45.75; Lemon, or rice with lemon flavours, 12 × 110-g sachets = £45.07; rice with apple, 24 × 55-g sachets = £43.46 Powder-balanced protein varieties, average nutritional content: protein 18.4 g, carbohydrate 63.9 g, fat 15 g, fibre 6 g, energy 1970 kJ (470 kcal)/110 g, with vitamins, minerals, and trace elements. Gluten-free, low lactose. Flavours: apple, chocolate, honey, or orange, net price 12 × 110-g sachets = £33.89. Nutritional supplement for short-bowel syndrome, intractable malabsorption, pre-operative preparation of undernourished patients, proven inflammatory bowel disease, following total gastrectomy, dysphagia, disease-related malnutrition. Not suitable for children under 12 years; use with caution in children 12–16 years |

Vitajoule (Vitaffio)

| Powder, Resource Thickened Drink | protein 12 g, carbohydrate 24 g, fat 54 g, energy 2610 kJ (630 kcal)/100 g. Net price 500 g = £3.48, 2.5 kg = £17.35, 25 kg = £101.97. For disease-related malnutrition; malabsorption states or other conditions requiring fortification with a high or readily available carbohydrate supplement |

Vitasavoury (Vitaffio)

| Powder, Resource ThickenUp | protein 12 g, carbohydrate 24 g, fat 54 g, energy 2610 kJ (630 kcal)/100 g. Net price 10 × 50-g sachets = £15.52, 24 × 33-g ready cups = £25.76. Flavours: chicken, leek and potato, mushroom, vegetable. Nutritional supplement for disease-related malnutrition, malabsorption states or other conditions requiring fortification with a fat/carbohydrate supplement. Not suitable for children under 1 year; use with caution in children 1–5 years |

Feed thickeners and pre-thickened foods

Carobel, Instant (Cow & Gate)

| Powder, Carobel ThickenUp | rice flour, net price 153 g = £2.81. For thickening feeds in the treatment of vomiting |

Enfamil AR (Mead Johnson)

| Powder, Resource Thickened Drink | protein 12.5 g, carbohydrate 56 g, fat 26 g, energy 2093 kJ (500 kcal)/100 g with vitamins, minerals, and trace elements; standard dilution (15%) provides protein 1.7 g, fat 3.5 g, carbohydrate 7.6 g, energy 285 kJ (68 kcal)/100 mL. Contains lactose; gluten-free. Net price 400 g = £2.90. For significant gastro-oesophageal reflux. For use not in excess of a 6-month period. Not to be used in conjunction with any other thickener or antacid product |

Nutilis (Nutricia Clinical)

| Powder, Nutilis ThickenUp | modified maize starch, gluten- and lactose-free, net price 20 × 9-g sachets = £5.71, 225 g = £4.38. For thickening of foods in dysphagia. Not suitable for children under 3 years |

Resource Thickened Drink (Nestlé)

| Liquid | carbohydrate 22 g, energy: orange 383 kJ (89 kcal); apple 375 kJ (89 kcal)/100 mL syrup and custard consistencies. Gluten-free; clinically lactose free, net price 12 × 114-mL cups = £7.08. For dysphagia. Not suitable for children under 1 year |

Resource ThickenUp (Nestlé)

| Powder, Resource Thickened Drink | modified maize starch, gluten- and lactose-free, net price 227 g = £4.11, 75 × 4.5-g sachet = £15.75. For thickening of foods in dysphagia. Not suitable for children under 1 year |

BNF 57
SLO Drinks (SLO Drinks)
Powder; carbohydrate content varies with flavour and chosen consistency (3 consistencies available), see product literature. Flavours: black currant, lemon, orange, or peach, net price 25-cups = £7.50.

For patient hydration in the dietary management of dysphagia. Not suitable as a sole source of nutrition. Not suitable for children under 3 years

SMA Staydown (SMA Nutrition)
Powder; protein (casein, whey) 12.4 g, fat 28 g, carbohydrate 54.3 g, energy 2166 kJ (518 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (12.9%) provides protein 1.6 g, carbohydrate 7 g, fat 3.6 g, energy 279 kJ (67 kcal)/100 mL. Contains lactose. Net price 900 g = £6.48.

For significant gastro-oesophageal reflux. Not to be used for more than 6 months or in conjunction with any other thickener or antacid product

Thick and Easy (Fresenius Kabi)
Modified maize starch, net price 225-g can = £4.15; 100 x 2.5-g sachets = £26.35; 4.54 kg = £70.53.

Thickened juices, liquid, modified food starch. Flavours: apple or orange, net price 118-mL pot = £54; 1.42-litre bottle = £3.61.

For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive

Vitapro (Vitaful)
Powder; skim milk proteins, containing all essential amino acids, 75%. Net price 250 g = £7.10, 2 kg = £55.73.

For biochemically proven hypoproteinaemia

Foods and supplements for special diets

Alcoholic Beverages
see under Rectified Spirit

Alembicol D (Alembic Products)
Fractionated coconut oil. Net price 5 kg = £115.55.

For steatohepatia associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, surgery of the intestine, chronic liver disease, liver cirrhosis, other proven malabsorption syndromes; in a ketogenic diet in the management of epilepsy, type I hyperlipoproteinaemia

Caprilon (SHS)
Powder; cows' milk 5.1 g, fat 28.3 g (of which MCT 75%) and 1494 kJ (357 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (12.7%) provides protein 1.5 g, carbohydrate 7 g, fat 3.6 g, energy 277 kJ (66 kcal)/100 mL. Net price 420 g = £14.28.

A sole source of nutrition or nutritional supplement for children with disorders for which a high intake of MCT is beneficial

Corn flour and corn starch
For hypoglycaemia associated with glycogen-storage disease

Energivit (SHS)
Powder, protein-free, carbohydrate 66.7 g, fat 25 g, energy 2059 kJ (492 kcal)/100 g with vitamins, minerals and trace elements, net price 400 g = £17.23.

Nutritional supplement for children requiring additional energy vitamins, minerals, and trace elements, following a protein-restricted diet

General Plus (SHS)
Powder; protein equivalent (whey, with added branched chain amino acids 33%) 76 g, carbohydrate 5 g, fat 5.5 g, energy 1596 kJ (374 kcal)/100 g with minerals. Net price 200 g (unflavoured) = £23.97. See also Modjul Flavour System, p. 878.

Nutritional supplement for patients with chronic liver disease and/or porto-hepatic encephalopathy, may be used for children over 6 months

Generalid (SHS)
Powder; protein equivalent (whey, with added branched chain amino acids 32%, and other essential amino acids) 11 g, energy 1494 kJ (357 kcal)/100 g with vitamins, minerals (low sodium), and trace elements; standard dilution (22%) provides protein equivalent 2.4 g, carbohydrate 13.6 g, fat 4.2 g, energy 428 kJ (102 kcal)/100 mL. Net price 400 g = £17.15. See also Modjul Flavour System, p. 878

A sole source of nutrition or nutritional supplement for children over 1 year with hepatic disorders

KetoCal (SHS)
Powder; protein 3.1 g, carbohydrate 600 mg, fat 14.6 g, energy 602 kJ (146 kcal)/100 mL serving (serving = 20 g powder reconstituted with water up to final volume of 100 mL, with vitamins, minerals, and trace elements. Vanilla or unflavoured, net price 300-g can = £23.87.

For use as part of the ketogenic diet in the management of epilepsy resistant to drug therapy. Only to be prescribed on the advice of a secondary care physician with experience of the ketogenic diet; not suitable for children under 1 year

Kindergen (SHS)
Powder; protein 7.5 g, carbohydrate 60.5 g, fat 26.1 g, energy 2060 kJ (492 kcal)/100 g with vitamins and minerals. Net price 400 g = £15.18.

For complete nutritional support or supplementary feeding for infants and children with chronic renal failure who are receiving peritoneal rapid overnight dialysis

Appendix 7: Borderline substances

and mineral content. Residual lactose; gluten-free. Net price 20-g sachet = £2.32.

Nutritional supplement for hypoproteinaemia and patients undergoing dialysis. Not suitable for children under 1 year

BNF 57
Appendix 7: Borderline substances

**Liquigen** (SHS)
- Emulsion, medium chain triglycerides 52%. Net price 250 mL = £7.26, 1 litre = £28.25.
- For steatorrhea associated with cystic fibrosis of the pancreas; intestinal lymphangiectasia, surgery of the intestine; chronic liver disease and liver cirrhosis; other proven malabsorption syndromes; ketogenic diet in the management of epilepsy; type I hyperlipoproteinaemia.

**MCT Oil**
- Triglycerides from medium chain fatty acids. For steatorrhoea associated with cystic fibrosis of the pancreas; intestinal lymphangiectasia; surgery of the intestine; chronic liver disease and liver cirrhosis; other proven malabsorption syndromes; in a ketogenic diet in the management of epilepsy; type I hyperlipoproteinaemia.

**MCT Pepdite** (SHS)
- Powder, protein equivalent (non-milk, low molecular-weight peptides and essential amino acids) 13.8 g, carbohydrate 59 g, fat (of which MCT 75%) 18 g, energy 1903 kJ (453 kcal)/100 g/ with vitamins, minerals, and trace elements. Unflavoured (see also Modju Flavour System, p. 878).
- MCT Pepdite. Standard dilution (15%) provides protein equivalent 2 g, carbohydrate 8.8 g, fat 2.7 g, energy 286 kJ (68 kcal)/100 mL. For use from birth, net price 400 g = £16.01.
- MCT Pepdite 1+. Standard dilution (20%) provides protein equivalent 2.8 g, carbohydrate 11.8 g, fat 3.6 g, energy 381 kJ (91 kcal)/100 mL. Available from SHS (net price 500 mL = £11.50).

**Metabolic Mineral Mixture** (SHS)
- Powder, essential mineral salts. Net price 100 g = £9.94.
- For mineral supplementation in synthetic diets.

**Monogen** (SHS)
- Powder, protein (whey) 11.4 g, carbohydrate 68 g, fat 11.8 g (of which MCT 90%), energy 1786 kJ (424 kcal)/100 g/ with vitamins, minerals and trace elements; standard dilution (17.5%) provides protein 2 g, carbohydrate 12 g, fat 2.1 g, energy 313 kJ (74 kcal)/100 mL. Net price 400 g = £15.91.
- A sole source of nutrition or nutritional supplement for disorders in which a high intake of medium chain triglyceride is beneficial.

**Nepro** (Abbot)
- Liquid, protein 7 g, carbohydrate 20.6 g, fat 9.6 g, fibre 1.56 g, energy 840 kJ (200 kcal)/100 ml with vitamins and minerals. Gluten- and lactose-free. Net price 500-ml ready-to-hang = £4.95 (vanilla); 200-mL carton = £2.28 (strawberry or vanilla).
- For patients with chronic renal failure who are on haemodialysis or continuous ambulatory peritoneal dialysis (CAPD), or patients with cirrhosis or other conditions requiring a high energy, low fluid, low electrolyte diet.

**Paediatric Seravit** (SHS)
- Powder, vitamins, minerals, low sodium and potassium, and trace elements. Net price 200 g (unflavoured) = £14.03; pineapple flavour, 250 g = £14.94.
- For vitamin and mineral supplementation in restrictive therapeutic diets in infants and children.

**Rectified Spirit**
- Where the therapeutic qualities of alcohol are required rectified spirit (suitably flavoured and diluted) should be prescribed.

**Renamil** (KoRa)
- Powder, protein (cows’ milk) 4.6 g, carbohydrate 7.08 g, fat 19.3 g, energy 2003 kJ (477 kcal)/100 g/ with vitamins (except vitamins A and D), minerals (low potassium, low phosphophate), and trace elements. Contains lactose; gluten-free. Net price 10 x 100 g = £25.40.
- A sole source of nutrition or nutritional supplement for use in chronic renal failure. Not suitable for children under 1 year.

**Suplepa** (Abbot)
- Liquid, protein 3 g, carbohydrate 25.5 g, fat 9.6 g, energy 841 kJ (201 kcal)/100 mL. Flavour: vanilla. Net price 237-mL can = £2.34.
- For patients with chronic or acute renal failure who are not undergoing dialysis; chronic or acute liver disease with fluid restriction; other conditions requiring a high-energy, low-protein, low-electrolyte, low-volume enteral feed.

**Special foods for conditions of intolerance**

**Colief** (Britannia)
- Liquid, lactase 50 000 units/g, net price 7-mL dropper bottle = £7.00.
- For the relief of symptoms associated with lactose intolerance in infants, provided that lactose intolerance is confirmed by the presence of reducing substances and/or excessive acid in stools, a low confirmed corresponding to the hydrolysis of the intestinal biopsy or by breath hydrogen test or lactose intolerance test. For dosage and administration details, consult product literature.

**Cow & Gate Pepti** (Cow & Gate)
- Powder, protein (whey, hydrolysed) 11.6 g, energy 52 g, fat 25.6 g, fibre 5.9 g, energy 2025 kJ (484 kcal)/100 g/ with vitamins, minerals, and trace elements; standard dilution (13.6%) provides protein 1.6 g, carbohydrate 7.1 g, fat 3.5 g, energy 800 mg, energy 275 kJ (66 kcal)/100 mL. Contains lactose. Net price 900 g = £19.39.
- A sole source of nutrition or nutritional supplement for established cows’ milk protein intolerance with or without proven secondary lactose intolerance.

**Cow & Gate Pepti-Junior** (Cow & Gate)
- Powder, protein (whey, hydrolysed) 14 g, energy 53.4 g, fat 27.3 g, energy 2155 kJ (515 kcal)/100 g/ with vitamins, minerals, and trace elements; standard dilution (12.8%) provides protein 1.8 g, carbohydrate 6.8 g, fat 3.5 g, energy 275 kJ (66 kcal)/100 mL. Residual lactose. Net price 450 g = £10.68.
- A sole source of nutrition or nutritional supplement for disorders and or whole protein intolerance or where amino acids and peptides are indicated in conjunction with medium chain triglycerides.

**Enfamil O-Lac** (Mead Johnson)
- Powder, protein (cows’ milk) 10.9 g, energy 55 g, fat 28 g, energy 2200 kJ (530 kcal)/100 g/ with vitamins, minerals, and trace elements; standard dilution provides protein 1.4 g, carbohydrate 7.2 g, fat 3.7 g, energy 280 kJ (68 kcal)/100 mL. Residual lactose. Net price 400 g = £3.86.
- A sole source of nutrition or nutritional supplement for proven lactose intolerance.

**Farley’s Soya Formula** (Heinz)
- Powder, protein 2%, carbohydrate 7%, fat 3.8% with vitamins and minerals when reconstituted. Gluten-, sucrose-, and milk-free. Net price 900 g = £6.17.
- For proven lactose and associated sucrose intolerance in preschool children, galactokienase deficiency, galactosaemia, and cow’s milk protein intolerance.

**Fructose** (Laevulose)
- For proven glucose/galactose intolerance.

**Galactamin 17 (SHS)**
- Powder, protein equivalent (cows’ milk) 12.3 g, energy 55.3 g, fat 27.2 g, energy 2155 kJ (515 kcal)/100 g/ with vitamins, minerals, and trace elements; standard dilution (13%) provides protein equivalent 1.7 g, carbohydrate 7.5 g, fat 3.7 g, energy 295 kJ (70 kcal)/100 mL. Residual lactose. Net price 400 g = £13.16.
- A sole source of nutrition or a nutritional supplement for proven lactose intolerance in preschool children, galactosaemia and galactokinase deficiency.

**Galactamin 19 (SHS)**
- Powder, protein equivalent (cows’ milk) 14.6 g, carbohydrate (fructose) 9 g, fat 30.8 g, energy 2233 kJ (534 kcal)/100 g/ with vitamins, minerals, and trace elements; standard dilution (12.9%) provides protein equivalent 1.9 g, carbohydrate 6.4 g.
Neocate Advance (SHS) 
Neocate Active (SHS) 
Locasol (SHS) 
Neocate (SHS) 
Neocate LCP (SHS) 
Neutramigen 1 (Mead Johnson) 
Neutramigen 2 (Mead Johnson) 
Neutramigen AA (Mead Johnson) 
Pepdite (SHS) 
Pepdite 1+ (SHS) 
Pragestimil (Mead Johnson) 
Prejomin (Milupa) 

Glucose (Dextrose monohydrate) 

Infasoy (Cow & Gate) 
Isomil (Abbott) 
Locasol (SHS) 
Neocate (SHS) 
Neocate Active (SHS) 
Neocate Advance (SHS) 
Neutramigen 1 (Mead Johnson) 
Neutramigen 2 (Mead Johnson) 
Neutramigen AA (Mead Johnson) 
Pepdite (SHS) 
Pepdite 1+ (SHS) 
Pragestimil (Mead Johnson) 
Prejomin (Milupa) 

BNF 57

Appendix 7: Borderline substances

875
(15%) provides protein 2 g, carbohydrate 8.6 g, fat 3.6 g, energy 315 kJ (75 kcal)/100 mL. Gluten- and lactose-free. Net price 400 g = £10.12. A sole source of nutrition or a nutritional supplement for diarrhoea and/or whole protein intolerance where additional medium chain triglyceride is not indicated

**SMA LF** *(SMA Nutrition)*

**Powder**; protein (casein, whey) 12 g, carbohydrate 55.6 g, fat 28 g. energy 2185 kJ (522 kcal)/100 g with vitamins, minerals and trace elements; **standard dilution (13%)** provides protein 1.48 g, carbohydrate 8.7 g, fat 3.6 g, energy 282 kJ (67 kcal)/100 mL. Residual lactose. Net price 430 g = £4.57. A sole source of nutrition or a nutritional supplement for proven lactose intolerance

**Wysoy** *(Wyeth)*

**Protein** (soya) 14 g, carbohydrate 54 g, fat 27 g, energy 2155 kJ (515 kcal)/100 g with vitamins, minerals and trace elements; **standard dilution (13.2%)** provides protein 1.8 g, carbohydrate 6.9 g, fat 3.6 g, energy 280 kJ (67 kcal)/100 mL. Lactose-free. Net price 430 g = £4.44; 860 g = £8.41. A sole source of nutrition or a nutritional supplement for proven lactose and associated sucrose intolerance in preschool children, galactokinase deficiency, galactosaemia and proven whole cows' milk sensitivity

**Gluten-sensitive enteropathies**

**Freebake** *(Freebake)*

**Gluten-free**. Bread mix, net price 2.4 kg = £12.15, cake mix, 2.4 kg = £11.90; pasta mix, 2.4 kg = £12.00; flour (plain), 2.4 kg = £11.50.

**Gadsby’s**

**Gluten-free**. White bread flour, net price 1 kg = £4.99. White bread rolls, 4 × 75 g = £2.00

**Glutafin** *(Nutrition Point)*

**Gluten-free**. Bread loaf, fibre or white (sliced or unleashed), 400 g = £3.25; rolls, fibre or white, 4 = £3.25. Biscuits, savoury, 125 g = £1.80; savoury shorts, 150 g = £2.47. Biscuits, digestives, sweet or tea, 150 g = £1.80. Biscuits, 200 g = £3.51. Fibre rolls, 100 g = £1.49. Mixes, fibre or white, 500 g = £5.65, cake, 500 g = £5.31. Crackers, 200 g = £2.93. High fibre crackers, 200 g = £2.46. Pasta (penne, shells, spirals, spaghetti), 500 g = £5.69; lasagne, tagliatelle, 250 g = £2.98. Pizza bases, 2 × 150 g = £7.40.

**Select Gluten-Free**

**Fibre loaf** (sliced or unleashed), 400 g = £2.89; paper-baked, 500 g = £3.25. Fresh bread, white or brown loaf, (sliced), 400 g = £3.03. Seeded loaf, 400 g = £3.15. White loaf (sliced or unleashed), 400 g = £2.89; part-baked, 400 g = £3.25. Fibre rolls, 4 = £3.25, part-baked, 4 = £3.25; long (part-baked), 2 = £3.25. White rolls, 4 = £3.25, part-baked 4 = £3.25; long (part-baked), 2 = £3.25. Mixes (bread, cake, fibre, fibre bread, pastry, and white), 500 g = £5.63

**Gluten-free** *(Gluten Free Foods Ltd)*

**Gluten-free**. Bread mix, organic (standard or fibre), net price 500 g = £4.12

**Il Pane di Anna** *(Gluten Free Foods Ltd)*

**Gluten-free**. Bread mix, white, net price 500 g = £5.25, cake mix, white 500 g = £5.25

**Juvela** *(Juvela)*

**Gluten-free**. Harvest mix, fibre mix, and flour mix, net price 500 g = £6.06. Bread (white or sliced), 400-g loaf = £2.92; part-baked loaf (with or without fibre), 400g = £3.13; fresh sliced loaf (white) 400 g = £0.34, (fibre) 400 g = £2.92. Bread (fibre unleashed), 400-g loaf = £2.92. Bread rolls, 5 × 85 g = £3.94, fibre bread rolls, 5 × 85 g = £3.94, part-baked rolls (with or without fibre), 5 × 75 g = £4.07. Crispbread, 210 g = £3.82. Pasta (Fibre Linguine, fibre Penne, fusilli, macaroni, spaghetti), 500 g = £5.94; lasagne, 250 g = £3.03; tagliatelle, 250 g = £2.96. Pasta bases, 2 × 180 g = £7.24. Digestive biscuits, 150 g = £2.51. Savoury biscuits, 150 g = £3.15. Sweet biscuits, 150 g = £2.38. Tea biscuits, 150 g = £2.51

**Gluten-free** *(Gluten Free Foods Ltd)*

**Gluten-free**. Bread, sliced (brown), net price 225 g = £2.25, (white), 200 g = £2.25; baguette (white) 250 g = £2.50; rolls (white), 4 = £2.50

**Lifestyle** *(Ultraplarm)*

**Gluten-free**. Brown bread (sliced and unleashed), net price 400 g = £2.82. White bread (sliced and unleashed), 400 g = £2.82. High fibre bread (sliced and unleashed), 400 g = £2.82. Bread rolls, (brown, white, or high-fibre) 400 g = £2.82

**Liwwell** *(Liwwell)*

**Gluten-free**. Bread, sliced, (brown), net price 225 g = £2.25, (white), 200 g = £2.25; baguette (white) 250 g = £2.50; rolls (white), 4 = £2.50

**Orange** *(Community)*

**Gluten-free**. Pasta: lasagne (corn, rice and maize), 150 g = £2.89; macaroni (rice and maize), 250 g = £2.25; shells (split pea and soya), 200 g = £2.25; spaghetti (corn, rice, and rice and maize), 250 g = £2.25; spirals (buckwheat, corn, rice, rice and millet, rice and maize), 250 g = £2.25, spirals (organic brown rice), 250 g = £2.90. Crispbread (corn or rice), 200 g = £2.56. Pizza and pastry mix, 375 g = £3.33. Flour, self-raising, 500 g = £2.89. Bread mix, 450 g = £3.10

**Pleniday** *(TOI)*

**Gluten-free**. Bread: loaf (sliced) net price 350 g = £1.18; country loaf (sliced), 500 g = £2.85; rustic loaf (sliced), 400 g = £2.09; petit pain (part baked), 2 × 150 g = £0.22. Pasta (penne), 250 g = £1.27; rigate, 250 g = £1.50

**Polial** *(Ultraplarm)*

**Gluten-free**. Biscuits. Net price 200-g pack = £2.85

**Procelli** *(Generpharm)*

**Gluten-free**. Bread, (white, sliced), net price 165 g = £2.24. Baguettes, sliced bread, 155 g = £1.18. Baguettes (part-baked), 2 × 125 g = £1.96; bread buns, 4 × 50 g = £1.25. Dinner rolls (white, part-baked), 4 × 35 g = £1.91. Flat bread (part-baked), 3 × 40 g = £3.99. Hotdog rolls (white, part-baked) 3 × 35 g = £1.95. Long rolls (white, part-baked), 3 × 83 g = £2.81. Lunch rolls (white), 6 × 45 g = £3.22. Flour (white), 1 kg = £6.88. Pasta (macaroni, small macaroni, penne, short spaghetti, spirals), 250 g = £2.99. Pizza bases, 3 × 125 g = £5.99. Rice
Gluten-sensitive enteropathies with coexisting established wheat sensitivity

ACBS indications: established gluten enteropathy with coexisting established wheat sensitivity only.

Ener-G (General Dietary)
Gluten-free, wheat-free. Pizza bases, 372 g = £3.75. Six flour bread loaf, 576 g = £3.60. Seattle brown rolls (round or long), 4 x 119 g = £1.00

Glutafin (Nutricia Dietary)
Gluten-free, wheat-free. Crisp bread, 2 x 125 g = £3.82. Mixes (fibre bread, bread), 500 g = £5.63; cake or pastry mix, 250 g = £5.63.

Heron Foods (Gluten Free Foods Ltd)
Gluten-free, wheat-free. Bread mix, organic (fibre), net price 500 g = £4.12; bread and cake mix, organic, 500 g = £4.12

Low protein

Protein (Ultrapharm)
Low protein. Low Na+ and K+. Benefits, net price 180 g (36) = £2.88; bread mix 250 g = £2.17; cake mix 300 g = £2.10; crispbread 260 g = £4.06; pasta (anellini, ditalini, rigatini, spaghetti) 500 g = £4.06; tagliatelle 250 g = £2.16.

Ener-G (General Dietary)
Low protein. Egg replacer, carbohydrate 94 g, energy 1574 kj (376 kcal)/100 g. Egg, gluten- and lactose-free, net price 454 g = £4.05. Rice bread, 600 g = £4.39.

Fate (Fat)
Low protein. All-purpose mix, net price 500 g = £6.35; Cake mix, 2 x 250 g = £6.35. Chocolate-flavour cake mix, 2 x 250 g = £6.35.

Hariffen (Ultrapharm)
Low protein. Cracker toast, net price 200 g = £2.75. Cookies, white chip, 200 g = £2.25.

Juelva (SHS)
Low Protein. Mix, net price 500 g = £6.66. Bread (sliced), 400-g loaf = £3.12. Bread rolls, 5 x 70 g = £3.87. Biscuits, orange and cinnamon flavour, 125 g = £5.61; chocolate chip, 130 g = £6.51. Pizza base, 2 x = £7.37.

Loprofin (SHS)
Low protein. Sweet biscuits, net price 150 g = £2.08; chocolate cream-filled biscuits, 125 g = £2.08; cookies (chocolate chip or cinnamon), 100 g = £5.51; crunch bar, 8 x 41 g = £11.09; wafers (orange, vanilla, or chocolate), 100 g = £0.22. Breakfast cereal, 375 g = £6.23. Egg replacer, 500 g = £12.14. Egg-white replacer, 100 g = £0.71. Bread (sliced), 400-g loaf = £3.12. Bread rolls (white) 4 x £2.91, (part-baked) 4 x 65 g = £3.28. Mix, 500 g = £6.61. Cake mix (chocolate or lemon), 500 g = £6.99. Dessert mix (chocolate, strawberry, vanilla), 150 g = £3.82. Crispbread, 150 g = £2.84. Herb crackers, 150 g = £2.84. Pasta (fusilli, penne, spaghetti), 500 g = £6.91. Pasta (macaroni, puntoni, tagliatelle) 250 g = £3.32. Pasta (conchiglie, gnocchi sardi) 500 g = £6.66. Pasta (lasagne), 250 g = £3.36. Pasta (vermicelli), 250 g = £3.44. Pasta (animal shapes) 500 g = £6.64. Snack Pot (curry or tomato and basil), 47 g = £3.67, Rice, 500 g = £6.71.

Low protein drink (Milupa)
Powder, whey protein 500 mg, carbohydrate 6 g, fat 3 g, energy 220 kJ (53 kcal)/10 g, with vitamins, minerals, and trace elements. Net price 400 g = £7.23.

For inherited disorders of amino acid metabolism in children over 1 year

Note Termed Milupa lpd by manufacturer

PK Foods (Gluten Free Foods Ltd)
Low-protein. Bread (white sliced) net price 500 g = £4.00. Crispbread, 75 g = £2.00. Pasta (spiral) 250 g = £2.00.

Aminex biscuits 150 g = £4.25; cookies, 200 g = £4.25; rusks, 200 g = £4.25

See also Phenylketonuria, p. 880

Promin (Firstplay Dietary)
Low protein. Burger mix, 2 x 62 g = £5.60, (lamb and mint), 4 x 72 g = £5.50. Sausage mix (apple and sage, tomato and basil, or original), 4 x 30 g = £6.30. Cous Cous, 500 g = £6.35. Pasta (alphabets, macaroni, shells, shortcut spaghetti, spirals); Pasta tricolour (alphabets, shells, spirals), net price 500 g = £6.35; Lasagne sheets, 200 g = £2.70. Pasta shells in tomato, pepper and herb sauce, 4 x 72 g-sachets = £7.32. Pasta elbows in cheese and broccoli sauce, 4 x 66-g sachets = £7.32. Pasta spirals in Moroccan sauce, 4 x 72 g = £7.32. Pasta spirals in tomato sauce, 4 x 72 g-sachets = £6.50. Pasta imitation rice, 500 g = £8.35. Rice puddling imitation (apple, banana, strawberry, and original flavours), 4 x 69-g sachets = £5.60. Dessert (chocolate and banana, strawberry and vanilla, custard, or caramel) 6 x 365 g = £5.60. Hot breakfast (apple and cinnamon, banana, chocolate, original) 6 x 57 g = £7.14. Spread, chocolate and hazelnut, 230 g = £6.80

Rite-Diet Low-protein (SHS)
Low protein. Baking mix. Net price 500 g = £6.61. Flour mix, 400 g = £5.68.
**Appendix 7: Borderline substances**

**1. Analog products are generally intended for use in children up to 1 year**

**2. Maxamaid products are generally intended for use in children 1–8 years, see also Modjul Flavour System, above**

**3. Maxamaid products are generally intended for use in children over 8 years**

---

**Homocystinuria or hypermethioninaemia**

**HCU cooler (Vitafo)**

Liquid, protein (essential and non-essential amino acids except methionine) 15 g, carbohydrate 7.8 g, fat trace, energy 386 kJ (92 kcal)/130 mL, with vitamins, minerals and trace elements. Orange flavour, net price 30 × 130-mL pouch = £258.30

A methionine-free protein substitute for use as a nutritional supplement in patients over 3 years of age with homocystinuria

**HCU Express (Vitafo)**

Protein, essential and non-essential amino acids except methionine) 15 g, carbohydrate 3.8 g, fat 30 mg, energy 315 kJ (75.3 kcal)/25 g with vitamins, minerals and trace elements. Unflavoured (see also FlavourPac, above), net price 30 × 25-g sachets = £253.24

A methionine-free protein substitute for use as a nutritional supplement in patients over 8 years of age with homocystinuria

**HCU gel (Vitafo)**

Protein, essential and non-essential amino acids except methionine) 8.4 g, carbohydrate 8.6 g, fat 30 mg, energy 286 kJ (68 kcal)/20 g with vitamins, minerals and trace elements. Unflavoured (see also FlavourPac, above), net price 30 × 20-g sachets = £141.51

A methionine-free protein substitute for use as a nutritional supplement in children 12 months–10 years with homocystinuria

**HCU LV (Vitafo)**

Powder, protein (essential and non-essential amino acids except methionine) 20 g, carbohydrate 2.5 g, fat 190 mg, energy 390 kJ (92 kcal)/27.8-g sachet, with vitamins, minerals and trace elements. Unflavoured (formulation varies slightly), net price 30 × 27.8-g sachets = £86.17

A nutritional supplement for hypermethioninaemia or vitamin B non-responsive homocystinuria in patients over 8 years.

**1. XMET Analog (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except methionine) 15 g, carbohydrate 54 g, fat 23 g, energy 1900 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, see also Modjul Flavour System, above, net price 400 g = £28.22.

For hypermethioninaemia or homocystinuria

**2. XMET Homidion (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except methionine) 77 g, carbohydrate 4.5 g, fat nil, energy 1386 kJ (326 kcal)/100 g. Net price 500 g = £145.76.

For hypermethioninaemia or homocystinuria

**3. XMET Maxamaid (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except methionine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, see also Modjul Flavour System, above. Net price 500 g = £123.34.

For hypermethioninaemia or homocystinuria

**4. XMET Maxumam (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except methionine) 39 g, carbohydrate 34 g, fat less than 0.5%, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, see also Modjul Flavour System, above. Net price 500 g = £123.34.

For hypermethioninaemia or homocystinuria

**Hyperlysinaemia**

**1. XLYS Analog (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except lysine) 39 g, carbohydrate 34 g, fat less than 0.5%, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, see also Modjul Flavour System, above. Net price 400 g = £28.22.

For hyperlysinaemia

**2. XLYS Maxamaid (SHS)**

Powder, protein equivalent (essential and non-essential amino acids except lysine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, see also Modjul Flavour System, above. Net price 400 g = £28.22.

For hyperlysinaemia

---

**Sno-Pro (SHS)**

Low-protein, Drink, protein 220 mg (phenylalanine 12.5 mg), carbohydrate 8 g, fat 3.8 g, energy 280 kJ (67 kcal)/100 mL. Net price 200 mL = £9.8p.

For phenylketonuria, chronic renal failure, and other inborn errors of metabolism

**Taranis (Firstplay Dietary)**

Low protein, Cake bars (lemon), net price 6 × 40g = £5.10

**Ultra (Ultrapharm)**

Low protein, PKU bread, 400 g = £2.25. PKU flour, 500 g = £3.07. PKU biscuits, 200 g = £2.21. PKU cookies, 250 g = £2.31. PKU pizza base, 400 g = £2.35. PKU savoy biscuits, 150 g = £2.06.

**Vita Bite (Vitafo)**

Low-protein, Bar, protein 30 mg (less than 2.5 mg phenylalanine), carbohydrate 15.35 g, fat 8.4 g, energy 572 kJ (137 kcal)/25 g. Chocolate flavoured, net price 25 g = £9.6p.

Not recommended for children under 1 year

### Metabolic Diseases

**Glutaric aciduria (type 1)**

**GA Gel (Vitafo)**

Gel, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 8.4 g, carbohydrate 8.6 g, fat trace, energy 286 kJ (68 kcal)/20 g, with vitamins, minerals, and trace elements. Net price 30 × 20-g sachets = £141.51.

**Modjul Flavour System (SHS)**

Powder, flavours: blackcurrant, lemon, orange, pineapple, 100 g = £9.54. Cherry-vanilla, grapefruit, lemon-lime, 20 × 5-g sachets = £9.54.

For use with unflavoured SHS products based on peptides or amino acids

**Flavour preparations**

**FlavourPac (Vitafo)**

Powder, flavours: blackcurrant, lemon, orange, tropical or raspberry, net price 4 × 30 × 4-g sachets = £43.84.

For use with Vitafo’s range of unflavoured protein substitutes for metabolic diseases

**Modjul Flavour System (SHS)**

Powder, flavours: blackcurrant, orange, pineapple, 100 g = £9.54. Cherry-vanilla, grapefruit, lemon-lime, 20 × 5-g sachets = £9.54.

For use with unflavoured SHS products based on peptides or amino acids

---

1. Analog products are generally intended for use in children up to 1 year

2. Maxamaid products are generally intended for use in children 1–8 years, see also Modjul Flavour System, above, for use with unflavoured amino acid and peptide products from SHS

3. Maxamaid products are generally intended for use in children over 8 years
than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, net price 500 g = £76.94.

For hyperlysinaemia

Isovaleric acidemia

1. XLEU Analog (SHS)
   Powder, protein equivalent (essential and non-essential amino acids except leucine) 15 g, carbohydrate 54 g, fat 23 g (of which MCT 4.5%), energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Glutên-, lactose-, fructose-free. Net price 400 g = £28.22.

For isovaleric acidemia

Ingredients: include arachis oil (peanut oil)

XLEU Faladon (SHS)
Powder, protein equivalent (essential and non-essential amino acids except leucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, net price 500 g = £76.94.

For isovaleric acidemia

2. XLEU Maxamaid (SHS)
   Powder, protein equivalent (essential and non-essential amino acids except leucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, net price 500 g = £76.94.

For isovaleric acidemia

Maple syrup urine disease

Isoleucine Amino Acid Supplement (Vitaflo)
Powder, isoleucine 0.05 g, carbohydrate 4 g, fat nil, energy 64 kJ (15 kcal)/4 g, net price 30 x 4-g sachets = £42.23.

For in use conjunction with a protein supplement for maple syrup urine disease in children over 1 year

Mapleflex (SHS)
Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 8.4 g, carbohydrate 11 g, fat 3.9 g, energy 474 kJ (113 kcal)/29 g, with vitamins, minerals, and trace elements. Unflavoured.

Net price 30 x 29-g sachets = £162.82.

For maple syrup urine disease in children 1–10 years

MSUD Aid III (SHS)
Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 77 g, carbohydrate 4.5 g, energy 1386 kJ (326 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 500 g = £145.76.

For maple syrup urine disease and related conditions where it is necessary to limit the intake of branched chain amino acids

1. MSUD Analog (SHS)
   Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 13 g, carbohydrate 54 g, fat 23 g (of which MCT 4.5%), energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 400 g = £28.22.

For maple syrup urine disease

MSUD express (Vitaflo)
Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 15 g, carbohydrate 3.8 g, fat less than 100 mg, energy 315 kJ (75 kcal)/25 g with vitamins, minerals, and trace elements. Unflavoured (see FlavourPac sachets, p. 878), net price 30 x 25-g sachets = £253.24.

For maple syrup urine disease in children over 8 years and adults

MSUD express cooler (Vitaflo)
Liquid, protein equivalent 15 g (essential and non-essential amino acids except isoleucine, leucine, and valine), carbohydrate 7.8 g, fat trace, energy 380 kJ (92 kcal)/130-mL.

1. Analog products are generally intended for use in children up to 1 year.

2. Maxamaid products are generally intended for use in children 1–8 years, see also Modjul Flavour System, p. 878, for use with unflavoured amino acid and peptide products from SHS

pouch, with vitamins, minerals, and trace elements. Orange flavour, net price 30 x 150-mL = £258.30.

For maple syrup urine disease in children over 3 years and adults

MSUD Gel (Vitaflo)
Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 8.4 g, carbohydrate 8.6 g, fat less than 100 mg, energy 286 kJ (68 kcal)/20 g with vitamins, minerals, and trace elements. Unflavoured (see FlavourPac sachets, p. 878), net price 30 x 20-g sachets = £141.51.

For maple syrup urine disease in children 1–10 years

2. MSUD Maxamaid (SHS)
   Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 39 g, carbohydrate 54 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Flavours: orange, unflavoured (see Modjul Flavour System, p. 878). Net price 500 g = £123.34.

For maple syrup urine disease

3. MSUD Maxamum (SHS)
   Powder, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, net price 500 g = £76.94.

For maple syrup urine disease

Valine Amino Acid Supplement (Vitaflo)
Powder, valine 0.05 g, carbohydrate 4 g, fat nil, energy 64 kJ (15 kcal)/4 g, net price 30 x 4-g sachets = £42.23.

For use in conjunction with a protein supplement for maple syrup urine disease in children over 1 year

Methylnalonic or propionic acidemia

1. XMVTI Analog (SHS)
   Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 12 g, carbohydrate 54 g, fat 23 g (of which MCT 4.5%), energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 500 g = £123.34.

For methylnalonic or propionic acidemia

XMVTI Asadon (SHS)
Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 77 g, carbohydrate 4.5 g, energy 1386 kJ (326 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 500 g = £145.76.

For methylnalonic or propionic acidemia

XMVTI Maxamaid (SHS)
Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 500 g = £76.94.

For methylnalonic or propionic acidemia

XMVTI Maxamum (SHS)
Powder, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 12 g, carbohydrate 54 g, fat less than 500 mg, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured (see also Modjul Flavour System, p. 878). Net price 500 g = £123.34.

For methylnalonic or propionic acidemia

Other errors of protein metabolism

Cystine Amino Acid Supplement (Vitaflo)
Powder, cystine 0.5 g, carbohydrate 3.4 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 x 4-g sachets = £42.23.

For dietary management of inborn errors of protein metabolism

EAA Supplement (Vitaflo)
Powder, protein equivalent (essential amino acids) 5 g, carbohydrate 4 g, fat nil, energy 151 kJ (36 kcal)/12.5 g, with trace elements.

3. Maxamaid products are generally intended for use in children over 8 years
Appendix 7: Borderline substances

Phenylketonuria

Add-Ins (SHS)

Powder, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 6.7 g, carbohydrate 5.1 g, fat 2 g, energy 275 kJ (65 kcal)/sachet, with vitamins, minerals, and trace elements. Unflavoured (see Modju Flavour System, p. 878), net price 60 x 18.2-g sachets = £294.00.

For the dietary management of proven phenylketonuria. Not suitable for children under 4 years

Lophlex LQ 10 (SHS)

Liquid, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 4.4 g, fibre 170 mg, energy 245 kJ (58 kcal)/62.5 mL with vitamins, minerals, and trace elements. Berry flavour, net price 60 x 62.5 mL = £243.00.

For the dietary management of phenylketonuria in children over 8 years and adults including pregnant women

Phenylketonuria

Appendix 7: Borderline substances

vitals, minerals, and trace elements. Tropical flavour, net price 50 x 12.5-g sachets = £165.67

For dietary management of disorders of protein metabolism including urea cycle disorders. Not suitable for children under 3 years

Leucine Amino Acid Supplement (Vitaflo)

Powder, leucine 0.1 g, carbohydrate 4 g, fat nil, energy 64 kJ (15 kcal)/4 g, net price 30 x 4-g sachets = £42.23

For the dietary management of inborn errors of protein metabolism

Capsules, protein equivalent (essential and non-essential amino acids except phenylalanine) 416 mg/capsule. Net price 200-cap pack = £33.23

Tablets, protein equivalent (essential and non-essential amino acids except phenylalanine) 1 g tablet. Net price 75-tab pack = £21.59

For use as a vitamin and mineral component of restricted therapeutic diets in children 11 years and over and adults with phenylketonuria and similar amino acid abnormalities

Tablets, vitamins, minerals, and trace elements, net price 180-tab pack = £68.69.

For the dietary management of phenylketonuria. Not suitable for children under 8 years

PK Aid-4 (SHS)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 75 g, carbohydrate 4.5 g, fat nil, energy 1420 kJ (334 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 500 g = £112.04. For phenylketonuria

PK Foods (Gluten Free Foods Ltd)

Cookies (chocolate chip, orange, or cinnamon). 150 g = £4.25. Egg replacer, 350 g = £4.25. Flour mix, 750 g = £9.60. Jelly (orange or cherry flavour), 4 x 80 g = £6.76. For phenylketonuria. See also Low-protein foods, p. 877.

PKU 2 (Milupa)

Granules, protein equivalent (essential and non-essential amino acids except phenylalanine) 66.8 g, carbohydrate 8.2 g, fat nil, energy 1274 kJ (300 kcal)/100 g with vitamins, minerals, and trace elements. Flavour: vanilla. Net price 500 g = £44.75. For phenylketonuria

PKU cooler10 (Vitaflo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 68 g, carbohydrate 3.9 g, fat nil, energy 1222 kJ (288 kcal)/100 g, with vitamins, minerals, and trace elements. Flavour: vanilla. Net price 500 g = £44.75. For phenylketonuria, not recommended for children under 8 years

PKU cooler15 (Vitaflo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 5.1 g, energy 250 kJ (62 kcal)/87-mL pouch, with vitamins, minerals, and trace elements. Orange or purple option. Net price 30 x 87 mL = £105.00. For the dietary management of phenylketonuria. Not recommended for children under 3 years

PKU cooler20 (Vitaflo)

Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 10.2 g, energy 517 kJ (124 kcal)/174 mL pouch, with vitamins, minerals, and trace elements. Orange or purple option. Net price 30 x 174 mL = £210.00. For the dietary management of phenylketonuria. Not recommended for children under 3 years

PKU express (Vitaflo)

Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 72 g, carbohydrate 15.1 g, energy 1260 kJ (301.5 kcal)/100 g with vitamins, minerals,
and trace elements. Lemon, orange, tropical or unflavoured, net price 30 x 25 g sachets = £15.53.

For phenylketonuria, not recommended for children under 3 years

PKU gel (Vitaflo)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.4 g, carbohydrate 8.6 g, fat 0.03 g, energy 285.5 kJ (68 kcal)/20 g with vitamins, minerals and trace elements. Orange or unflavoured, net price 30 x 20-g sachets = £88.51.

For use as part of the low-protein dietary management of phenylketonuria in children 1–10 years

PKU Start (Vitaflo)
Liquid, ready-to-feed formula, phenylalanine-free containing essential and non-essential amino acids, carbohydrate, fat, vitamins, minerals, and trace elements. Includes long-chain polyunsaturated fatty acids. Net price 500-mL bottle = £5.30.

For the dietary management of phenylketonuria in children under 1 year

L-Tyrosine (SHS)
Powder, net price 100 g = £12.53.

For use as a supplement in maternal phenylketonurics who have low plasma tyrosine concentrations

Tyrosine Amino Acid Supplement (Vitaflo)
Powder, tyrosine 1 g, carbohydrate 2.9 g, energy 62 kJ (15 kcal)/4-g sachet, net price 30 x 4-g sachets = £37.80.

For the dietary management of phenylketonuria. Not suitable as a sole source of nutrition.

XP Analog (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 13 g, carbohydrate 54 g, fat 23 g (of which MCT 4.5%), energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 400 g = £22.54.

For phenylketonuria

XP Analog LCP (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Gluten- and lactose-free. Net price 400 g = £25.64.

For phenylketonuria in children under 2 years

XP Maxamaid (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 25 g, carbohydrate 51 g, fat less than 0.5 g, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Net price 400 g = £22.54.

For phenylketonuria

XP Maxamum (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 39 g, carbohydrate 34 g, fat less than 0.5 g, energy 1260 kJ (297 kcal)/100 g, with vitamins, minerals, and trace elements. Flavours: orange, unflavoured (see Modiflavour System, p. 878). Net price 30 x 50-g sachets = £21.14, 500 g = £70.39.

For phenylketonuria.

Tyrosinaemia

TYR express (Vitaflo)
Powder, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 15 g, carbohydrate 3.8 g, fat less than 0.1 g, energy 315 kJ (76 kcal)/25 g, with vitamins, minerals, and trace elements. Unflavoured (see Flavourpacs, p. 878), net price 30 x 25-g sachets = £25.24.

A tyrosine- and phenylalanine-free protein substitute for use in the dietary management of tyrosinaemia. Not recommended for children under 8 years

TYR Gel (Vitaflo)
Gel, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 8 g, carbohydrate 6.6 g, fat 0.03 g, energy 285.5 kJ (68 kcal)/20 g, with vitamins, minerals and trace elements. Unflavoured (see Flavourpacs, p. 878) net price 30 x 20-g sachets = £141.51.

A tyrosine- and phenylalanine-free protein substitute for use in the dietary management of tyrosinaemia in children 1–10 years

XPHEN TYR Analog (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured (for child over 6 months, Modiflavour System, can be used, see p. 878). Net price 400 g = £28.22.

For tyrosinaemia

XPHEN TYR Maxamaid (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 25 g, carbohydrate 51 g, fat less than 0.5 mg, energy 1311 kJ (309 kcal)/100 g with vitamins, minerals, and trace elements. Unflavoured. Net price 500 g = £76.94.

For tyrosinaemia

XPHEN TYR Tyrosidon (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine and tyrosine) 77 g, carbohydrate 4.3 g, fat nil, energy 1386 kJ (326 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured (for child over 6 months, Modiflavour System can be used, see p. 878). Net price 500 g = £145.76.

For tyrosinaemia where plasma methionine concentrations are normal

XPTM Analog (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine, tyrosine, and methionine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements. Modiflavour System can be used, see p. 878). Net price 400 g = £28.22.

For tyrosinaemia

XPTM Tyrosidon (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine, tyrosine, and methionine) 77 g, carbohydrate 4.3 g, fat nil, energy 1386 kJ (326 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured (for child over 6 months, Modiflavour System can be used, see p. 878). Net price 500 g = £145.76.

For tyrosinaemia type 1 where plasma concentrations are above normal

Urea cycle disorders (other than arginase deficiency)

L-Arginine (SHS)
Powder, net price 100 g = £10.64.

For use as a supplement in urea cycle disorders other than arginase deficiency, such as hyperammonaemia types I and II, citrullinaemia, argininosuccinic aciduria, and deficiency of N-acetyl glutamate synthetase
Conditions for which toilet preparations may be prescribed on FP10, GP10 (Scotland), WP10 (Wales)

Note This is a list of clinical conditions for which the ACBS has approved toilet preparations. For details of the preparations see Chapter 13.

Birthmarks  See Disfiguring skin lesions, below

Dermatitis  Aveeno Bath Oil; Aveeno Cream; Aveeno Colloidal; Aveeno Lotion; E45 Emollient Bath Oil; E45 Emollient Wash Cream; E45 Lotion

Dermatitis herpetiformis  See also Gluten-sensitive enteropathies, p. 876

Disfiguring skin lesions (birthmarks, mutilating lesions, scars, vitiligo)  Covermark classic foundation and finishing powder; Dermacolor Camouflage cream and fixing powder; Keromask masking cream and finishing powder; Veil Cover cream and Finishing Powder. (Cleansing Creams, Cleansing Milks, and Cleansing Lotions are excluded)

Disinfectants (antiseptics)  May be prescribed on an FP10 only when ordered in such quantities and with such directions as are appropriate for the treatment of patients, but not for general hygenic purposes.

Eczema  See Dermatitis, above

Photodermatoses (skin protection in)  Delph Sun Lotion SPF 30; E45 Sun SPF 50; Spectran Ultra; Sunsense Ultra; Uvistat Lipscreen SPF 50, Uvistat Suncream SPF 30 and 50.

Pruritus  See Dermatitis, above
A8 Wound management products and elastic hosiery

A8.1 Wound dressings

A8.1.1 Alginate dressings
A8.1.2 Foam dressings
A8.1.3 Hydrogel dressings
A8.1.4 Hydrocolloid dressings
A8.1.5 Vapour-permeable films and membranes
A8.1.6 Low adherence dressing and wound contact materials
A8.1.7 Odour absorbent dressings
A8.1.8 Dressing packs
A8.1.9 Surgical absorbents
A8.1.10 Capillary dressings
A8.1.11 Other dressings
A8.2 Bandages and adhesives

An overview of the management of chronic wounds (including venous ulcers and pressure sores) and the role of different dressings is given below, as is the NICE guidance on difficult-to-heal surgical wounds; the notes do not deal with the management of clean surgical wounds which usually heal very rapidly. The correct dressing for wound management depends not only on the type of wound but also on the stage of the healing process. The principal stages of healing are:

1. Cleansing, removal of debris;
2. Granulation, vascularisation;
3. Epithelialisation.

Greater understanding of the requirements of a wound dressing, including recognition of the benefits of maintaining a moist environment for wound healing, has improved the management of chronic wounds.

The ideal dressing needs to ensure that the wound remains:

1. Moist with exudate, but not macerated;
2. Free of clinical infection and excessive slough;
3. Free of toxic chemicals, particles or fibres;
4. At the optimum temperature for healing;
5. Undisturbed by the need for frequent changes;
6. At the optimum pH value.

As wound healing passes through its different stages, variations in dressing type may be required to satisfy better one or other of these requirements. The type of dressing depends on the type of wound or the stage of the healing process.

### Functions of dressings

<table>
<thead>
<tr>
<th>Type of wound</th>
<th>Role of dressing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moisture retention or rehydration</td>
<td></td>
</tr>
<tr>
<td>If dry, moisture retention or rehydration</td>
<td></td>
</tr>
<tr>
<td>If moist, fluid absorption</td>
<td></td>
</tr>
<tr>
<td>Possibly odour absorption</td>
<td></td>
</tr>
<tr>
<td>Possibly antimicrobial activity</td>
<td></td>
</tr>
<tr>
<td>Fluid absorption</td>
<td></td>
</tr>
<tr>
<td>Thermal insulation</td>
<td></td>
</tr>
<tr>
<td>Possibly antimicrobial activity</td>
<td></td>
</tr>
<tr>
<td>Moisture retention or rehydration</td>
<td></td>
</tr>
<tr>
<td>Low adherence</td>
<td></td>
</tr>
<tr>
<td>Thermal insulation</td>
<td></td>
</tr>
</tbody>
</table>

Alginates, foam, hydrogel and hydrocolloid dressings are designed to absorb wound exudate and thus to control the state of hydration of a wound. There have been few clinical trials able to establish a clear advan-
Dressings impregnated with an antiseptic, such as iodine, can be used to treat clinically infected wounds. Dressings containing silver should be used when clinical signs or symptoms of infection are present, or when infection has been confirmed by microbiological investigation.

Medical grade honey has antimicrobial properties; it may improve healing time in mild to moderate superficial and partial thickness burns.

Protease modulating matrix dressings (section A8.1.3) alter the activity of proteolytic enzymes in chronic wounds; the clinical significance of this approach is yet to be demonstrated.

Practices such as the use of irritant cleansers may be harmful and are largely obsolete; removal of debris and dressing remnants should need minimal irrigation with physiological saline.

A8.1.1 Alginate dressings

The gelling characteristics of alginate dressings vary according to the product used. Some products only gel to a limited extent to form a partially gelled sheet that can be lifted off; others form an amorphous gel that can be rinsed off with water or physiological saline. A secondary covering is needed. They are highly absorptive and are therefore suitable for moderately or heavily exuding wounds, but not for eschars or for dry wounds.

Dressings containing silver should be used when infection is suspected as a result of clinical signs or symptoms, or when infection has been confirmed by microbiological investigation.

Acticoat Absorbent (S&N Hlth.)
Calcium alginate dressing with a silver coated antimicrobial barrier, 5 cm × 5 cm = £4.91, 10 cm × 10 cm = £11.78; cavity dressing, 2 cm × 30 cm = £1.45
Uses antimicrobial dressing for moderately to heavily exuding wounds

ActiHeal (MedLogic)
ActiveHeal Alginate, calcium sodium alginate dressing, 5 cm × 5 cm = 57p, 10 cm × 10 cm = £1.11, 10 cm × 20 cm = £2.73; cavity dressing, 2 cm × 30 cm = £0.05
ActiveHeal Aquafiber, non-woven, calcium sodium alginate dressing, 5 cm × 5 cm = 73p, 10 cm × 10 cm = £1.74, 15 cm × 15 cm = £3.28; cavity dressing, 2 cm × 42 cm = £1.75
Uses moderately to heavily exuding wounds

Algisite (S&N Hlth.)
Algisite Ag, calcium alginate dressing, with silver, 5 cm × 5 cm = £1.53, 10 cm × 10 cm = £3.85, 10 cm × 20 cm = £7.04; cavity dressing 2 g, 30 cm = £5.28
Uses antimicrobial dressing for moderately to heavily exuding wounds

Algisite M, calcium alginate fibre, non-woven dressing, 5 cm × 5 cm = 85p, 10 cm × 10 cm = £1.75, 15 cm × 20 cm = £4.71; cavity dressing, 2 cm × 30 cm = £3.18
Uses moderately to heavily exuding wounds

Algosteril (S&N Hlth.)
Calcium alginate dressing, 5 cm × 5 cm = £3.25; cavity dressing, 2 g, 30 cm = £3.47
Uses moderately to heavily exuding wounds

Curasorb (Covidien)
Curasorb Alginate dressing, 5 cm × 5 cm = 69p, 10 cm × 10 cm = £1.46, 10 cm × 14 cm = £2.36, 10 cm × 20 cm = £2.87, 15 cm × 25 cm = £5.05, 30 cm × 61 cm = £26.50
(Other sizes £)
Curasorb Plus, calcium alginate dressing, 10 cm × 10 cm = £2.00
Curasorb Rope, calcium alginate cavity dressing, 30 cm = £2.78, 61 cm = £4.88, 91 cm = £5.25
Curasorb Zn, calcium alginate and zinc dressing, 5 cm × 5 cm = 78p, 10 cm × 10 cm = £1.65, 10 cm × 20 cm = £3.24
(Other sizes £)

Flaminal (Ark Therapeutics)
Forte gel, alginate with glucose oxidase and lactoperoxidase, 15 g = £7.13
Uses moderately to heavily exuding wounds

Hydro gel, alginate with glucose oxidase and lactoperoxidase, 15 g = £7.13
Uses lightly to moderately exuding wounds

Kaltostat (Convatec)
(Alginate Dressing, BP 1993, type C) Calcium alginate fibre, non-woven, 5 cm × 5 cm, = £87p, 7.5 cm × 12 cm = £1.91, 10 cm × 20 cm = £3.77, 15 cm × 25 cm = £6.48, (other sizes £)
Calcium alginate dressing, 5 cm × 5 cm = £1.53, 10 cm × 10 cm = £3.85, 10 cm × 20 cm = £7.04
Uses moderately to heavily exuding wounds

Melgisorb (Mölnlycke)
Calcium sodium alginate fibre, highly absorbent, gelling dressing, non-woven, 5 cm × 5 cm = 84p, 10 cm × 10 cm = £1.64, 10 cm × 20 cm = £3.08; cavity dressing, 32 cm × 2.2 cm, (2 g) = £3.30
Uses moderately to heavily exuding wounds including leg ulcers, dermal lesions and traumatic wounds

SeaSorb (Coloplast)
SeaSorb Soft, alginate containing hydrocolloid dressing, highly absorbent, gelling dressing, 5 cm × 5 cm = 90p, 10 cm × 10 cm = £2.14, 15 cm × 15 cm = £4.05
Uses heavily exuding wounds

SeaSorb Soft Filler, calcium sodium alginate fibre, highly absorbent, gelling filler, 44 cm = £2.52
Uses moderately to heavily exuding cavity wounds

Sorbalgon (Hartmann)
Calcium alginate dressing, 5 cm × 5 cm = £7.4p, 10 cm × 10 cm = £1.55; cavity dressing, net price 2 g, 32 cm = £3.17
Uses for moderately to heavily exuding wounds

Sorbsan (Unomedical)
Sorbsan Flat, calcium alginate fibre, highly absorbent, flat non-woven pads, 5 cm × 5 cm = 78p, 10 cm × 10 cm = £1.64, 10 cm × 20 cm = £3.08; with silver, 5 cm × 5 cm = £1.50, 10 cm × 10 cm = £3.80, 10 cm × 20 cm = £6.94
Uses moderately to heavily exuding wounds; with silver, antimicrobial dressing for moderately to heavily exuding wounds

Sorbsan Plus, alginate dressing bonded to a secondary absorbent viscose pad, 7.5 cm × 10 cm = £1.66, 10 cm × 15 cm = £2.93, 10 cm × 20 cm = £3.74, 15 cm × 20 cm = £5.20
Uses moderately to heavily exuding shallow wounds and ulcers

Sorbsan Plus SA, alginate dressing with adhesive border and absorbent backing, 11.5 cm × 14 cm = £2.89, 14 cm ×
Foam dressings vary from products that are suitable for lightly exuding wounds to highly absorbent structures for heavily exuding wounds. They may also be used as secondary dressings. In hypergranulating (or overgranulating) tissue (which may arise from the use of occlusive dressings such as hydrocolloids), changing to a more permeable product such as a foam dressing may be beneficial.

Dressings containing silver should be used when infection is suspected as a result of clinical signs or symptoms, or when infection has been confirmed by microbiological investigation.

**Polyurethane Foam Dressing, BP 1993**
Absorbent foam dressing of low adherence

- **Lyfoam**, 7.5 cm x 7.5 cm = £1.02; 10 cm x 10 cm = £1.17, 10 cm x 17.5 cm = £1.88, 15 cm x 20 cm = £2.54, other sizes (\(\geq 10\) cm) 10 cm x 25 cm = £4.79 (hospital only), 25 cm x 30 cm = £11.35 (Medlock)

**Uses**
- Treatment of burns, decubitus ulcers, donor sites, granulating wounds

### For lightly to non-exuding wounds

**Polyurethane Foam Dressing with Adhesive Border**

- **Avazorb Border**, 6 cm x 10 cm = £1.10, 8 cm x 12 cm = £1.90 (Advancis)
- **PolyMem**, 5 cm x 5 cm = 48p (Unomedical)
- **Tielle Lite**, 11 cm x 11 cm = £2.24; 7 cm x 9 cm = £1.19; 8 cm x 15 cm = £2.76; 8 cm x 20 cm = £2.91 (J&J)

### For lightly to moderately exuding wounds

**Polyurethane Foam Dressing with Adhesive Border**

- **Lyfoam Extra Adhesive**, 9 cm x 9 cm = £1.27, 15 cm x 15 cm = £2.39, 22 cm x 22 cm = £4.70; sacral, 15 cm x 13 cm = £1.95; (Medlock)
- **Suprasorb P**, 7.5 cm x 7.5 cm = £1.16, 10 cm x 10 cm = £1.25, 15 cm x 15 cm = £2.24 (Synergy Healthcare)
- **Tielle**, 11 cm x 11 cm = £2.53; 15 cm x 15 cm = £3.81; 18 cm x 18 cm = £4.85; 7 cm x 9 cm = £1.25; 15 cm x 20 cm = £4.77; **Tielle Sacrum** 18 cm x 18 cm = £3.53 (J&J)
- **Trufoam**, 7 cm x 9 cm = £1.13; 11 cm x 11 cm = £2.16 (Unomedical)

### For moderately to heavily exuding wounds

**Polyurethane Foam Dressing without Adhesive Border**

- **Allevyn Lite**, 5 cm x 5 cm = £1.04; 10 cm x 10 cm = £1.88; 10 cm x 20 cm = £3.22; 15 cm x 20 cm = £4.02 (S&N Hlth.)
- **Allevyn Thin** (adhesive), net price 5 cm x 6 cm = 98p, 10 cm x 10 cm = £1.98, 15 cm x 15 cm = £3.26, 15 cm x 20 cm = £3.96 (S&N Hlth.)
- **Flexipore** (adhesive), 6 cm x 7 cm = 93p; 10 cm x 10 cm = £1.73, 15 cm x 20 cm = £3.70; 20 cm x 20 cm = £5.06; 10 cm x 30 cm = £3.60 (MedLogic)
- **Lyfoam Extra**, 10 cm x 10 cm = £2.02; 17.5 cm x 10 cm = £3.43; 20 cm x 15 cm = £4.44 (Medlock)
- **Suprasorb M**, 10 cm x 10 cm = £1.72, 10 cm x 20 cm = £3.03, 20 cm x 20 cm = £5.05 (Synergy Healthcare)
- **Suprasorb P**, 5 cm x 5 cm = 90p, 7.5 cm x 7.5 cm = 96p, 10 cm x 10 cm = £1.13, 15 cm x 15 cm = £3.01 (Synergy Healthcare)
- **Transorbert** (adhesive), 5 cm x 7 cm = £1.00; 10 cm x 10 cm = £1.89; 15 cm x 15 cm = £3.47; 20 cm x 20 cm = £5.55 (Unomedical)

### For moderately to heavily exuding wounds

**Polyurethane Foam Dressing with Adhesive Border**

- **ActivHeal Foam Island**, 10 cm x 10 cm = £1.57, 12.5 cm x 12.5 cm = £1.50, 15 cm x 15 cm = £1.92, 20 cm x 20 cm = £4.34 (MedLogic)
- **Allevyn Plus Adhesive**, 12.5 cm x 12.5 cm = £3.08; 17.5 cm x 17.5 cm = £5.93; 22.5 cm x 22.5 cm = £5.45; (sacral) 17 cm x 17 cm = £4.48, 22 cm x 22 cm = £6.49 (S&N Hlth.)
- **Biatain Adhesive**, 10 cm x 10 cm = £1.62; 12 cm x 12 cm = £2.38, 18 cm x 18 cm = £4.77, 20 cm x 20 cm = £7.06; 23 cm x 23 cm (sacral) = £4.08, 19 cm x 20 cm (heel) = £4.76, 17 cm diameter (contour) = £4.59 (Coloplast)
- **Copa Island**, 10 cm x 10 cm = £1.51, 15 cm x 15 cm = £2.84, 20 cm x 20 cm = £5.36 (Covidien)

**Appendix 8: Wound management**

**A8.1.2 Foam dressings**

- **Suprasorb A** (Synergy Healthcare)
  - Calcium alginate dressing, 5 cm x 5 cm = £1.10; cavity dressing, 2 g x 30 cm = £2.04
  - Uses: moderately to heavily exuding wounds

- **Tegaderm Alginate** (3M)
  - 5 cm x 5 cm = 76p, 10 cm x 10 cm = £1.61; cavity dressing, 2 g x 30 cm = £2.68
  - Uses: moderately to heavily exuding wounds

- **Tielle Packing** (J&J)
  - Tielle Packing, 9.5 cm x 9.5 cm = £2.08

- **Urgosorb** (Urgo)
  - Alginate containing hydrocolloid dressing without adhesive border, 5 cm x 5 cm = 81p, 10 cm x 10 cm = £1.93, 10 cm x 20 cm = £3.55; cavity dressing, 30 cm = £2.58
  - Uses: moderately to heavily exuding wounds

- **Urgosorb Silver** (Urgo)
  - Alginate containing hydrocolloid dressing, impregnated with silver, 5 cm x 5 cm = £1.42, 10 cm x 10 cm = £3.39, 10 cm x 20 cm = £6.39; cavity dressing, 2.5 cm x 10 cm = £3.41
  - Uses: antifungal dressing for heavily exuding wounds

- **Algivon** (Advancis)
  - Absorbent, non-adherent calcium alginate dressing impregnated with medical grade manuka honey, 5 cm x 5 cm = £2.09, 10 cm x 10 cm = £3.53
  - Uses: lightly to heavily exuding wounds; use with suitable secondary dressing

- **Medihoney** (Medihoney)
  - Gel sheet, sodium alginate dressing impregnated with medical grade honey, 5 cm x 5 cm = £1.75, 10 cm x 10 cm = £4.20
  - Uses: lightly to moderately exuding wounds
<table>
<thead>
<tr>
<th>Polyurethane Foam Film Dressing without Adhesive Border</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PermaFoam</strong>, concave 16.5 cm × 18 cm = £3.67; sacral 18 cm × 18 cm = £3.02, 22 cm × 22 cm = £3.47; PermaFoam Comfort 8 cm × 8 cm = £1.02, 10 cm × 20 cm = £3.06, 11 cm × 11 cm = £1.94, 15 cm × 15 cm = £3.16, 20 cm × 20 cm = £4.59 (Hartmann)</td>
<td></td>
</tr>
<tr>
<td><strong>PolyMem</strong>, 5 cm × 7.6 cm = £1.07, 8.8 cm × 12.7 cm = £1.90, 10 cm × 13 cm = £2.06, 15 cm × 15 cm = £2.77, 16.5 cm × 20.9 cm = £6.25, 18.4 cm × 20 cm (sacral) = £4.28 (Unomedical)</td>
<td></td>
</tr>
<tr>
<td><strong>Tegaderm Foam Adhesive</strong>, 10 cm × 11 cm = £2.28, 14 cm × 14 cm = £3.37, 15 cm × 15 cm = £4.05, 19 cm × 22.5 cm = £6.64, 14 cm × 14 cm (heel) = £4.06 (3M)</td>
<td></td>
</tr>
<tr>
<td><strong>Tielle Plus</strong>, 11 cm × 11 cm = £2.58; 15 cm × 15 cm = £4.21; 20 cm × 20 cm = £5.28; 25 cm × 25 cm (sacrum) = £3.07; Tielle Plus Heel Hydropolymer Adhesive Dressing 20 cm × 26.5 cm = £4.37 (J&amp;J)</td>
<td></td>
</tr>
<tr>
<td><strong>Trofoam</strong>, 11 cm × 11 cm = £2.16, 15 cm × 15 cm = £3.62, 7 cm × 9 cm = £1.15, 15 cm × 20 cm = £4.53 (Unomedical)</td>
<td></td>
</tr>
</tbody>
</table>

**Cavi-Care** (S&N Hlth.)

Soft, conforming cavity wound dressing prepared by mixing thoroughly for 15 seconds immediately before use and allowing to expand its volume within the cavity. 20 g = £18.12

**Silver-containing foam film dressings**

**Acticoat Moisture Control** (S&N Hlth.)

Three layer polyurethane dressing consisting of a silver coated layer, a foam layer, and a waterproof layer, 5 cm × 5 cm = £8.58, 10 cm × 10 cm = £15.39, 15 cm × 20 cm = £29.99

**Uses** antimicrobial dressing for lightly to moderately exuding wounds

**Allevyn Ag** (S&N Hlth.)

Silver sulfadiazine impregnated polyurethane foam film dressing with adhesive border, 7.5 cm × 7.5 cm = £3.15, 10 cm × 10 cm = £4.96, 12.5 cm × 12.5 cm = £6.25, 17.5 cm × 17.5 cm = £12.54, 17 cm × 17 cm (sacral) = £9.79, 22 cm × 22 cm (sacral) = £13.12; without adhesive border, 5 cm × 5 cm = £2.94, 10 cm × 10 cm = £5.54, 15 cm × 15 cm = £10.50, 20 cm × 20 cm = £15.38, 10.5 cm × 13.5 cm (heel) = £9.90

**Uses** antimicrobial dressing for moderately to heavily exuding wounds

**Avance** (Medlock)

Silver impregnated polyurethane foam dressing, without adhesive border, 10 cm × 10 cm = £2.75, 15 cm × 17.5 cm = £4.38, 15 cm × 20 cm = £6.05; with adhesive border, 9 cm × 9 cm = £2.31, 12 cm × 12 cm = £3.83, 15 cm × 15 cm = £4.69, 16.5 cm × 13 cm (sacral) = £4.45

**Uses** antimicrobial dressing for lightly to moderately exuding wounds

**Blatiain Ag** (Coloplast)

(S formerly Contrexx Foam) Silver impregnated polyurethane foam dressing with adhesive border, 12.5 cm × 12.5 cm = £8.55, 18 cm × 18 cm = £17.14, 19 cm × 20 cm (heel) = £16.91, 23 cm × 23 cm (sacral) = £17.97; without adhesive border, 10 cm × 10 cm = £7.47, 5 cm × 7 cm = £3.07, 10 cm × 20 cm = £13.73, 15 cm × 15 cm = £15.00, 20 cm × 20 cm = £21.15, cavity dressing 5 cm × 8 cm = £3.72

**Uses** antimicrobial dressing for moderately to heavily exuding wounds

**PolyMem** (Unomedical)

Silver impregnated polyurethane foam film dressing, with adhesive border, 5 cm × 7.6 cm (oval) = £2.15, 12.7 cm × 8.8 cm (oval) = £5.30; without adhesive border, 10.8 cm × 10.8 cm = £8.20, 17 cm × 19 cm = £16.80

**Uses** antimicrobial dressing for moderately to heavily exuding wounds

**Vacuum assisted closure products**

**Exsu-Fast** (Synergy Healthcare)

**Dressing kit**, Kit 1 (small wound, low exudate) = £28.04; Kit 2 (large wound, heavy exudate) = £35.83; Kit 3 (large wound, medium to low exudate) = £25.83; Kit 4 (small wound, heavy exudate) = £28.04

**V.A.C. Granufoam** (KCI Medical)

**Dressing kit**, polyurethane foam dressing (with adhesive drapes and pad connector), 10 cm × 7.5 cm × 3.3 cm (small) = £21.41, 18 cm × 12.5 cm × 3.3 cm (medium) = £25.49, 26 cm × 15 cm × 3.3 cm (large) = £29.57

**Venturi** (Talley)

**Wound sealing kit**, flat drain, standard = £15.00, large = £17.50; channel drain = £15.00

**VISTA** (S&N Hlth.)

**Dressing kit**, flat drain, small = £16.52, medium = £20.70, large = £26.28; round drain, small = £16.52, large = £26.28; channel drain, medium = £20.70

**WoundASSIST** (Huntleigh)

**Wound pack**, small-medium = £20.50, medium-large = £23.50
Appendix 8: Wound management

**Wound drainage collection devices**
- **V.A.C Freedom** , canister (with gel), 300 mL = £26.51 (KCI Medical)
- **Venturi** , canister kit (with solidifier) = £12.50 (Tailley)
- **V1STA** , canister kit, 250 mL (with solidifier) = £18.63, 800 mL (with solidifier) = £20.70 (S&N Hlth.)
- **WoundASSIST** , canister, 500 mL = £20.00 (Huntleigh)

**A8.1.3 Hydrogel dressings**

Hydrogel dressings are most commonly supplied as an amorphous, cohesive material that can take up the shape of a wound. A secondary covering is needed. These dressings are generally used to donate liquid to dry sloughy wounds and facilitate autolytic debridement but they may also have the ability to absorb limited amounts of exudate. Hydrogel sheets are also available which have a fixed structure; such products have limited fluid handling capacity. Hydrogel sheets are best avoided in the presence of infection. Hydrogel products that do not contain propylene glycol should be used if the wound is to be treated with larval therapy.

- **ActiFormCool** (Activa)
  - Hydrogel dressing, 5 cm × 6.5 cm = £1.65, 10 cm × 10 cm = £2.43, 15 cm × 15 cm = £3.49
  - Uses: exuding or necrotic wounds; with compression bandaging for moderately to heavily exuding wounds

- **ActivHeal Hydrogel** (MedLogic)
  - Hydrogel containing guar gum and propylene glycol, 15 g = £1.36
  - Uses: dry or lightly exuding sloughy or necrotic wounds

- **Aquaform** (Unomedical)
  - Hydrogel containing modified starch copolymer, 8 g = £1.57, 15 g = £1.91
  - Uses: for dry, sloughy or necrotic wounds, lightly exuding wounds, granulating wounds

- **Aquaflo** (Coviden)
  - Hydrogel dressing, 7.5 cm diameter = £2.50, 12 cm = £5.16

- **Askin Gel** (Braun)
  - Hydrogel containing modified starch and glycerol, 15 g = £1.89
  - Uses: exuding, sloughy, or necrotic wounds

- **Citrugel** (Advancis)
  - Hydrogel containing polysaccharides, 15 g = £1.35
  - Uses: sloughy or necrotic wounds, lightly exuding wounds

- **Coolie** (Zeroderma)
  - Hydrogel dressing with lint backing, 7 cm diameter = £1.96
  - Uses: for sloughy or necrotic wounds, lightly exuding wounds, granulating wounds

- **Curageel** (Coviden)
  - Hydrogel dressing, without adhesive border, 5 cm × 7.5 cm = £1.74, 10 cm × 10 cm = £2.71; with adhesive border, 7.5 cm × 10 cm = £2.47, 12.5 cm × 12.5 cm = £3.58

- **Cutimed** (BSN Medical)
  - **Hydrogel**, 8 g = £1.56, 15 g = £1.90, 25 g = £2.80

- **Cutinova Hydro** (S&N Hlth.)
  - Polyurethane gel sheet with waterproof polyurethane film, 5 cm × 6 cm = £1.16, 10 cm × 10 cm = £2.33, 15 cm × 20 cm = £4.94
  - Uses: lightly to moderately exuding wounds

- **Flexigran** (A1 Pharmaceuticals)
  - Hydrogel containing starch polymer and glycerol, 15 g = £1.90

**Gel FX** (Synergy Healthcare)
- Hydrogel dressing (without adhesive border) 10 cm × 10 cm = £1.60, 10 cm × 15 cm = £2.20, 15 cm × 15 cm = £3.20

**Geliperm** (Geistlich)
- Hydrogel sheets, 10 cm × 10 cm = £2.27, 12 cm × 26 cm = £9.31
  - Uses: wound and ulcer dressing, burns, donor sites

**GranuGel** (ConvacTec)
- Hydrogel containing carboxymethylcellulose, pectin, and propylene glycol, 15 g = £2.13
  - Uses: dry, sloughy or necrotic wounds, lightly exuding wounds, granulating wounds

**Hydrosorb** (Hartmann)
- Absorbent, transparent, hydrogel sheets containing polyurethane polymers covered with a semi-permeable film
  - **Hydrosorb 5**, 5 cm × 7.5 cm = £1.43; 10 cm × 10 cm = £2.04; 20 cm × 20 cm = £6.12
  - **Hydrosorb comfort** (with adhesive border, waterproof), 4.5 cm × 6.5 cm = £1.69; 7.5 cm × 10 cm = £2.24; 12.5 cm × 12.5 cm = £3.26
  - Uses: second degree burns, donor sites; chronic wounds where granulation is unsatisfactory, including leg ulcers, pressure sores

**Intrasite Conformable** (S&N Hlth.)
- Soft non-woven dressing impregnated with Intrasite gel, 10 cm × 10 cm = £1.66; 10 cm × 20 cm = £2.23; 10 cm × 40 cm = £3.99
  - Uses: for dry, sloughy or necrotic wounds, lightly exuding wounds; granulating wounds

**Intrasite Gel** (S&N Hlth.)
- Hydrogel containing modified carmelllose polymer and propylene glycol, 8-g sachet = £1.66, 15-g sachet = £2.25, 25-g sachet = £3.29
  - Uses: for dry, sloughy or necrotic wounds, lightly exuding wounds; granulating wounds

**Mesitran** (Unomedical)
- Absorbent, semi-permeable dressings impregnated with medical grade honey, 10 cm × 10 cm = £2.51, 10 cm × 15 cm = £4.52, 15 cm × 15 cm = £5.22; with adhesive border, 10 cm × 10 cm = £2.61, 15 cm × 13 cm (sacral) = £4.42, 15 cm × 15 cm = £4.62
  - Uses: pressure ulcers, diabetic ulcers, fungating wounds, donor sites, surgical wounds, abrasions, and first and second degree burns

**Mesitran Mesh**
- Non-adherent wound contact layer, without adhesive border, 10 cm × 10 cm = £2.41
  - Uses: pressure ulcers, diabetic ulcers, donor sites, abrasions, trauma wounds, post-operative wounds, and first and second degree burns

**Novogel** (Ford)
- Glycerol hydrogel sheets, 10 × 10 cm = £3.01; 30 cm × 30 cm, standard = £12.74, thin = £12.03, 5 cm × 7.5 cm = £1.91; 10 cm × 20 cm = £5.74; 20 cm × 40 cm = £10.94; 7.5 cm diameter = £2.73
  - Uses: diabetic wounds, burns, leg ulcers, decubitus ulcers, donor sites

**Nu-Gel** (IBI)
- Hydrogel containing alginates and propylene glycol, 15 g = £2.05
  - Uses: dry, sloughy or necrotic, lightly exuding or granulating wounds

**Prontosan Wound Gel** (Braun)
- Hydrogel containing betaine surfactant and polyhexanide, 30 mL = £5.97

**Purilon Gel** (Coloplast)
- Hydrogel containing carboxymethylcellulose and calcium alginate, 8 g = £1.61, 15 g = £2.10
  - Uses: for dry, sloughy or necrotic wounds, lightly exuding wounds; granulating wounds

**Suprasorb G** (Synergy Healthcare)
- Hydrogel dressing containing carboxymethylcellulose and propylene glycol (without adhesive border) 5 cm × 7.5 cm = £1.73, 10 cm × 10 cm = £2.22, 20 cm × 20 cm = £6.71; (amorphous gel) 6 g = £1.10, 20 g = £1.80
Appendix 8: Wound management

A8.1.4 Hydrocolloid dressings

**Vacuette** (Proex)
Non-adherent, hydrogel coated polyester net dressing, 10 cm × 10 cm = £1.93, 10 cm × 15 cm = £2.86
*Uses* lacerations, abrasions, pressure ulcers, burns, surgical and malignant wounds.

**With iodine**

**Iodoflex** (S&N Hlth.)
*Paste*, iodine 0.9% as cadexomer–iodine in a paste basis with gauze backing, 5-g unit = £7.46; 17 g = £11.81
*Uses* for treatment of chronic exuding wounds, such as leg ulcers, apply to wound surface, remove gauze backing and cover; renew when saturated (usually 2–3 times weekly, daily for heavily exuding wounds); max. single application 50 g, max. weekly application 150 g; max. duration up to 3 months in any single course of treatment
*Cautions* iodine may be absorbed, particularly from large wounds or during prolonged use; severe renal impairment; history of thyroid disorder
*Contra-indications* children; pregnancy and breast-feeding

**Iodosorb** (S&N Hlth.)
*Ointment*, iodine 0.9% as cadexomer–iodine in an ointment basis, 10 g = £4.04; 20 g = £8.24
*Powder*, iodine 0.9% as cadexomer–iodine microbeads, 3-g sachet = £1.76
*Uses* for treatment of chronic exuding wounds, such as leg ulcers, apply to wound surface to depth of approx. 3 mm and cover; renew when saturated (usually 2–3 times weekly, daily for heavily exuding wounds); max. single application 50 g, max. weekly application 150 g, max. duration up to 3 months in any single course of treatment
*Cautions* iodine may be absorbed, particularly from large wounds or during prolonged use; severe renal impairment; history of thyroid disorder
*Contra-indications* children; patients receiving lithium, thyroid disorders; pregnancy and breast-feeding

**Iodozyme** (Insense)
*Hydrogel* (two-component dressing containing glucose oxidase and iodide ions), 10 cm × 10 cm = £12.50
*Uses* antimicrobial dressing for lightly to moderately exuding wounds
*Contra-indications* children; pregnancy and breast-feeding

**Oxyzyme** (Insense)
*Hydrogel* (two-component dressing containing glucose oxidase and iodide ions), 10 cm × 10 cm = £10.00
*Uses* non-infected, dry to moderately exuding wounds
*Cautions* children; pregnancy and breast-feeding

**Protease modulating matrix**
Protease modulating matrix dressings alter the activity of proteolytic enzymes in chronic wounds; the clinical significance of this approach is yet to be demonstrated.

**Cadesorb** (S&N Hlth.)
*Ointment*, starch-based, 10 g = £4.96, 20 g = £8.46
*Uses* chronic wounds free of necrotic tissue and infection

**Promogran** (J&J)
Collagen and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing, 28 cm (hexagonal) = £5.09, 123 cm (hexagonal) = £15.32
*Uses* chronic wounds free of necrotic tissue and infection

**Promogran Prisma Matrix** (J&J)
Collagen, silver and oxidised regenerated cellulose matrix, applied directly to wound and covered with suitable dressing, 28 cm (hexagonal) = £6.19, 123 cm (hexagonal) = £17.63
*Uses* chronic wounds free of necrotic tissue

**Sorbin S** (H&R)
Absorbent polymers in cellulose matrix, hypoallergenic fleece envelope, 7.5 cm × 7.5 cm = £1.74, 10 cm × 10 cm = £2.20, 20 cm × 20 cm = £6.85, 20 cm × 10 cm = £3.63, 30 cm × 10 cm = £5.25, 30 cm × 20 cm = £9.85, 12 cm × 5 cm = £1.85
*Uses* moderately to heavily exuding chronic wounds

**Suprasorb C** (Synergy Healthcare)
Collagen, 4 cm × 6 cm = £2.55, 6 cm × 8 cm = £3.90, 8 cm × 12 cm = £7.65
*Uses* lightly to moderately exuding chronic uninfected wounds

**Tegaderm Matrix** (3M)
Cellulose acetate matrix, impregnated with polyhydrated ionogens ointment in polyethylene glycol basis, 5 cm × 6 cm = £4.75, 8 cm × 10 cm = £9.75
*Uses* chronic uninfected wounds

---

**A8.1.4 Hydrocolloid dressings**

Hydrocolloid dressings are usually presented as a hydrocolloid layer on a vapour-permeable film or foam. Because of their impermeable nature, hydrocolloid dressings facilitate rehydration and autolytic debridement of dry, sloughy, or necrotic wounds; they are also suitable for promoting granulation. Fibrous dressings made from modified carmellose fibres resemble alginate dressings (e.g. *Aquace®*, *Aquacell®*); these are not occlusive.

Dressings containing *silver* should be used when infection is suspected as a result of clinical signs or symptoms, or when infection has been confirmed by microbiological investigation.

**ActivHeal**

**Hydrocolloid** (MedLogic)
Semi-permeable polyurethane film backing, hydrocolloid wound contact layer, 5 cm × 7.5 cm = 75p, 10 cm × 10 cm = £1.52, 15 cm × 15 cm = £3.31, 15 cm × 18 cm (sacral) = £3.84; with polyurethane foam layer, 5 cm × 7.5 cm = 94p, 10 cm × 10 cm = £1.49, 15 cm × 15 cm = £2.81, 15 cm × 18 cm (sacral) = £3.24
*Uses* lightly to moderately exuding wounds

**Aline** (Coloplast)
Semi-permeable hydrocolloid dressing with adhesive border, 10 cm × 10 cm = £2.96, 12.5 cm × 12.5 cm = £4.07, 12 cm × 20 cm = £5.34, 15 cm × 15 cm = £5.14, 20 cm × 20 cm = £7.68; without adhesive border 10 cm × 10 cm = £2.96, 12.5 cm × 12.5 cm = £4.07, 12 cm × 20 cm = £5.34, 15 cm × 15 cm = £5.14, 20 cm × 20 cm = £7.68
*Uses* chronic and exuding wounds

**Aquadex** (Convatec)
Soft non-woven pad containing hydrocolloid fibres, 4 cm × 10 cm = £1.38, 4 cm × 20 cm = £2.04, 4 cm × 30 cm = £3.05, 5 cm × 5 cm = £1.07, 10 cm × 10 cm = £2.54, 15 cm × 15 cm = £4.78
*Uses* moderately to heavily exuding wounds

**Aquadex Ag** (silver impregnated), 4 cm × 10 cm = £2.65, 4 cm × 20 cm = £3.46, 4 cm × 30 cm = £5.17, 5 cm × 5 cm = £1.81, 10 cm × 10 cm = £4.32, 15 cm × 15 cm = £8.13, 20 cm × 30 cm = £20.17
*Uses* antimicrobial dressing for moderately to heavily exuding wounds

**Aquadex Ag Ribbon** (silver impregnated), 2 cm × 45 cm = £4.34
*Uses* antimicrobial dressing for moderately to heavily exuding cavity wounds

**Aquadex Ribbon** (silver impregnated), 2 cm × 45 cm = £2.59
*Uses* moderately to heavily exuding cavity wounds
Askina Biofilm Transparent (Braun)  
Semi-permeable, polyurethane film dressing with hydrocolloid adhesive, 10 cm × 10 cm = £1.02, 15 cm × 15 cm = £2.31, 20 cm × 20 cm = £3.02  
Biofilm S (Braun)  
Hydrocolloid dressing with polyurethane-polyester backing; also in powder form for direct application into wound, 10 cm × 10 cm = £1.65, 20 cm × 20 cm = £5.70  
Biofilm powder, 1 sachet = £1.82  
Comfeel Plus (ConvaTec)  
Hydrocolloid dressing with polyurethane-polyester backing; also in powder form for direct application into wound, 10 cm × 10 cm = £1.65, 20 cm × 20 cm = £5.70  
Comfeel powder, 1 sachet = £1.82  
Combiderm (Convatec)  
Semi-permeable, hydrocolloid dressing with carmellose sodium and colloid adhesive, 5 cm = £0.66, 10 cm = £1.27, 15 cm = £1.88, 20 cm = £2.49; without adhesive border (in powder form) 10 cm × 10 cm = £1.05, 15 cm × 15 cm = £2.36  
Uses lightly to moderately exuding wounds  
Hydrocolloid dressing with adhesive border and absorbent wound contact pad, 10 cm × 10 cm = £1.53, 14 cm × 14 cm = £2.13, 15 cm × 18 cm (triangular) = £3.66, 20 cm × 20 cm = £4.08, 20 cm × 23 cm (triangular) = £4.92  
Uses lightly to moderately exuding wounds  
Comfeel (Coloplast)  
Soft elastic, latex-free dressing consisting of carmellose sodium particles embedded in adhesive mass; smooth outer layer and polyurethane film backing; available as sheets, powder in plastic blister units and paste for direct application into the wound: ulcer dressing, 10 cm × 10 cm = £2.41, 15 cm × 15 cm = £4.83, 20 cm × 20 cm = £7.39; other sizes (\( \text{mm} \) × 6 cm × 6 cm = £1.19; powder 6 g = £4.04; paste 12-g sachet = £1.61; 50 g = £6.33  
Uses lightly to moderately exuding wounds  
Comfeel Plus (Coloplast)  
Hydrocolloid dressings containing carmellose sodium and calcium alginate. Contour dressing, 6 cm × 6 cm = £0.24, 9 cm × 11 cm = £3.54; Ulcer Dressing, 4 cm × 6 cm = £8.80, 10 cm × 10 cm = £2.25, 15 cm × 15 cm = £4.82, 16 cm × 20 cm (triangular) = £5.25, 20 cm × 20 cm = £8.94; Trans- 
parent Dressing, 5 cm × 7 cm = £1.61, 5 cm × 15 cm = £1.46, 5 cm × 25 cm = £2.37, 9 cm × 14 cm = £2.24, 9 cm × 25 cm = £3.18, 10 cm × 10 cm = £1.17, 15 cm × 15 cm = £3.06, 15 cm × 20 cm = £3.11, 17 cm × 17 cm (sacral) = £3.44, 20 cm × 20 cm = £3.15; Pressure Relieving Dressing:  
Diameter = £4.26, 15 cm × 15 cm = £6.62  
Uses light to moderately exuding wounds  
Comfeel Hydrocolloid (Coloplast)  
Semi-permeable, antimicrobial barrier dressing with ionic silver (silver sodium thiosulphate). 10 cm × 10 cm = £2.13, 15 cm × 15 cm = £3.12, 20 cm × 20 cm = £6.94; Concave dressing, 8 cm × 10 cm = £1.90, 12 cm × 12 cm (heel) = £3.12, 15 cm × 18 cm (sacral) = £4.37; without adhesive border, thin, 10 cm × 10 cm = £1.04  
Uses lightly to moderately exuding wounds  
Suprasorb H (Synergy Healthcare)  
Semi-permeable hydrocolloid dressing with adhesive border, 10 cm × 10 cm = £1.65, 15 cm × 15 cm = £3.30; without adhesive border, thin 5 cm × 10 cm = £1.15, 10 cm × 10 cm = £1.00, 20 cm × 20 cm = £7.53, 11 cm × 11 cm = £4.06  
Uses antimicrobial dressing for moderate to heavily exuding wounds  
Versiva (Convatec)  
Semi-permeable hydrocolloid dressing with hydrocolloid and alginate dressing impregnated with silver, 2.5 cm × 3.5 cm = £4.37, 5 cm × 5 cm = £1.64, 10 cm × 20 cm = £6.73; Sacral dressing, 15 cm × 18 cm = £4.32  
Uses lightly to moderately exuding wounds  
Silvercel (J&J)  
Hydrocolloid and alginate dressing impregnated with silver, 9 cm = £3.89, 14 cm = £2.24, 9 cm = £2.44, 11 cm = £2.25, 10 cm × 10 cm = £2.39, 15 cm × 15 cm = £4.42  
Uses chronic wounds such as leg ulcers and pressure sores  
Tegaderm Hydrocolloid Thin (3M)  
Hydrocolloid dressing with adhesive border, 10 cm × 12 cm (oval) = £2.42, 13 cm × 15 cm (oval) = £4.19, 17.1 cm × 16.1 cm (sacral) = £4.68; without adhesive border, 10 cm × 10 cm = £2.29, 15 cm × 15 cm = £4.42  
Uses chronic wounds such as leg ulcers and pressure sores  
Tegaderm Hydrocolloid Thin, semi-permeable, clear film dressing with hydrocolloid and adhesive border, 10 cm × 12 cm (oval) = £1.49, 13 cm × 15 cm (oval) = £2.79; without adhesive border, 10 cm × 10 cm = £1.50  
Uses lightly to moderately exuding wounds  
Ultec Pro (Covidien)  
Semi-permeable hydrocolloid dressing with adhesive border, 10 cm × 10 cm = £1.39, 14 cm × 14 cm = £2.24, 21 cm × 21 cm = £4.94, 15 cm × 10 cm (sacral) = £3.17, 19.5 cm × 23 cm (sacral) = £4.88; without adhesive border 10 cm × 20 cm = £2.19, 15 cm × 15 cm = £4.27, 20 cm × 20 cm = £6.43  
Uses lightly to moderately exuding wounds  
Versiva XC (Convatec)  
Semi-permeable hydrocolloid dressing with fibre layer and polyurethane foam backing with adhesive border, 9 cm × 9 cm = £2.44, 11 cm × 19 cm (oval) = £2.42, 14 cm × 14 cm = £4.55, 19 cm × 19 cm = £7.08, 19 cm × 24 cm = £8.56, 18 cm × 17.7 cm (oval) = £5.99, 21 cm × 25 cm (capsule) = £8.56, 19.5 cm × 18.5 cm (heel) = £7.27  
Uses chronic and acute exuding wounds  
Versiva, hydrocolloid gelling foam dressing, with adhesive border, 10 cm × 10 cm = £2.30, 14 cm × 14 cm = £3.10, 19 cm × 19 cm = £4.95, 22 cm × 22 cm = £5.50, 18.5 cm × 17.7 cm (oval) = £5.99; without adhesive border, 7.5 cm × 7.5 cm = £1.35, 11 cm × 11 cm = £2.25, 15 cm × 15 cm = £4.15, 20 cm × 20 cm = £6.20  
Uses lightly to moderately exuding wounds  
Hydrocolloid (Hartmann)  
Hydrocolloid dressing with adhesive border and absorbent wound contact pad, 5 cm × 5 cm = £0.92, 7.5 cm × 7.5 cm = £1.51, 10 cm × 10 cm = £2.20, 15 cm × 15 cm = £4.13; Concave dressing, 8 cm × 12 cm = £1.93; Sacral dressing, 12 cm × 18 cm = £3.29; Basic dressing without adhesive border, 10 cm × 10 cm = £2.23, Thin film dressing, 7.5 cm × 7.5 cm = £3.63, 10 cm × 10 cm = £1.01, 15 cm × 15 cm = £2.36  
Uses lightly to moderately exuding wounds  
Nu Derm (J&J)  
Semi-permeable hydrocolloid dressing without adhesive border, 5 cm = £0.63, 10 cm × 10 cm = £1.53, 15 cm × 15 cm = £3.12, 20 cm × 20 cm = £6.24, 8 cm × 12 cm (heel/ 
elbow) = £3.12, 15 cm × 18 cm (sacral) = £4.37; without adhesive border, thin, 10 cm × 10 cm = £1.04  
Replicare Ultra (S&N Hlth.)  
Adhesive hydrocolloid dressing with outer semi-permeable polyurethane film backing, 10 cm × 10 cm = £2.29, 15 cm × 15 cm = £4.56, 20 cm × 20 cm = £6.73; Sacral dressing, 15 cm × 18 cm = £4.32  
Uses lightly to moderately exuding wounds  
Bio-cellulose dressings  
Suprasorb X (Synergy Healthcare)  
Biosynthetic cellulose fibre dressing, 5 cm × 5 cm = £1.87, 9 cm × 9 cm = £3.89, 14 cm × 20 cm = £7.71, 2 cm × 21 cm (rape) = £5.99  
Uses lightly to moderately exuding wounds  
Appendix 8: Wound management
Appendix 8: Wound management

**Vapour-permeable films and membranes**

Vapour-permeable films and membranes allow the passage of water vapour and oxygen but not of water or micro-organisms, and are suitable for mildly exuding wounds. They are highly conformable, convenient to use, provide a moist healing environment, and some may permit constant observation of the wound. However, water vapour loss may occur at a slower rate than exudate is generated, so that fluid accumulates under the dressing, which can lead to tissue maceration and to wrinkling at the adhesive contact site (with risk of bacterial entry). Newer versions have increased moisture vapour permeability, some also contain water-soluble antimicrobials. Despite these advances vapour-permeable films and membranes remain less suitable for large heavily exuding wounds and are probably not suitable for chronic leg ulcers. They are most commonly used as secondary dressings over alginate or gel; they are also sometimes used to protect fragile skin of patients at risk of developing minor skin damage.

**Vapour-permeable Adhesive Film Dressing, BP 1993**
(Semi-permeable Adhesive Dressing)

Extendable, waterproof, water-vapour-permeable polyurethane film coated with synthetic adhesive mass; transparent. Supplied in single-use pieces.

**Advise! Conform** (Advancis)

Self-adhesive silicone gel sheet with polyurethane backing, 10 cm × 10 cm = £5.20, 10 cm × 15 cm = £9.17

**Cica-Care** (S&B Hith.)

Soft, self-adhesive, semi-occlusive silicone gel sheet with backing, 6 cm × 12 cm = £13.42; 15 cm × 12 cm = £26.16

**Clitech** (Su-Med)

Silicone gel sheet, 10 cm × 10 cm = £7.50, 15 cm × 15 cm = £14.00, 10 cm × 20 cm = £12.50

Silicone gel, 15 g = £17.50, 60 g = £50.00

**Dermatix**

(Decompression)

(ConvaTec)

Siligel (Mölnlycke)

Sage of water vapour and oxygen but not of water or insulation

**Advasil Conform** (Advancis)

Dermatix

Clitech

Ciltech

Cica-Care

Advasil Conform

(Advancis)

890 A8.1.5 Vapour-permeable films and membranes

BNF 57

Keloid dressings

Silicone gel and gel sheets are used to reduce or prevent hypertrophic and keloid scarring. They should not be used on open wounds. Application times should be increased gradually. Silicone sheets can be washed and reused.

**Hyaluronic acid**

**Hyalo-lift** (ConvaTec)

Hyalofill R, flat, non-woven, absorbent fibrous fleece of Hyaff (an ester of hyaluronic acid), 5 cm × 5 cm = £9.98, 10 cm × 10 cm = £27.68

**Hyalofill-F** (Mölnlycke)

Uses for treatment of chronic or acute wounds, place on surface inside cavity and cover with sterile dressing, renew daily or when saturated (at least every 2–3 days)

**Hyalofill-R** (Mölnlycke)

absorbent fibrous rope of Hyaff (an ester of hyaluronic acid), 500 mg = £27.68

**Uses** for treatment of chronic or acute wounds, position gently inside cavity and cover with sterile dressing, renew daily or when saturated (at least every 2–3 days)

**Hyaluronic acid**

**Hyalo-lift** (ConvaTec)

Hyalofill R, flat, non-woven, absorbent fibrous fleece of Hyaff (an ester of hyaluronic acid), 5 cm × 5 cm = £9.98, 10 cm × 10 cm = £27.68

**Uses** for treatment of chronic or acute wounds, place on surface of lesion and cover with sterile dressing, renew daily or when saturated (at least every 2–3 days)

**Hyalo-lift** (ConvaTec)

(ConvaTec)

Hyalofill R, flat, non-woven, absorbent fibrous fleece of Hyaff (an ester of hyaluronic acid), 5 cm × 5 cm = £9.98, 10 cm × 10 cm = £27.68

**Uses** for treatment of chronic or acute wounds, place on surface inside cavity and cover with sterile dressing, renew daily or when saturated (at least every 2–3 days)
Omiderm (Chemical Search)

Water-vapour permeable polyurethane film (plain and meshed versions). 5 cm × 7 cm = £2.00; 8 cm × 10 cm = £3.50, meshed = £4.75; 18 cm × 10 cm = £6.40, meshed = £9.50; 60 cm × 10 cm = £23.50; 21 cm × 31 cm = £24.00, meshed = £32.00; 23 cm × 39 cm = £48.75

Uses: ulcers; donor sites; superficial and partial thickness burns; meshed: donor sites, skin grafts

For intravenous and subcutaneous catheter sites

Central Gad (Unomedical)

16 cm × 7 cm (central venous catheter) = 92p, 16 cm × 8.8 cm (central venous catheter) = £1.01.

IV3000 (S&N Hlth.)

5 cm × 6 cm (1-hand) = 39p, 6 cm × 7 cm (non-winged peripheral catheter) = 51p, 7 cm × 9 cm (ported peripheral catheter) = 67p, 9 cm × 12 cm (PICC line) = £1.54, 10 cm × 12 cm (central venous catheter) = £1.28.

Mepore IV (Möllycse)

5 cm × 5.5 cm = 29p, 8 cm × 9 cm = 37p, 10 cm × 11 cm = 97p.

Niko Fix (Unomedical)

7 cm × 8.5 cm (intra-venous ported peripheral catheter) = 38p.

PharmaPre-PU IV (Wallace Cameron)

8.5 cm × 7 cm = 7p, 6 cm × 7 cm (ported peripheral cannula) = 8p, 7 cm × 9 cm (peripheral cannula, hand) = 17p.

Tegaderm IV (3M)

7 cm × 8.5 cm (peripheral catheter) = 57p, 8.5 cm × 10.5 cm (central venous catheter) = £1.11, 10 cm × 15.5 cm (peripherally inserted central venous catheter) = £1.60.

A8.1.6 Low adherence dressing and wound contact materials

Low adherence dressings and wound contact materials are used as interface layers under secondary absorbent dressings.

Tulle dressings are manufactured from cotton or viscose fibres which are impregnated with white or yellow soft paraffin to prevent the fibres from sticking, but this is only partly successful and it may be necessary to change the dressings frequently. The paraffin reduces the problems of adherence but they are suitable for heavily exuding wounds; they are not appropriate for leg ulcers or for other lesions that produce large quantities of viscous exudate.

Absorbent dressings should be used when infection is suspected as a result of clinical signs or symptoms, or when infection has been confirmed by microbiological investigation.

Absorbent Cellulose Dressing with Fluid Repellent Backing

Eclipse, 15 cm × 15 cm = £1.52; 20 cm × 30 cm = £2.14; 60 cm × 30 cm = £8.15; Eclipse Adherent with silicone wound contact layer, 10 cm × 10 cm = £2.99; 10 cm × 20 cm = £3.75, 15 cm × 15 cm = £4.99; 20 cm × 30 cm = £9.99 (Advancis)

Uses: primary or secondary dressing for medium to heavily exuding wounds.

Exu-Dry, 10 cm × 15 cm = £1.03, 15 cm × 23 cm = £2.11, 23 cm × 38 cm = £4.90 (S&N Hlth.)

Uses: primary or secondary dressing for medium to heavily exuding wounds.

Mesorol cellulose wadding pad with gauze wound contact layer and non-woven repellent backing, 10 cm × 10 cm = 58p, 10 cm × 15 cm = 75p, 10 cm × 20 cm = 93p, 15 cm × 20 cm = £1.32. 15 cm × 25 cm = £2.08, 20 cm × 30 cm = £2.36 (Möllycse)

Uses: post-operative use for heavily exuding wounds.

Telfa Max, 15 cm × 22.8 cm = £1.96, 22.8 cm × 38 cm = £4.53, 38 cm × 45.7 cm = £5.50, 38 cm × 60.9 cm = £8.00 (Covidien)

Uses: primary or secondary dressing for medium to heavily exuding wounds.

Zetuvit, non-sterile, 10 cm × 10 cm = 6p, 10 cm × 20 cm = 8p, 20 cm × 20 cm = 13p, 20 cm × 40 cm = 25p; sterile, 10 cm × 10 cm = £1.19, 10 cm × 20 cm = 22p, 20 cm × 20 cm = 35p, 20 cm × 40 cm = 98p (Hartmann)

Uses: primary or secondary dressing for medium to heavily exuding wounds.

Absorbent Perforated Dressing with Adhesive Border

Low adherence dressing consisting of viscose and rayon absorbent pad with adhesive border.

Cosmopore E, 5 cm × 7.2 cm = 7p, 6 cm × 10 cm = 14p, 8 cm × 10 cm = 16p, 6 cm × 15 cm = 18p, 8 cm × 15 cm = 25p, 8 cm × 20 cm = 34p, 10 cm × 20 cm = 41p, 10 cm × 25 cm = 59p, 10 cm × 35 cm = 71p (Hartmann)

Medipore + Pad, 5 cm × 7.2 cm = 7p, 10 cm × 10 cm = 15p, 10 cm × 15 cm = 24p, 10 cm × 20 cm = 36p, 10 cm × 25 cm = 45p, 10 cm × 35 cm = 62p (3M)

Medisafe, 6 cm × 8 cm = 8p, 8 cm × 10 cm = 13p, 8 cm × 12 cm = 23p, 9 cm × 15 cm = 29p, 9 cm × 20 cm = 34p, 9 cm × 25 cm = 36p (Neomeric)

Mepore, 7 cm × 8 cm = 10p, 10 cm × 11 cm = 20p, 11 cm × 15 cm = 34p, 9 cm × 20 cm = 41p, 9 cm × 25 cm = 57p, 9 cm × 30 cm = 65p, 9 cm × 35 cm = 71p (Möllycse)

Primapore, 6 cm × 8.3 cm = 16p, 8 cm × 10 cm = 18p, 8 cm × 15 cm = 30p, 10 cm × 20 cm = 40p, 10 cm × 25 cm = 46p, 10 cm × 30 cm = 57p, 10 cm × 35 cm = 85p (S&N Hlth.)

Softpore, 6 cm × 7 cm = 6p, 10 cm × 10 cm = 13p, 10 cm × 15 cm = 20p, 10 cm × 20 cm = 35p, 10 cm × 25 cm = 40p, 10 cm × 30 cm = 59p, 10 cm × 35 cm = 85p (Richardson)

Sterifix, 5 cm × 7 cm = 16p, 7 cm × 10 cm = 30p, 10 cm × 14 cm = 53p (Hartmann)

Telfa Island, 5 cm × 10 cm = 8p, 10 cm × 12.5 cm = 26p, 10 cm × 20 cm = 34p, 10 cm × 25 cm = 45p, 10 cm × 35 cm = 60p; Telfa AMD Island (with polyhexamethylene biguanide—antimicrobial), 10 cm × 12.5 cm = 57p, 10 cm × 20 cm = 83p, 10 cm × 25 cm = 94p, 10 cm × 35 cm = £1.17 (Covidien)

Uses: lightly exuding and post-operative wounds.
Appendix 8: Wound management

Absorbent Perforated Plastic Film Faced Dressing

(Drug Tariff specification 43). Knitted viscose primary dressing impregnated with povidone–iodine ointment 10%, 5 cm × 5 cm = 32p, 9.5 cm × 9.5 cm = 62p (J&J)

Uses wound contact layer for abrasions and superficial burns

Contraindications iodoine may be absorbed particularly if large wounds treated, children under 6 months, thyroid disease

Para-indications severe renal impairment, pregnancy, breastfeeding

Acticoat (S&N Hlth.)

Three layer antimicrobial barrier dressing consisting of a polyester core between low adherent silver coated high density polyethylene mesh, 5 cm × 5 cm = £3.22, 10 cm × 10 cm = £7.85, 10 cm × 20 cm = £12.28, 20 cm × 40 cm = £42.01

Acticoat 7 five layer antimicrobial barrier dressing consisting of a polyester core between low adherent silver coated high density polyethylene mesh, 5 cm × 5 cm = £5.59, 10 cm × 12.5 cm = £16.65, 15 cm × 15 cm = £29.93

Uses pressure ulcers, venous ulcers, diabetic ulcers, burns, donor and recipient graft sites; with silver, antimicrobial dressing for exuding wounds

Allevyn Gentle (S&N Hlth.)

Soft gel wound contact dressing, with polyurethane foam film backing, 5 cm × 5 cm = £1.21, 10 cm × 10 cm = £2.38, 10 cm × 20 cm = £3.83, 15 cm × 15 cm = £4.31, 20 cm × 20 cm = £6.39

Allevyn Gentle Border, silicone gel wound contact dressing, with polyurethane foam film backing, 7.5 cm × 7.5 cm = £1.40, 10 cm × 10 cm = £2.39, 12.5 cm × 12.5 cm = £3.08, 17.5 cm × 17.5 cm = £5.99

Atrauman (Hartmann)

Non-adherent knitted polyester primary dressing impregnated with neutral triglycerides, 5 cm × 5 cm = 26p, 7.5 cm × 10 cm = 25p, 10 cm × 20 cm = 57p, 20 cm × 30 cm = £1.57

Uses abrasions, burns, and other injuries of skin, and ulcerative conditions; postoperatively for granulating wounds

Atrauman Ag, non-adherent polyamide fabric impregnated with silver and neutral triglycerides, 5 cm × 5 cm = 47p, 7 cm × 7 cm = £1.14, 10 cm × 20 cm = £2.23

Uses antimicrobial dressing for burns, acute or chronic wounds, donor graft sites, diabetic ulcers

Cutimed Sorbact (BSN Medical)

Low adherence acetate tissue impregnated with dialkylcarbamoyl chloride, (dressing pad) 7 cm × 9 cm = £3.70, 20 cm × 20 cm = £7.80; (swabs) 4 cm × 6 cm = £1.50, 7 cm × 9 cm = £2.50, (round swabs) 3 cm, 5 pad pack = £3.00; (cavity dressing, cotton) 2 cm × 5 cm = £5.74, 3 cm × 200 cm = £7.37

Use wound contact dressing with polyurethane foam film backing, 7.5 cm × 7.5 cm = £1.19, 10 cm × 10 cm = £2.16, 10 cm × 20 cm = £2.90, 10 cm × 30 cm = £4.25, 15 cm × 15 cm = £3.15, 15 cm × 20 cm = £4.10

KerraMax (Ark Therapeutics)

Super absorbent polyacrylate primary dressing, 10 cm × 22 cm = £1.02, 20 cm × 22 cm = £1.80

Uses moderate to heavily exuding wounds

Mepilex (Mölnlycke)

Absorbent soft silicone dressing with polyurethane foam film backing, 10 cm × 11 cm = £2.53, 11 cm × 20 cm = £4.16, 15 cm × 20 cm = £4.59, 20 cm × 21 cm = £6.93, 20 cm × 50 cm = £27.24

Mepilex Border, with soft silicone adhesive border, 7 cm × 7.5 cm = £1.31, 10 cm × 12.5 cm = £2.59, 10 cm × 20 cm = £3.47, 10 cm × 30 cm = £5.21, 15 cm × 17.5 cm = £4.46, 17 cm × 20 cm = £5.78

Mepilex Border Lite, thin absorbent soft silicone dressing with adhesive border, 4 cm × 5 cm = £8.66, 7.5 cm × 7.5 cm = £1.33, 10 cm × 20 cm = £1.92, 10 cm × 10 cm = £2.42, 15 cm × 15 cm = £3.95

Mepilex Border Sacrum, soft silicone dressing with adhesive border, 18 cm × 18 cm = £4.56, 23 cm × 23 cm = £7.44

Mepilex Heel, soft silicone adhesive dressing, 13 cm × 20 cm = £5.15

Mepilex Lite, thin absorbent soft silicone dressing, 6 cm × 8.5 cm = £1.69, 10 cm × 10 cm = £2.02, 15 cm × 15 cm = £3.92, 20 cm × 50 cm = £24.77

Mepilex Transfer, soft silicone exudate transfer dressing, 7.5 cm × 8.5 cm = £2.10, 10 cm × 12 cm = £3.30, 15 cm × 20 cm = £9.89, 20 cm × 50 cm = £25.27

Mepilex Ag, soft silicone wound contact dressing with polyurethane foam film backing, with silver, 10 cm × 10 cm = £5.80, 10 cm × 20 cm = £9.57, 15 cm × 15 cm = £10.77, 20 cm × 20 cm = £15.96

Chlorhexidine Gauze Dressing, BP 1993

Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with povidone–iodine ointment 10%, 5 cm × 5 cm = £1.78, 10 cm × 10 cm = £3.01 (Advancis)

Uses leg ulcers, pressure sores

Actilite (B&G), impregnated with medical grade manuka honey 10% (normal loading); S&N Hlth.—Paratex, soft silicone adhesive dressing, 13 cm × 20 cm = £5.15

Uses moderate to heavily exuding wounds

Cutisorb LA, 5 cm × 5 cm = 8p, 10 cm × 10 cm = 14p, 10 cm × 20 cm = 29p (BSN Medical)

Interpose, 5 cm × 5 cm = 9p, 10 cm × 10 cm = 15p, 10 cm × 20 cm = 32p (Frontier)

Melolin, 5 cm × 5 cm = 16p, 10 cm × 10 cm = 25p, 20 cm × 10 cm = 49p (S&N Hlth.)

Release, 5 cm × 5 cm = 14p, 10 cm × 10 cm = 23p, 20 cm × 10 cm = 43p (J&J)

Skinfact, 5 cm × 5 cm = 10p, 10 cm × 10 cm = 17p, 20 cm × 10 cm = 34p (Robinson)

Solvaline N, 5 cm × 5 cm = 9p, 10 cm × 10 cm = 16p, 20 cm × 10 cm = 32p (Synergy Healthcare)

Paragauze, yellow soft paraffin, 10 cm × 10 cm = £3.22, 10 cm × 20 cm = £3.47, 10 cm × 30 cm = £5.00

Uses leg ulcers, pressure sores, and other granulating wounds with superimposed absorbent pad

Antiseptic/infectious

Melolin, 5 cm × 5 cm = £3.22, 10 cm × 10 cm = £5.00

Uses severe renal impairment; pregnancy; breast-feeding

Paraffin Gauze Dressing, BP 1993

(Tulle Gras). Fabric of leno weave, weft and warp threads of cotton and/or viscose yarn, impregnated with white or yellow soft paraffin, 10 cm × 10 cm, (light loading) = 25p; (normal loading) = 37p (most suppliers including Synergy Healthcare—Paragon; BSN Medical—Cuticell Classic (normal loading); S&N Hlth.—Jelonet (normal loading); Neomedic—Netullle (normal loading); C D Medical—Paragauze (normal loading))

Povidone–iodine Fabric Dressing

(Drug Tariff specification 43). Knitted viscose primary dressing impregnated with povidone–iodine ointment 10%, 5 cm × 5 cm = 32p, 9.5 cm × 9.5 cm = 47p (J&J—Intodine )

Uses wound contact layer for abrasions and superficial burns

Contraindications iodoine may be absorbed particularly if large wounds treated, children under 6 months, thyroid disease

Uses wound contact dressing of low adherent dressing and wound contact materials BNF 57

Appendix 8: Wound management

892 A8.1.6 Low adherence dressing and wound contact materials BNF 57
Mepitel (Mölnlycke)
Soft silicone wound contact dressing, 5 cm × 7 cm = £1.52, 8 cm × 10 cm = £3.05, 12 cm × 15 cm = £6.17, 20 cm × 30 cm = £16.61
Uses leg ulcers, decubitus ulcers, burns, fixation of skin grafts; should be covered with simple absorbent secondary dressing

Physiostulle (Coloplast)
Non-adherent soft polyurethane wound contact dressing, 10 cm × 10 cm = £2.09, 15 cm × 20 cm = £6.37
Uses leg ulcers, pressure sores, burns, postoperative wounds, donor sites, skin abrasions

Physiostulle Ag (Coloplast)
Non-adherent polyester fabric with hydrocolloid and silver sulphadiazine, 10 cm × 10 cm = £2.10
Uses antimicrobial dressing for leg ulcers, diabetic ulcers, pressure sores, burns, postoperative wounds, donor sites, skin abrasions

Proguide (S&N Hith.)
Non-adherent polyurethane wound contact layer, 10 cm × 10 cm = £2.00

Silon-TSR (Job skin)
Soft silicone wound polymer wound contact dressing, 13 cm × 13 cm = £3.52, 13 cm × 25 cm = £5.47, 28 cm × 30 cm = £7.37
Uses non-exuding to heavily exuding wounds; use suitable secondary dressing

Siltex (Advancis)
Soft silicone-coated polyurethane wound contact dressing, 5 cm × 7 cm = £1.25, 8 cm × 10 cm = £2.55, 12 cm × 15 cm = £5.15, 20 cm × 30 cm = £13.25
Uses non-exuding to heavily exuding wounds; use suitable secondary dressing

SURGIPAD (3M)
Except in Sterile Dressing Pack with Non-woven Pads

Tegaderm Contact (3M)
Non-adherent soft polyurethane wound contact dressing, 7.5 cm × 10 cm = £2.13, 7.5 cm × 20 cm = £4.17, 20 cm × 25 cm = £10.16

UrgoCell (Urgo)
Non-adherent soft polyurethane wound contact dressing with polyurethane foam film backing, 10 cm × 12 cm = £4.44, 15 cm × 20 cm = £9.00; with adhesive border 13 cm × 13 cm = £4.44, 15 cm × 20 cm = £9.00; with silver, 6 cm × 6 cm = £4.00, 10 cm × 10 cm = £5.50, 15 cm × 20 cm = £9.90
Uses moderately to heavily exuding wounds; with silver, antimicrobial dressing for moderately to heavily exuding wounds

UrgoCell Start (Urgo), soft polymer wound contact dressing with polyurethane foam backing, 6 cm × 6 cm = £4.30, 10 cm × 10 cm = £9.95, 15 cm × 20 cm = £10.70

Urgotul (Urgo)
Non-adherent soft polyurethane wound contact dressing, 11 cm × 11 cm = £2.98, 10 cm × 40 cm = £9.69, 16 cm × 21 cm = £8.43; with silver, 10 cm × 12 cm = £3.52, 15 cm × 20 cm = £9.03
Uses dry or lightly exuding wounds; with silver, antimicrobial dressing for dry or lightly exuding wounds

Urgotul Duo, non-adherent, soft polymer wound contact dressing, 5 cm × 10 cm = £2.39, 10 cm × 12 cm = £3.54, 15 cm × 20 cm = £8.22; with silver, 5 cm × 7 cm = £1.94, 11 cm × 11 cm = £3.85, 15 cm × 20 cm = £9.28
Uses dry or lightly exuding wounds; with silver, antimicrobial dressing for dry or lightly exuding wounds

Urgotul Duo Border, soft polymer wound contact dressing with absorbent pad and adhesive polyurethane film backing, 8 cm × 8 cm = £2.24, 10 cm × 12 cm = £3.47, 15 cm × 20 cm = £8.05

Urgotul 500, with silver sulphadiazine, 11 cm × 11 cm = £2.95, 16 cm × 21 cm = £8.35
Uses antimicrobial dressing for dry or lightly exuding wounds

A8.1.7 Odour absorbent dressings

Dressings containing activated charcoal are used to absorb odour from wounds. Wound odour is most effectively reduced by debridement of slough, reduction in bacterial levels, and frequent dressing changes.

Actisorb Silver 220 (J&J)
Knitted fabric of activated charcoal, with one-way stretch, with antimicrobial silver, within spun-bonded nylon sleeve. 6.5 cm × 9.5 cm = £1.61, 10.5 cm × 10.5 cm = £2.53, 15.5 cm × 19 cm = £4.60

Askina Carbosorb (Braun)
Activated charcoal absorbent dressing, 10 cm × 10 cm = £2.72, 10 cm × 20 cm = £5.25

CarboFLEX (Convatec)
Dressing in 5 layers: wound-facing absorbent layer containing alginate and hydrocolloid; water-resistant second layer; third layer containing activated charcoal; non-woven absorbent fourth layer; water-resistant backing layer. 10 cm × 10 cm = £2.95, 8 cm × 15 cm = £3.55, 15 cm × 20 cm = £6.72

Carbonet (S&N Hith.)
Activated charcoal dressing, 10 cm × 10 cm = £3.13, 10 cm × 20 cm = £6.10

Carbopad VC (Synergy Healthcare)
Activated charcoal non-absorbent dressing, 10 cm × 10 cm = £1.59, 10 cm × 20 cm = £2.15

CliniSorb Odour Control Dressings (CliniMed)
Layer of activated charcoal cloth between viscose rayon with outer polyamide coating. 10 cm × 10 cm = £1.75, 10 cm × 20 cm = £2.33, 15 cm × 25 cm = £3.75

Lyfoam C (Medipal)
Lyfoam sheet with layer of activated charcoal cloth and additional outer envelope of polyurethane foam. 10 cm × 10 cm = £2.85, 15 cm × 20 cm = £6.47

Sorbpan Plus Carbon (Unomedical)
Alginite dressing with activated carbon, 7.5 cm × 10 cm = £2.42, 10 cm × 10 cm = £4.70, 10 cm × 20 cm = £5.62, 15 cm × 20 cm = £6.47

A8.1.8 Dressing packs

The role of dressing packs is very limited. They are used to provide a clean or sterile working surface; packs shown below include cotton wool balls, but they are not recommended for use on wounds.

Non-Drug Tariff Specification Sterile Dressing Pack
Dressit contains vilutex gloves, large apron, disposable bag, paper towel, softswabs, absorbent pad, sterile field = 60p (Richardson)

Polyfield Nitrile Patient Pack contains powder-free nitrile gloves, laminate sheet, non-woven swabs, towel, polythene disposable bag, apron = 52p (Shermond)

Polyfield Soft Vinyl Patient Pack contains powder-free soft vinyl gloves, polythene sheet, non-woven swabs, towel, polythene disposable bag, apron = 52p (Shermond)

Propax SDP contains paper towel, disposable bag, gauze swabs, dressing pad, sterile field = 45p (BSN Medical)

Sterile Dressing Pack
(Drug Tariff specification 10). Contains gauze and cotton tissue pads, gauze swabs, absorbent cotton wool balls, absorbent paper towel, water repellent inner wrapper. 1 pack = 49p (Synergy Healthcare—Vernad )
Appendix 8: Wound management

**A8.1.9 Surgical absorbents**

Surgical absorbents, applied directly to the wound, have many disadvantages, since they adhere to the wound, shed fibres into it, and dehydrate it; they also permit leakage of exudate (‘strike through’) with an associated risk of infection. Surgical absorbents may be used as secondary absorbent layers in the management of heavily exuding wounds.

**Absorbent Cotton, BP**

Carded cotton fibres of not less than 10 mm average staple length, available in rolls and balls, 2.5 g = 69p; 100 g = £1.58; 500 g = £5.31. 25-g pack to be supplied when weight not stated. Uses general purpose cleansing and swabbing, pre-operative skin preparation, application of medications; supplementary absorbent pad to absorb excess wound exudate.

**Absorbent Cotton Gauze, BP 1988**

Cotton fabric of plain weave, in rolls and as swabs (see below), usually Type 13 light, sterile, 90 cm (all) × 1 m = £1.04; 3 m = £2.17; 5 m = £3.38; 10 m = £6.47. 1-m packet supplied when no size stated. Uses pre-operative preparation, for cleansing and swabbing; absorbs more quickly than gauze.

**Absorbent Cotton Ribbon Gauze, BP 1993**

Woven fabric in ribbon form with fast selvedge edges. Uses post-surgery cavity packing for sinus, dental, throat cavities etc. See also below.

**Absorbent Cotton and Viscose Ribbon Gauze, BP 1993**

Consists of absorbent cotton gauze type 12 or absorbent cotton and viscose gauze type 2. 500 g = £6.74. Uses absorbent and protective pad, as burns dressing on non-adherent layer.

**Absorbent Cotton and Viscose Ribbon Gauze, BP 1993**

Woven fabric in ribbon form with fast selvedge edges, warp threads of cotton, weft threads of viscose or combined cotton and viscose yarn, sterile. 5 m (both) × 1.25 cm = 78p; 2.5 cm = 86p. Uses post-surgery cavity packing for sinus, dental, throat cavities etc.

**Gauze and Cotton Tissue, BP 1988**

Consists of absorbent cotton enclosed in absorbent cotton gauze type 12 or absorbent cotton and viscose gauze type 2. 500 g = £6.74. Uses absorbent and protective pad, as burns dressing on non-adherent layer.

**Gauze and Cotton Tissue**

(Drug Tariff specification 14). Similar to above. 500 g = £4.92. Uses absorbent and protective pad, as burns dressing on non-adherent layer.

**Absorbent Lint, BPC**

Cotton cloth of plain weave with nap raised on one side from warp yarns. 25 g = 66p; 100 g = £2.63; 500 g = £11.07. 25-g pack supplied where no quantity stated. Note Not recommended for wound management.

**Absorbent Muslin, BP 1988**

Fabric of plain weave, warp threads of cotton, weft threads of cotton and/or viscose. Uses wet dressing, soaked in 0.9% sterile sodium chloride solution.

**Gauze Swab, BP 1988**

Consists of absorbent cotton gauze type 13 light or absorbent cotton and viscose gauze type 1 folded into squares or rectangles of 8-ply with no cut edges exposed, sterile, 7.5 cm × 7.5 cm 5-pad packet = 88p; non-sterile, 10 cm × 10 cm 100-pad packet = £1.31 (most suppliers).

**Filmed Gauze Swab, BP 1988**

As for Gauze Swab, but with thin layer of Absorbent Cotton enclosed within, non-sterile, 10 cm × 10 cm, 100-pad packet = £3.52 (Synergy Healthcare—Cofide).

**Non-woven Fabric Swab**

(Drug Tariff specification 28). Consists of non-woven fabric folded 4-ply; alternative to gauze swabs, type 13 light, sterile, 7.5 cm × 7.5 cm, 5-pad packet = 24p; non-sterile, 10 cm × 10 cm, 100-pad packet = 76p. Uses general purpose swabbing and cleansing.

**Filmed Non-woven Fabric Swab**

(Drug Tariff specification 29). Film of viscose fibres enclosed within non-woven viscose fabric folded 8-ply, non-sterile, 10 cm × 10 cm, 100-pad packet = £3.52 (J & J—Regal). Uses general purpose swabbing and cleansing.

**A8.1.10 Capillary dressings**

Capillary dressings consist of an absorbent core of hydrophilic fibres sandwiched between two low-adherent wound-contact layers. Wound exudate is taken up by the dressing and retained within the highly absorbent central layer. The dressing may be applied intact to relatively superficial areas, but for deeper wounds or cavities it may be cut to shape to ensure good contact with the wound base. Multiple layers may be applied to heavily exuding wounds to further increase the fluid-absorbing capacity of the dressing.

Capillary dressings can be applied to a variety of wounds but they are contra-indicated for heavily bleeding wounds or arterial bleeding.

**Advadraw**

Non-adherent dressing consisting of a soft viscose and polyester absorbent pad with central wicking layer between two perforated permeable wound contact layers. 5 cm × 7.5 cm = 56p, 10 cm × 10 cm = 87p, 10 cm × 15 cm = £1.17, 15 cm × 15 cm = £1.54.

**Advadraw Spiral**

0.5 cm × 40 cm = 81p.

**Cerdak Basic**

Non-adhesive wound contact sachet containing ceramic spheres. 5 cm × 5 cm = 70p, 10 cm × 10 cm = £1.56, 10 cm × 15 cm = £2.08; cavity dressing 10 cm × 10 cm = £2.10, 10 cm × 15 cm = £2.63.

**Cerdak Aerocloth**

Non-adhesive wound contact sachet containing ceramic spheres, with non-woven fabric adhesive backing. 5 cm × 5 cm = £1.37, 5 cm × 10 cm = £1.94.

**Cerdak Aerofilm**

Non-adhesive wound contact sachet containing ceramic spheres, with waterproof transparent adhesive film backing. 5 cm × 5 cm = £1.51, 5 cm × 10 cm = £2.07.

**Sumar**

Lite. For light to moderately exuding wounds and cavities, 10 cm × 10 cm = £1.59, 10 cm × 15 cm = £2.12.

**Sumar Max**

For heavily exuding wounds, 10 cm × 10 cm = £1.61, 10 cm × 15 cm = £2.15.
A8.1.11 Other dressings

Honey-based topical application
Medical grade honey is applied directly to the wound and covered with a primary low adherence wound dressing; an additional secondary dressing may be required for exuding wounds. Honey has an osmotic effect that may help to deslough wounds and maintain required for exuding wounds. Honey has an osmotic effect that may help to deslough wounds and maintain

Antibacterial Medical Honey
Manuka honey, (medical grade), 25-g tube = £1.99
Medihoney
Antibacterial Medical Honey, honey (medical grade, Lep- tosparsum sp), 20-g tube = £3.96
Antibacterial Wound Gel, honey (medical grade, Leptosper- sum sp), 80% in natural waxes and oils, 10-g tube = £2.69, 20-g tube = £4.02
Note Antibacterial Wound Gel is not recommended for use in deep wounds or body cavities where removal of waxes may be difficult
Melladerm
Honey (medical grade; S. African, Fynbos) 45% in basis containing polyethylene glycol, 50-g tube = £7.50
Melladerm Plus, honey (medical grade; Bulgarian, moun- tain flower) 45% in basis containing polyethylene glycol, 20-g tube = £4.49, 50-g tube = £8.50
Mesitran
Ointment, honey (medical grade) 47%, 15-g tube = £3.47, 50-g tube = £9.55
Ointment S, honey (medical grade) 40%, 15-g tube = £3.46
Excipients include lanolin

A8.2 Bandages and adhesives

According to their structure and performance bandages are used for dressing retention, for support, and for compression.

A8.2.1 Non-extensible bandages
Bandages made from non-extensible woven fabrics have generally been replaced by more conformable products, therefore their role is now extremely limited. Triangular calico bandage has a role as a sling.

Domette Bandage, BP 1988
Fabric, plain weave, cotton warp and wool weft (hospital quality also available, all cotton). 5 m (all), 5 m = 54p; 7.5 cm × 5 cm = 81p; 10 cm = £1.08; 15 cm = £1.61 (Seraid)
Uses protection and support where warmth required

Multiple Pack Dressing No. 1
(Drug Tariff). Contains absorbent cotton, absorbent cotton gauge type 13 light (sterile), open-wove bandages (banded). 1 pack = £3.93
Appendix 8: Wound management

Elasticated Tubular Bandage, BP 1993

...Venous leg ulcers and should be considered after wound healing.

Compression hosiery (section A8.3.1) reduces the recurrence of venous leg ulcers and should be considered after wound healing.

Elasticated Surgical Tubular Stockinette, Foam packed

(Drug Tariff specification 25). Fabric as for Elasticated Tubular Bandage with polyurethane foam lining. ...Series: Synergy—Comfigrip; Easigrip—Easigrip; Sallis—Easiband; Sigma—Sigma ETB; S&N Hilton—Tenosigrip, JLB—Textex; Medlock—Tubigrip. Where no size stated by prescriber the 50 cm length should be supplied and width endorsed.

Elasticated Surgical Stockinette

(Drug Tariff specification 46). Lightweight plain-knit elasticated tubular bandage.

Acti-Fast .3.5 cm red line (small limb), length 1 m = 62p; 5 cm green line (medium limb), length 1 m = 65p, 3 m = £1.90, 5 m = £3.30; 7.5 cm blue line (large limb), length 1 m = £3.15, 5 cm = £4.89, 9 cm = £6.50; 10.75 cm beige line (adult trunks), length 1 m = £2.15 (Activa).

CliniFast .3.5 cm red line (small limb), length 1 m = 56p; 5 cm green line (medium limb), length 1 m = 58p, 3 m = £1.62, 5 m = £2.81; 7.5 cm blue line (large limb), length 1 m = 71p, 3 m = £2.13, 5 m = £3.74; 10.75 cm yellow line (child trunk), length 1 m = £1.45, 3 m = £4.10, 5 m = £7.10; 17.5 cm beige line (adult trunk), length 1 m = £2.15 (Activa).

Uses: retention of dressings on limbs, abdomen, trunk.

Elasticated Viscose Stockinette

(Drug Tariff specification 100). Light support bandages, which include the various forms of crepe bandage, are used in the prevention of oedema; they are also used to provide support for mild sprains and joints but their effectiveness has not been proven for this purpose. Since they have limited extensibility, they are able to provide light support without

their use as the only means of applying pressure to an oedematous limb or to a varicose ulcer is not appropriate, since the pressure they exert is inadequate. Compression hosiery (section A8.3.1) reduces the recurrence of venous leg ulcers and should be considered after wound healing.

Cotton Stockinette, Bleached, BP 1988

Knitted fabric, cotton yarn, tubular, 1 m × 2.5 cm = 33p; 5 cm = 51p; 7.5 cm = 62p; 6 m × 10 cm = £4.23 (J&J, Medlock)

Uses: 1 lengths, basis (with wadding) for Plaster of Paris bandages etc.; 6 m length, compression bandage.

Elasticated Tubular Bandage, BP 1993

(formerly Elasticated Surgical Tubular Stockinette). Knitted fabric, elasticated threads of rubber-cored polyamide or polyester yarns and viscose or cotton yarns; tubular. Lengths 50 cm and 1 m, widths 6.25 cm, 6.75 cm, 7.5 cm, 8.75 cm, 10 cm, 12 cm (other sizes); Synergy—Comfigrip; Easigrip—Easigrip; Sallis—Easiband; Sigma—Sigma ETB; S&N Hilton—Tenosigrip, JLB—Textex; Medlock—Tubigrip. Where no size stated by prescriber the 50 cm length should be supplied and width endorsed.

Elasticated Viscose Stockinette

(Drug Tariff specification 46). Lightweight plain-knit elasticated tubular bandage.

Acti-Fast .3.5 cm red line (small limb), length 1 m = 62p; 5 cm green line (medium limb), length 1 m = 65p, 3 m = £1.90, 5 m = £3.30; 7.5 cm blue line (large limb), length 1 m = £3.15, 5 cm = £4.89, 9 cm = £6.50; 10.75 cm beige line (adult trunks), length 1 m = £2.15 (Activa).

CliniFast .3.5 cm red line (small limb), length 1 m = 56p; 5 cm green line (medium limb), length 1 m = 58p, 3 m = £1.62, 5 m = £2.81; 7.5 cm blue line (large limb), length 1 m = 71p, 3 m = £2.13, 5 m = £3.74; 10.75 cm yellow line (child trunk), length 1 m = £1.45, 3 m = £4.10, 5 m = £7.10; 17.5 cm beige line (adult trunk), length 1 m = £2.15 (Activa).

Uses: retention of dressings on limbs, abdomen, trunk.

Elasticated Viscose Stockinette

(Drug Tariff specification 46). Lightweight plain-knit elasticated tubular bandage.

Acti-Fast .3.5 cm red line (small limb), length 1 m = 62p; 5 cm green line (medium limb), length 1 m = 65p, 3 m = £1.90, 5 m = £3.30; 7.5 cm blue line (large limb), length 1 m = 90p, 3 m = £2.50, 5 m = £4.40; 10.75 cm yellow line (child trunk), length 1 m = £1.45, 3 m = £4.10, 5 m = £7.10; 17.5 cm beige line (adult trunk), length 1 m = £2.15 (Activa).

Uses: retention of dressings on limbs, abdomen, trunk.

Elasticated Viscose Stockinette

(Drug Tariff specification 46). Lightweight plain-knit elasticated tubular bandage.

Acti-Fast .3.5 cm red line (small limb), length 1 m = 62p; 5 cm green line (medium limb), length 1 m = 65p, 3 m = £1.90, 5 m = £3.30; 7.5 cm blue line (large limb), length 1 m = £3.15, 5 cm = £4.89, 9 cm = £6.50; 10.75 cm beige line (adult trunks), length 1 m = £2.15;...
exerting undue pressure. For a warning against injudicious compression see section A8.2.5.

**Crepe Bandage, BP 1988**
Fabric, plain weave, warp of wool threads and crepe-twisted cotton threads, weft of cotton threads; stretch bandage. 4.5 m stretched (all): 5 cm = 90p; 7.5 cm = £1.20; 10 cm = £1.85; 15 cm = £2.39 (most suppliers)

**Uses** light support system for strains, sprains, compression over paste bandages for varicose veins

**Cotton Crepe Bandage**
Light support bandage, 4.5 m stretched (all): 5 cm = 48p; 7.5 cm = 67p; 10 cm = 87p; 15 cm = £1.27 (Steraid—Hospiacrepe 239)

**Cotton Crepe Bandage, BP 1988**
Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton and/or viscose threads; stretch bandage. 4.5 m stretched (both): 7.5 cm = £2.81; 10 cm = £3.62; other sizes (most suppliers)

**Uses** light support system for strains, sprains, compression over paste bandages for varicose ulcers

**Cotton, Polyamide and Elastane Bandage**
Fabric, cotton, polyamide, and elastane; light support bandage (Type 2). 4.5 m stretched (all): 5 cm = 54p; 7.5 cm = £73p; 10 cm = 91p; 15 cm = £1.12 (Neomedic—Neoprot); 5 cm = 64p; 7.5 cm = 91p; 10 cm = £1.16; 15 cm = £1.67 (BSN Medical—Jiffipore); 10 cm = £1.10 (Medlock—Setocrepe); 10 cm = £1.24, latex-free = £1.31 (S&N Hlth.—Profore #2)

**Uses** light support for sprains and strains; retention of dressings

**Cotton Stretch Bandage, BP 1988**
Fabric, plain weave, warp of crepe-twisted cotton threads, weft of cotton threads; stretch bandage, lighter than cotton crepe. 4.5 m stretched (all): Hospipore 233, 5 cm = 52p; 7.5 cm = 72p; 10 cm = 96p; 15 cm = £1.36 (Steraid)

**PremierBand** 6, 5 cm = 45p; 7.5 cm = 63p; 10 cm = 79p; 15 cm = £1.18 (Shermond)

**Uses** light support system for strains, sprains, compression over paste bandages for varicose ulcers

**Cotton Suspensory Bandage**
(Drug Tariff). Type 1: cotton net bag with draw tapes and webbing waistband; small, medium, and large (all) = £1.55, extra large = £1.65. Type 2: cotton net bag with elastic edge and webbing waistband; small = £1.77, large = £1.83, extra large = £1.91. Type 3: cotton net bag with elastic edge and webbing waistband with elastic insertion; small, medium, and large (all) = £1.86; extra large = £1.92. Type supplied to be endorsed

**Uses** support of scrotum

**Knitted Elastomer and Viscose Bandage**
Knitted fabric, viscose and elastomer yarn. **Type 2** (light support bandage)
Clinilite, 4.5 m (all), 5 cm = 44p; 7.5 cm = 61p; 10 cm = 80p; 15 cm = £1.16 (Clinisupplies)

**K-Lite** 4.5 m stretched, 5 cm = 51p; 7 cm = 71p; 10 cm = 93p; 15 cm = £1.34; 5.2 m stretched, 10 cm = £1.06 (Urgo)

**Knit-Firm** 4.5 m stretched, 5 cm = 36p; 7 cm = 51p; 10 cm = 66p; 15 cm = 96p (Steraid)

**Uses** light support for sprains and strains

**Type 3a (light compression bandage):**
CliniPlus, all 5 cm = £1.80 (Clinisupplies)

**Elset** 6 m stretched, 10 cm = £2.39; 15 cm = £2.59; 8 m stretched, 10 cm = £3.06; 12 m stretched, 15 cm = £5.13 (Medlock)

**K-Plus** 8.7 m stretched, 10 cm = £2.08; 10.25 m stretched, 10 cm = £2.36 (Urgo)

**K-Plus Long** 10.25 m stretched, 10 cm = £2.41 (Urgo)

**Profore #3** 8.7 m stretched, 10 cm = £3.60, latex-free = £3.91 (S&N Hlth.)

**High compression bandages**

**PEC High Compression Bandage**
Polyamide, elastane, and cotton compression (high) extensible bandage, 3 m (unstretched) (all): 7.5 cm = £2.52; 10 cm = £3.25 (Medlock—Setocrepe)

**VEC High Compression Bandage**
Viscose, elastane, and cotton compression (high) extensible bandage, 3 m unstretched (both): 7.5 cm = £2.52; 10 cm = £3.25; 15 cm = £3.95 (S&N—Tensopress)

**High Compression Bandage**
Cotton, viscose, nylon, and Lycra extensible bandage, 3 m (unstretched), 10 cm (red) = £3.33 (ConvaTec—SurePres); 3 m (unstretched), 10 cm = £2.64 (Urgo—K-ThreeC); 3.5 m (unstretched), 10 cm = £1.82 (Advancis—Adva-Co)

**ProGuide #2** (S&N Hlth.)
Woven, elastomer, cohesive, extensible, compression bandage, 3 m (unstretched), 10 cm (red) = £5.37, 10 cm (yellow) = £5.85, 10 cm (green) = £6.34

**Short stretch compression bandage**
Short stretch bandages help to reduce oedema and promote healing of venous leg ulcers. They are also used to reduce swelling associated with lymphoedema. They are applied at full stretch over padding (see Sub-compression Wadding Bandage below) which protects areas of high pressure and sites at high risk of pressure damage.

**Actiban** (Activa)
All 5 m, 8 cm = £3.08; 10 cm = £3.31; 12 cm = £4.02

**Actico** (Activa)
Cohesive, all 6 m, 4 cm = £2.19, 6 cm = £2.57, 8 cm = £2.95, 10 cm = £3.07, 12 cm = £3.91

**Comprilan** (BSN Medical)
All 5 m, 6 cm = £2.52; 8 cm = £2.96; 10 cm = £3.18; 12 cm = £3.87

**Rosidal K** (Synergy Healthcare)
All 5 m, 4 cm = £1.70, 6 cm = £2.37, 8 cm = £2.83, 10 cm = £3.09, 12 cm = £3.75; 10 m x 10 cm = £5.38

**Silkolan** (Urgo)
All 5 m, 8 cm = £3.00; 10 cm = £3.39

**Sub-compression wadding bandage**
Advasoft (Advancis)
3.5 m unstretched, 10 cm = 37p

**Cellona Undercast Padding** (Synergy Healthcare)
2.75 m unstretched (all): 5 cm = 26p, 7.5 cm = 34p; 10 cm = 42p; 15 cm = 54p

**Flexi-Ban** (Activa)
Padding, 3.5 m unstretched, 10 cm = 46p
Multi-layer compression bandaging systems are an alternative to High Compression Bandages (section A8.2.5) for the treatment of venous leg ulcers. Compression is achieved by the combined effects of two or three extensible bandages applied over a layer of orthopaedic wadding and a wound contact dressing.

### Four layer systems

**K-Four** (Urgo)  
K-Four Wound Dressing (Paratex — see Knitted Viscose Primary Dressing, p. 892); K-Four #1 (K-Soft — see Sub-compression Wadding Bandage, above); K-Four #2 (K-Lite — see Knitted Elastomer and Viscose Bandage, p. 897); K-Four #3 (K-Plus — see Knitted Elastomer and Viscose Bandage, p. 897); K-Three C — see High compression bandages, p. 897; K-Four #4 (K-Flex ), 6 m (stretched), 10 cm = £2.76; 7.6 (stretched), 10 cm = £3.16

Multi-layer compression bandaging kit, four layer system, for ankle circumference up to 18 cm = £6.93, 18–25 cm = £6.51, 25–30 cm = £6.64, above 30 cm = £9.05, reduced compression, 18 cm+ = £4.43

**Profore** (S&N Hlth.)  
Profore wound contact layer (see Knitted Viscose Primary Dressing, p. 892); Profore #1 (see Sub-compression Wadding Bandage, above); Profore #2 (see Cotton, Polyamide and Elastane Bandage, p. 897); Profore #3 (see Knitted Elastomer and Viscose Bandage, p. 897); Profore #4 (see Cohesive bandages, p. 899); Profore Plus 3 m (unstretched), 10 cm = £3.37, latex-free = £3.60

Multi-layer compression bandaging kit, four layer system, for ankle circumference up to 18 cm = £9.32, 18–25 cm = £6.69, 25–30 cm = £7.21, above 30 cm = £10.79, latex-free, 18–25 cm = £9.28, Profore Lite above 18 cm = £5.01, latex-free = £5.45

**System 4** (Mölnlycke)  
System 4 wound contact layer (Setoprime — see Knitted Viscose Primary Dressing, p. 892); System 4 #1 (Softex — see Sub-compression Wadding Bandage, above); System 4 #2 (Strocrepe — see Cotton, Polyamide and Elastane Bandage, p. 897); System 4 #3 (Ellet — see Knitted Elastomer and Viscose Bandage, p. 897); System 4 #4 (Coban — see Cohesive Bandages, p. 899)

### Two layer systems

**Coban** (3M)  
Multi-layer compression bandaging kit, two layer system (latex-free, foam bandage and cohesive compression bandage), one size = £8.08

**K-Two** (Urgo)  
K-Tech (see Sub-compression Wadding Bandages, above); K-Press (see Cohesive Bandages, p. 899)

Multi-layer compression bandaging kit, two layer system, for ankle circumference 18–25 cm (short) = £6.50, ankle circumference 18–25 cm = £7.70, ankle circumference 25–32 cm = £8.35

**ProGuide** (S&N Hlth.)  
ProGuide wound contact layer (see Low Adherence Dressing and Wound Contact Materials, p. 893); ProGuide #1 (see Sub-compression Wadding Bandage, above); ProGuide #2 (see High Compression Bandages, p. 897)

Multi-layer compression bandaging kit, two layer system, for ankle circumference 18–22 cm (red) = £8.98, 22–28 cm (yellow) = £9.48, 28–32 cm (green) = £9.96

### Adhesive bandages

Elastic adhesive bandages are used to provide compression in the treatment of varicose veins and for the support of injured joints; they should no longer be used for the support of fractured ribs and clavicles. They have also been used with zinc paste bandage in the treatment of venous ulcers, but they can cause skin reactions in susceptible patients and may not produce sufficient pressures for healing (significantly lower than those provided by other compression bandages).

**Elastic Adhesive Bandage, BP 1993**  
Woven fabric, elastic in warp (crepe-twisted cotton threads), weft of cotton and/or viscose threads spread with adhesive mass containing zinc oxide. 4.5 m stretched (all): 5 cm = £3.51; 7.5 cm = £4.80; 10 cm = £6.36 (Robinsons—Flexoplast); S&N Hlth.—Elastoplast Bandage. 7.5 cm width supplied when size not stated

**Uses** compression for chronic leg ulcers, compression and support for swollen or sprained joints

### Cohesive bandages

Cohesive bandages adhere to themselves, but not to the skin, and are useful for providing support for sports use where ordinary stretch bandages might become displaced and adhesive bandages are inappropriate. Care is needed in their application, however, since the loss of ability for movement between turns of the bandage to equalise local areas of high tension carries the potential for creating a tourniquet effect. They should not be used if arterial disease is suspected.
Cohesive extensible bandages

These elastic bandages adhere to themselves and not to skin; this prevents slipping during use.

**Uses**: support of sprained joints; outer layer of multi-layer compression bandaging

**Coban** (3M)

6 m (stretched), 10 cm = £2.76; other sizes £4.5 m stretched (all): 2.5 cm = £1.29; 5 cm = £1.81; 7.5 cm = £2.74; 10 cm = £3.61; 15 cm = £5.33

**K-Press** (Urgo)

6.5 m × 10 cm (0, short) = £2.76, 7.5 m × 10 cm (18–25 cm ankle circumference) = £3.22, 10.5 m × 10 cm (25–32 cm ankle circumference) = £3.50

**Profore #4** (S&N Hlth.)

2.5 m (unstretched) = £2.97, latex-free = £3.23

Ultra Fast (Robinsons)

6.3 m (stretched), 10 cm = £2.59

A8.2.9 Medicated bandages

**Zinc Paste Bandage** has been used with compression bandaging for the treatment of venous leg ulcers. However, paste bandages are associated with hypersensitivity reactions and should be used with caution.

Zinc paste bandages are also used with coal tar or ichthammol in chronic lichenified skin conditions such as chronic eczema (ichthammol often being preferred since its action is considered to be milder). They are also used with calamine in milder eczematous skin conditions.

**Zinc Paste Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide; requires additional bandaging, 6 m × 7.5 cm = £3.23 (Medlock—Zincaband 15%), excipients: include hydroxybenzoates; £3.55 (S&N Hlth.—Viscopaste PB7 (10%), excipients: include cetostearyl alcohol, hydroxybenzoates)

**Zinc Paste and Calamine Bandage** (Drug Tariff specification 5). Cotton fabric, plain weave, impregnated with suitable paste containing calamine and zinc oxide; requires additional bandaging. 6 m × 7.5 cm = £3.33 (Medlock—Caloband).

**Zinc Paste and Ichthammol Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide and ichthammol; requires additional bandaging, 6 m × 7.5 cm = £3.31 (Medlock—Icthaband 15%/25%), excipients: include hydroxybenzoates; £3.55 (S&N Hlth.—Icthopaste 6%/2%, excipients: include cetostearyl alcohol

**Uses** see section 13.5

**Steripaste** (Medlock)

Cotton fabric, selvedge weave impregnated with paste containing zinc oxide (requires additional bandaging), 6 m × 7.5 cm = £3.24

**Excipients** include polysorbate 80

**Medicated stocking**

**Ziploc** (S&N Hlth.)

Sterile rayon stocking impregnated with ointment containing zinc oxide 20%. 4-pouch carton = £12.52; 10-pouch carton = £31.30

**Uses** chronic leg ulcers; can be used under appropriate compression bandages or hosiery in chronic venous insufficiency.

A8.2.10 Surgical adhesive tapes

Adhesive tapes are useful for retaining dressings on joints or awkward body parts. These tapes, particularly those containing rubber, can cause irritant and allergic reactions in susceptible patients; synthetic adhesives have been developed to overcome this problem, but they, too, may sometimes be associated with reactions. Adhesive tapes that are occlusive may cause skin maceration. Care is needed not to apply these tapes under tension, to avoid creating a tourniquet effect. If applied over joints they need to be orientated so that the area of maximum extensibility of the fabric is in the direction of movement of the limb.

### Permeable adhesive tapes

**Elastic Adhesive Tape, BP 1988**

(Elastic Adhesive Plaster). Woven fabric, elastic in warp (crepe-twisted cotton threads), web of cotton and/or viscose threads, spread with adhesive mass containing zinc oxide. 4.5 m stretched × 2.5 cm = £1.64 (Robinsons—Flexoplast; S&N—Elastoplast).

**Uses** securing dressings.

For 5 cm width, see Elastic Adhesive Bandage

**Permeable, Apertured Non-Woven Synthetic Adhesive Tape, BP 1988**

Non-woven fabric with a polyacrylate adhesive.

**Hyfaja** (all) 2.5 cm = £1.56, 5 cm = £2.48, 10 cm = £4.33, 15 cm = £6.42, 20 cm = £8.51, 30 cm = £12.31 (BSN Medical).

**Mefix** 2.5 cm = 95p, 5 cm = £1.68, 10 cm = £2.69, 15 cm = £3.66, 20 cm = £4.69, 30 cm = £6.72 (Molnlycke).

**Omnifix** 2.5 cm = £1.79, 10 cm = £3.69, 15 cm = £5.44 (Hartmann).

**Uses** securing dressings.

**Permeable Non-woven Synthetic Adhesive Tape, BP 1988**

Backing of paper-based or non-woven textile material spread with a polymeric adhesive mass:

**Clinipore** 5 m (all) 1.25 cm = 35p, 2.5 cm = 59p, 5 cm = 99p; 2.5 cm × 10 m = 73p (Clinisupplies).

**Leukofix** 5 m (all) 1.25 cm = 52p, 2.5 cm × 83p, 5 cm = £1.45 (BSN Medical).

**Leukopore** 5 m (all) 1.25 cm = 46p, 2.5 cm = 72p, 5 cm = £1.26 (BSN Medical).

**Mediplast** 5 m (all) 1.25 cm = 30p, 2.5 cm = 50p (Neomedic).

**Microprop** 5 m (all) 1.25 cm = 60p, 2.5 cm = 89p, 5 cm = £1.57 (3M).

**Scanpor** 5 m (all) 1.25 cm = 40p, 2.5 cm = 64p, 5 cm = £1.11, 10 cm (all) 1.25 cm = 52p, 2.5 cm = 86p, 5 cm = £1.64, 7.5 cm = £2.40 (BioDiagnosics).

Where no brand stated by prescriber, net price of tape supplied not to exceed 35p (1.25 cm), 59p (2.5 cm), 99p (5 cm).

**Uses** securing dressings; skin closures for small incisions for patients with skin reactions to other plasters and strapping, which require use for long periods.

**Permeable Woven Synthetic Adhesive Tape, BP 1988**

Non-extendible closely woven fabric, spread with a polymeric adhesive. 5 m (all): 1.25 cm = 77p, 2.5 cm = £1.12, 5 cm = £1.95 (Beiersdorf—Leukosilk).

**Uses** securing dressings for patients with skin reactions to other plasters and strapping, which require use for long periods.

**Silicone adhesive tape**

Soft silicone, water-resistant, knitted fabric, polyurethane film adhesive tape.

**Insil** 2 cm × 3 m = £5.60, 4 cm × 1.5 m = £6.60 (Insight).

**Mepitac** 2 cm × 3 m = £6.39, 4 cm × 1.5 m = £6.39 (Molnlycke).

**Uses** securing dressings and appliances, skin protection under devices.

**Zinc Oxide Adhesive Tape, BP 1988**

(Zinc Oxide Plaster). Fabric, plain weave, warp and weft of cotton and/or viscose, spread with an adhesive containing...
Appendix 8: Wound management

Vapour permeable adhesive dressings

Vapour-permeable Waterproof Plastic Wound Dressing, BP 1993
(former Drug Tariff title: Semipermeable Waterproof Plastic Wound Dressing). Consists of absorbent pad, may be dyed and impregnated with suitable antiseptic (see under Elastic Adhesive Dressing), attached to a piece of permeable plastic surgical adhesive tape, to leave a suitable adhesive margin; both pad and margin covered with suitable protector (most suppliers)

Use general purpose waterproof dressing, permeable to air and water vapour

Occlusive adhesive tapes

Impermeable Plastic Wound Dressing, BP 1993

Consists of absorbent pad, may be dyed and impregnated with suitable antiseptic (see under Elastic Adhesive Dressing), attached to piece of impermeable plastic surgical adhesive tape, to leave suitable adhesive margin; both pad and margin covered with suitable protector (most suppliers)

Uses protective covering for wounds requiring an occlusive dressing

A8.2.11 Adhesive dressings

A8.2.12 Skin closure dressings

Skin closure strips are used as an alternative to sutures for minor cuts and lacerations.

Skin closure strips, sterile

Leukostrip, 6.4 mm × 76 mm, 3 strips per envelope. 10 envelopes = £5.79 (S&N Hlth.)

Steri-strip, 6 mm × 75 mm, 3 strips per envelope. 12 envelopes = £8.52; 5.5 mm × 75 mm, 12 envelopes = £8.32; 12 mm × 100 mm, 12 envelopes = £8.52 (3M)

Drug Tariff specifies that these are specifically for personal administration by the prescriber

A8.3 Elastic hosiery

Before elastic hosiery can be dispensed, the quantity (single or pair), article (including accessories), and compression class must be specified by the prescriber. There are different compression values for graduated compression hosiery and lymphoedema garments (see table below). All dispensed elastic hosiery articles must state on the packaging that they conform with Drug Tariff technical specification No. 40, for further details see Drug Tariff.

Note Graduated compression tights are

A8.3.1 Graduated compression hosiery

Class 1 Light Support

Hosiery, compression at ankle 14–17 mmHg, thigh length or below knee with knitted in heel. 1 pair, circular knit (standard), thigh length = £7.44, below knee = £6.80, (made-to-measure), thigh length = £36.95, below knee = £23.12, lightweight elastic net (made-to-measure), thigh length = £19.93, below knee = £15.55

Uses superficial or early varices, varicosis during pregnancy

Class 2 Medium Support

Hosiery, compression at ankle 18–24 mmHg, thigh length or below knee with knitted in heel. 1 pair, circular knit (standard), thigh length = £11.06, below knee = £9.94, (made-to-
measure), thigh length = £36.95, below knee = £23.12; net
(made-to-measure), thigh length = £19.93, below knee = £15.55; flat bed (made-to-measure, only with closed heel and open toe), thigh length = £36.95, below knee = £23.12
Uses varices of medium severity, ulcer treatment and prophylaxis, mild oedema, varicosis during pregnancy

Class 3 Strong Support
Hosiery, compression at ankle 25–35 mmHg, thigh length or below knee with open or knitted in heel. 1 pair, circular knit (standard), thigh length = £13.11, below knee = £11.27, (made-to-measure) thigh length = £36.95, below knee = £23.12
Uses gross varices, post thrombotic venous insufficiency, gross oedema, ulcer treatment and prophylaxis

A8.3.2 Accessories
Suspenders
Suspenders, for thigh stockings = 65p, belt (specification 13), = £4.96, fitted (additional price) = 62p

A8.3.3 Anklets
Class 2 Medium Support
Anklets, compression 18–24 mmHg, circular knit (standard and made-to-measure), 1 pair = £6.51; flat bed (standard and made-to-measure) = £11.33; net (made-to-measure) = £12.80
Uses soft tissue support

Class 3 Strong Support
Anklets, compression 25–35 mmHg, circular knit (standard and made-to-measure), 1 pair = £9.09; flat bed (standard) = £9.09, (made-to-measure) = £13.53
Uses soft tissue support

A8.3.4 Knee caps
Class 2 Medium Support
Kneecaps, compression 18–24 mmHg, circular knit (standard and made-to-measure), 1 pair = £6.51; flat bed (standard and made-to-measure) = £12.80
Uses soft tissue support

Class 3 Strong Support
Kneecaps, compression 25–35 mmHg, circular knit (standard and made-to-measure), 1 pair = £8.68; flat bed (standard) = £8.68, (made-to-measure) = £13.53
Uses soft tissue support

A8.3.5 Lymphoedema garments
In addition to the products listed below, made-to-measure garments up to compression 90 mmHg and accessories also available; see Drug Tariff for details. There are different compression values for lymphoedema garments and graduated compression hosiery, see table, p. 900

Low Compression
Armsleeves (with grip top), compression 12–16 mmHg, small, medium, and large sizes all available short or long, 1 pair = £16.70

Class 1 Light support
Hosiery and armsleeves, compression 18–21 mmHg, small, medium, and large sizes all available short or long, 1 pair = £16.70

Class 2 Medium support
Hosiery and armsleeves, compression 23–32 mmHg, small, medium, large, and extra large sizes all available standard length (some available petite), 1 pair below knee closed or open toe (no top band) = £25.50, thigh closed or open toe (with top band) = £49.00; 1 piece armsleeve (no top band) = £14.50, armsleeve (with top band) = £19.00, combined armsleeve (no top band) = £25.50, combined armsleeve (with top band) = £30.00

Class 3 Strong support
Hosiery, compression 34–46 mmHg, small, medium, large, and extra large sizes all available standard length (some available petite), 1 pair below knee open toe (no top band) = £28.00, thigh open toe (with top band) = £51.00
Appendix 9: Cautionary and advisory labels for dispensed medicines

Numbers following the preparation entries in the BNF correspond to the code numbers of the cautionary labels that pharmacists are recommended to add when dispensing. It is also expected that pharmacists will counsel patients when necessary.

Counselling needs to be related to the age, experience, background, and understanding of the individual patient. The pharmacist should ensure that the patient understands how to take or use the medicine and how to follow the correct dosage schedule. Any effects of the medicine on driving or work, any foods or medicines to be avoided, and what to do if a dose is missed should also be explained. Other matters, such as the possibility of staining of the clothes or skin by a medicine should also be mentioned.

For some preparations there is a special need for counselling, such as an unusual method or time of administration or a potential interaction with a common food or domestic remedy, and this is indicated where necessary.

Original packs Most preparations are now dispensed in unbroken original packs (see Patient Packs, p. x) that include further advice for the patient in the form of patient information leaflets. Label 10 may be of value in unbroken original packs (see Patient Packs, p. x) that include further advice for the patient in the form of patient information leaflets. Label 10 may be of value where appropriate. More general leaflets advising on the administration of preparations such as eye drops, eye ointments, inhalers, and suppositories are also available.

Scope of labels In general no label recommendations have been made for injections on the assumption that they will be administered by a healthcare professional or a well-instructed patient. The labelling is not exhaustive and pharmacists are recommended to use their professional discretion in labelling new preparations and those for which no labels are shown.

Individual labelling advice is not given on the administration of the large variety of antacids. In the absence of instructions from the prescriber, and if on enquiry the patient has had no verbal instructions, the directions given under ‘Dose’ should be used on the label.

It is recognised that there may be occasions when pharmacists will use their knowledge and professional discretion and decide to omit one or more of the recommended labels for a particular patient. In this case counselling is of the utmost importance. There may also be an occasion when a prescriber does not wish additional cautionary labels to be used, in which case the prescription should be endorsed ‘NCL’ (no cautionary labels). The exact wording that is required instead should then be specified on the prescription.

Pharmacists label medicines with various wordings in addition to those directions specified on the prescription. Such labels include ‘Shake the bottle’, ‘For external use only’, and ‘Store in a cool place’, as well as ‘Discard . . . days after opening’ and ‘Do not use after . . . ,’ which apply particularly to antibiotic mixtures, diluted liquid and topical preparations, and to eye-drops. Although not listed in the BNF these labels should continue to be used when appropriate; indeed, ‘For external use only’ is a legal requirement on external liquid preparations, while ‘Keep out of the reach of children’ is a legal requirement on all dispensed medicines. Care should be taken not to obscure other relevant information with adhesive labelling.

It is the usual practice for patients to take standard tablets with water or other liquid and for this reason no separate label has been recommended.

The label wordings recommended by the BNF apply to medicines dispensed against a prescription. Patients should be aware that a dispensed medicine should never be taken by, or shared with, anyone other than for whom the prescriber intended it. Therefore, the BNF does not include warnings against the use of a dispensed medicine by persons other than for whom it was specifically prescribed.

The label or labels for each preparation are recommended after careful consideration of the information available. However, it is recognised that in some cases this information may be either incomplete or open to a different interpretation. The Executive Editor will therefore be grateful to receive any constructive comments on the labelling suggested for any preparation.

Recommended label wordings

Wordings which can be given as separate warnings are labels 1–19 and labels 29–33. Wordings which can be incorporated in an appropriate position in the directions for dosage or administration are labels 21–28. A label has been omitted for number 20.

If separate labels are used it is recommended that the wordings be used without modification. If changes are made to suit computer requirements, care should be taken to retain the sense of the original.

1 Warning. May cause drowsiness

To be used on preparations for children containing antihistamines, or other preparations given to children where the warnings of label 2 on driving or alcohol would not be appropriate.

2 Warning. May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink

To be used on preparations for adults that can cause drowsiness, thereby affecting the ability to drive and operate hazardous machinery; label 1 is more appropriate for children. It is an offence to drive while under the influence of drink or drugs.
Some of these preparations only cause drowsiness in the first few days of treatment and some only cause drowsiness in higher doses. In such cases the patient should be told that the advice applies until the effects have worn off. However many of these preparations can produce a slowing of reaction time and a loss of mental concentration that can have the same effects as drowsiness. Avoidance of alcoholic drink is recommended because the effects of CNS depressants are enhanced by alcohol. Strict prohibition however could lead to some patients not taking the medicine. Pharmacists should therefore explain the risk and encourage compliance, particularly in patients who may think they already tolerate the effects of alcohol (see also label 3). Queries from patients with epilepsy regarding fitness to drive should be referred back to the patient's doctor.

Side-effects unrelated to drowsiness that may affect a patient's ability to drive or operate machinery safely include blurred vision, dizziness, or nausea. In general, no label has been recommended to cover these cases but the patient should be suitably counselled.

3 Warning. May cause drowsiness. If affected do not drive or operate machinery
To be used on preparations containing monoamine-oxidase inhibitors; the warning to avoid alcohol and dealcoholised (low alcohol) drink is covered by the patient information leaflet. Also to be used as for label 2 but where alcohol is not an issue.

4 Warning. Avoid alcoholic drink
To be used on preparations where a reaction such as flushing may occur if alcohol is taken (e.g. metronidazole and chlorpropamide). Alcohol may also enhance the hypoglycaemia produced by some oral antidiabetic drugs but routine application of a warning label is not considered necessary.

5 Do not take indigestion remedies at the same time of day as this medicine
To be used with label 25 on preparations coated to resist gastric acid (e.g. enteric-coated tablets). This is to avoid the possibility of premature dissolution of the coating in the presence of an alkaline pH.
Label 5 also applies to drugs such as ketoconazole where the absorption is significantly affected by antacids; the usual period of avoidance recommended is 2 to 4 hours.

6 Do not take indigestion remedies or medicines containing iron or zinc at the same time of day as this medicine
To be used on preparations containing oflixacin and some other quinolones, doxycycline, lymecycline, minocycline, and penicillamine. These drugs chelate calcium, iron and zinc and are less well absorbed when taken with calcium-containing antacids or preparations containing iron or zinc. These incompatible preparations should be taken 2 to 3 hours apart.

7 Do not take milk, indigestion remedies, or medicines containing iron or zinc at the same time of day as this medicine
To be used on preparations containing ciprofloxacin, norfloxacin or tetracyclines that chelate calcium, iron, magnesium, and zinc and are thus less available for absorption; these incompatible preparations should be taken 2 to 3 hours apart. Doxycycline, lymecycline and minocycline are less liable to form chelates and therefore only require label 6 (see above).

8 Do not stop taking this medicine except on your doctor's advice
To be used on preparations that contain a drug which is required to be taken over long periods without the patient necessarily perceiving any benefit (e.g. anti-tuberculous drugs).
Also to be used on preparations that contain a drug whose withdrawal is likely to be a particular hazard (e.g. clonidine for hypertension). Label 10 (see below) is more appropriate for corticosteroids.

9 Take at regular intervals. Complete the prescribed course unless otherwise directed
To be used on preparations where a course of treatment should be completed to reduce the incidence of relapse or failure of treatment. The preparations are antimicrobial drugs given by mouth. Very occasionally, some may have severe side-effects (e.g. diarrhoea in patients receiving clindamycin) and in such cases the patient may need to be advised of reasons for stopping treatment quickly and returning to the doctor.

10 Warning. Follow the printed instructions you have been given with this medicine
To be used particularly on preparations containing anticoagulants, lithium and oral corticosteroids. The appropriate treatment card should be given to the patient and any necessary explanation given. This label may also be used on other preparations to remind the patient of the instructions that have been given.

11 Avoid exposure of skin to direct sunlight or sun lamps
To be used on preparations that may cause phototoxic or photoallergic reactions if the patient is exposed to ultraviolet radiation. Many drugs other than those listed in Appendix 9 (e.g. phenothiazines and sulphonamides) may, on rare occasions, cause reactions in susceptible patients. Exposure to high intensity ultraviolet radiation from sunray lamps and sun-beds is particularly likely to cause reactions.

12 Do not take anything containing aspirin while taking this medicine
To be used on preparations containing probenecid and sulfinpyrazone whose activity is reduced by aspirin.
Label 12 should not be used for anticoagulants since label 10 is more appropriate.

13 Dissolve or mix with water before taking
To be used on preparations that are intended to be dissolved in water (e.g. soluble tablets) or mixed with water (e.g. powders, granules) before use. In a few cases other liquids such as fruit juice or milk may be used.

14 This medicine may colour the urine
To be used on preparations that may cause the patient's urine to turn an unusual colour. These include phenolphthalein (alkaline urine pink), triamterene (blue under some lights), levodopa (dark red dish), and rifampicin (red).

15 Caution flammable: keep away from fire or flames
To be used on preparations containing sufficient flammable solvent to render them flammable if exposed to a naked flame.

16 Allow to dissolve under the tongue. Do not transfer from this container. Keep tightly closed. Discard eight weeks after opening
To be used on glyceryl trinitrate tablets to remind the patient not to transfer the tablets to plastic or less suitable containers.

17 Do not take more than . . . in 24 hours
To be used on preparations for the treatment of acute migraine except those containing ergotamine, for which label 18 is used. The dose form should be specified, e.g. tablets or capsules. It may also be used on preparations for which no dose has been specified by the prescriber.

18 Do not take more than . . . in 24 hours or . . . in any one week
To be used on preparations containing ergotamine. The dose form should be specified, e.g. tablets or suspensions.

19 Warning. Causes drowsiness which may continue the next day. If affected do not drive or operate machinery. Avoid alcoholic drink
To be used on preparations containing hypnotics (or some other drugs with sedative effects) prescribed to be taken at night. On the rare occasions (e.g. nitrazepam in epilepsy) when hypnotics are prescribed for...
daytime administration this label would clearly not be appropriate. Also to be used as an alternative to the label 2 wording (the choice being at the discretion of the pharmacist) for anxiolytics prescribed to be taken at night.

It is hoped that this wording will convey adequately the problem of residual morning sedation after taking ‘sleeping tablets’. A

21 . . . with or after food
To be used on preparations that are liable to cause gastric irritation, or those that are better absorbed with food. Patients should be advised that a small amount of food is sufficient.

22 . . . half to one hour before food
To be used on some preparations whose absorption is thereby improved. Most oral antibacterials require label 23 instead (see below).

23 . . . an hour before food or on an empty stomach
To be used on oral preparations whose absorption may be reduced by the presence of food and acid in the stomach.

24 . . . sucked or chewed
To be used on preparations that should be sucked or chewed. The pharmacist should use discretion as to which of these words is appropriate.

25 . . . swallowed whole, not chewed
To be used on preparations that are enteric-coated or designed for modified-release. Also to be used on preparations that taste very unpleasant or may damage the mouth if not swallowed whole.

26 . . . dissolved under the tongue
To be used on preparations designed for sublingual use. Patients should be advised to hold under the tongue and avoid swallowing until dissolved. The buccal mucosa between the gum and cheek is occasionally specified by the prescriber.

27 . . . with plenty of water
To be used on preparations that should be well diluted (e.g. chloral hydrate), where a high fluid intake is required (e.g. sulphonamides), or where water is required to aid the action (e.g. methylcellulose). The patient should be advised that ‘plenty’ means at least 150 mL (about a tumblerful). In most cases fruit juice, tea, or coffee may be used.

28 To be spread thinly . . .
To be used on external preparations that should be applied sparingly (e.g. corticosteroids, dithranol).

29 Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
To be used on containers of dispensed solid dose preparations containing paracetamol for adults when the instruction on the label indicates that the dose can be taken on an ‘as required’ basis. The dose form should be specified, e.g. tablets or capsules. This label has been introduced because of the serious consequences of overdose with paracetamol.

30 Do not take with any other paracetamol products
To be used on all containers of dispensed preparations containing paracetamol.

31 Contains aspirin and paracetamol. Do not take with any other paracetamol products
To be used on all containers of dispensed preparations containing aspirin and paracetamol.

32 Contains aspirin
To be used on containers of dispensed preparations containing aspirin when the name on the label does not include the word ‘aspirin’.

33 Contains an aspirin-like medicine
To be used on containers of dispensed preparations containing aspirin derivatives.

### Products and their labels

Products introduced or amended since publication of BNF No. 56 (September 2008) are underlined. Proprietary names are in italic.

= counselling advised; see BNF = consult product entry in BNF

C

<table>
<thead>
<tr>
<th>Product</th>
<th>Description</th>
<th>Label</th>
</tr>
</thead>
</table>
| Acupan, 2, 14, (urine pink) | Adalat LA, 25 | C
| Adalat Retard, 25 | Adalimumb, C, tuberculosis |
| Adcal, 24 | Adcal-D, 24 |
| Adcortyl with Graneodin, 28 | Adipine MR, 21, 25 |
| Adipine XL, 25 | Adizem, 25 |
| Advagraf, 23, 25, C, driving | Aliorin, C, dose, change to CFC-free inhaler, see BNF |
| Alledzam, 9 | Alconetasone external prep. |
| Allopurinol, 21 | C, application, see BNF |
| Alprazolam, 2 | Aldactone, 21 |
| Almogran, 2 | Aldara, 10, patient information leaflet |
| Alphaderm, 2 | Aldomet, 3, 8 |
| Alphosyl HC, 28 | Alendronic acid, C, administration, see BNF |
| Alpar, 28 | Alfuzosin, 3, 25, C, dose, see BNF |
| Alvederon, 30 | Alfuzosin m/r, 3, 21, 25, C, dose, see BNF |
| Alvases, 8, C, dose | Alimemazine, 2 |
| Amantadine, C, driving | Aliskiren, 2 |
| Amiodarone, 11 | Amimpiricin, 2 |
| Amisulpride, 2 | Amiotrptan, 3 |
| Ammonia, 2 | Alphosyl HC, 28 |
| Amorolfine, 10 | Alprazolam, 2 |
| Amitriptyline m/r, 2, 25 | Alperlon, 2 |
| Amorolfine, 10, patient information leaflet | Alprozolam, 2 |
| Acetazolamide, 3 | Alperlon, 2 |
| Acetazolamide m/r, 3, 25 | Amisulpride, 2 |
| Acetaminophen, 2, 9 | Alprazolam, 2 |
| Acetaminol, 10, patient information leaflet | Alperlon, 2 |
| Acetaminol, 2 | Alprazolam, 2 |
| Acetaminol, 3, 25, C, dose, see BNF | Alprazolam, 2 |
| Acetaminol, 3, 25, C, dose, see BNF | Alprazolam, 2 |
Amoxicillin, 9
Amoxicillin chewable tabs, 9, 10, patient information leaflet
Amoxicillin dispersible sachets, 9, 13
Amoxil, 9
Asmafansol dispersible sachets, 9, 13
Asmafan poed susp, 9, C, use of pipette
Amphoterin loz, 9, 24, C, after food
Amphotericin tabs, 21, 29, also 31 (if 'aspirin' not on label)
Aspirin dispersible tabs, 13, 21, also 32 (if 'aspirin' not on label)
Aspirin e/c, 5, 25, also 32 (if 'aspirin' not on label)
Aspirin supps, 32, (if 'aspirin' not on label)
Aspirin tabs, 21, also 32 (if 'aspirin' not on label)
Aspirin, paracetamol and codeine tabs, 21, 29, also 31 (if 'aspirin' and 'paracetamol' not on label)
Atarax, 2
Atazanavir, 5, 21
Atenolol, 8
Atorvastatin, C, muscle effects, see BNF
Atovaquone, 21
Atriola, 23, 25
Atrone inhalations, C, dose, see BNF
Augmentin susp and tabs, 9
Augmentin Duo, 9
Augmentin dispersible tabs, 9, 13
Auranofin, 11, 21, C, blood disorder symptoms
Androcure, 21
Andropatch, C, administration, see BNF
Angettes-75, 32
Angitil SR, 25
Angitil XL, 25
Anhydrol Forte, 15
Anquil, 2
Antabuse, 2, C, alcohol reaction, see BNF
Antacids, see BNF dose statements
Antepsin, 5
Anthranel preps, 28
Anticoagulants, oral, 10, anti-coagulant card
Antihistamines, (see individual preparations)
Anturane, 12, 21
Aptivus, 5, 21
Araza, 4
Ariept Evesa, C, administration
Aripiprazole, 2
Aripiprazole o.r. dispersible tabs, 2, C, administration, see BNF
Arlvert, 2
Aromasin, 21
Arpicolin, C, driving
Artane, C, before or after food, driving, see BNF
Artemether with lumefantrine, 21, C, driving
Arythmol, 21, 25
Arthrotec, 21, 25
Asocol MR tabs, 5, 25, C, blood disorder symptoms, see BNF
Asocol enema and supps, C, blood disorder symptoms, see BNF
Asasantin Retard, 21, 25
Ascorbic acid, effervescent, 13
Ascorbic acid tabs (500mg), 24
Asmabec preps, 8, C, dose; with high doses, 10, steroid card
Asmanex, 8, 10, steroid card, C, dose
Asmasal, C, dose, see BNF
Aspav, 2, 13, 21, 32
Aspirin and papaveretum dispersible tabs, 2, 13, 21, also 32 (if 'aspirin' not on label)
Betamethasone tab, 10, steroid card, 21
Betamethasone external preps, 28, C, application, see BNF
Betamethasone scalp application, 15, 28, C, application, see BNF
Betamethasone tab, 10, steroid card, 13, 21, (when used as a mouthwash, Label: 10, 13, C, administration)
Betnovate external preps, 28, C, application, see BNF
Betnovate scalp application, 15, 28, C, application, see BNF
Betnovate-RO, 28, C, application, see BNF
Bettamousse, 28, C, application, see BNF
Bezafibrate, 21
Bezafibrate m/r, 21, 25
Bezalip, 21
Bezalip-Mono, 21, 25
Biorphen, C, driving
Bisacodyl tabs, 5, 25
Bisoprolol, 8
Bolamyn SR, 21, 25
Bonronat tabs, C, administration, see BNF
Bonefoss caps and tabs, C, food and calcium, see BNF
Bonviva tabs, C, administration, see BNF
Brexidol, 21
Bricanyl inhalations, C, dose, see BNF
Bricanyl SA, 25
Briliftex, 2
Broflex, C, driving, see BNF
Bromocriptine, 21, C, hypotensive reactions, see BNF
Brunen, 21
Brufen gran, 13, 21
Brunen Retard, 25, 27
Buccastem, 2, C, administration, see BNF
Budensol, 5, 10, steroid card, 22, 25
Budesonide inhalations, 8, C, dose; with high doses, 10, steroid card
Budesonide caps, 5, 10, steroid card, 22, 25
Budesonide m/r caps, 5, 10, steroid card, 25
Buprenorphine, 2, 26
Buproprion, 25, C, driving
Buserelin nasal spray, C, nasal dose; with high doses, 10, steroid card
BuTrans, 2
Appendix 9: Cautionary and advisory labels

Byetta, C, administration, see BNF

Cabaser, 21, C, driving, hypotensive reactions, see BNF
Cabergoline, 21, C, driving, hypotensive reactions, see BNF
Cacit, 13
Cacit D3, 13
Cafergot, 18, C, dosage
Calceos, 24
Calcicard CR, 25
Calcichew preps, 24
Calcisorb, 13, 21, C, may be sprinkled on food
Calcium-500, 25
Calcium and ergocalciferol tabs, 3, 8, C, blood, hepatic or renal disorder symptoms, see BNF
Calcium phosphate sachets, 13
Calcium Resonium, C
Calcium carbonate tabs, chewable, 24
Calcium carbonate tabs and gran effervescent, 13
Calcium gluconate tabs, 24
Calcium phosphate sachets, 13
Calcium Resonium, 13
Calcium and ergocalciferol tabs, C, administration, see BNF
Calict, 5, 10, steroid card
Calfovit D3, 10, lithium prophylaxis, see BNF
Calgirol
Calceos, 18, C, dose; with high doses, 10, steroid card
Climamycin, 9, 27, C, diarrhoea, see BNF
Climper, 25
Clobazam, 2 or 19, 8, C, driving (see BNF)
Clobetasol external preps, 28, C, application, see BNF
Clobetasol scalp application, 28, C, application, see BNF
Clofazimine, 8, 14, (urine red), 21
Clonazepam, 2, 8, C, driving, alcohol, see BNF
Clonidine, see Catapres
Clopixol, 2
Clotam Rapid, 21
Clotrimazole spray, 15
Clopam, 14, (urine reddish), C, administration
Colazide, 21, 25
Codexal, 14, (urine red), C, driving
Codine phosphate syr and tabs, 14, (urine red), C, administration, see BNF
Codelux, 15, 28, C, application, see BNF
Dalmane, 19
Dantrolen, 2, C, driving, hepatotoxicity (see BNF)
Dantrolene, 2, C, driving, hepatotoxicity (see BNF)
Dapsone, 8
Darifenacin m/r, 3, 25
Darunavir, 21, C, missed dose, see BNF
Dasatinib, 25
DDAVP Melt, 26, C, fluid intake, see BNF
DDAVP tabs and intranasal, C, fluid intake, see BNF
Deferasirox, 13, 22
Deferiprone, 14, C, blood disorders
deflazacort, 5, 10, steroid card
deltacortril e/c, 5, 10, steroid card, 25
deltastab inj, 10, steroid card
demeclocycline, 7, 9, 11, 23
de-Noltab, C, administration, see BNF
denzapine, 2, 10, patient information leaflet
depakote, 25
depoxil, 2
depo Medrone (systemic), 10, steroid card
dermestril, C, administration, see BNF
dermovate cream and oint, 28, C, application, see BNF
dermovate scalp application, 28, C, application, see BNF
desmoMelt, 26, C, fluid intake, see BNF
desmopressin sublingual tabs, 26, C, fluid intake, see BNF
desmopressin sublingual tabs and intranasal, C, fluid intake, see BNF
desmospray, C, fluid intake, see BNF
desmotabs, C, fluid intake, see BNF
destolit, 21
detrusin, 3
detrusinorm XL, 1, 8, 21, 25
diatrizoate meglumine and diatrizoate meglumine hydroxide, see BNF
diazepam, 2 or 19
diclofenac dispersible tabs, 13, 21
diclofenac e/c, 5, 25
diclofenac m/r, 21, 25
dicloflex retard, 21, 25
diclomax 75 mg SR and Retard, 21, 25
diconal, 2
didanosine e/c caps, 25, C, administration
didronel, C, food and calcium, see BNF
didronel POMO, 10, patient leaflet, C, food and calcium, see BNF
diflucan 500 mg, 9
diflucan susp, 9
diflucortolone external preps, 28, C, application, see BNF
digoxin elixir, C, use of pipette
dihydrocodeine, 2, 21
dihydrocodeine m/r, 2, 25
dilacardia SR, 25
diloxanide, 9
diltiazem, 25
dilzem preps, 25
dindevan, 10, antiagulant card, 14, (urine pink or orange)
dioderm, 28, C, application, see BNF
dipentum, 21, C, blood disorder symptoms, see BNF
diprosalic, 28, C, application, see BNF
diprosone, 28, C, application, see BNF
dipyriramol, 22
dipyriramol m/r, 21, 25
dispal, C, driving
disodium etidronate, C, food and calcium, see BNF
disopyramide m/r, 25
dispersol, 30
distacol, 9
distacol MR, 9, 21, 25
distalsalicyclic acid, 2, 10, patient information leaflet, 29, 30
distamene, 22, C, blood disorder symptoms, see BNF
distigmine, 22
disulfiram, 2, C, alcohol reaction, see BNF
dithranol preps, 28
dithrocream preps, 28
dithrolean, 28
ditropan, 3
diumide K Continus, 25, 27
dolmatil, 2
dolobid, 21, 25, C, avoid aluminium hydroxide
doloxene, 2
doloxene Compound, 2, 21, 32
donepezil orodispersible tabs, C, administration
doralese, 2
dostinex, 21, C, hypertensive reactions, see BNF
dosulepin, 2
dovobet, 28
doxazosin, C, driving
Appendix 9: Cautionary and advisory labels for dispensed medicines

Doxazosin m/r, 25, C, driving

Doxepin, 2

Doxepin topical, 2, 10, patient information leaflet

Doxycycline caps, 6, 9, 11, 27, C, posture, see BNF

Doxycycline dispersible tabs, 6, 9, 11, 13

Doxycycline tabs, 6, 11, 27, C, posture, see BNF

Doxil, 2

Dropper, 2

Drosera, 2

Drosera, C, administration

Drosera, C, postural

Drosera, C, posture

Drosera, C, food and calcium, see BNF

Drosera, C, administration

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Drosera, C, posture

Epanutin caps, 8, C, administration, blood or skin disorder symptoms (see BNF), driving (see BNF)

Epanutin Infatabs, 8, 24, C, blood or skin disorder symptoms (see BNF), driving (see BNF)

Epanutin susp, 8, C, administration, blood or skin disorder symptoms (see BNF), driving (see BNF)

Eripil Chrono, 8, 25, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)

Eripil Chronosphere, 8, 25, C, administration, blood or hepatic disorder symptoms (see BNF), driving (see BNF)

Eripil crushable tabs, liquid and syrup, 8, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)

Eripil e/c tabs, 5, 8, 25, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)

Eripil, 8, 25, C, administration, blood or hepatic disorder symptoms (see BNF), driving (see BNF)

Erosartan, 21

Equanil, 2

Equasym XL, 2

Erythromycin caps, 5, 9, 25

Erythromycin ethyl succinate, 9

Erythromycin ethyl succinate, 9

Erythrocin, 9

Erythromycin tabs, 5, 8, 25, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)

Eystals, 8, 25, C, administration, blood or skin disorder symptoms (see BNF), driving (see BNF)

Etravirine, 21

Etravirin, 28, C, application, see BNF

Eucardic, 8

Eucrast, 21

Eumovate external preps, 28, C, application, see BNF

Eurax-Hydrocortisone, 28, C, application, see BNF

EvoRel preps, C, administration, see BNF

Efexor, 21

Efexor, 21

Efexor XL, 3, 25, C, driving

Elantan preps, 25

Elidel, 4, 28

Elleste Solo MX patches, C, administration, see BNF

Eloxan, 28, C, application, see BNF

Emlor preps, 8

Emeside, 8, C, blood disorder symptoms (see BNF), driving (see BNF)

Emflex, 21, C, driving

Emselex, 3, 25

En-De-Kay mouthwash, C, food and drink, see BNF

Endoxana, 23, 25, 27

Enfuvirtide, C, hypersensitivity reactions, see BNF

Entacapone, 14, (urine reddish-brown), C, driving, avoid iron-containing preparations at the same time of day

Entecavic, C, administration

Entencort CR, 5, 10, steroid card, 25

Ethambutol, 8, C, food and calcium, see BNF

Etidronate, C, food and calcium, see BNF

Etoconazole, C, food and calcium, see BNF

Etoconazole, C, food and calcium, see BNF

Etonogestrel implant, C, see BNF

Etoposide caps, 23

Etravirine, 21

Etravirin, 28, C, application, see BNF

Eucardic, 8

Eucrast, 21

Eumovate external preps, 28, C, application, see BNF

Eurax-Hydrocortisone, 28, C, application, see BNF

Evorel preps, C, administration, see BNF

Exelon caps, 21, 25

Exelon solution, 21

Exemestane, 21

Exenatide, C, administration, see BNF

Exjade, 13, 22, C, administration, see BNF

Famciclovir, 9

Famvir, 9

Farlutal 500-mg tabs, 27

Fasigyn, 6, 9, 21, 25

Favorin, C, driving, see BNF

F felon, 25

Fefol-Vit, 25

Felbinac foam, 15

Feldene caps, 21

Feldene Melt, 10, patient information leaflet, 21

Feldope, 25

Ferrograd Folic, 25

Ferrograd C, 25

Ferrograd, 25

Ferrograd, 25

Ferrograd, 25

Ferrograd, 25

FermoPax, 25

FemSeven, C, administration, see BNF

FenBid, 25

Fenbufen, 21

Fenobamate, 21

Fenogal, 21

Fenoprofen, 21

Fenoprofen, 21

Fentanyl patches and lozenges, 2

Fenogal, 21

Fencol, 25

Fenofibrate, 21

Fenofibrate, 21

Fenofibrate, 21

Fenotrol, 21

Fentazin

Fentanyl sublingual tablets, 2, 26

Fendole, 25

Fenbid, 25

Fenbufen, 21

Fenofibrate, 21

Fenogal, 21

Fenoprofen, 21

Fenoprofen, 21

Fentanyl patches and lozenges, 2

Fenofibrate, 25

Fenofibrate, 25
Flucloxacillin, 9, 23
Fluconazole susp, 9
Fluconazole 50 and 200mg, 9
Flucloxacillin, 9, 23
Fluconazole, 9, 24, C, after food
Fluocortolone external preps, 28, C, application, see BNF
Fluocinonide external preps, 28, C, application, see BNF
Fludrocortisone, 10, steroid card
Fluconazole 50 and 200mg, 9
Flucloxacillin, 9, 23
Fluconazole, 9, 14, (urine yellow or brown), 21
Flurazepam, 19
Flurbiprofen m/r, 21
Flurbiprofen m/r, 21, 25
Fluticasone inhalations (CFC-free), 8, C, dose, change to CFC-free inhaler (see BNF); with high doses, 10, steroid card
Fluticasone inhalations, 8, C, dose; with high doses, 10, steroid card
Fluticasone external preps, 28, C, application, see BNF
Flubiprofen m/r, 21, C, to be chewed
Fostair, 8, C, dose, 10, steroid card
Fosrenol, 21, C, to be chewed
Fosnavance, C, administration, see BNF
Fosamax, 21, C, administration, see BNF
Fosaparc, 15
Fosamprenavir susp, C, administration, see BNF
Fosavance, C, administration, see BNF
Fosamax, 21, C, administration, see BNF
Flurazepam, 19
Flurbiprofen m/r, 21
Flurbiprofen m/r, 21, 25
Fluticasone inhalations, 8, C, dose; with high doses, 10, steroid card
Fluticasone inhalations (CFC-free), 8, C, dose, change to CFC-free inhaler (see BNF); with high doses, 10, steroid card
Fluvastatin, C, food
Flubiprofen m/r, 21, 25
Fluticasone external preps, 28, C, application, see BNF
Fluticasone inhalations (CFC-free), 8, C, dose, change to CFC-free inhaler (see BNF); with high doses, 10, steroid card
Fluvastatin, C, muscle effects, see BNF
Fluvastatin m/r, 25, C, muscle effects, see BNF
Fluvastatin, C, administration, see BNF
Fluvastamine, C, driving, see BNF
Foradil, 8, C, dose, see BNF
Forceval caps, 25
Formoterol fumarate, C, dose, see BNF
Fortipine LA 40, 21, 25
Fortral caps and tabs, 2, 21
Fortral susp, 2
Fosamax, C, administration, see BNF
Fosamprenavir susp, C, administration, see BNF
Fosavance, C, administration, see BNF
Fosrenol, 21, C, to be chewed
Fostair, 8, C, dose, 10, steroid card
Frisium, 2 or 19, 8, C, driving (see BNF)
Frobén, 21
Frobén SR, 21, 25
Frovatriptan, 3
Fruisene, 14, (urine blue in some lights), 21
Fucibet, 28, C, application, see BNF
Fucidin susp, 9, 21
Fucidin tabs, 9
Fucidin H, 28, C, application, see BNF
Furosemide, 14, (urine yellow or brown), 21
Furamidine, 9
Fuzeon, C, hypersensitivity reactions, see BNF
Fybogel, 13, C, administration, see BNF
Fybogel Mebeverine, 13, 22, C, administration, see BNF
Gabapentin, 3, 5, 8, C, driving (see BNF)
Gabitril, 21
Galantamine, 3, 21
Galantamine m/r, 3, 21, 25
Ganciclovir, 21
Garbien, 21
Gemfibrozil, 22
Glucophage, 21
Glucophage SR, 21, 25
Glyceryl trinitrate patch, see preps
Glyceryl trinitrate m/r, 25
Glyceryl trinitrate tabs, 16
Griseofulvin spray, 15
Griseofulvin tabs, 9, 21, C, driving
Grisofulvin, 15
Grisol AF, 15
Grisovin, 15
Glyceryl trinitrate m/r, 25
Glyceryl trinitrate tabs, 16
Griseofulvin spray, 15
Griseofulvin tabs, 9, 21, C, driving
Grisofulvin spray, 15
Grisol AF, 15
Grisovin, 15, 21, C, driving
GTN 300 mcg, 16
Haelan, 28, C, application, see BNF
Haldol, 2
Half-Inderal LA, 8, 25
Half-Securon SR, 25
Half-Sinemet CR, 14, (urine red-dish), 25
Haloperidol, 2
Heminevrin, 19
Hiprex, 9
Humira, 10, steroid card
Hydrocortisone inj, 10, steroid card
Hydrocortisone external preps, 28, C, application, see BNF
Hydrocortisone tabs, 10, steroid card, 21
Hydrocortisone butyrate external preps, 28, C, application, see BNF
Hydrocortisone butyrate scalp lotion, 15, 28, C, application, see BNF
Hydromorphine caps, 21, C, administration, see BNF
Hydromorphine m/r, 21, C, administration, see BNF
Hydromorphone m/r, 21, C, administration, see BNF
Hydroxyzine, 2
Hyoscine hydrobromide tabs, 2, 24
Hyoscine hydrobromide patches, 19, C, application, see BNF
Hyponex, 2
Hypogon, 25
Hypotensive, 25
Ibuprofen, 21
Ibuprofen gran, 13, 21
Ibuprofen m/r, 25, 27
Ibupray, 15
Idarubicin caps, 25
Imatinib, 21, 27
Imdur, 25
Imigran, 3, 10, patient information leaflet
Imigran RADIS, 3, 10, patient information leaflet
Imipramine, 2
Imiquimod, 10, patient information leaflet
Imodium Plus, 24
Implanon, 3, C, patient information leaflet
Imuran, 21
Increlex, C, administration, see BNF
Indapamide m/r, 25
Inderal-LA, 8, 25
Indinavir, 27, C, administration, see BNF
Indinavir caps, and mixt, 21, C, driving
Indomethacin caps and mixt, 21, C, driving
Indomethacin m/r, see preps
Indomethacin suptts, C, driving
Indoramin, 2
Industrial methylated spirit, 15
Inferno, C, muscle effects, see BNF
Infacol, 21, C, use of dropper
Infliximab, 10, Alert card, C, tuberculosis and hypersensitivity reactions
Inosine pranobex, 9
Iovelon, 21, C, driving, see BNF
Insulin, C, see BNF
Inovelon, 21, C, driving, see BNF
Intal, 8, C, change to CFC-free inhaler
Appendix 9: Cautionary and advisory labels for dispensed medicines

Intencence, 21
Invega, 2, 25
Invirase, 21
Iodine Solution, Aqueous, 27
Ionomim, 25, C, driving
Ipocol, 5, 25, C, blood disorder symptoms, see BNF
Ipratropium inhalations, C, dose, see BNF
Ketoprofen m/r caps, 21, 25
Ketotifen, 2, 21
Ketorolac, 17, 21
Ketoval, 21, 25
Kineret, C, blood disorder symptoms, see BNF
Kivexa, C, hypersensitivity reactions, see BNF
Klaricid, 9
Klaricid sachets, 9, 13
Klaricid XL, 9, 21, 25
Kleen-Prep, 10, patient information leaflet, 13, C, administration
Konakion tabs, 24
Kwells, 2, 24
Labetalol, 8, 21
Lacosamide tabs and syrup, 8, C, driving, see BNF
Lamictal dispersible tabs, 8, 13, C, driving (see BNF), skin reactions
Lamictal tabs, 8, C, driving (see BNF), skin reactions
Lamisil, 9
Lamotrigine dispersible tabs, 8, 13, C, driving (see BNF), skin reactions
Lansoprazole caps, 5, 22, 25
Lansoprazole oro-dispersible tabs, 5, 22, C, administration, see BNF
Lanthanum, 21, C, to be chewed
Lapatinib, C, see BNF
Lapropam SR, 2, 25
Largactil, 2, 11
Larium, 21, 25, 27, C, driving, malaria prophylaxis, see BNF
Laxido, 13
Lederfen, 21
Ledermycin, 7, 9, 11, 23
Lefunomide, 4
Lenalidomide, 25, C, symptoms of thromboembolism, neutropenia, or thrombocytopenia, patient information leaflet
Lercanidipine, 22
Lescal, C, muscle effects, see BNF
Lescal XL, 25, C, muscle effects, see BNF
Levetiracetam, 8
Levocetirizine, C, driving
Levoflaxacin, 6, 9, 25, C, driving
Levomepromazine, 2
Librium, 2
Li-Liquid, 10, lithium card, C, fluid and salt intake, see BNF
Linezolid susp and tabs, 9, 10, patient information leaflet
Lioresal, 2, 8
Lipantil, 21
Lipitor, C, muscle effects, see BNF
Lipostat, C, muscle effects, see BNF
Liquid paraffin, C, administration, see BNF
Liskonum, 10, lithium card, 25, C, fluid and salt intake, see BNF
Litorax, 10, lithium card, 25, C, fluid and salt intake, see BNF
Lithium carbonate, 10, lithium card, C, fluid and salt intake, see BNF
Lithium carbonate m/r, 10, lithium card, 25, C, fluid and salt intake, see BNF
Lithium citrate liq, 10, lithium card, C, fluid and salt intake, see BNF
Lithium citrate m/r, 10, lithium card, 25, C, fluid and salt intake, see BNF
Lithium carbonate card, 25, C, fluid and salt intake, see BNF
Lithium paraffin card, 25, C, fluid and salt intake, see BNF
Loperamide, 2 or 19
Lorazepam, 2 or 19
Lormetazepam, 19
Lorcanilb, 10, patient information leaflet
Loratadine, 10, C, administration, see BNF
Lorazepam, 2 or 19
Lornoxicam, 10, patient information leaflet, C, food and calcium, see BNF
Losec, C, administration, see BNF
Lotriderm, 28, C, application, see BNF
Lugol's solution, 27
Lustral, C, driving, see BNF
Lyclear Dermal cream, 10, patient information leaflet
Lymecycline, 7, 9, 11, 23
Macrolide card, 25, C, fluid and salt intake, see BNF
Macrogols, 13
Macrobid, 9, 14, (urine yellow or brown), 21, 25
Macrodantin, 9, 14, (urine yellow or brown), 21, 25
Macroplax, 13
Madopar, 14, (urine reddish), C, driving
Madopar dispersible tabs, 14, (urine reddish), C, administration, driving, see BNF
Mabron, 2, 25
Macrobid, 9, 14, (urine yellow or brown), 21, 25
Macroplax, 13
Madopar, 14, (urine reddish), C, driving
Madopar dispersible tabs, 14, (urine reddish), C, administration, driving, see BNF
Methylprednisolone external
Methylphenidate m/r, 25
Methyldopa, 3, 8
Methylcellulose tabs (anorectic),
Methylcellulose (constipation or
Methotrexate tabs, C, NSAIDs
Methocarbamol, 2
Methenamine, 9
Methadose
Methadone, 2
Metformin m/r, 21, 25
Metformin, 21
Mesren MR
Mesalazine gran, see preps
Mesalazine enema and supps, C,
Mesalazine m/r, see preps
Mesalazine e/c, see preps
Mesalazine m/r, see preps
Mesalazine enema and supps, C,
Methylene blue, 2, 21, 25
Mecasermin, C, administration,
Mebeverine, C, administration,
Maxtrex (methotrexate)
Maxolon SR
Maxolon paed liquid
Maxitram SR
Malarivon
Magnapen
Madopar CR, 5, 14, (urine red-
Meprobamate, 2
Mepacrine, 4, 9, 21
Meloxicam tabs, 21
Melatonin, 2, 21, 25
Mefloquine, 21, 25, 27, C, driv-
Medrone tabs
Medikinet XL
Mecasermin, C, administration,
Mepacrine, 4, 9, 14, 21
Mepidol, 3, 8
Methylphenidate m/r, 25
Methylprednisolone external
preps, 28
BNF 57  Appendix 9: Cautionary and advisory labels for dispensed medicines

Appendix 9: Cautionary and advisory labels
Salofalk enema and supps, C, blood disorder symptoms, see BNF
Salofalk gran, 25, C, administration, blood disorder symptoms, see BNF
Salofalk tabs, 5, 25, C, blood disorder symptoms, see BNF
Sandimmun, C, administration, see BNF
Sandrena, C, administration, see BNF
Sando-K, 13, 21
Sandocol, 13
Sanomigran, 2
Saqunivair, 21
Scopoderm TTS, 19, C, administration, see BNF
Sebivo, C, muscle effects
Sebomin MR, 6, 25
Secobarbital, 19
Secoval, 19
Sectral, 8
Securon SR, 25
Selegiline (freeze-dried tablets), 21, 27, C, administration, see BNF
Selegiline (oral), 22, C, soft lenses
Seldane, 21, 27, C, driving (see BNF)
Seldane (oral), 21, C, food and calcium, see BNF
Selderan, 21, C, may be sprinkled on food
Selingine, 21, C, food and calcium, see BNF
Selenace, 2
Serec, 21
Serenace, 2
Sertid, 8, 10, steroid card (250- and 500-Accuphaler only), C, dose
Sertid E沃haler, 8, C, dose, change to CFC-free inhaler (see BNF), 10, steroid card (125- and 250-E沃haler only)
Serevent, C, dose, see BNF
Serevent (CFC-free), C, dose, change to CFC-free inhaler, see BNF
Seroquel, 2
Seroquel XL, 2, 23, 25
Seroxat tabs, 21, C, driving
Seroxat susp, 5, 21, C, driving
Sertraline, C, driving, see BNF
Serovital, C, muscle effects
Simeprevir, see paediatric prep
Simvastatin, C, muscle effects, see BNF
Sinemet CR, 14, (urine reddish), 25, C, driving
Sinemet preps, 14, (urine reddish), C, driving
Sinupret, 2
Sinvir, 2
Sivir, 2
Sivum, 2
Sjogren's syndrome, 2
Slo-Fe, 25
Slo-Fe Folic, 25
Slo-K, 25, 27, C, posture, see BNF
Slow-Trasicor, 8, 25
Slozem, 25
Sodium Amytal, 19
Sodium aurothiomalate, 11, C, blood disorder symptoms, see BNF
Sodium cellulose phosphate, 13, 21, C, may be sprinkled on food
Sodium chloride m/r, 25
Sodium chloride tabs, 13
Sodium chloride and glucose oral pady, cpd, 13
Sodium chloride solution-tabs, 13
Sodium clofibrate, 5, 25, C, blood disorder symptoms (see BNF), driving (see BNF)
Sodium valproate e/c, 5, 8, 25, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)
Sodium valproate m/r and granules, 8, 25, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)
Sodium valproate erythrocrystals, 8, 25, C, blood or hepatic disorder symptoms (see BNF), driving (see BNF)
Sola, 2
Sofi, 19
Somnites, 2
Sonarc, 8
Sotalol, 8
Sporanox caps, C
Sporanox liq, 9, 23, C, administration, hepatotoxicity
Spryce, 25
Appendix 9: Cautionary and advisory labels for dispensed medicines

Trimpan, 9
Trimovate, 28, C, application, see BNF
Tripotassium dicitratobismuthate, C, administration, see BNF
Tripolidine m/r, 2, 25
Triptafen preps, 2
Trizivir, C, hypersensitivity reactions, see BNF
Tropium, 2
Trosipm chloride, 23
Trudua, 21, C, administration, see BNF
Tryptophan
Truvada, 21, C, administration
Trospium chloride, 23
Tropium
Trizivir
Triprolidine m/r, 2, 25
Tripotassium dicitratobismuthate, 23, C, administration, see BNF
Viazem XL
Vfend
Vesanoid
Vertab SR
Vertapres
Vepesid caps, 25
Verapamil m/r, 25
Verapress, 25
Vertab SR, 25
Vesanoid, 21, 25
Vescicare, 3
Vjend, 9, 11, 23
Viazem XL, 25
Vibramycin caps, 6, 9, 11, 27, C, posture, see BNF
Vibramycin-D, 6, 9, 11, 13
Videx, 23, C, administration, see BNF
Videx e/c caps, 25, C, administration
Videx tabs, 23, C, administration
Vigabatrin sachets, 3, 8, 13, C, driving (see BNF)
Vigabatrin tabs, 3, 8, C, driving (see BNF)
Vimpat tabs and syrup, 8, C, driving, see BNF
Vinorelbine caps, 21, 25
Vioform Hydrocortisone, 21, C, application, see BNF
Virocept tabs, 21
Viramune, C, hypersensitivity reactions, see BNF
Viread, 21, C, administration, see BNF
Visclair, 5, 22, 25
Vikaludix, 8
Visken, 8
Vivotif, 23, 25, C, administration, see BNF
Voltarol dispersible tabs, 13, 21
Voltarol 75 mg SR and Retard, 21, 25
Voltarol tabs, 5, 25
Voriconazole, 9, 11, 23
Warfarin, 10, anticoagulant card
Warfarin WBP, 10, anticoagulant card
Warticon, 15
Welldorm, 19, 27
Wellvone, 21
Wenzin, 23
Xagrid, C, driving
Xamotil, 28
Xanax, 2
Xatrol, 3, C, dose, see BNF
Xatrol XL, 3, 21, 25, C, dose, see BNF
Xeloda, 21
Xepin, 2, 10, patient information leaflet
Xismox XL, 25
Xyzal, C, driving
Yentreve, 2
Zaditen, 2, 21
Zadstat supps, 4, 9
Zaflurlyast, 23
Zaleplon, 2
Zamadol, 2
Zamadol 24 hr, 2, 25
Zamadol SR, 2, C, administration, see BNF
Zanaflex, 2
Zanidip, 22
Zantac effervescent tabs, 13
Zapone, 2, 10, patient information leaflet
Zarontin, 8, C, blood disorder symptoms (see BNF), driving (see BNF)
Zavedos caps, 25
Zelapac, C, administration, see BNF
Zemon XL, 25
Zemtard XL, 25
Zerit, 23
Ziagen, C, hypersensitivity reactions, see BNF
Zidovudine oral solution, C, use of oral syringe
Zimical XL, 21, 25
Zimovane, 19
Zinamide, 8
Zinc acetate, 23
Zinc sulphate, see preps
Zinnat susp, 9, 21
Zinnat tabs, 9, 21, 25
Zispin SolTab, 2
Zithromax caps, 5, 9, 23
Zithromax susp, 5, 9
Zocor, C, muscle effects, see BNF
Zofran Melt, C, administration, see BNF
Zolpidem, 19
Zonamisapril, C, administration, see BNF
Zolmitriptan orodispersible tabs, C, administration, see BNF
Zolpidem, 19
Zolmitriptan orodispersible tabs, C, administration, see BNF
Zovirax susp and tabs, 9
Zuclopenthixol, 2
Zyban, 25, C, driving
Zydoil, 2
Zydol solubile, 2, 13
Zydol SR, 2, 25
Zydol XL, 2, 25
Zyloric
Zyproxa tabs, 2
Zyproxa Velotab, 2, C, administration, see BNF
Zyvox susp and tabs, 9, 10, patient information leaflet
List of Dental Preparations

The following list has been approved by the appropriate Secretaries of State, and the preparations therein may be prescribed by dental practitioners on form FP10D (GP14 in Scotland, WP10D in Wales).

Sugar-free versions, where available, are preferred.

- Aciclovir Cream, BP
- Aciclovir Oral Suspension, BP, 200 mg/5 mL
- Aciclovir Tablets, BP, 200 mg
- Aciclovir Tablets, BP, 800 mg
- Amoxicillin Capsules, BP
- Amoxicillin Oral Powder, DPF
- Amoxicillin Oral Suspension, BP
- Amphotericin Lozenges, BP
- Ampicillin Capsules, BP
- Ampicillin Oral Suspension, BP
- Artificial Saliva, DPF
- Artificial Saliva Substitutes as listed below (to be prescribed only for indications approved by ACBS):
  - AS Saliva Orthana®
  - Glandosane®
  - BioXtra®
  - Saliveze®
  - Salivix®
- Aspirin Tablets, Dispersible, BP
- Azithromycin Oral Suspension, 200 mg/5 mL, DPF
- Beclometasone Pressurised Inhalation, BP, 50 micrograms/metered inhalation, CFC-free, as:
  - Clenil Modulite®
- Benzylamine Mouthwash, BP, 0.15%
- Benzylamine Oromucosal Spray, BP, 0.15%
- Betamethasone Soluble Tablets, 500 micrograms, DPF
- Carbamazepine Tablets, BP
- Carmellose Gelatin Paste, DPF
- Cefalexin Capsules, BP
- Cefalexin Oral Suspension, BP
- Cefalexin Tablets, BP
- Cefadroxil Capsules, BP
- Cefadroxil Oral Solution, DPF
- Cefazolin Hydrochloride Tablets, 10 mg, DPF
- Chlorhexidine Gluconate 1% Gel, DPF
- Chlorhexidine Mouthwash, BP
- Chlorhexidine Oral Spray, DPF
- Chlorphenamine Oral Solution, BP
- Chlorphenamine Tablets, BP
- Choline Salicylate Dental Gel, BP
- Clindamycin Capsules, BP
- Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)
- Diazepam Oral Solution, BP, 2 mg/5 mL
- Diazepam Tablets, BP
- Diclofenac Sodium Tablets, BP
- Dihydrocodeine Tablets, BP, 30 mg
- Doxycycline Capsules, BP, 100 mg
- Doxycycline Tablets, BP, 20 mg, DPF
- Ephedrine Nasal Drops, BP
- Erythromycin Ethyl Succinate Oral Suspension, BP
- Erythromycin Ethyl Succinate Tablets, BP
- Erythromycin Stearate Tablets, BP
- Erythromycin Tablets, BP
- Fluconazole Capsules, 50 mg, DPF
- Fluconazole Oral Suspension, 50 mg/5 mL, DPF
- Hydrocortisone Cream, BP, 1%
- Hydrocortisone Oromucosal Tablets, BP
- Hydrogen Peroxide Mouthwash, BP
- Ibuprofen Oral Suspension, BP, sugar-free
- Ibuprofen Tablets, BP
- Lansoprazole Capsules, DPF
- Lidocaine 5% Ointment, DPF
- Lidocaine Spray 10%, DPF
- Loratadine Tablets, 10 mg, DPF
- Menthol and Eucalyptus Inhalation, BP 1980
- Metronidazole Oral Suspension, BP
- Metronidazole Tablets, BP
- Miconazole Cream, BP
- Miconazole Oromucosal Gel, BP
- Miconazole and Hydrocortisone Cream, BP
- Miconazole and Hydrocortisone Ointment, BP
- Mouthwash Solution-tablets, BP
- Nitrazepam Tablets, BP
- Nystatin Oral Suspension, BP
- Gastro-resistant Omeprazole Capsules, BP
- Oxytetracycline Tablets, BP
- Paracetamol Oral Suspension, BP
- Paracetamol Tablets, BP
- Paracetamol Tablets, Soluble, BP
- Phenoxymethylpenicillin Cream, DPF
- Phenoxymethylpenicillin Oral Solution, BP
- Phenoxymethylpenicillin Tablets, BP
- Promethazine Hydrochloride Tablets, BP
- Promethazine Oral Solution, BP
- Saliva Stimulating Tablets, DPF
- Sodium Chloride Mouthwash, Compound, BP
- Sodium Fluoride Mouthwash, BP
- Sodium Fluoride Oral Drops, BP
- Sodium Fluoride Tablets, BP
- Sodium Fluoride Toothpaste 0.619%, DPF
- Sodium Fluoride Toothpaste 1.1%, DPF

1. Amoxicillin Dispersible Tablets are no longer available
2. Supplies may be difficult to obtain
3. Indications approved by the ACBS are: patients suffering from dry mouth as a result of having (or having undergone) radiotherapy or sicca syndrome
4. The BP directs that when soluble aspirin tablets are prescribed, dispersible aspirin tablets should be dispensed
5. This preparation does not appear in subsequent editions of the BP
6. The BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed and no strength stated Paracetamol Oral Suspension 120 mg/5 mL should be dispensed
Sodium Fusidate Ointment, BP
Temazepam Oral Solution, BP
Temazepam Tablets, BP
Tetracycline Tablets, BP
Triamcinolone Dental Paste, BP

Preparations in this list which are not included in the BP or BPC are described under Details of DPF preparations, below

Details of DPF preparations

Preparations on the List of Dental Preparations which are specified as DPF are described as follows in the DPF. Although brand names have sometimes been included for identification purposes preparations on the list should be prescribed by non-proprietary name.

Amoxicillin Oral Powder (proprietary product: Amoxicillin Trio)
amoxicillin (as trihydrate) 3 g sachet

Artificial Saliva (proprietary product: laborant) consists of sorbitol 1.8 g, carmellose sodium (sodium carboxymethylcellulose) 390 mg, dibasic potassium phosphate 48.23 mg, potassium chloride 37.5 mg, monobasic potassium phosphate 21.97 mg, calcium chloride 9.972 mg, magnesium chloride 3.528 mg, sodium fluoride 258 micrograms/60 mL, with preservatives and colouring agents

Azithromycin Oral Suspension 200 mg/5 mL (proprietary product: Zithromax); azithromycin (as dihydrate) 200 mg/5 mL when reconstituted with water

Betamethasone Soluble Tablets 500 micrograms (proprietary product: Betnesol Soluble Tablets), beta-methasone (as sodium phosphate) 500 micrograms

Carmellose Gelatin Paste (proprietary product: Orabase Oral Paste), gelatin, pectin, carmellose sodium, 16.58% of each in a suitable basis

Cefradine Oral Solution (proprietary product: Velosef Syrup), cefradine 250 mg/5mL when reconstituted with water

Cetirizine Hydrochloride Tablets cetirizine hydrochloride 10 mg

Chlorhexidine Gluconate 1% Gel (proprietary product: Corsodyl Dental Gel), chlorhexidine gluconate 1%

Chlorhexidine Oral Spray (proprietary product: Corsodyl Oral Spray), chlorhexidine gluconate 0.2%

Doxycycline Tablets 20 mg (proprietary product: Periostal), doxycycline (as hyclate) 20 mg

Fluconazole Capsules 50 mg (proprietary product: Diflucan), fluconazole 50 mg

Fluconazole Oral Suspension 50 mg/5 mL (proprietary product: Diflucan), fluconazole 50 mg/5 mL when reconstituted with water

Lansoprazole Capsules (proprietary product: Protonix), lansoprazole 15 mg and 30 mg capsules, enclosing e/c granules

Lidocaine 5% Ointment lidocaine 5% in a suitable basis

Lidocaine Spray 10% (proprietary product: Xylocaine Spray), lidocaine 10% supplying 10 mg lidocaine/spray

Loratadine Tablets loratadine 10 mg

Mouthwash Solution-tablets consist of tablets which may contain antimicrobial, colouring and flavouring agents in a suitable soluble effervescent basis to make a mouthwash suitable for dental purposes

Penciclovir Cream (proprietary product: Vectavir Cream), penciclovir 1%

Saliva Stimulating Tablets (proprietary product: Sst), citric acid, malic acid and other ingredients in a sorbitol base

Sodium Fluoride Toothpaste 0.619% (proprietary product: Duraphat ‘2800 ppm’ Toothpaste), sodium fluoride 0.619%

Sodium Fluoride Toothpaste 1.1% (proprietary product: Duraphat ‘5000 ppm’ Toothpaste), sodium fluoride 1.1%

Changes to Dental Practitioners’ Formulary since September 2008

Additions
Beclometasone Pressurised Inhalation, BP, 50 micrograms/metered inhalation, CFC-free, as: Clenil Modulite®
Cetirizine Hydrochloride Tablets, 10 mg, DPF
Chlorphenamine Oral Solution, BP
Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)
Lansoprazole Capsules, DPF
Loratadine Tablets, 10 mg, DPF
Gastro-resistant Omeprazole Capsules, BP

Deletions
Ascorbic Acid Tablets, BP
Beclometasone Dipropionate Aerosol Inhalation 50 micrograms/metered dose, DPF
Nystatin Ointment, BP
Pethidine Tablets, BP
Vitamin B Tablets, Compound, Strong, BPC

Changes of title
Old New
Metronidazole Oral Suspension, DPF Metronidazole Oral Suspension, BP

918 Dental Practitioners’ Formulary BNF 57
Nurse Prescribers’ Formulary for Community Practitioners

Nurse Prescribers’ Formulary Appendix (Appendix NPF). List of preparations approved by the Secretary of State which may be prescribed on form FP10P (form HS21(N) in Northern Ireland, form GP10(N) in Scotland, forms FP10(CN) and FP10(PN) in Wales or, when available, WP10CN and WP10PN in Wales) by Nurses for National Health Service patients.

Community practitioners who have completed the necessary training may only prescribe items appearing in the nurse prescribers’ list set out below. Community Practitioner Nurse Prescribers are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved generic name.

Medicinal Preparations

Preparations on this list which are not included in the BP or BPC are described on p. 920

Almond Oil Ear Drops, BP
Arachis Oil Enema, NPF
1 Aspirin Tablets, Dispersible, 300 mg, BP
Bisacodyl Suppositories, BP (includes 5-mg and 10-mg strengths)
Bisacodyl Tablets, BP
Catheter Maintenance Solution, Chlorhexidine, NPF
Catheter Maintenance Solution, Sodium Chloride, NPF
Catheter Maintenance Solution, ‘Solution G’, NPF
Catheter Maintenance Solution, ‘Solution R’, NPF
Chlorhexidine Gluconate Alcoholic Solutions containing at least 0.05%
Chlorhexidine Gluconate Aqueous Solutions containing at least 0.05%
Choline Salicylate Dental Gel, BP
Clotrimazole Cream 1%, BP
Co-danthramer Capsules, NPF
Co-danthramer Capsules, Strong, NPF
Co-danthramer Oral Suspension, NPF
Co-danthramer Oral Suspension, Strong, NPF
Co-danthrusate Capsules, BP
Co-danthrusate Oral Suspension, NPF
Crotamiton Cream, BP
Crotamiton Lotion, BP
Dimeticone barrier creams containing at least 10%
Dimeticone Lotion, NPF
Docusate Capsules, BP
Docusate Enema, NPF
Docusate Oral Solution, BP
Docusate Oral Solution, Paediatric, BP
Econazole Cream 1%, BP

Emollients as listed below:
Aqueous Cream, BP
Arachis Oil, BP
Cetraben® Emollient Cream
Decubal® Clinic
Dermamist®
Diprobase® Cream
Diprobase® Ointment
Doublebase®
E45® Cream
Emulsifying Ointment, BP
Epaderm®
Hydromol® Cream
Hydromol® Ointment
Hydrous Ointment, BP
Linola® Gamma Cream
Lipobase®
Liquid and White Soft Paraffin Ointment, NPF
Neutrogena® Dermatological Cream
Oilatum® Cream
Oilatum® Junior Cream
Paraffin, White Soft, BP
Paraffin, Yellow Soft, BP
QV® Cream
QV® Lotion
QV® Wash
Ultrabase®
Unguentum M®
Zerobase® Cream

Emollient Bath Additives as listed below:
Alpha Ker® Bath Oil
3 Balneum®
Cetraben® Emollient Bath Additive
Dermalo® Bath Emollient
Diprobath®
Doublebase® Emollient Bath Additive
Doublebase® Emollient Shower Gel
Hydromol® Emollient
Imuderm® Bath Oil
Oilatum® Emollient
Oilatum® Junior Emollient Bath Additive
Oilatum® Gel
QV® Bath Oil
Folic Acid 400 micrograms/5 mL Oral Solution, NPF
Folic Acid Tablets 400 micrograms, BP
Glycerol Suppositories, BP
Ibuprofen Oral Suspension, BP
Ibuprofen Tablets, BP
Isaphagus Husk Granules, BP
Isaphagus Husk Granules, Effervescent, BP
Isaphagus Husk Oral Powder, BP
Lactulose Solution, BP
Lidocaine Ointment, BP

1. Max. 96 tablets; max. pack size 32 tablets
2. Included in the Drug Tariff, Scottish Drug Tariff, and Northern Ireland Drug Tariff
3. Except pack sizes that are not to be prescribed under the NHS (see Part XVIIIA of the Drug Tariff, Part XI of the Northern Ireland Drug Tariff)
4. Except for indications and doses that are...
Paracetamol Tablets, BP
Miconazole Oomucosal Gel, BP
Methbendazole Tablets, NPF
Methbendazole Tablets, BP
Miconazole Cream 2%, BP
Miconazole Oomucosal Gel, BP
Mouthwash Solution-tablets, NPF
Nicotine Inhalation Cartridge for Oomucosal Use, NPF
Nicotine Lozenges, NPF
Nicotine Medicated Chewing Gum, NPF
Nicotine Inal Spray, NPF
Nicotine Sublingual Tablets, NPF
Nicotine Transdermal Patches, NPF
Nyosstat Oral Suspension, BP
Olive Oil Ear Drops, BP
Paracetamol Oral Suspension, BP (includes 120 mg/5 mL and 250 mg/5 mL strengths—both of which are available as sugar-free formulations)
Spermicidal contraceptives as listed below:
Sodium Picosulfate Elixir, NPF
Sodium Picosulfate Capsules, NPF
Sodium Citrate Compound Enema, NPF
Sodium Chloride Solution, Sterile, BP
Senna and Ispaghula Granules, NPF
Senna Tablets, BP
Senna Tablets, BP
Senna and Ispaghula Granules, NPF
Sodium Chloride Solution, Sterile, BP
Sodium Citrate Compound Enema, NPF
Sodium Picosulfate Capsules, NPF
Sodium Picosulfate Elixir, NPF
Spermicidal contraceptives as listed below: Gygel® Contraceptive Jelly
Sterculia and Frangula Granules, NPF
Sterculia Granules, NPF
Sterculia and Frangula Granules, NPF
Titanium Ointment, BP
Water for Injections, BP
Zinc and Castor Oil Ointment, BP
Zinc Cream, BP
Zinc Ointment, BP
Zinc Oxide and Dimeticone Spray, NPF
Zinc Oxide Impregnated Medicated Bandage, NPF
Zinc Oxide Impregnated Medicated Stocking, NPF
Zinc Paste Bandage, BP 1993
Zinc Paste and Calamine Bandage
Zinc Paste and Ichthammol Bandage, BP 1993

Appliances and Reagents (including Wound Management Products)

Community Practitioner Nurse Prescribers in England, Wales and Northern Ireland can prescribe any appliance or reagent in the relevant Drug Tariff. In the Scottish Drug Tariff, Appliances and Reagents which may not be prescribed by Nurses are annotated Nx.

The Drug Tariffs can be accessed online at:
National Health Service Drug Tariff for England and Wales: www.ppa.org.uk/ppa/edt_intro.htm
Health and Personal Social Services for Northern Ireland Drug Tariff: www.centralservicesagency.com/display/ni_drug_tariff
Scottish Drug Tariff: www.isdscotland.org/isd/2245.html

Appliances (including Contraceptive Devices) as listed in Part IXA of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 3 (Appliances) and Part 2 (Dressings) of the Scottish Drug Tariff)
Incontinence Appliances as listed in Part IXB of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 5 of the Scottish Drug Tariff)
Stoma Appliances and Associated Products as listed in Part IXC of the Drug Tariff (Part III of the Northern Ireland Drug Tariff, Part 6 of the Scottish Drug Tariff)
Chemical Reagents as listed in Part IXR of the Drug Tariff (Part II of the Northern Ireland Drug Tariff, Part 9 of the Scottish Drug Tariff)

Details of NPF preparations

Preparations on the Nurse Prescribers’ Formulary which are not included in the BP or BPC are described as follows in the Nurse Prescribers’ Formulary.

Although brand names have sometimes been included for identification purposes, it is recommended that non-proprietary names should be used for prescribing medicinal preparations in the NPF except where a non-proprietary name is not available.

Arachis Oil Enema

archois oil 100%

Catheter Maintenance Solution, Chlorhexidine

(proprietary products: Uro-Tainer Chlorhexidine, Uroflex C), chlorhexidine 0.02%

Catheter Maintenance Solution, Sodium Chloride

(proprietary products: OptiFlo S, Uro-Tainer Sodium Chloride, Uriflex-S), sodium chloride 0.9%

Catheter Maintenance Solution, ‘Solution G’

(proproprietary products: OptiFlo G, Uro-Tainer Suby G, Uriflex G), citric acid 3.23%, magnesium oxide 0.38%, sodium bicarbonate 0.7%, disodium edetate 0.01%

Catheter Maintenance Solution, ‘Solution R’

(proproprietary products: OptiFlo R, Uro-Tainer Solution R, Uriflex R), citric acid 6%, gluconolactone 0.6%, magnesium carbonate 2.8%, disodium edetate 0.01%

Chlorhexidine gluconate alcoholic solutions

(proproprietary products: Hydrex Solution, Hydrex spray), chlorhexidine gluconate in alcoholic solution

Chlorhexidine gluconate aqueous solutions

(proproprietary product: Unisept) chlorhexidine gluconate in aqueous solution

1. Max. 96 tablets; max. pack size 32 tablets

2. Nurse Prescribers in Family Planning Clinics—where it is not appropriate for nurse prescribers in family planning clinics to prescribe contraceptive devices using form FP10F(PS) for FP10(PS and CN) and FP10(PN), or when available WP10(CN and WP10(PN, in Wales), they may prescribe using the same system as doctors in the clinic.
Co-danthramer Capsules
co-danthramer 25/200 (dantrone 25 mg, poloxamer '188' 200 mg)

Co-danthramer Capsules, Strong
co-danthramer 37.5/500 (dantrone 37.5 mg, poloxamer '188' 500 mg)

Co-danthramer Oral Suspension
(proprietary product: Codalax), co-danthramer 25/200 in 5 mL (dantrone 25 mg, poloxamer '188' 200 mg/5 mL)

Co-danthramer Oral Suspension, Strong
(proprietary product: Codalax Forte), co-danthramer 75/1000 in 5 mL (dantrone 75 mg, poloxamer '188' 1 g/5 mL)

Co-danthrusate Oral Suspension
(proprietary product: Normac), co-danthrusate 50/60 (dantrone 50 mg, docusate sodium 60 mg/5 mL)

Dimeticone Barrier creams
(proprietary products: Conotrine Cream, dimeticone '350' 22%, Siopel Barrier Cream, dimeticone '1000' 10%; Vasogen Barrier Cream, dimeticone 20%), dimeticone 10–22%

Dimeticone Lotion
(proprietary product: Hedin), dimeticone 4%

Docusate Enema
(proprietary product: Norgalax Micro-ema) docusate sodium 120 mg in 10 g

Folic Acid Oral Solution 400 micrograms/5 mL
(proprietary product: Folicare), folic acid 400 micrograms/5 mL

Liquid and White Soft Paraffin Ointment
liquid paraffin 50%, white soft paraffin 50%

Macrogol Oral Powder
macrogol '4000' (polyethylene glycol '4000') 10 g/sachet

Macrogol Oral Powder, Compound
macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 46.6 mg/sachet (proprietary products: Movicol, Movicol Plain, Laxido (orange or natural flavour)) or macrogol '3350' (polyethylene glycol '3350') 13.125 g, sodium bicarbonate 178.5 mg, sodium chloride 350.7 mg, potassium chloride 31.7 mg/sachet (proprietary product: Movicol Chocolate)

Macrogol Oral Powder, Compound, Half-strength
(proprietary product: Movicol-Half), macrogol '3350' (polyethylene glycol '3350') 6.563 g, sodium bicarbonate 89.3 g, sodium chloride 175.4 mg, potassium chloride 23.3 mg/sachet

Malathion alcoholic lotions
(proprietary product: Prioderm Lotion), malathion 0.5% in an alcoholic basis

Malathion aqueous lotions
(proprietary products: Derbac-M Liquid, Quellada M Liquid), malathion 0.5% in an aqueous basis

Mebendazole Oral Suspension
(proprietary product: Vermox), mebendazole 100 mg/5 mL

Mebendazole Tablets
(proprietary products: Ovek, Vermax), mebendazole 100 mg

Mouthwash Solution-tablets
consist of tablets which may contain antimicrobial, colouring and flavouring agents in a suitable soluble effervescent basis to make a mouthwash

Nicotine Inhalation Cartridge for Oromucosal Use
(proprietary products: Nicorette Inhalator), nicotine 10 mg

Nicotine Lozenge
nicotine (as bitartrate) 1 mg or 2 mg (proprietary product: Nicotinell Mint Lozenge) or nicotine (as polacrilex) 2 mg or 4 mg (proprietary product: Nicotinell Lozenges), or nicotine (as resinate complex) 1.5 mg (proprietary product: Nicopass Lozenge)

Nicotine Medicated Chewing Gum
(proprietary products: Nicorette Gum, Nicotinell Gum, NiQuitin Gum), nicotine 2 mg or 4 mg

Nicotine Nasal Spray
(proprietary product: Nicorette Nasal Spray), nicotine 500 micrograms/metered spray

Nicotine Sublingual Tablets
(proprietary product: Nicorette Microtab), nicotine (as a cyclodextrin complex) 2 mg

Nicotine Transdermal Patches
releasing in each 16 hours, nicotine approx. 5 mg, 10 mg, or 15 mg (proprietary product: Boots NicAssist Patch, Nicorette Patch) or releasing in each 24 hours nicotine approx. 7 mg, 14 mg, or 21 mg (proprietary products: Nicopatch, Nicotinell TTS, NiQuitin)

Permethrin Cream
(proprietary product: Lyclear Dermal Cream), permethrin 5%

Phenothrin Alcoholic Lotion
(proprietary product: Full Marks Lotion), phenothrin 0.2% in a basis containing isopropyl alcohol

Phenothrin Aqueous Lotion
(proprietary product: Full Marks Liquid), phenothrin 0.5% in an aqueous basis

Phosphate Suppositories
(proprietary product: Carbalax), sodium acid phosphate (anhydrous) 1.3 g, sodium bicarbonate 1.08 g

Piperazine and Senna Powder
(proprietary product: Pripsen Oral Powder), piperazine phosphate 4 g, sennosides 15.3 mg/sachet

Senna Oral Solution
(proprietary product: Senokot Syrup), sennosides 7.5 mg/5 mL

Senna and Ispaghula Granules
(proprietary product: Manevac Granules), senna fruit 12.4%, ispaghula 54.2%

1. For exemption, see p. 364
2. For use with inhalation mouthpiece; to be prescribed as either a starter pack (6 cartridges with inhalator device and holder) or refill pack (42 cartridges with inhalator device)
3. To be prescribed as either a starter pack (2 x 15-tablet discs with dispenser) or refill pack (7 x 15-tablet discs)
4. Prescriber should specify the brand to be dispensed
Sodium Citrate Compound Enema
(proprietary products: Micolette Micro-enema, Micralax Micro-enema, Relaxit Micro-enema), sodium citrate 450 mg with glycerol, sorbitol and an anionic surfactant

Sodium Picosulfate Capsules
(proprietary products: Dulco-lax Perles), sodium picosulfate 2.5 mg

Sodium Picosulfate Elixir
(proprietary products: Dulco-lax Liquid, Laxoberal), sodium picosulfate 5 mg/5 mL

Sterculia Granules
(proprietary product: Normacol Granules), sterculia 62%

Sterculia and Frangula Granules
(proprietary product: Normacol Plus Granules), sterculia 62%, frangula (standardised) 8%

Zinc Oxide and Dimeticone Spray
(proprietary product: Sprilon), dimeticone 1.04%, zinc oxide 12.5% in a pressurised aerosol unit

Zinc Oxide Impregnated Medicated Bandage
(proprietary product: Steripaste), sterile cotton bandage impregnated with paste containing zinc oxide 15%

Zinc Oxide Impregnated Medicated Stocking
(proprietary product: Zipzoc), sterile rayon stocking impregnated with ointment containing zinc oxide 20%

Nurse Independent Prescribing
Nurse Independent Prescribers (formerly known as Extended Formulary Nurse Prescribers) are able to prescribe any licensed medicine for any medical condition, including some Controlled Drugs (see below).

Nurse Independent Prescribers must work within their own level of professional competence and expertise. They are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved non-proprietary name.

Nurse Independent Prescribers are also able to prescribe independently the Controlled Drugs in the table below, solely for the medical conditions indicated.

Up-to-date information and guidance on nurse independent prescribing is available on the Department of Health website at www.dh.gov.uk/nonmedicalprescribing

Controlled drugs prescribable by Nurse Independent Prescribers solely for the medical conditions indicated

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Route of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buprenorphine</td>
<td>Transdermal use in palliative care</td>
<td>Transdermal</td>
</tr>
<tr>
<td>Chlordiazepoxide hydrochloride</td>
<td>Treatment of initial or acute withdrawal symptoms caused by the withdrawal of alcohol from persons habituated to it</td>
<td>Oral</td>
</tr>
<tr>
<td>Codeine phosphate</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Co-phenotrope</td>
<td></td>
<td>Oral, parenteral</td>
</tr>
<tr>
<td>Diamorphine hydrochloride</td>
<td>Use in palliative care, pain relief in respect of suspected myocardial infarction or for relief of acute or severe pain after trauma, including in either case postoperative pain relief</td>
<td>Oral, parenteral, rectal</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Use in palliative care, treatment of initial or acute withdrawal symptoms caused by the withdrawal of alcohol from persons habituated to it, tonic-clonic seizures</td>
<td>Oral, parenteral, rectal</td>
</tr>
<tr>
<td>Dihydrocodeine tartrate</td>
<td></td>
<td>Oral</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Transdermal use in palliative care</td>
<td>Transdermal</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Use in palliative care, tonic-clonic seizures</td>
<td>Oral, parenteral</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Use in palliative care, tonic-clonic seizures</td>
<td>Parenteral, buccal</td>
</tr>
<tr>
<td>Morphine hydrochloride</td>
<td>Use in palliative care, pain relief in respect of suspected myocardial infarction or for relief of acute or severe pain after trauma, including in either case postoperative pain relief</td>
<td>Rectal</td>
</tr>
<tr>
<td>Morphine sulphate</td>
<td>Use in palliative care, pain relief in respect of suspected myocardial infarction or for relief of acute or severe pain after trauma, including in either case postoperative pain relief</td>
<td>Oral, parenteral, rectal</td>
</tr>
<tr>
<td>Oxycodone hydrochloride</td>
<td>Use in palliative care</td>
<td>Oral, parenteral</td>
</tr>
</tbody>
</table>
A range of non-medical healthcare professionals are able to prescribe medicines for patients as either Independent or Supplementary Prescribers.

Independent prescribers are practitioners responsible and accountable for the assessment of patients with previously undiagnosed or diagnosed conditions and for decisions about the clinical management required, including prescribing. They are recommended to prescribe generically, except where this would not be clinically appropriate or where there is no approved non-proprietary name.

Supplementary prescribing is a partnership between an independent prescriber (a doctor or a dentist) and a supplementary prescriber to implement an agreed individual Clinical Management Plan with the patient’s agreement.

Independent and Supplementary Prescribers are identified by an annotation next to their name in the relevant professional register.

Up-to-date information and guidance on non-medical prescribing is available on the Department of Health website at www.dh.gov.uk/nonmedicalprescribing.

**Nurses**

For further information on Nurse Independent Prescribing, see Nurse Prescribers’ Formulary, p. 922.

**Optometrists**

Optometrist Independent Prescribers are able to prescribe any licensed medicine for ocular conditions affecting the eye and the tissues surrounding the eye, except Controlled Drugs or medicines for parenteral administration. Optometrist Independent Prescribers must work within their own level of professional competence and expertise.

**Pharmacists**

Pharmacist Independent Prescribers are able to prescribe any licensed medicine, except Controlled Drugs, for any medical condition. Pharmacist Independent Prescribers must work within their own level of professional competence and expertise.
Index of manufacturers

3M
3M Health Care Ltd
3M House
Morley St
Loughborough
Leics, LE11 1EP.
tel: (01509) 611611
fax: (01509) 237288

A&H
Allen & Hanburys Ltd
See GSK

A1 Pharmaceuticals
A1 Pharmaceuticals Plc
Units 20+21 Easter Park
Site 8A Beam Reach
Ferry Lane South, Rainham
Essex, RM13 9BP.
tel: (01708) 528 900
fax: (01708) 528 928
sales@a1plc.co.uk

Abbott
Abbott Laboratories Ltd
Abbott House
Norden Rd, Maidenhead
Berks, SL6 4XE.
tel: (01628) 773 355
fax: (01628) 644 185
ukmedinfo@abbott.com

ABT Healthcare
ABT Healthcare UK Ltd
Springwood Booths Hall
Booths Park
Chelford Rd
Knutsford, WA16 8QZ.
tel: (01565) 757783

Acorus
Acorus Therapeutics Ltd
Office Village
Chester Business Park
Chester, CH4 9QZ.
tel: (01244) 625 152
fax: (01244) 625 151
enquiries@acorus-therapeutics.com

Actavis
Actavis UK Ltd
Whiddon Valley
Barnstaple
Devon, EX31 8NS.
tel: (0870) 311 257
fax: (01271) 346 106
medinfo@actavis.co.uk

Actelion
Actelion Pharmaceuticals UK Ltd
BSI Building, 13th Floor
389 Chiswick High Rd, London, W4 4AL.
tel: (020) 8987 3333
fax: (020) 8987 3322

Activa
Activa Healthcare
1 Lancaster Park
Newborough Rd, Needwood
Burton-upon-Trent, Staffs, DE13 9PD.
tel: (0845) 060 6707
fax: (01283) 576 808
advice@activahealthcare.co.uk

Advancis
Advancis Medical Ltd
Lowmoor Business Park
Kirkby-in-Ashfield, Nottingham, NG17 7JZ.
tel: (01623) 751 500
fax: (0871) 284 8238
info@advancis.co.uk

Agepha
Agepha GmbH
9 High St
Woburn Sands, MK17 8RF.
tel: (01934) 835 694
fax: (01934) 876 790
info@agepha.com

Aguettant
Aguettant Ltd
The Barn
41a Main Rd, Cleeve
Somerset, BS49 4NZ.
tel: (01934) 835 694
fax: (01934) 876 790
info@aguettant.co.uk

Air Products
Air Products plc
Medical Group
2 Millennium Gate
Westmere Drive, Crewe
Cheshire, CW1 6AP.
tel: (0800) 373 580
fax: (0800) 214 709

Alan Pharmaceuticals
Alan Pharmaceuticals
2 Kingsgate Ave
London, N3 2BH.
tel: (020) 8346 4311
fax: (020) 8346 5218

Alcon
Alcon Laboratories (UK) Ltd
Pentagon Park
Boundary Way
Hemel Hempstead, Herts, HP2 7UD.
tel: (01442) 341 234
fax: (01442) 341 200

Alembic Pharmaceuticals
Alembic Pharmaceuticals Ltd
River Lane
Saltney, Chester, Cheshire, CH4 9QR.
tel: (01244) 680 147
fax: (01244) 680 155

Alexion
Alexion Pharma UK Ltd
3000 Cathedral Hill
Guildford
Surrey, GU2 7YB.
tel: (01483) 246 641
fax: (01483) 245 130
alexion.uk@alxn.com

Allergan
Allergan Ltd
1st Floor Marlow International
The Parkway
Marlow
Bucks, SL7 1YL.
tel: (01628) 494 026
fax: (01628) 494 449

Allergy
Allergy Therapeutics Ltd
Dominion Way
Worthing, West Sussex, BN14 8SA.
tel: (01903) 844 702
fax: (01903) 844 744
infoservices@allergytherapeutics.com

Alliance
Alliance Pharmaceuticals Ltd
Avonbridge House
2 Bath Rd
Chippingham, Wilts, SN15 2BB.
tel: (01249) 466 977
fax: (01249) 466 977
medinfo@alliancepharma.co.uk

Almirall
Almirall Ltd
4 The Square
Stockley Park
Uxbridge, UB11 1ET.
tel: (0800) 0087399
almirall@professionalinformation.co.uk

Alphapharma
See Actavis

Alphashow
Alphashow Ltd
10 South Rd
Amersham
Bucks, HP6 5LX.
tel: (01672) 515 614
info@alphashow.co.uk

Altacor
Altacor Ltd
St. John’s Innovation Centre
Cowley Road
Cambridge, CB4 0WS.
tel: (01223) 421 411
fax: (01223) 420 844
info@altacor-pharma.com

Altana
See Nycomed

Amdipharm
Amdipharm plc
Regency House
Miles Grey Rd
Basildon, Essex, SS14 3AF.
tel: (0870) 777 7675
fax: (0870) 777 7875
medinfo@amdipharm.com

Ampen
Ampen Ltd
240 Cambridge Science Park
Milton Rd, Cambridge, CB4 0WD.
tel: (01223) 420 305
fax: (01223) 426 314
infoline@uk.amgen.com
Anglian
Anglian Pharma Sales & Marketing
Titmore Court
Titmore Green
Little Wymondley, Hitchin
Herts, SG4 7XJ.
tel: (01438) 743 070
fax: (01438) 743 080
mail@anglianpharma.com

Anpharm
See Goldshield

Antigen
See Goldshield

APS
See TEVA UK

Archimedes
Archimedes Pharma UK Ltd
250 South Oak Way
Green Park
Reading
Berk, RG2 6UG.
tel: (0118) 931 5060
fax: (0118) 931 5065
medicalinformation@archimedespharma.com

Ardana
Ardana Bioscience Ltd
58 Queen St
Edinburgh, EH2 3NS.
tel: (0131) 226 8550
fax: (0131) 226 8551
info@ardana.co.uk

Ardern
Ardern Healthcare Ltd
Pipers Brook Farm
Eastham
Tenbury Wells, Worcs, WR15 8NP.
tel: (01584) 883 100
fax: (01584) 881 640
info@ardernhealthcare.com

Ark Therapeutics
Ark Therapeutics Group Plc
79 New Cavendish St
London, W1 1إل.
tel: (020) 7388 7722
fax: (020) 7388 7805
info@arktherapeutics.com

Ashbourne
Ashbourne Pharmaceuticals Ltd
The Drummonds
Spring Hill Office Park
Harborough Rd
Pitsford, Northampton, NN6 9AA.
tel: (01604) 883 100
fax: (01604) 881 640

AS Pharma
AS Pharma Ltd
PO Box 181
Polegate, East Sussex, BN26 6WD.
tel: (08700) 664 117
fax: (08700) 664 118
info@aspharma.co.uk

Astellas
Astellas Pharma Ltd
Lovett House, Lovett Rd
Staines, TW18 3AZ.
tel: (01784) 419 615
fax: (01784) 419 401

AstraZeneca
AstraZeneca UK Ltd
Horizon Place
600 Capability Green
Luton, Beds, LU1 3LU.
tel: 0800 7830 033
fax: (01582) 838 003
medical.informationuk@astrapzeneca.com

Auden Mckenzie
Auden Mckenzie (Pharma Division) Ltd
30 Stadium Business Centre
North End Rd
Wembley, Middx, HA9 0AT.
tel: (020) 8900 2122
fax: (020) 8903 9620

Aurum
Aurum Pharmaceuticals Ltd
Hubert Rd
Brentwood
Essex, CM14 4LZ.
tel: (01277) 266600
fax: (01277) 848 976
info@martindalepharma.co.uk

Aventis Pharma
See Sanofi-Aventis

Ayrton Saunders
Ayrton Saunders Ltd
Ayrton House
Commerce Way
Parliament Business Park
Liverpool, Merseyside, L8 7BA.
tel: (0151) 709 2074
fax: (0151) 709 7336
info@ayrtons.com

Bard
Bard Ltd
Forest House
Brighton Rd
Crawley, West Sussex, RH11 9BP.
tel: (01293) 527 888
fax: (01293) 552 428

Basilea
Basilea Pharmaceuticals Ltd
14/16 Frederick Sanger Road
The Surrey Research Park
Guildford
Surrey, GU2 7YD.
tel: (01483) 790 023
fax: (01483) 505 345
ukmedinfo@basilea.com

Bausch & Lomb
Bausch & Lomb UK Ltd
106 London Rd
Kingston-upon-Thames
Surrey, KT2 6TN.
tel: (020) 8781 2900
fax: (020) 8781 2901

Baxter
Baxter Healthcare Ltd
Wallingford Rd
Compton
Newbury
Berk, RG20 7GW.
tel: (01635) 206 345
fax: (01635) 206 071
surecall@baxter.com

Bayer
Bayer plc
Bayer Schering Pharma
Bayer House, Strawberry Hill
Newbury, Berks, RG14 1JA.
tel: (01635) 563 000
fax: (01635) 563 393
medical.science@bayer.co.uk

Bayer Consumer Care
See Bayer

Bayer Diabetes Care
See Bayer

Bayer Diagnostics
See Bayer

BBI Healthcare
BBI Healthcare
Unit A
Kestrel Way
Garnpoch Industrial Estate
Gorseinon, Swansea, SA4 5WN.
tel: (01792) 229 333
fax: (01792) 897 311
info@bbihealthcare.com

Beacon
Beacon Pharmaceuticals Ltd
85 High St
Tunbridge Wells, TN1 1YG.
tel: (01892) 600 930
fax: (01892) 600 937
info@beaconpharma.co.uk

Beckton Dickinson
Becton Dickinson UK Ltd
The Danby Building
Edmund Halley
Oxford Science Park
Oxford, Oxon, OX4 4DQ.
tel: (01865) 781 510
fax: (01865) 781 551

Beiersdorf
Beiersdorf UK Ltd
2010 Solihull Parkway
Birmingham Business Park
Birmingham, B37 7YS.
tel: (0121) 329 8800
fax: (0121) 329 6801

Bell and Croyden
John Bell and Croyden
50-54 Wigmore St
London, W1U 2AJ.
tel: (020) 7935 5555
fax: (020) 7935 9605
jbc@johnbellcroyden.co.uk

Berk
See TEVA UK

BNF 57

BHR

BHR Pharmaceuticals Ltd
41 Centenary Business Centre
Hammond Close
Aitleborough Fields, Nuneaton
Warwickshire, CV11 6RY.
tel: (024) 7635 3742
fax: (024) 7632 7812
info@bhr.co.uk

Bioacellerate
Bioacellerate Ltd
11-12 Charles II St
Savanah House
London, SW1Y 4QU.
tel: (020) 7451 2488
fax: (020) 7451 2469
info@bioacellerate.com
<table>
<thead>
<tr>
<th>Bioenvision</th>
<th>Bioenvision Ltd</th>
<th>10 Lockside Place</th>
<th>Edinburgh Park</th>
<th>Edinburgh, EH12 9RG.</th>
<th>tel: (0131) 248 3555</th>
<th>fax: (0131) 2483300</th>
<th><a href="mailto:info@bioenvision.com">info@bioenvision.com</a></th>
</tr>
</thead>
<tbody>
<tr>
<td>Biogen</td>
<td>Biogen Idc Ltd</td>
<td>Innovation House</td>
<td>70 Norden Rd</td>
<td>Maidenhead</td>
<td>Berks, SL6 4AY.</td>
<td>tel: (0800) 008 7401</td>
<td>fax: (01628) 501 010</td>
</tr>
<tr>
<td>Biocut</td>
<td>Biocut Ltd</td>
<td>75-100 Lockside Place</td>
<td>Edinburgh Park</td>
<td>Edinburgh, EH12 9RG.</td>
<td>tel: (0131) 248 3555</td>
<td>fax: (0131) 2483300</td>
<td><a href="mailto:info@bioenvision.com">info@bioenvision.com</a></td>
</tr>
<tr>
<td>Biocut</td>
<td>Biocut Ltd</td>
<td>75-100 Lockside Place</td>
<td>Edinburgh Park</td>
<td>Edinburgh, EH12 9RG.</td>
<td>tel: (0131) 248 3555</td>
<td>fax: (0131) 2483300</td>
<td><a href="mailto:info@bioenvision.com">info@bioenvision.com</a></td>
</tr>
<tr>
<td>Biocut</td>
<td>Biocut Ltd</td>
<td>75-100 Lockside Place</td>
<td>Edinburgh Park</td>
<td>Edinburgh, EH12 9RG.</td>
<td>tel: (0131) 248 3555</td>
<td>fax: (0131) 2483300</td>
<td><a href="mailto:info@bioenvision.com">info@bioenvision.com</a></td>
</tr>
<tr>
<td>Bioenvision</td>
<td>Bioenvision Ltd</td>
<td>10 Lockside Place</td>
<td>Edinburgh Park</td>
<td>Edinburgh, EH12 9RG.</td>
<td>tel: (0131) 248 3555</td>
<td>fax: (0131) 2483300</td>
<td><a href="mailto:info@bioenvision.com">info@bioenvision.com</a></td>
</tr>
<tr>
<td>Boehringer Ingelheim</td>
<td>Boehringer Ingelheim Ltd</td>
<td>Ellesfield Ave</td>
<td>Bracknell</td>
<td>Berks, RG12 8YS.</td>
<td>tel: (01344) 424 600</td>
<td>fax: (01344) 741 444</td>
<td><a href="mailto:medicalinfo@bra.boehringer-ingelheim.com">medicalinfo@bra.boehringer-ingelheim.com</a></td>
</tr>
<tr>
<td>Boots</td>
<td>Boots The Chemists</td>
<td>Medical Services</td>
<td>Thane Rd</td>
<td>D90 East S10</td>
<td>Nottingham, NG90 1BS.</td>
<td>tel: (0115) 959 5165</td>
<td>fax: (0115) 959 2565</td>
</tr>
<tr>
<td>Borg</td>
<td>Borg Medicare</td>
<td>PO Box 99</td>
<td>Hitchin</td>
<td>Herts, SG5 2GF</td>
<td>tel: (01462) 442 993</td>
<td>fax: (01462) 441 293</td>
<td></td>
</tr>
<tr>
<td>BPC 100</td>
<td>The Bolton Pharmaceutical 100 Ltd</td>
<td>2 Chapel Drive</td>
<td>Ambrosden</td>
<td>Oxfordshire, OX25 2RS.</td>
<td>tel: (0845) 602 3907</td>
<td>fax: (01462) 442 993</td>
<td><a href="mailto:info@bpc100.com">info@bpc100.com</a></td>
</tr>
<tr>
<td>BPL</td>
<td>Bio Products Laboratory</td>
<td>Dagger Lane</td>
<td>Elstree, Herts, WD6 3BX.</td>
<td>tel: (020) 8258 2200</td>
<td>fax: (020) 8258 2601</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Braun</td>
<td>B Braun (Medical) Ltd</td>
<td>Brookdale Rd</td>
<td>Thornciffe Park Estate</td>
<td>Chapeltown, Sheffield, S35 2FW.</td>
<td>tel: (0114) 225 9000</td>
<td>fax: (0114) 225 9111</td>
<td><a href="mailto:info@bbraun.com">info@bbraun.com</a></td>
</tr>
<tr>
<td>Braun Biotrol</td>
<td>See Braun</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bray</td>
<td>Bray Health &amp; Leisure</td>
<td>1 Regal Way</td>
<td>Faringdon</td>
<td>Oxon, SN7 7BX.</td>
<td>tel: (01367) 240 736</td>
<td>fax: (01367) 242 625</td>
<td><a href="mailto:info@bray.co.uk">info@bray.co.uk</a></td>
</tr>
<tr>
<td>Bristol-Myers Squibb</td>
<td>Bristol-Myers Squibb Pharmaceuticals Ltd</td>
<td>Uxbridge Business Park</td>
<td>Sanderson Rd</td>
<td>Uxbridge</td>
<td>Middx, UB8 1DH.</td>
<td>tel: (01895) 523 000</td>
<td>fax: (01895) 523 010</td>
</tr>
<tr>
<td>Britannia</td>
<td>Britannia Pharmaceuticals Ltd</td>
<td>41-51 Brighton Rd</td>
<td>Redhill</td>
<td>Surrey, RH1 6YS.</td>
<td>tel: (01737) 773 741</td>
<td>fax: (01737) 762 672</td>
<td><a href="mailto:medicalservices@britannia.pharm.com">medicalservices@britannia.pharm.com</a></td>
</tr>
<tr>
<td>BR Pharma</td>
<td>BR Pharma Ltd</td>
<td>Unit 7, Capital Business Park</td>
<td>Manor Way</td>
<td>Borehamwood</td>
<td>Herts, WD6 1GW.</td>
<td>tel: (020) 8238 6770</td>
<td>fax: (020) 8238 6786</td>
</tr>
<tr>
<td>BSIA</td>
<td>See Torbet</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSN Medical</td>
<td>BSN Medical Ltd</td>
<td>PO Box 258</td>
<td>Willerby</td>
<td>Hull, HU10 6WT.</td>
<td>tel: (0845) 1223 600</td>
<td>fax: (0845) 1223 666</td>
<td></td>
</tr>
<tr>
<td>Cambridge</td>
<td>Cambridge Laboratories</td>
<td>Deltic House, Kingfisher Way</td>
<td>Silverlink Business Park, Wallsend Tyne &amp; Wear, NE28 9NX.</td>
<td>tel: (0191) 296 9300</td>
<td>fax: (0191) 296 9368</td>
<td><a href="mailto:customer.services@camb-labs.com">customer.services@camb-labs.com</a></td>
<td></td>
</tr>
<tr>
<td>Castlemead</td>
<td>See Sanofi-Aventis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C D Medical</td>
<td>C D Medical Ltd</td>
<td>Aston Grange</td>
<td>Oker, Matlock, DE4 2JJ.</td>
<td>tel: (01629) 733 860</td>
<td>fax: (01629) 733 414</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Celgene</td>
<td>Celgene Ltd</td>
<td>Morgan House</td>
<td>Madeira Walk</td>
<td>Windsor</td>
<td>Berks, SL4 1EP.</td>
<td>tel: (08448) 010 045</td>
<td>fax: (08448) 010 046</td>
</tr>
<tr>
<td>Centrapharm</td>
<td>See Derma UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cephalon</td>
<td>Cephalon Ltd</td>
<td>1 Albany Place</td>
<td>Hyde Way</td>
<td>Welwyn Garden City</td>
<td>Herts, AL7 3BT.</td>
<td>tel: (0800) 783 4869</td>
<td>fax: (01483) 765 008</td>
</tr>
<tr>
<td>Company</td>
<td>Address</td>
<td>Contact Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceuta</td>
<td>Ceuta Healthcare Ltd, Hill House, 41 Richmond Hill, Bournemouth, Dorset, BH2 6HS</td>
<td>tel: (01202) 780 558, fax: (01202) 780 559</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chatten UK</td>
<td>Chatten UK Ltd, Quarry House, Ringway Centre, Edison Rd, Basingstoke, RG24 6YH</td>
<td>tel: (01256) 844 144, fax: (01256) 844 145</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chauvin</td>
<td>See Bausch &amp; Lomb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chefaro UK</td>
<td>Chefaro UK Ltd, Unit 1, Tower Close, St. Peter’s Industrial Park, Huntingdon</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemical Search</td>
<td>Chemical Search International Ltd, 29th floor, 1 Canada Square, Canary Wharf, London, E14 5DY</td>
<td>tel: (020) 7712 1758, fax: (020) 7712 1759</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chirin</td>
<td>See Novartis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chiron Vaccines</td>
<td>See Novartis Vaccines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHS</td>
<td>Cambridge Healthcare Supplies Ltd, 14D Wendover Rd, Rackheath Industrial Estate, Rackheath</td>
<td>tel: (01603) 735 200, fax: (01603) 735 217</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chugai</td>
<td>Chugai Pharma UK Ltd, Mulliner House, Flanders Rd, Turnham Green, London, W4 1NN</td>
<td>tel: (020) 8987 5680, fax: (020) 8987 5661</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clement Clarke</td>
<td>Clement Clarke International Ltd, Edinburgh Way, Harlow, Essex, CM20 2TT</td>
<td>tel: (01279) 414 969, fax: (01279) 456 304</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinimed</td>
<td>Clinimed Ltd, Cavel House, Knaves Beech Way, Loudwater, High Wycombe, Bucks, HP10 9QY</td>
<td>tel: (01628) 850 100, fax: (01628) 850 331</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinisupplies</td>
<td>Clinisupplies Ltd, 9 Crystal Way, Elimgrove Rd, Harrow, Middx, HA1 2HP</td>
<td>tel: (020) 8863 4168, fax: (020) 8426 0768</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clonmel</td>
<td>Clonmel Healthcare Ltd, Waterford Rd, Clonmel, Co. Tipperary, Ireland</td>
<td>tel: (00353) 52 77777, fax: (00353) 52 77799</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colgate-Palmolive</td>
<td>Colgate-Palmolive Ltd, Guildford Business Park, Middleton Rd, Guildford</td>
<td>tel: (01483) 302 222, fax: (01483) 303 003</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coloplast</td>
<td>Coloplast Ltd, Peterborough Business Park, Peterborough, PE2 6FX</td>
<td>tel: (01733) 392 000, fax: (01733) 233 348</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Community</td>
<td>Community Foods Ltd, Micross, Brent Terrace, London, NW2 1LT</td>
<td>tel: (020) 8450 9411, fax: (020) 8208 1803</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Concord</td>
<td>See Archimedes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ConvaTec</td>
<td>ConvaTec Ltd, Harrington House, Milton Rd, Ickenham, Middx, UB10 8PU</td>
<td>tel: (01895) 628 400, fax: (01895) 628 456</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coviden</td>
<td>Coviden UK Commercial Ltd, 154 Fareham Rd, Gosport, Hants, PO13 0AS</td>
<td>tel: (01329) 224 226, fax: (01329) 224 334</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cow &amp; Gate</td>
<td>See Nutricia Clinical</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crawford</td>
<td>Crawford Pharmaceuticals, Cheshire House, 164 Main Rd, Goostrey, Cheshire, CW4 8NP</td>
<td>tel: (01477) 537 596, fax: (01477) 534 262</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crookes</td>
<td>See Reckitt Benckiser</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSL Behring</td>
<td>CSL Behring UK Ltd, Hayworth House, Market Place, Haywards Heath, West Sussex, RH16 1DB</td>
<td>tel: (01444) 447 400, fax: (01444) 447 403</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daiichi Sankyo</td>
<td>Daiichi Sankyo UK Ltd, Chiltern Place, Chalfont Park, Gerrards Cross, SL9 0BG</td>
<td>tel: (01753) 893 600, fax: (01753) 893 694</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danetre</td>
<td>Danetre Health Products Ltd, Office 4, Broad March, Long March Industrial Estate, Daventry</td>
<td>tel: (01327) 310 909, fax: (01327) 310 311</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DDD</td>
<td>DDD Ltd, 94 Rickmansworth Rd, Watford, Herts, WD18 7JL</td>
<td>tel: (01923) 229 251, fax: (01923) 220 728</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Denfleet</td>
<td>Denfleet Pharmaceuticals Ltd, 260 Centennial Park, Elstree Hill South, Elstree, Herts, WD6 3SR</td>
<td>tel: (020) 8236 0000, fax: (020) 8236 3501</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dental Health</td>
<td>Dental Health Products Ltd, Maidstone, Kent, ME15 9QS</td>
<td>tel: (01622) 749 222, fax: (01622) 744 672</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company Name</td>
<td>Address</td>
<td>Phone</td>
<td>Fax</td>
<td>Email</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>-------</td>
<td>-----</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dentsply</td>
<td>Dentsply Ltd, Hamm Moor Lane, Addlestone, Weybridge, Surrey, KT15 2SE.</td>
<td>(01932) 837 279</td>
<td>(01932) 858 970</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Dermal Laboratories Ltd, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR.</td>
<td>(01462) 458 866</td>
<td>(01462) 420 565</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derma UK</td>
<td>Derma UK Ltd, ARC Progress Mill Lane, Stotfold, Beds, SG5 4NY.</td>
<td>(01462) 733 500</td>
<td>(01462) 733 600</td>
<td><a href="mailto:info@dermauk.co.uk">info@dermauk.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Vilbiss</td>
<td>De Vilbiss Health Care UK Ltd, High Street, Wollaston, West Midlands, DY8 4PS.</td>
<td>(01384) 446 688</td>
<td>(01384) 446 699</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Witt</td>
<td>E C De Witt &amp; Co Ltd, Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire, WA4 4HS.</td>
<td>(01928) 756 800</td>
<td>(01928) 756 818</td>
<td><a href="mailto:info@ecdewitt.com">info@ecdewitt.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexcel</td>
<td>Dexcel-Pharma Ltd, 1 Cottesbrooke Park, Heartlands Business Park, Daventry, Northamptonshire, NN11 8YL.</td>
<td>(01327) 312 266</td>
<td>(01327) 312 262</td>
<td><a href="mailto:office@dexcelpharma.co.uk">office@dexcelpharma.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHP Healthcare</td>
<td>DHP Healthcare Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QZ.</td>
<td>(01622) 749 222</td>
<td>(01622) 743 816</td>
<td><a href="mailto:sales@dphhealthcare.co.uk">sales@dphhealthcare.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diatos</td>
<td>Diatos SA, Immeuble Paris BioPark - 2 etage, 11 Rue Watt, 75013 Paris, France</td>
<td>(00800) 3286 6966</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethaid</td>
<td>Dimethaid International c/o Benoliel Partners, Linden House, Ewelme, Oxfordshire, OX10 6HQ.</td>
<td>(01491) 825 016</td>
<td>(01491) 834 592</td>
<td><a href="mailto:medinfo@dimethaid.com">medinfo@dimethaid.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Falk</td>
<td>Dr Falk Pharma UK Ltd, Bourne End Business, Cores End Rd, Bourne End, Bucks, SL8 5AS.</td>
<td>(01628) 536 600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durbin</td>
<td>Durbin plc, 180 Northolt Rd, South Harrow, Middx, HA2 0LT.</td>
<td>(020) 8869 6500</td>
<td>(020) 8869 6565</td>
<td><a href="mailto:info@durbin.co.uk">info@durbin.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Dermal Laboratories Ltd, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR.</td>
<td>(01462) 458 866</td>
<td>(01462) 420 565</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derma UK</td>
<td>Derma UK Ltd, ARC Progress Mill Lane, Stotfold, Beds, SG5 4NY.</td>
<td>(01462) 733 500</td>
<td>(01462) 733 600</td>
<td><a href="mailto:info@dermauk.co.uk">info@dermauk.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Vilbiss</td>
<td>De Vilbiss Health Care UK Ltd, High Street, Wollaston, West Midlands, DY8 4PS.</td>
<td>(01384) 446 688</td>
<td>(01384) 446 699</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Witt</td>
<td>E C De Witt &amp; Co Ltd, Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire, WA4 4HS.</td>
<td>(01928) 756 800</td>
<td>(01928) 756 818</td>
<td><a href="mailto:info@ecdewitt.com">info@ecdewitt.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexcel</td>
<td>Dexcel-Pharma Ltd, 1 Cottesbrooke Park, Heartlands Business Park, Daventry, Northamptonshire, NN11 8YL.</td>
<td>(01327) 312 266</td>
<td>(01327) 312 262</td>
<td><a href="mailto:office@dexcelpharma.co.uk">office@dexcelpharma.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHP Healthcare</td>
<td>DHP Healthcare Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QZ.</td>
<td>(01622) 749 222</td>
<td>(01622) 743 816</td>
<td><a href="mailto:sales@dphhealthcare.co.uk">sales@dphhealthcare.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diatos</td>
<td>Diatos SA, Immeuble Paris BioPark - 2 etage, 11 Rue Watt, 75013 Paris, France</td>
<td>(00800) 3286 6966</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethaid</td>
<td>Dimethaid International c/o Benoliel Partners, Linden House, Ewelme, Oxfordshire, OX10 6HQ.</td>
<td>(01491) 825 016</td>
<td>(01491) 834 592</td>
<td><a href="mailto:medinfo@dimethaid.com">medinfo@dimethaid.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dr Falk</td>
<td>Dr Falk Pharma UK Ltd, Bourne End Business, Cores End Rd, Bourne End, Bucks, SL8 5AS.</td>
<td>(01628) 536 600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Durbin</td>
<td>Durbin plc, 180 Northolt Rd, South Harrow, Middx, HA2 0LT.</td>
<td>(020) 8869 6500</td>
<td>(020) 8869 6565</td>
<td><a href="mailto:info@durbin.co.uk">info@durbin.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Dermal Laboratories Ltd, Tatmore Place, Gosmore, Hitchin, Herts, SG4 7QR.</td>
<td>(01462) 458 866</td>
<td>(01462) 420 565</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Derma UK</td>
<td>Derma UK Ltd, ARC Progress Mill Lane, Stotfold, Beds, SG5 4NY.</td>
<td>(01462) 733 500</td>
<td>(01462) 733 600</td>
<td><a href="mailto:info@dermauk.co.uk">info@dermauk.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Vilbiss</td>
<td>De Vilbiss Health Care UK Ltd, High Street, Wollaston, West Midlands, DY8 4PS.</td>
<td>(01384) 446 688</td>
<td>(01384) 446 699</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>De Witt</td>
<td>E C De Witt &amp; Co Ltd, Aegon House, Daresbury Park, Daresbury, Warrington, Cheshire, WA4 4HS.</td>
<td>(01928) 756 800</td>
<td>(01928) 756 818</td>
<td><a href="mailto:info@ecdewitt.com">info@ecdewitt.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexcel</td>
<td>Dexcel-Pharma Ltd, 1 Cottesbrooke Park, Heartlands Business Park, Daventry, Northamptonshire, NN11 8YL.</td>
<td>(01327) 312 266</td>
<td>(01327) 312 262</td>
<td><a href="mailto:office@dexcelpharma.co.uk">office@dexcelpharma.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHP Healthcare</td>
<td>DHP Healthcare Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QZ.</td>
<td>(01622) 749 222</td>
<td>(01622) 743 816</td>
<td><a href="mailto:sales@dphhealthcare.co.uk">sales@dphhealthcare.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diatos</td>
<td>Diatos SA, Immeuble Paris BioPark - 2 etage, 11 Rue Watt, 75013 Paris, France</td>
<td>(00800) 3286 6966</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dimethaid</td>
<td>Dimethaid International c/o Benoliel Partners, Linden House, Ewelme, Oxfordshire, OX10 6HQ.</td>
<td>(01491) 825 016</td>
<td>(01491) 834 592</td>
<td><a href="mailto:medinfo@dimethaid.com">medinfo@dimethaid.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company Name</td>
<td>Address</td>
<td>Telephone</td>
<td>Fax Number</td>
<td>Email</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------------------------------------------</td>
<td>----------------------------------------------</td>
<td>-----------------</td>
<td>-----------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gluten Free Foods Ltd</td>
<td>Unit 270 Centennial Park, Centennial Ave, Elstree, Borehamwood, Herts, WD6 3SS.</td>
<td>Tel: (020) 8953 4444</td>
<td>Fax: (020) 8953 8285</td>
<td><a href="mailto:info@glutenfree-foods.co.uk">info@glutenfree-foods.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Goldshield</td>
<td>Goldshield Pharmaceuticals Ltd, NLA Tower 12-16 Addiscombe Rd, Croydon, CR0 0XT.</td>
<td>Tel: (020) 8649 8500</td>
<td>Fax: (020) 8686 0897</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP Pharma</td>
<td>See Derma UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grifols</td>
<td>Grifols UK Ltd, Byron House, Cambridge Business Park, Cowley Road, Cambridge, CB4 0AZ.</td>
<td>Tel: (0223) 395 700</td>
<td>Fax: (0223) 395 766</td>
<td><a href="mailto:reception.uk@grifols.com">reception.uk@grifols.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grünenthal</td>
<td>Grünenthal Ltd, 2 Beacon Heights Business Park, Ibstone Rd, Stonkenchurch, Bucks, HP14 3XR.</td>
<td>Tel: (0870) 351 8960</td>
<td>Fax: (01494) 486 298</td>
<td><a href="mailto:medicalinformationuk@gruenenthal.com">medicalinformationuk@gruenenthal.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline, Stockley Park West, Uxbridge, Middx, UB4 8AL.</td>
<td>Tel: 0800 221 441</td>
<td>Fax: (020) 8990 4328</td>
<td><a href="mailto:customercontactuk@gsk.com">customercontactuk@gsk.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSK Consumer Healthcare</td>
<td>GlaxoSmithKline Consumer Healthcare, GSK House, 980 Great West Rd, Brentford, Middx, TW8 9GS.</td>
<td>Tel: (0500) 888 878</td>
<td>Fax: (020) 8047 6860</td>
<td><a href="mailto:customer.relations@gsk.com">customer.relations@gsk.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H&amp;R Healthcare Ltd</td>
<td>H&amp;R Healthcare Ltd, Melton Court, Gibson Lane, Melton, East Yorkshire, HU14 3HH.</td>
<td>Tel: (01482) 638 491</td>
<td>Fax: (01482) 638 485</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hameln</td>
<td>Hameln Pharmaceuticals Ltd, Nexus, Gloucester Business Park, Gloucester, GL3 4AG.</td>
<td>Tel: (01452) 621 661</td>
<td>Fax: (01452) 632 732</td>
<td><a href="mailto:enquiries@hameln.co.uk">enquiries@hameln.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartmann</td>
<td>Paul Hartmann Ltd, Unit P2, Parklands, Heywood Distribution Park, Pilsworth Rd, Heywood, Lancs, OL10 2TT.</td>
<td>Tel: (01706) 363 200</td>
<td>Fax: (01706) 363 201</td>
<td><a href="mailto:info@uk.hartmann.info">info@uk.hartmann.info</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthcare Logistics</td>
<td>See Movianto</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heinz</td>
<td>H. J. Heinz Company Ltd, South Building, Hayes Park, Hayes, UB4 8AL.</td>
<td>Tel: (020) 8573 7757</td>
<td>Fax: (020) 8848 2325</td>
<td><a href="mailto:Farleys_Heinz@Heinz.co.uk">Farleys_Heinz@Heinz.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Henleys</td>
<td>Henleys Medical Supplies Ltd, Brownfields, Welwyn Garden City, Herts, AL7 1AN.</td>
<td>Tel: (01707) 333 164</td>
<td>Fax: (01707) 334 795</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hilcross</td>
<td>AAH Pharmaceuticals Ltd, Walsgrave Triangle, Coventry, CV2 2TX.</td>
<td>Tel: (024) 7643 2000</td>
<td>Fax: (024) 7643 2001</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HK Pharma</td>
<td>HK Pharma Ltd, PO Box 105, Hitchin, Herts, SG5 2GG.</td>
<td>Tel: (01462) 433 993</td>
<td>Fax: (01462) 450 755</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hochtsthan Monro Rossell</td>
<td>See Sanofi-Aventis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Home Diagnostics</td>
<td>Home Diagnostics (UK) Ltd, 25 Barnes Wallis Road, Segensworth East, Fareham, Hants, PO15 5TT.</td>
<td>Tel: (01489) 569 469</td>
<td>Fax: (01489) 569 424</td>
<td><a href="mailto:info@homediagnostics-uk.com">info@homediagnostics-uk.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospira</td>
<td>Hospira UK Ltd, PO Box 122, Richmond, YO10 5DH.</td>
<td>Tel: (01904) 435 228</td>
<td>Fax: (01904) 435 229</td>
<td><a href="mailto:paul@infast.co.uk">paul@infast.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Innovative Solutions UK Ltd</td>
<td>Unit 28, Transpennine Industrial Estate, Garsorey Way, Queensway, Rochdale, Lancs, OL11 2QR.</td>
<td>Tel: (01706) 7467 13</td>
<td><a href="mailto:enquiries@innovative-solutions.org.uk">enquiries@innovative-solutions.org.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insaense</td>
<td>Insaense Ltd, Colworth Science Park, Sharnbrook, Bedford, MK44 1LQ.</td>
<td>Tel: (01234) 782 870</td>
<td>Fax: (01234) 783 444</td>
<td><a href="mailto:enquiries@insaense.co.uk">enquiries@insaense.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insight</td>
<td>Insight Medical Products Ltd, Units 1-4 Silk Mill Studios, 2 Charlton Road, Tidbury, GL5 8DY.</td>
<td>Tel: (01666) 500 055</td>
<td>Fax: (01666) 500 115</td>
<td><a href="mailto:info@insightmedical.net">info@insightmedical.net</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapharm</td>
<td>Intrapharm Laboratories Ltd, 60 Boughton Lane, Maidstone, Kent, ME15 9QS.</td>
<td>Tel: (01622) 749 222</td>
<td>Fax: (01622) 744 672</td>
<td><a href="mailto:sales@intraphamlabs.com">sales@intraphamlabs.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Address</td>
<td>Contact Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------</td>
<td>---------</td>
<td>---------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ipsen</td>
<td>Ipsen Ltd 190 Bath Rd Slough Berks, SL1 3XE. tel: (01753) 627 777 fax: (01753) 627 778 <a href="mailto:medical.information.uk@ipsen.com">medical.information.uk@ipsen.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IS Pharmaceuticals</td>
<td>IS Pharmaceuticals Ltd Office Village Chester Business Park Chester, CH4 9QQ. tel: (01244) 625 152 fax: (01244) 625 151 <a href="mailto:enquiries@ispharma.plc.uk">enquiries@ispharma.plc.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IVAX</td>
<td>See TEVA UK</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J&amp;J</td>
<td>Johnson &amp; Johnson Ltd Foundation Park Roxborough Way Maidenhead Berks, SL6 3UG. tel: (01628) 822 222 fax: (01628) 821 222</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J&amp;J Medical</td>
<td>Johnson &amp; Johnson Medical Coronation Rd Ascot Berks, SL5 9EY. tel: (01344) 871 000 fax: (01344) 872 599</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Janssen-Cilag</td>
<td>Janssen-Cilag Ltd 50-100 Holmers Farm Way High Wycombe Bucks, HP12 4EG. tel: (01494) 567 444 fax: (01494) 567 568</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Javelin Pharmaceuticals</td>
<td>Javelin Pharmaceuticals UK Ltd Compass House, Vision Park Chivers Way Histon Cambs, CB4 9AD. tel: (0800) 066 5446 fax: (01223) 527 800</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jerini</td>
<td>Jerini AG Invalidenstrasse 130 10115 Berlin Germany tel: (08000) 7020 7020</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JIC</td>
<td>See Sanofi-Aventis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>JLB</td>
<td>B. Braun JLB Ltd Unit 2A St Columb Industrial Estate St Columb Major Cornwall, TR9 6SF. tel: (01637) 880 065 fax: (01637) 881 549</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jobskin</td>
<td>Jobskin Ltd Unit 13 Harrington Mill Leopold St Long Eaton Nottingham, NG10 4GQ. tel: (0115) 973 4300 fax: (0115) 973 3902 <a href="mailto:dw@jobskin.co.uk">dw@jobskin.co.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Juvela</td>
<td>Juvela (Hero UK) Ltd 19 De-Havilland Dr Liverpool, L24 8RN. tel: (0151) 432 5300 fax: (0151) 432 5335 <a href="mailto:info@juvela.co.uk">info@juvela.co.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K/L</td>
<td>K/L Pharmaceuticals Ltd 21 Macadam Place South Newmoor Irvine Ayrshire, KA11 4HP. tel: (01294) 215 951 fax: (01294) 221 600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KCI Medical</td>
<td>KCI Medical Ltd Langford Business Park Langford Locks Kidlington Oxon, OX5 1GF. tel: (01865) 840 600 fax: (01865) 840 626</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kestrel</td>
<td>Kestrel Ltd Ashfield House Resolution Rd Ashby de la Zouch Leics, LE65 1HW. tel: (01530) 562 301 fax: (01530) 562 430 <a href="mailto:kestrel@ventiv.co.uk">kestrel@ventiv.co.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kestrel Ophthalmics</td>
<td>Kestrel Ophthalmics Ltd Kestrel House 7 Moor Rd Broadstone Dorset, BH18 8AZ. tel: (01202) 658 444 fax: (01202) 659 599 <a href="mailto:info@kestrelophthalmics.co.uk">info@kestrelophthalmics.co.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>King</td>
<td>King Pharmaceuticals Ltd 2nd Floor, The Maltings Bridge St Hitchin Herts, SG5 2DE. tel: (01462) 434 366 fax: (01462) 450 755</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KoGEN</td>
<td>KoGEN Ltd Seago Industrial Estate Craigavon, BT63 5UA. tel: (028) 383 33933 fax: (028) 383 33665 <a href="mailto:info@kogen.co.uk">info@kogen.co.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>KoRa</td>
<td>KoRa Healthcare Ltd Frans Maas House Swords Business Park, Swords Co. Dublin Ireland tel: (00353) 1890 0406 fax: (00353) 1890 3016 <a href="mailto:kora@ireland.com">kora@ireland.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kyowa Hakko</td>
<td>Kyowa Hakko UK Ltd 258 Bath Rd Slough Berks, SL1 4DX. tel: (01753) 566 020 fax: (01753) 566 030</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lab</td>
<td>Laboratories for Applied Biology 91 Amburk Park London, N16 5DR. tel: (020) 8800 2252 fax: (020) 8809 6884 <a href="mailto:enquiries@cerumol.com">enquiries@cerumol.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Labopharm</td>
<td>Labopharm Europe Ltd Unit 5, The Seapoint Building 44-45 Clonarf Road Dublin 3 Ireland tel: (0800) 678 3765 (UK only) or (01908) 542 374 <a href="mailto:labopharm.uk@canreginc.com">labopharm.uk@canreginc.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lantar</td>
<td>Lantar UK Ltd 73 St Helens Rd Bolton Lancs, BL3 3PR. tel: (01204) 855 000 <a href="mailto:help@lantor.co.uk">help@lantor.co.uk</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lederle</td>
<td>See Wyeth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEO</td>
<td>LEO Pharma Longwick Rd Princes Risborough Bucks, HP27 9RR. tel: (01844) 347 333 fax: (01844) 342 278 <a href="mailto:medical-info.uk@leo-pharma.com">medical-info.uk@leo-pharma.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LifeScan</td>
<td>LifeScan 50-100 Holmers Farm Way High Wycombe Bucks, HP12 4DP. tel: (01494) 658 750 fax: (01494) 658 751</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lilly</td>
<td>Eli Lilly &amp; Co Ltd Lilly House Priestley Rd Basingstoke Hampshire, RG24 9NL. tel: (01256) 315 999 <a href="mailto:ukmedinfo@lilly.com">ukmedinfo@lilly.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lincoln Medical</td>
<td>Lincoln Medical Ltd 13 Boathouse Meadow Business Park Cherry Orchard Lane Salisbury Wilts, SP2 7LD tel: (01722) 410 443</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linderma</td>
<td>Linderma Ltd Canon Bridge House Canon Bridge Madley Hereford, HR2 9JE. tel: (01981) 250 124 fax: (01981) 251 412 <a href="mailto:linderma@virgin.net">linderma@virgin.net</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Link</td>
<td>See Archimedes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Address</td>
<td>Telephone</td>
<td>Fax</td>
<td>Email</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>---------</td>
<td>-----------</td>
<td>-----</td>
<td>-------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morningside Healthcare Ltd</td>
<td>115 Narborough Rd, Leicester, LE3 0PA</td>
<td>(0116) 204 5950</td>
<td>(0116) 247 0756</td>
<td><a href="mailto:movianto.uk@movianto.com">movianto.uk@movianto.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordic Pharma UK Ltd</td>
<td>1650 Arlington Business Park, Theale</td>
<td>(0118) 929 8233</td>
<td>(0118) 929 8234</td>
<td><a href="mailto:info@nordicpharma.co.uk">info@nordicpharma.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis Pharmaceuticals UK Ltd</td>
<td>Frimley Business Park, Frimley</td>
<td>(01276) 692 255</td>
<td>(01276) 692 508</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordisk</td>
<td>Novo Nordisk Ltd</td>
<td>(01293) 613 555</td>
<td>(01293) 613 535</td>
<td><a href="mailto:customercareuk@novonordisk.com">customercareuk@novonordisk.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutricia Clinical Care</td>
<td>Nutricia Ltd</td>
<td>(01252) 532 333</td>
<td>(01252) 533 344</td>
<td><a href="mailto:networkm@globalnet.co.uk">networkm@globalnet.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrition Point</td>
<td>Nutrition Point Ltd</td>
<td>(07041) 544 044</td>
<td>(07041) 544 055</td>
<td><a href="mailto:info@nutritionpoint.co.uk">info@nutritionpoint.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nycomed</td>
<td>Nycomed UK Ltd</td>
<td>(01628) 646 400</td>
<td>(01628) 646 401</td>
<td><a href="mailto:nycomed@medinformation.co.uk">nycomed@medinformation.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis Consumer Health</td>
<td>Novartis Consumer Health</td>
<td>(01707) 226 094</td>
<td>(01707) 226 194</td>
<td><a href="mailto:OPIUK@orphan-mpi.com">OPIUK@orphan-mpi.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NeoMed</td>
<td>NeoMed Ltd</td>
<td>(0208) 8847 7800</td>
<td>(0208) 8847 7828</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nestlé Nutrition</td>
<td>Nestlé's House, Park Lane, Croydon</td>
<td>(0208) 8867 5130</td>
<td>(0208) 8867 5616</td>
<td><a href="mailto:nutrition.uk@nestle.com">nutrition.uk@nestle.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NeoLab</td>
<td>Neolab Ltd</td>
<td>57 High St, Odiham, Hampshire, RG29 1LF</td>
<td>(01256) 701 144</td>
<td><a href="mailto:info@neolab.co.uk">info@neolab.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novartis Vaccines</td>
<td>Novartis Vaccines Ltd</td>
<td>(0151) 7055 669</td>
<td><a href="mailto:serviceuk@chiron.com">serviceuk@chiron.com</a></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nordpharma</td>
<td>Nordic Pharma UK Ltd</td>
<td>(01252) 532 333</td>
<td>(01252) 533 344</td>
<td><a href="mailto:networkm@globalnet.co.uk">networkm@globalnet.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OPI</td>
<td>OPI Ltd</td>
<td>(01223) 424 444</td>
<td>(01223) 424 441</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral B</td>
<td>Oral B Laboratories Ltd</td>
<td>(0208) 8847 7800</td>
<td>(0208) 8847 7828</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omnus</td>
<td>Omnus Laboratories Ltd</td>
<td>(01223) 432 700</td>
<td>(01223) 424 368</td>
<td><a href="mailto:medrequest@omnus.co.uk">medrequest@omnus.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Organon</td>
<td>Organon Laboratories Ltd</td>
<td>(01252) 532 300</td>
<td>(01252) 520 319</td>
<td><a href="mailto:medicalinformation@organonpharma.com">medicalinformation@organonpharma.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orion</td>
<td>Orion Pharma (UK) Ltd</td>
<td>(0116) 204 5950</td>
<td>(0116) 247 0756</td>
<td><a href="mailto:movianto.uk@movianto.com">movianto.uk@movianto.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Octapharma | Octapharma Ltd | (01276) 692 255 | (01276) 692 508 |奥林匹亚健康

**BNF 57**

**Index of manufacturers 933**
<table>
<thead>
<tr>
<th>Company Name</th>
<th>Address</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orphan Europe</td>
<td>Orphan Europe (UK) Ltd</td>
<td>Oxon, RG9 1AT.</td>
<td>(01491) 414 443</td>
<td><a href="mailto:info.uk@orphan-europe.com">info.uk@orphan-europe.com</a></td>
</tr>
<tr>
<td>Ortho Biotech</td>
<td>Ortho Biotech PO Box 79</td>
<td>High Wycombe</td>
<td>(0800) 389 2926</td>
<td><a href="mailto:info.uk@orphan-europe.com">info.uk@orphan-europe.com</a></td>
</tr>
<tr>
<td>Otsuka</td>
<td>Otsuka Pharmaceutical (UK) Ltd</td>
<td>BSI Tower</td>
<td>(020) 8742 4300</td>
<td><a href="mailto:info@otsuka.co.uk">info@otsuka.co.uk</a></td>
</tr>
<tr>
<td>Ovation</td>
<td>Ovation Healthcare International Ltd</td>
<td>Dublin 2 Ireland</td>
<td>(00353) 161 39 707</td>
<td><a href="mailto:customerservices@owenmumford.co.uk">customerservices@owenmumford.co.uk</a></td>
</tr>
<tr>
<td>Oxford Nutrition</td>
<td>Oxford Nutrition Ltd</td>
<td>Woodstock Oxford</td>
<td>(01270) 582 255</td>
<td><a href="mailto:info@peckforton.com">info@peckforton.com</a></td>
</tr>
<tr>
<td>Owen Mumford</td>
<td>Owen Mumford Ltd</td>
<td>Brook Hill Oxford</td>
<td>(01945) 711 222</td>
<td><a href="mailto:info@peckforton.com">info@peckforton.com</a></td>
</tr>
<tr>
<td>Pfizer</td>
<td>Pfizer Ltd</td>
<td>Walton Oaks</td>
<td>(01304) 616 161</td>
<td><a href="mailto:info@peckforton.com">info@peckforton.com</a></td>
</tr>
<tr>
<td>Pfizer Consumer</td>
<td>Pfizer Consumer PO Box 214</td>
<td>Walton-on-the-Hill Surrey</td>
<td>(01304) 656 221</td>
<td><a href="mailto:info@peckforton.com">info@peckforton.com</a></td>
</tr>
<tr>
<td>PGR Health Foods</td>
<td>PGR Health Foods Ltd</td>
<td>Herford, SG14 2ZX.</td>
<td>(01992) 536594</td>
<td><a href="mailto:info@pharmaglobal.ie">info@pharmaglobal.ie</a></td>
</tr>
<tr>
<td>Pharmacia</td>
<td>Pharmacia</td>
<td>Hudson Rd Sandyvore Co. Dublin Ireland</td>
<td>0436 580</td>
<td><a href="mailto:eyecare@pharmaglobal.ie">eyecare@pharmaglobal.ie</a></td>
</tr>
<tr>
<td>Pharma Mar</td>
<td>Pharma Mar</td>
<td>Northway, Walworth Industrial Estate Andover, Hampshire, SP10 5AZ.</td>
<td>(01264) 363 117</td>
<td><a href="mailto:info@pharmar.co.uk">info@pharmar.co.uk</a></td>
</tr>
<tr>
<td>Pharmaco</td>
<td>Pharmaco</td>
<td>Northway, Walworth Industrial Estate Andover, Hampshire, SP10 5AZ.</td>
<td>(01264) 332 223</td>
<td><a href="mailto:info@pharmar.co.uk">info@pharmar.co.uk</a></td>
</tr>
<tr>
<td>Pharmasecur</td>
<td>Pharmasecur</td>
<td>28 Watford Metro Centre Dwight Rd Watford, WD18 9SB.</td>
<td>(01923) 233 113</td>
<td><a href="mailto:info@pharmasecur.co.uk">info@pharmasecur.co.uk</a></td>
</tr>
<tr>
<td>Pharmexx UK</td>
<td>Pharmexx UK Ltd</td>
<td>Oxon, OX10 6SL.</td>
<td>(01748) 828 888</td>
<td><a href="mailto:pharmaexx@professionalinformation.co.uk">pharmaexx@professionalinformation.co.uk</a></td>
</tr>
<tr>
<td>Pickers</td>
<td>J. Pickles Healthcare</td>
<td>Beech House</td>
<td>(01423) 867 314</td>
<td><a href="mailto:pickers@pharmaglobal.ie">pickers@pharmaglobal.ie</a></td>
</tr>
<tr>
<td>Pinewood</td>
<td>Pinewood Healthcare Ballymacabry Clonmel, Co Tipperary, Eire</td>
<td>(01730) 710900</td>
<td><a href="mailto:info@pinewood.ie">info@pinewood.ie</a></td>
<td></td>
</tr>
<tr>
<td>PLIVA</td>
<td>PLIVA Pharma Ltd</td>
<td>Vision House Bedford Rd Petersfield Hampshire, GU32 3QB.</td>
<td>(01730) 710901</td>
<td><a href="mailto:info@pliva-pharma.co.uk">info@pliva-pharma.co.uk</a></td>
</tr>
<tr>
<td>Potters</td>
<td>Potters Herbal Medicines 1 Botanic Court</td>
<td>Martland Park Wigan, WN5 0JZ.</td>
<td>(01942) 219 960</td>
<td><a href="mailto:info@pottersherbals.co.uk">info@pottersherbals.co.uk</a></td>
</tr>
<tr>
<td>Procter &amp; Gamble</td>
<td>Procter &amp; Gamble UK</td>
<td>The Heights Brooklands Weybridge</td>
<td>(01932) 896 000</td>
<td><a href="mailto:info@pottersherbals.co.uk">info@pottersherbals.co.uk</a></td>
</tr>
<tr>
<td>Procter &amp; Gamble Pharm.</td>
<td>Procter &amp; Gamble Technical Centres Medical Dept</td>
<td>Rusham Park Whitehall Lane Egham, Surrey, TW20 9NW.</td>
<td>(01784) 474 705</td>
<td><a href="mailto:info@profilepharma.com">info@profilepharma.com</a></td>
</tr>
<tr>
<td>Profile</td>
<td>Profile Pharma Ltd</td>
<td>98 Cromwell Battle Barns Preston Cromwell Wallingford Oxon, OX10 6SL.</td>
<td>(01748) 828 888</td>
<td>profilepharma.com</td>
</tr>
<tr>
<td>Profile Respiratory</td>
<td>Profile Respiratory</td>
<td>Respiration</td>
<td>(01983) 896 000</td>
<td><a href="mailto:info@respiration.co.uk">info@respiration.co.uk</a></td>
</tr>
<tr>
<td>Company</td>
<td>Address</td>
<td>Phone</td>
<td>Fax</td>
<td>Email</td>
</tr>
<tr>
<td>------------------</td>
<td>----------------------------------------------</td>
<td>----------------------</td>
<td>-------------------</td>
<td>------------------------------</td>
</tr>
<tr>
<td>ProStrakan</td>
<td>ProStrakan Ltd Galabank Business Park Galashiels, TD1 1QH. tel: (01896) 664 000 fax: (01896) 664 001 <a href="mailto:medinfo@prostrakan.com">medinfo@prostrakan.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protex</td>
<td>Protex Healthcare (UK) Ltd Unit 5, Molly Millars Lane Wokingham Berks, RG41 2Q2. tel: (01870) 114 112 <a href="mailto:orders@protexhealthcare.co.uk">orders@protexhealthcare.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Provalis</td>
<td>See KoGEN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ranbaxy</td>
<td>Ranbaxy Ltd CP House 97-107 Uxbridge Rd Ealing London, W5 5TL. tel: (020) 8280 1600 fax: (020) 8280 1996 <a href="mailto:mediinfoeurope@ranbaxy.com">mediinfoeurope@ranbaxy.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ransom</td>
<td>Ransom Consumer Healthcare Alexander House 40A Wilbury Way Hitchin Herts, SG5 1LY. tel: (01462) 437 615 fax: (01462) 420 528 <a href="mailto:info@williamransom.com">info@williamransom.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratiopharm UK</td>
<td>Ratiopharm UK Ltd 5 Jackson Close Grove Rd Cosham Portsmouth, Hants, PO6 1UP. tel: (02392) 313 587 fax: (02392) 386 208 <a href="mailto:info@ratiopharmdirect.co.uk">info@ratiopharmdirect.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reckitt Benckiser</td>
<td>Reckitt Benckiser Healthcare Dansom Lane Hull, HU8 7DS. tel: (01482) 326 151 fax: (01482) 582 526 <a href="mailto:miu@reckittbenckiser.com">miu@reckittbenckiser.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Recordati</td>
<td>Recordati Pharmaceuticals Ltd Knyvett House The Causeway Staines Middx, TW18 3BA. tel: (01784) 898 300 fax: (01784) 895 103</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regent Medical</td>
<td>See Molnycke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ReSource Medical</td>
<td>ReSource Medical UK Ltd 2 Thorne Rd Thornton Lodge Huddersfield, HD1 3JJ. tel: (01484) 531 489 fax: (01484) 531 584 <a href="mailto:info@resource-medical.co.uk">info@resource-medical.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respironics</td>
<td>Respironics (UK) Ltd Chichester Business Park City Fields Way Tangmere, Chichester West Sussex, PO20 2FT. tel: (0800) 1300 840 fax: (0800) 1300 841 <a href="mailto:rukmarketing@respironics.com">rukmarketing@respironics.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhône-Poulenc Rorer</td>
<td>See Sanofi-Aventis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richardson</td>
<td>Richardson Healthcare Ltd Devonshire House Manor Way Borehamwood Herts, WD6 1QQ. tel: (08700) 111 126 fax: (08700) 111 127 <a href="mailto:info@richardsonhealthcare.com">info@richardsonhealthcare.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Riems</td>
<td>Riems Arzneimittel AG An der Wiek 7 17493 Greifswald - Insel Riems Germany tel: (0049) 38351 76 679 fax: (0049) 38351 76 778 <a href="mailto:info@RIEMSER.DE">info@RIEMSER.DE</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RIS Products</td>
<td>RIS Products Ltd 10 Prospect Place Welwyn Herts, AL6 9EW. tel: (01438) 840 135 fax: (01438) 716 067 <a href="mailto:info@risproducts.co.uk">info@risproducts.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robinsons</td>
<td>Robinson Healthcare Ltd Lawn Rd Carlton-in-Lindrick Industrial Estate Workop Notts, S81 9LB. tel: (01909) 735 001 fax: (01909) 731 103 <a href="mailto:enquiries@robinsoncare.com">enquiries@robinsoncare.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche</td>
<td>Roche Products Ltd Hexagon Place 6 Falcon Way, Shire Park Welwyn Garden City Herts, AL7 1TW. tel: (0800) 328 1629 fax: (01707) 384 555 <a href="mailto:mediinfo.uk@roche.com">mediinfo.uk@roche.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche Consumer Health</td>
<td>See Bayer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Roche Diagnostics</td>
<td>Roche Diagnostics Ltd Charles Avenue Burgess Hill West Sussex, RH15 9RY. tel: (01444) 256 000 fax: (01444) 256 239 <a href="mailto:burgesshill.accu-check@roche.com">burgesshill.accu-check@roche.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rosemont</td>
<td>Rosemont Pharmaceuticals Ltd Rosemont House Yorkdale Industrial Park Braithwaite St Leeds, LS11 9XE. tel: (0113) 244 1999 fax: (0113) 246 0738 <a href="mailto:infodesk@rosemontpharma.com">infodesk@rosemontpharma.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rowa</td>
<td>Rowa Pharmaceuticals Ltd Bantry Co Cork Ireland tel: (00 353 27) 50077 fax: (00 353 27) 50417 <a href="mailto:rowa@rowa-pharma.ie">rowa@rowa-pharma.ie</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S &amp; N Lith.</td>
<td>Smith &amp; Nephew Healthcare Ltd Healthcare House Goulton St Hull, HU9 4DJ. tel: (01482) 222 200 fax: (01482) 222 211 <a href="mailto:advice@smith-nephew.com">advice@smith-nephew.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saganl</td>
<td>Saganl Ltd Unit 9 Park House 15-19 Greenhill Crescent Watford Business Park Watford, WD18 8PF. tel: (01923) 251 777 fax: (01923) 251 999 <a href="mailto:sales@saganl.co.uk">sales@saganl.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sallis</td>
<td>Sallis Healthcare Ltd Vernon Works Waterford St Basford Nottingham, NG6 0DH. tel: (0115) 978 7841 fax: (0115) 942 2272</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sandoz</td>
<td>Sandoz Ltd Unit 37 Woolmer Way Bordon Hants, GU35 9QE. tel: (01420) 478 301 fax: (01420) 474 427</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sankyo</td>
<td>See Daiichi Sankyo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanochemia</td>
<td>Sanochemia Diagnostics UK Ltd Argentum 510 Bristol Business Park Coldharbour Lane Bristol, BS16 1EJ. tel: (0117) 906 3562 fax: (0117) 906 3709</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi-Aventis</td>
<td>Sanofi-Aventis Ltd 1 Odnlow St Guildford Surrey, GU1 4YS. tel: (01483) 505 515 fax: (01483) 535 432 uk-medicalinformation@ sanofi-aventis.com</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi-Pasteur</td>
<td>Sanofi Pasteur MSD Ltd Mallards Reach Bridge Avenue Maidenhead Berks, SL6 1QP. tel: (01628) 785 291 fax: (01628) 671 722</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanofi-Synthelabo</td>
<td>See Sanofi-Aventis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schering Health</td>
<td>See Bayer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Company</td>
<td>Address</td>
<td>Telephone</td>
<td>Fax Number</td>
<td>Email Address</td>
</tr>
<tr>
<td>---------------</td>
<td>--------------------------------------------------------------------------</td>
<td>-----------</td>
<td>------------</td>
<td>---------------------------------------------------</td>
</tr>
</tbody>
</table>
| Schering-Plough | Schering-Plough Ltd  
Shire Park  
Welwyn Garden City  
Herts, AL7 1TW,  
tel: (01707) 363 636  
fax: (01707) 363 763  
medical.info@spcorp.com |             |            |                                                   |
| Schuco        | Schuco International Ltd  
Challenge House  
1 Lyndhurst Ave  
London, N12 0NE,  
tel: (020) 8368 1642  
fax: (020) 8361 3761  
sales@schuco.co.uk |             |            |                                                   |
| Serono        | See Merck Serono                                                         |             |            |                                                   |
| Servier       | Servier Laboratories Ltd  
Gallions  
Wexham Springs  
Framework Rd  
Wexham, SL3 6RJ,  
tel: (01753) 666 409  
fax: (01753) 666 204  
medical.information@uk.netgrs.com |             |            |                                                   |
| Seven Seas    | Seven Seas Ltd  
Hedon Rd  
Marfleet  
Hull, HU9 SNJ,  
tel: (01482) 375 234  
fax: (01482) 374 345 |             |            |                                                   |
| Shermond      | Shermond  
Castle House  
Sea View Way  
Woodingdean  
Brighton, East Sussex, BN2 6NT,  
tel: (0870) 242 7701  
fax: (01273) 391 028  
sales@shermond.com |             |            |                                                   |
| Shire         | Shire Pharmaceuticals Ltd  
Hampshire International Business Park  
Chineham  
Basingstoke  
Hants, RG24 8EP,  
tel: (0800) 055 6614  
fax: (01256) 894 708  
medinfo@shire.com |             |            |                                                   |
| Sigma         | Sigma Pharmaceuticals plc  
PO Box 233  
Unit 1-7 Colonial Way  
Warford  
Herts, WD24 4YR,  
tel: (01923) 444 999  
fax: (01923) 444 998  
info@sigpharm.co.uk |             |            |                                                   |
| Sigma-Tau     | Sigma-Tau Pharma Ltd (UK)  
Abbey House  
1650 Arlington Business Park  
Reading  
Berks, RG7 4SA,  
tel: (0118) 929 8075  
fax: (0118) 929 8076  
medical.information@sigt-tau.co.uk |             |            |                                                   |
| Sinclair      | Sinclair Pharmaceuticals Ltd  
4 Godalming Business Centre  
Woolwack Way  
Godalming  
Surrey, GU7 1XW,  
tel: (01483) 410 600  
fax: (01485) 410 620  
info@sinclairpharma.com |             |            |                                                   |
| Skin Camouflage Co. | The Skin Camouflage Company Ltd  
Moor Lane  
Soby  
Market Rasen, LN8 5LR,  
tel: (01507) 343 091  
fax: (01507) 343 092  
smcovermark@aol.com |             |            |                                                   |
| SLO Drinks    | SLO Drinks Ltd  
Unit 1  
Torr Top St  
New Mills  
High Peak, SK22 4BS,  
tel: (08452) 22 22 05  
fax: (08452) 22 22 06  
info@slodrinks.com |             |            |                                                   |
| SMA Nutrition | See Wyeth  
SNBTS  
Scottish National Blood Transfusion Service  
Hotel Fractionation Centre  
Ellen’s Glen Rd  
Edinburgh, EH7 7QT,  
tel: (0131) 536 5700  
fax: (0131) 536 5781  
Contact.pfc@snbts.csa.scot.nhs.uk |             |            |                                                   |
| Solvay        | Solvay Healthcare Ltd  
Mansbridge Rd  
West End  
Southampton, SO18 3JQ,  
tel: (023) 8046 7000  
fax: (023) 8046 5350  
medinfo.shl@solvay.com |             |            |                                                   |
| Sovereign     | See Amudiphar  
SpePharm  
SpePharm UK Ltd  
28a New Yatt Rd  
Witney  
Oxon, OX28 1NZ,  
tel: (0844) 800 7579  
fax: (0844) 800 7336  
medinfo.uk@spepharm.com |             |            |                                                   |
| Squibb        | See Bristol-Myers Squibb  
SSL  
SSL International plc  
Venus, 1 Old Park Lane  
Trafford Park  
Urmston  
Manchester, M41 7HA,  
tel: (08701) 222 690  
fax: (08701) 222 692  
medical.information@ssl-international.com |             |            |                                                   |
| Standard Drug Products | STD Pharmaceutical Products Ltd  
Plough Lane  
Hereford, HR4 6EL,  
tel: (01432) 373 555  
fax: (01432) 373 556  
enquiries@stpharm.co.uk |             |            |                                                   |
| Steraid       | Steraid (Gainsborough) Ltd  
Unit 42  
Corringham Road Industrial Estate  
Gainsborough, DN21 1QB,  
tel: (01427) 677 659  
Fax: (01427) 677 654 |             |            |                                                   |
| Sterling Health | See GSK Consumer Healthcare  
Sterwin | See Winthrop |             |            |                                                   |
| Stiefel       | Stiefel Laboratories (UK) Ltd  
Holtspur Lane  
Woodburn Green  
High Wycombe  
Bucks, HP10 0AL,  
tel: (01628) 524 966  
Fax: (01628) 810 021  
general@stiefel.co.uk |             |            |                                                   |
| Stragen       | Stragen UK Ltd  
Castle Court  
41 London Rd  
Reigate  
Surrey, RH2 9RJ,  
tel: (01707) 351 8744  
Fax: (01707) 351 8745  
info@stragenuk.com |             |            |                                                   |
| Strakan       | See ProStrakan  
Su-Med | See MedPharm |             |            |                                                   |
| Sutherland    | Sutherland Health Ltd  
Unit 1, Rivermead  
Pipers Way  
Thatcham  
Berks, RG19 4EP,  
tel: (01635) 874 488  
Fax: (01635) 877 622 |             |            |                                                   |
| Swedish Orphan | Swedish Orphan International Ltd  
1 Fordham House Court  
Fordham House Estate  
Newmarket Rd  
Fordham, Cambs, CB7 5LL,  
tel: (01638) 722 380  
Fax: (01638) 723 167 |             |            |                                                   |
Synergy Healthcare
Synergy Healthcare (UK) Ltd
Lion Mill
Flitton St
Royton
Oldham, OL2 5JX.
tel: (0161) 624 5641
fax: (0161) 627 0902
healthcaresolutions@synergyhealthplc.com

Syner-Med
Syner-Med (Pharmaceutical Products) Ltd
Beech House
840 Brighton Rd
Purley, CR8 2BH.
tel: (0845) 634 2100
fax: (0845) 634 2101
mail@syner-med.com

Takeda
Takeda UK Ltd
Takeda House, Mercury Park
Wycombe Lane
Wooburn Green
High Wycombe, Bucks, HP10 0HH.
tel: (01628) 537 900
fax: (01628) 526 615

Taro
Taro Pharmaceuticals (UK) Ltd
Lakeside
1 Furzeground Way
Stockley Park East
Uxbridge, Middx, UB11 1BD.
tel: (0870) 369 544
fax: (0870) 369 545
customerservice@taro-pharma.co.uk

Taru
See Chemidex

Teofarma
Teofarma S.r.l.
c/o Professional Information Ltd
Olliver
Richmond
North Yorkshire, DL10 5HX.
tel: (01748) 828 857
info@teofarma@professionalinformation.co.uk

Teva
Teva Pharmaceuticals Ltd
The Gate House
Gatehouse Way
Aylesbury
Bucks, HP19 8DB.
medinfo@tevapharma.co.uk

TEVA UK
TEVA UK Ltd
Building V
The London Road Campus
London Rd
Harlow, Essex, CM17 9LP.
tel: (08705) 320 034
fax: (08705) 323 334
medinfo@tevauk.com

Thornton & Ross
Thornton & Ross Ltd
Linthwaite Laboratories
Huddersfield, HD7 5QH.
tel: (01484) 842 217
fax: (01484) 847 301
mail@thorntonross.com

Tillomed
Tillomed Laboratories Ltd
3 Howard Rd
Eaton Socon, St Neots
Cambs, PE19 3ET.
tel: (01480) 402 400
fax: (01480) 402 402
info@tillomed.co.uk

TOL
Tree of Life
Coaldale Rd
Lymedale Business Park
Newcastle Under Lyme
Staffs, ST5 9QX.
tel: (01782) 367 100
fax: (01782) 367 199
health@tol-europe.com

TopoTarget
TopoTarget A/S
Synbiont Science Park
Fruebjergvej 3
DK-2100
Copenhagen, Denmark
tel: (00 45) 49 178 392
fax: (00 45) 49 179 492

Torbet
Torbet Laboratories Ltd
14D Wendover Rd
Rackheath Industrial Estate
Rackheath
Norwich, NR13 6LH.
tel: (01603) 735 217
fax: (01603) 735 217
torbet@typharm.com

Transdermal
Transdermal Ltd
35 Grimwade Ave
Croydon
Surrey, CR0 5DJ.
tel: (020) 8654 2251
fax: (020) 8654 2252
transdermal@transdermal.co.uk

TRB Chemedica
TRB Chemedica (UK) Ltd
MED IC3
Keene University Science Park
Keene
Staffordshire, ST5 5NP.
tel: (0845) 330 7556
fax: (0845) 330 7557
phunt@trbchemedica.co.uk

Trinity
Trinity Pharmaceuticals Ltd
See Trinity-Chiesi

Trinity-Chiesi
Trinity-Chiesi Pharmaceuticals Ltd
Cheadle Royal Business Park
Highfield
Cheadle, SK8 3GY.
tel: (0161) 488 5555
fax: (0161) 488 5565

TSL
Tissue Science Laboratories plc
Victoria House
Victoria Rd
Aldershot
Hants, GU11 1EJ.
tel: (01252) 333 002
fax: (01252) 333 010
enquiries@tissuescience.com

Typharm
Typharm Ltd
14D Wendover Rd
Rackheath Industrial Estate
Rackheath
Norwich, NR13 6LH.
tel: (01603) 735 217
fax: (01603) 735 217
customerservices@typharm.com

UCB Pharma
UCB Pharma Ltd
208 Bath Rd
Slough, SL1 3WE.
tel: (01753) 334 653
fax: (01753) 447 647
medicalinformationuk@ucb-group.com

Ultrapharma
Ultrapharma Ltd
Centenary Business Park
Henley-on-Thames
Oxon, RG9 1DS.
tel: (01491) 578 016
fax: (01491) 570 001
orders@glutenfree.co.uk

Univar
Univar Ltd
International House
Zenith, Paycocke Rd
Basildon
Essex, SS14 3DW.
tel: (01268) 594 400
fax: (01268) 594 481
trientine@univareurope.com

Unomedical
Unomedical Ltd
Thornhill Rd
Redditch, B98 7NL.
tel: (01527) 587 700
fax: (01527) 592 111

Urgo
Urgo Ltd
Sullington Road
Shepshed
Loughborough
Leics, LE12 9JL.
tel: (01509) 502 051
fax: (01509) 650 898
medical@parema.com

Valeant
Valeant Pharmaceuticals Ltd
Cedarwood
Chineham Business Park
Crockford Lane, Basingstoke
Hants, RG24 8WD.
tel: (01256) 707 744
fax: (01256) 707 334
valeantuk@valeant.com

Vegenat
c/o Archealis Ltd
23 Pembroke Gardens
London, W2 4ER.
tel: (0870) 803 2484
info@vegenat.co.uk
<table>
<thead>
<tr>
<th>Company</th>
<th>Address</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Viatris</strong></td>
<td>Sealed Barn, School Lane, Shutterton, Tamworth, Staffs, B79 0DX. tel: (01827) 896 996 fax: (0870) 705 8153 <a href="mailto:info@viridianpharma.co.uk">info@viridianpharma.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Viridian</strong></td>
<td>Viridian Pharma Ltd, Seales Barn, School Lane, Shutterton, Tamworth, Staffs, B79 0DX. tel: (01827) 896 996 fax: (0870) 705 8153 <a href="mailto:info@viridianpharma.co.uk">info@viridianpharma.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitaflow</strong></td>
<td>Vitaflow Ltd, 11 Century Building, Brunswick Business Park, Liverpool, L3 4BL. tel: (0151) 709 9020 fax: (0151) 709 9727 <a href="mailto:vitaflow@vitaflow.co.uk">vitaflow@vitaflow.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitaline</strong></td>
<td>Vitaline Pharmaceuticals UK Ltd, 8 Ridge Way, Drakes Drive, Credon Business Park, Long Credon, Bucks, HP18 9BF. tel: (01604) 202 044 fax: (01604) 202 077 <a href="mailto:vitalineinfo@aol.com">vitalineinfo@aol.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vitalograph</strong></td>
<td>Vitalograph Ltd, Maids Moreton, Buckingham, MK18 1SW. tel: (01280) 827 110 fax: (01280) 823 302 <a href="mailto:sales@vitalograph.co.uk">sales@vitalograph.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wallace Cameron</strong></td>
<td>Wallace Cameron Ltd, 26 Netherhall Rd, Netherton Industrial Estate, Wishaw, ML2 0JG. tel: (01698) 354 600 fax: (01698) 354 700 <a href="mailto:sales@wallacecameron.com">sales@wallacecameron.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wallace Mfg</strong></td>
<td>Wallace Manufacturing Chemists Ltd, Wallace House, New Abbey Court, 51-53 Stert St, Abingdon, Oxon, OX14 3JF. tel: (01235) 538 700 fax: (01235) 538 800 <a href="mailto:info@alinter.co.uk">info@alinter.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wellfoods</strong></td>
<td>Wellfoods Ltd, Towngate, Mapplewell, Barnsley, South Yorks, S75 6AS. tel: (01226) 381 712 fax: (01226) 390 087 <a href="mailto:wellfoods@talk21.com">wellfoods@talk21.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Winthrop</strong></td>
<td>Winthrop Pharmaceuticals UK Ltd, PO Box 611, Guildford, Surrey, GU1 4YS. tel: (01483) 554 101 fax: (01483) 554 810 <a href="mailto:winthropsales@sanofi-aventis.com">winthropsales@sanofi-aventis.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wockhardt</strong></td>
<td>Wockhardt UK Ltd, Ash Rd North, Wrexham Industrial Estate, Wrexham, LL13 9UF. tel: (01978) 661 261 fax: (01978) 660 130</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wyeth</strong></td>
<td>Wyeth Pharmaceuticals, Huntercombe Lane South, Taplow, Maidenhead, Berks, SL6 2DR. tel: (01628) 604 377 fax: (01628) 666 368 <a href="mailto:ukmedinfo@wyeth.com">ukmedinfo@wyeth.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wynlit</strong></td>
<td>Wynlit Laboratories, 153 Furzehill Rd, Borehamwood, Herts, WD6 2DR. tel: (07903) 370 130 fax: (020) 8292 6117</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Wyvern</strong></td>
<td>Wyvern Medical Ltd, PO Box 17, Ledbury, Herefordshire, HR8 2ES. tel: (01531) 631 105 fax: (01531) 634 844</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zeal</strong></td>
<td>G. H. Zeal Ltd, Deer Park Rd, London, SW19 3UU. tel: (020) 845 42283 fax: (020) 845 7840 <a href="mailto:scientiffc@zeal.co.uk">scientiffc@zeal.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zeneus</strong></td>
<td>Zeneus Ltd, The Manor House, Victor Barns, Northampton Rd, Brixworth, Northampton, NN6 9DQ. tel: (01604) 889 855 fax: (01604) 883 199 <a href="mailto:info@ixlpharma.com">info@ixlpharma.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zeroderma</strong></td>
<td>Zeroderma Ltd, The Manor House, Victor Barns, Northampton Rd, Brixworth, Northampton, NN6 9DQ. tel: (01604) 889 855 fax: (01604) 883 199 <a href="mailto:info@ixlpharma.com">info@ixlpharma.com</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ZooBiotic</strong></td>
<td>ZooBiotic Ltd, Biosurgical Research Unit, Surgical Materials Testing Laboratory, Princess of Wales Hospital, Coity Rd, Briggend, Mid Glamorgan, South Wales, CF31 1RQ. tel: (0845) 230 1810 fax: (01656) 752 830 <a href="mailto:maggote@smtl.co.uk">maggote@smtl.co.uk</a></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Zurich</strong></td>
<td>See Trinity-Chiesi</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Unlicensed medicines are available from 'special-order' manufacturers and specialist-importing companies; the MHRA maintains a register of these companies at www.mhra.gov.uk

Licensed hospital manufacturing units also manufacture 'special-order' products as unlicensed medicines, the principal NHS units are listed below. A database (Pro-File; www.pro-file.nhs.uk) provides information on medicines manufactured in the NHS; access is restricted to NHS pharmacy staff.

The MHRA recommends that an unlicensed medicine should only be used when a patient has special requirements that cannot be met by use of a licensed medicine

### England

#### London

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Company</th>
<th>Address</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr P. Forsey</td>
<td>Production Manager</td>
<td>Guy's and St. Thomas' NHS Foundation Trust</td>
<td>Lambeth Palace Rd, London, SE1 7EH.</td>
<td>(020) 7188 5003</td>
<td>(020) 7188 5013</td>
<td><a href="mailto:paul.forsey@gett.nhs.uk">paul.forsey@gett.nhs.uk</a></td>
</tr>
<tr>
<td>Mr A. Krol</td>
<td>Director of Commercial Services</td>
<td>Pharmaceutical Manufacturing Unit</td>
<td>Moorfields Eye Hospital NHS Trust, 34 Nile St, London, N1 7LX.</td>
<td>(020) 7684 8561</td>
<td>(020) 328 8191</td>
<td><a href="mailto:alan.krol@moorfields.nhs.uk">alan.krol@moorfields.nhs.uk</a></td>
</tr>
<tr>
<td>Mr M. Lillywhite</td>
<td>Director of Technical Services</td>
<td>Barts and the London NHS Trust</td>
<td>St Bartholomew's Hospital, West Smithfield, London, EC1A 7BE.</td>
<td>(020) 7601 7486</td>
<td>(020) 7601 7486</td>
<td><a href="mailto:mike.lillywhite@bartsandthelondon.nhs.uk">mike.lillywhite@bartsandthelondon.nhs.uk</a></td>
</tr>
</tbody>
</table>

#### Midlands and Eastern

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Company</th>
<th>Address</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr C. Trehan</td>
<td>Production Manager</td>
<td>Pharmacy Manufacturing Unit</td>
<td>The Ipswich Hospital NHS Trust, Heath Rd, Ipswich, IP4 5PD.</td>
<td>(01473) 703 603</td>
<td>(01473) 703 609</td>
<td><a href="mailto:con.hanson@ipswichhospital.nhs.uk">con.hanson@ipswichhospital.nhs.uk</a></td>
</tr>
<tr>
<td>Ms J. Kendall</td>
<td>Assistant Chief Pharmacist</td>
<td>Pharmacy Production Units</td>
<td>Nottingham University Hospitals NHS Trust, Queens Medical Centre Campus, Nottingham, NG7 2UH.</td>
<td>(0115) 875 4521</td>
<td>(0115) 970 9744</td>
<td><a href="mailto:jeannette.kendall@nuh.nhs.uk">jeannette.kendall@nuh.nhs.uk</a></td>
</tr>
<tr>
<td>Mrs R. Newton</td>
<td>Head of Production</td>
<td>Pharmacy Manufacturing Unit</td>
<td>University Hospital of North Staffs, City General Site, Stoke-on-Trent, ST4 6QG.</td>
<td>(01782) 552 290</td>
<td>(01782) 552 916</td>
<td><a href="mailto:ruth.newton@uhns.nhs.uk">ruth.newton@uhns.nhs.uk</a></td>
</tr>
<tr>
<td>Dr S. Langford</td>
<td>Principal Pharmacist (Technical Services)</td>
<td>UHB Medicines (SFMU), 32–34 Melchett Rd, Kings Norton Business Centre, Kings Norton, Birmingham, B30 3HS.</td>
<td>(0121) 627 2326</td>
<td>(0121) 627 2168</td>
<td><a href="mailto:stephen.langford@uhb.nhs.uk">stephen.langford@uhb.nhs.uk</a></td>
<td></td>
</tr>
</tbody>
</table>

#### North East

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Company</th>
<th>Address</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ms S. Klein</td>
<td>Production Manager</td>
<td>Pharmacy Production Unit</td>
<td>Royal Victoria Infirmary, Queen Victoria Rd, Newcastle-upon-Tyne, NE1 4LP.</td>
<td>(0191) 282 0377</td>
<td>(0191) 282 0376</td>
<td><a href="mailto:stephanie.klein@nuth.nhs.uk">stephanie.klein@nuth.nhs.uk</a></td>
</tr>
</tbody>
</table>

#### North West

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
<th>Company</th>
<th>Address</th>
<th>Telephone</th>
<th>Fax</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mr M.D. Booth</td>
<td>Principal Pharmacist</td>
<td>Production &amp; Aseptic Services Manager</td>
<td>Stockport Pharmaceuticals, Stepping Hill Hospital, Stockport, Cheshire, SK2 7JE.</td>
<td>(0161) 419 5657</td>
<td>(0161) 419 5664</td>
<td><a href="mailto:mike.booth@stockport.nhs.uk">mike.booth@stockport.nhs.uk</a></td>
</tr>
<tr>
<td>Mr N. Fletcher</td>
<td>Deputy Director of Pharmacy, Technical Services</td>
<td>Preston Pharmaceuticals, Royal Preston Hospital, Fulwood, Preston, PR2 9HT.</td>
<td>(01772) 522 505</td>
<td>(01772) 522 602</td>
<td><a href="mailto:neil.fletcher@tbtr.nhs.uk">neil.fletcher@tbtr.nhs.uk</a></td>
<td></td>
</tr>
</tbody>
</table>
South East
Mr F. Brown
Head of Production
Pharmacy Department
St Peter’s Hospital
Guildford Rd
Chertsey
Surrey, KT16 0PZ.
tel: (01932) 722 886
fax: (01932) 723 209
fraser.brown@aspnhs.uk

Ms G. Middlehurst
Quality Assurance and Business Manager
Pharmacy Manufacturing Unit
Queen Alexandra Hospital
Southwick Hill Rd
Cosham
Portsmouth
Hants, PO6 3LY.
tel: (02392) 286 335
fax: (02392) 378 288
gillian.middlehurst@porthosp.nhs.uk

Mr M. Sherwood
Principal Pharmacist (Production)
Eastbourne DGH Pharmaceuticals
Eastbourne DGH Hospital
East Sussex Hospitals NHS Trust
Kings Drive, Eastbourne
East Sussex, BN21 2UD.
tel: (01323) 414 906
fax: (01323) 414 931
mike.sherwood@esht.nhs.uk

Yorkshire
Mr R.W. Brookes
Technical Services Manager
Pharmacy Department
Royal Hallamshire Hospital
Glossop Rd
Sheffield, S10 2JF.
tel: (0114) 271 3104
fax: (0114) 271 2783
roger.brookes@sth.nhs.uk

Dr J. Harwood
Production Manager
Pharmacy Manufacturing Unit
Calderdale and Huddersfield NHS Foundation Trust
Gate 2 School St
Lindley
Huddersfield
West Yorks, HD3 3ET.
tel: (01484) 355 371
fax: (01484) 355 377
john.harwood@cht.nhs.uk

Northern Ireland
Ms C. McBride
Assistant Director of Pharmaceutical Services
Manufacturing and Royal Group of Hospitals Belfast
77 Boucher Crescent
Belfast, BT12 6HU.
tel: (028) 9063 3310 or (028) 9055 3407
fax: (028) 9055 3498
collette.mcbride@royalhospitals.n-i.nhs.uk

South West
Mr P. S. Bendell
Pharmacy Manufacturing Services Manager
Torbay PMU
South Devon Healthcare
Kemmings Close, Long Rd
Paignton
Devon, TQ4 7TW.
tel: (01803) 664 707
fax: (01803) 664 354
phil.bendell@nhs.net

Scotland
Mr G. Conkie
Manager, Pharmacy Production Unit
Western Infirmary
Dumbarton Road
Glasgow, G11 6NT.
tel: (0141) 211 2882
fax: (0141) 211 1967
graham.conkie@northglasgow.scot.nhs.uk

Mr B. W. Millar
General Manager
Tayside Pharmaceuticals
Ninewells Hospital
Dundee, DD1 9SY.
tel: (01382) 632 183
fax: (01382) 632 060
baxter.w.millar@tuht.scot.nhs.uk

Wales
Mr P. Spark
Principal Pharmacist (Production)
Cardiff and Vale NHS Trust
University Hospital of Wales
Heath Park
Cardiff, CF14 4XW.
tel: (029) 2074 4828
fax: (029) 2074 5114
paul.spark@cardiffandvale.wales.nhs.uk
Antiplatelet drugs, 131
Antiprotease drugs, 352
Antiprostaglandins, topical, 621
Antipsychotics, 192
depot injections, 202
equivalent doses
depot, 202
oral, 194
high doses, 191
manic, 204
withdrawal, 192
Antipyretics, 229
Antirabies immunoglobulin, 682
Antitussives, 180
Antituberculous drugs, 316
Antithyroid drugs, 387
Antithrombin III concentrate,
Antithrombin alfa, 138
Antitetanus immunoglobulin, 683
Antispasmodics, 41
Antiserum, 663, 681
Antiseptics, 656
Antiretrovirals, 334, 335, 342
Antirabies immunoglobulin, 682
Apo-go
Aplastic anaemia, 509
Apidra
Aphthous ulcers, 608
Anzemet
Anxiolytics, 183,
Bowel cleansing solutions, 64, 65
Bowel irrigation, 28
Bradycardia, 80
anaesthesia, 691
Bran, 59
Brand names, symbol, 1
Braisol, 640
Breast cancer, 497
bone metastases, 417
tratuzumab, 485
Brexidol, 593
Brolene, 272
Brolec, 585
Bromocriptine, 421, 426
acromegaly, 421
galactorrhoea, 421
hyperprolactinaemia, 422
necroplastic malignant syndrome, 193
parkinsonism, 264, 265
prolactinoema, 422
Bronchiectasis, 179
Bronchitis, 179, 285
bronchodilators, 151
Bronchodilators
adrenoceptor agonist, 152
antimuscarinic, 157
surgery, 686
sympathomimetic, 152
theophylline, 158
Bronchospasm, 152
Brucellosis, 303, 319
Brucellosis
animal, 287
intraoperative analgesia, 235
Brexit, 235
Butylbromide, 42
Butoconazole, 423
Bupropion, 276
Buprenorphine, 274
Burinex, 76
Burinex A, 78
Burns, infected, 648
Buscopan preparations (Hyoscine butylbromide), 42
Buserelin, 425, 501
detomidrosis, 425
IVF, 425
prostate cancer, 500, 501
Busilex, 464
Buspirone, 191
Buxiprime, 190, 191
Buxulafan, 463, 464
infusion table, 856
Buxulfan, 463, 464
Butyrophenones, 193
Byetta, 380

C

C1 esterase inhibitor, 175
Cabaser, 265
Cabergoline
hyperprolactinaemia, 421, 422, 423
parkinsonism, 264, 265
Calcit, 418, 533
Calcit D3, 542
Cadesorb, 888
Cadexomer–iodine, 888
Caelyx, 467
Cafegot, 247
Calfeine, 230
Calaband, 899
Calamine, 621
coral tar with, 633
Calcex, 542
Calcien MR (nifedipine), 117
Calciscr, 114
Calcichew, 533
Calcichew D3, 542
Calcichew D3 Forte, 542
Calciferol, 541
Calcijex, 542
Calcipotriol, 630, 631, 632
betamethasone with, 632
Calcitonin, 415
hypercalcaemia, 416, 534
infusion table, 856
osteoporosis, 416
Calcitriol, 541, 542
osteoporosis, 415
psoriasis, 630, 631, 632
Calcium
colecalciferol with, 541, 542
ergocalciferol with, 541
Calcium acetate, 542
Calcium alginate dressings, 884, 885
Calcium and vitamin D tablets, 541
Calcium balance, maintenance, 416
Calcium carbonate, 533, 542
antacid, 38
disodium edetionate with, 418
risedronate and colecalciferol with, 419
Calcium chloride, 533
Calcium citrate, 542
Calcium folinate, 508
infusion table, 856
Calcium gluconate, 533
infusion table, 856
Calcium lactate tablets, 533
Calcium leucovorin seen Calcium folin-ate
Calcium levofolinate, 462
infusion table, 856
Calcium phosphate, 542
Calcium polystrene sulphonate, 520
Child-resistant containers, 3
Chloretone, 705
Chloramphenicol
  eye, 583
genital, 286
macrolides, in, 307
quinolones, in, 323
tetracyclines, in, 303
Chlorothiazide (chlorothalidone), 194
Chloral hydrate, see also Chloral betaine, 187
Chloral hydrate, 186, 187
Chlorambucil, 463, 464
ChlorampHENicol, 310, 311
ear, 600, 602
eye, 583, 584
infusion table, 857
skin, hydrocortisone with, 640
Chloraprep
Chlorphenamine, 169,
  223
Chlorpheniramine
see Chlorphenamine, 169,
  223
Chloroxylenol, 659
Chloroquine, 358
Chloroquine, 358
malaria
  prophylaxis, 354–6, 357
treatment, 354, 357
proguanil with, 358
rheumatic disease, 563, 566
Chlorox, 659
Chlorphenamine, 169, 171
Chlorphenamine see Chlorphenamine, 169, 171
Chlorpromazine, 193, 194
hiccup, 194
nausea, 224
nausea and vertigo, 222
psychosis, 193
Chlorpromazine, 376
diabetes insipidus, 412
Chlorotardione, 74, 75
atenolol with, 87, 88
diabetes insipidus, 412
triamterene with, 79
Chlorella algal, see Chlorotardione
Cholecalciferol see Cholecalciferol
Cholecalciferol see Cholecalciferol
Cholera vaccine, 665
travel, 685
Cholestagel, 143
Cholesterol see Colesterol
Choline, 539
Choline salicylate
dental gel, 608, 610
CholinerGic crises, 575
Cholinesterase inhibitors, 575, 700
Choragon, 408
Choreas, 273
Choriocarcinoma, 468
Choriongonadotropin alfa, 408
Chorionic gonadotrophin, 408
Chronic eosinophilic leukaemia, 480
Chronic myeloid leukaemia, 480
Chronic obstructive pulmonary disease, 151, 176
Chlosis, 458
Clobar 60XL (isosorbid mononitrate), 112
Cica-Care, 890
Ciclosporin
  oral infections, 310
  pneumonia, 363
  vaginal infections, 437
Clinafast, 897
Clininorm, 527
Clindamycin, 309, 310
  acne, 638, 639
  benzoyl peroxide with, 638
  infusion table, 857
  malaria treatment, 353
  oral infections, 310
  pneumocystis pneumonia, 363
  skin, hydrocortisone with, 640
Clotenap, 657
Chloroform, 541
Ciclesonide, 166
Clindamycin
  oral infections, 310
  pneumonia, 363
  vaginal infections, 437
Clenbuterol
  hernia, 187
  medical treatment, 187
Clonidine
  hypertension, 96, 97
  menopause, 248, 395
  migraine, 247, 248
  Tourette syndrome, 273
Clonazepam, 260
  status epilepticus, 261
  infusion table, 857
Clonidine
  hypertension, 96, 97
  menopause, 248, 395
  migraine, 247, 248
  Tourette syndrome, 273
Clonazepam, 260
  status epilepticus, 261
  infusion table, 857
Clomipramine, 407, 408
Clomiphene see Clomiphene, 407, 408
Clomipramine, 207, 208, 209
Clonazepam, 260, 261
  epilepsy, 250, 260
Clotam, 596
Clontrex
  60XL, 596
  Clofazimine, 408
  Clindamycin, 309, 310
  acne, 638, 639
  benzoyl peroxide with, 638
  infusion table, 857
  malaria treatment, 353
  oral infections, 310
  pneumocystis pneumonia, 363
  skin, hydrocortisone with, 640
Clotam Rapid, 244
Clomethiazole, 321
Clomiphene
  see also Clomiphene, 407, 408
  Analgesics, 293
  Clonidine, 250
  Clomipramine, 407, 408
  Clofazimine, 408
  Clindamycin, 309, 310
  acne, 638, 639
  benzoyl peroxide with, 638
  infusion table, 857
  malaria treatment, 353
  oral infections, 310
  pneumocystis pneumonia, 363
  skin, hydrocortisone with, 640
Clotam Rapid, 244
Corticosteroids (continued)—
osteoarthritis, 552
pneumocystis pneumonia, 363
pregnancy, 391
proctitis, 56
proctosigmoiditis, 56
psychiatric reactions, 391
replacement therapy, 388
rheumatic disease, 561
septic shock, 398
side-effects, 392
skin
acne, 640
eczema, 622, 629
psoriasis, 622
suitable quantities, 623
surgery, 390
thrombocytopenic purpura, 515
ulcerative colitis, 56, 57
withdrawal of, 390
Corticosteroids—Decongestants
BNF 57
Index

Cytotoxic drugs, 459
alopecia, 461
bladder instillation, 455
bone-marrow suppression, 461
dosage, 460
evrapivation, 460
handling guidelines, 459
hyperuricaemia, 460
nausea and vomiting, 460
pregnancy, 461
regimens, 460
thrombomembolism, 461

D

d4T see Stavudine, 335, 337, 338
Dabigatran, 130
Dacarbazine, 476, 477
infusion table, 857
Daclizumab—discontinued
Dactinomycin, 466
infusion table, 857
Dakotacort, 624
Daktarin, 607
oral gel, 611
skin, 651
Deltacortril preparations, 310
acne, 639
vaginal, 437
Dalfopristin, quinupristin with, 313, 314
infusion table, 863
Daliv, 544
Dalmine, 185
Dalteparin, 125
Danaparoid, 126, 127
infusion table, 857
Danazol, 423, 424
Danrazol (ketoconazole), 646
Dantrium, 547
Dantrium SR, 578
Intravenous, 702
Dantrolene, 578
malignant hyperthermia, 702
muscle spasm, 577
neuroleptic malignant syndrome, 193
Dantron, 60, 61
Dantrium, 578

Daptomycin, 312, 313
infusion table, 857
Daraprim, 360
Daraprim, 360
Darbopeptin, 509, 510, 511
Darier’s disease, 631
Darifenacin, 451, 452
Darunavir, 480, 481
Danol, 424
Dantracon see Dantron, 60, 61
Dantracon, 578
Dantracon, 578

Decapeptyl SR, 426, 502
Decapeptyl SR, 426, 502
Decan, 551
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Decapeptyl, 502
Digitoxin, 72
Digitoxin, 71, 72
heart failure, 100
infusion table, 858
Digitoxin-specific antibody fragments, 72, 73
infusion table, 858
Dihydrocodeine, 234, 236
paracetamol with, 233
Dihydroxypropyldine calcium-channel blockers, 113
Dihydrotachysterol, 541, 542
Dihexylohydroxycalciferol, 541, 542, 632
Dicitadene SR, 114
Dilantin, 133, 114, 115
anal fissure, 67
poisoning by, 32
see also Calcium-channel blockers
Dilzem preparations, 115
Dimitrihydrate, cinnarizine with, 223
Dimercaprol, 34
Dimethadione, 386
Dimenhydrinate, cinnarizine with, 236
preparations, 115
Dilzem
Diphenoxylate, 51, 234
Dipeptiven
Dipentum
Dip/Ser, 667
Diovan
Diovan preparations, 520
Diovan, 223
Diovan preparations, 520
Dioralyte
Dioderm
Dioctyl sodium sulphosuccinate
Dioctyl
Dimethicon, activated
Dimercaprol, 34
Dimethicone, activated
Dimethicone, activated
dimethyl sulfoxide
Dimethyl sulfoxide
Dimethystat
Dimethyl sulfoxide
Dimethyl sulfoxide
DIMUZE
Dipterix
Dinoprostone, 429, 430, 431
infusion table, 858
Diocap, 61
Diocyl, 61
Diocyl sodium sulphosuccinate see
Docusate sodium
Dioderm, 624
Dioderex, 520
Diovan, 108
Dip/Ser, 667
Dipetidum, 55
Dipetipvien, 531
Diphenoxylate, 15, 234
see also Analgesics, opioid
Diphenylbutylyperidine, 193
Diphenylphosphonates see Bisphosphonates
Diphtharia, 290, 665
antibacterial prophylaxis, 288
antitoxin, 667
immunisation
travel, 666
vaccines, 665
vaccines, combined, 666
Diphtheria vaccines, combined, 666
misusers, notification of, 9
interactions, 708
malaria
Diphenoxylate, 51, 234
preparations, 115
Diphenoxylate, 51, 234
DOPAC, 61
Dopamine, 121
infusion table, 858
Dopamine receptor agonists
parkinsonism, 264
Dopamineergic drugs
endocrine, 421
parkinsonism, 264
Dopexamine, 121, 122
infusion table, 858
Dopram, 176
Doraise, 450
Doribax, 301
Doripenem, 301
infusion table, 858
Dormase alfa, 179
Dorzolamide, 592, 593
with timolol, 593
Dose changes, xi
Doses, 2
children, 14
elderly, 20
liver disease, 790
renal impairment, 801
Doxapram, 176
respiratory depression, 176
Doxazoxin cardiovascular, 98
urinary tract, 449, 450
Doxepin, 207, 209
topical, 621
Doxorubicin, 465, 467
bladder, 455
infusion table, 858
Doxycycline, 304
acne, 640
aphthous ulcers, 609
Lyme disease, 293
malaria
prophylaxis, 355, 356, 357,
361
treatment, 353
mouth, 609
oral infections, 303
periodontitis, 609
rosacea, 638
Doxylar (doxycycline), 304
Doxic, 195
Droamlone, 620
Dressing packs, 893, 894, 895
Dressings, 883
Dressit, 893
Drinor, 659
Dried prothrombin complex, 129, 138
Droserone
Drospirenone
contraception
ethinylestradiol with, 442,
443
HRT, estradiol with, 398
Drotricogin alfa (activated), 138
Drug
allergy, 169
dependence, 7
management, 275
interactions, 708
misusers, notification of, 9
Drug
allergy, 169
dependence, 7
management, 275
interactions, 708
misusers, notification of, 9
Dry mouth, 613
Duc, 638
Dual block, 700
Ductus arteriosus closure, 432
patency, 432

International travel, immunisation for, 684
Interpose, 892
Intracranial pressure, raised corticosteroids, 389
palliative care, 16 thipental, 688
Intralipid preparations, 527
Intravit products, 687
Intra-u-terine devices, 447
copper-bearing, 447, 448
progestogen-releasing, 446
Intravenous infusions, 521
addition to, 853
Intravenous nutrition, 526
Intrinsa, 405
Itron A, 492
Ivanz, 302
Ivega, 200
Invirase, 341
locare, 596
Iodine, 387, 388
oral solution, 388
radioactive, 387
topical, 658
Iodosol, 888
Iodosorb products, 888
Iodozyme, 888
IONYS, 237
Japidine, 597
Ipecacuanha mixture, 28
Ipcol, 54
Ipratropium, 157
asthma, 157
fenoterol with, 159
rhinorrhoea, 606, 690
salbutamol with, 159
Steri-Neb, 157
IPV see Poliovaccines, immunisation
Irbesartan, 106, 107
hydrochlorothiazide with, 107
Iridocyclitis see Anterior uveitis, 588
Irinotecan, 884
infusion table, 860
Iron
deficiency, 504
folic acid and, 505
overload, 513
poisoning by, 32
therapy
oral, 504, 505, 506
parenteral, 506, 507
Iron dextran, 506, 507
infusion table, 860
Iron sucrose, 506, 507
infusion table, 860
Ironorm, 505
Irtilex, 656
Irripod, 656
Irritable bowel syndrome, 41, 53
Iresent, 343
Istb 60XL, 112
Island dressings, 900
Ismelin, 98
Ismo preparations, 112
Isocarboxazid, 112
Isocarbazine, 690, 691
Isogel, 60
Isobet preparations, 111
Isocarboxazid, 112
Isocarboxazid
Isometric therapy
poisoning by, 32
Isostencel, 884
infusion table, 860

Isoprenaline, 121
Isotox
Alkaline, 595
Plain, 595
Isosorbid dinitrate, 110, 111
infusion table, 861
Isosorbid mononitrate, 110, 112, 113
Insoluble preparations, 868
Isotard preparations, 112
Isotretinoin
acne
oral, 637, 641, 642
topical, 639, 640
erthythromycin with, 640
rosacea, 638
Isotrex
Isotrexin, 640
Isoverin, 640
Isovanic acid, 879
Isovirin, 462
Isopaglurula
constipation, 59, 60
diarrhoea, 51
mebeverine with, 42
Isradipine, 113, 115, 116
see also Calcium-channel blockers
Istin, 114
Itraconazole, 327, 328, 331, 332
infusion table, 861
IUDs see Intra-uterine devices
IV3000, 891
Ivabradine, 119
Ivermectin
larva migrans, 366
onchocerciasis, 366
scabies, 653
strongyloidesis, 366
IIZS see Insulin, zinc suspension

Januvia, 381
Japanese encephalitis, 685
Jelonet, 892
Jet nebulisers, 161
Jevity preparations, 868, 869
Joint prostheses
endocarditis prophylaxis, 290
Joy Rides, 228
Juvela
gluten-free, 876
low-protein, 877

K
Kabiven preparations, 527
Kala-azar, 362
Kalatre, 340
Kalipare, 79
Kalten, 88
Kaltostat products, 884
Kao lin, 51
mixture, 51
morphine with, 52
poultices, 581
Kapake, 232
Kaplon (captopril), 102
Karvel preparations, 180
Katyra 30/75, 443
Kawasaki syndrome, 681
Kaye-Cee-L, 519
K-Band, 895
Kefadim, 300
Keflex, 296
Kefid (cefalexin), 296
Keloc SR (felodipine), 115
Kelo-cote, 890
Keloïd dressings, 890
Kemadrin preparations, 272
Kemicetine, 311
Kenalog, 394, 563
Kentero, 453
Kontine MR (nifedipine), 117
Kepivance, 463
Keppra, 255
Keral, 355
Keratitis, 583
Keratocon, 697
Keratolytics, warts and calluses, 642
Keratitis follicularis, 631
Keromask preparations, 645
Kerastix, 886
KerrMax, 892
Ketalar, 689
Ketamine, 688, 689
infusion table, 861
neuropathic pain, 243
Ketek, 309
Ketoacidosis, diabetic, 382
KetoCalc, 873
Ketocid, 559
Ketoconazole, 328, 332
anogenital, 437
Cushing’s syndrome, 427
scalp, 645, 646
skin, 649, 650, 651
Ketodastix, 386
Ketodil, 307
Ketoprofen, 558, 559
gout, 573
pain, 558
postoperative, 695
rheumatoid disease, 552, 558
topical, 581
Ketorolac
eye, 597
postoperative, 695
Ketostix, 385
Ketotifen, 171
eye, 587, 588
Ketovail, 559
Ketorol, 544
Ketur Test, 385
K-Four products, 898
Kidney see Renal
Kindergem, 873
Kineret, 571
Kivexa, 336
Klaricid preparations, 309
Klean-Prep, 65
Klofem, 399
Klovance, 399
K-Lite, 897, 898
Klourf—discontinued
Knit Fix, 895
Knit-Band, 895
Knit-Firm, 897
Knitted viscose dressing, primary, 892
Knit-Flx, 898
Kogenate Bayer (factor VIII fraction), 139
Koantico, 41
Konakion preparations, 544
Konturn, 895
Korsakov’s psychosis, 539
K-Flus, 897, 898
K-Press, 898, 899
K-Soft, 898
K-Tech, 898
K-Tee, 897
K-Two, 898
Menadione sodium phosphate, 543
Mendelson's syndrome, 45, 687
Meniere's disease, 223
Meningeal carcinoma, 468
Menigitic, 674
Meningitis
cryptococcal, 330
haemophilus, 286, 310
immunisation, 673
Hib with, 667
vaccine, 674
initial therapy, 286
listerial, 286
meningococcal, 286
prophylaxis, 288
travel, 674, 684
pneumococcal, 286
Meningococcal see Meningitis
Menitorix
Menjugate
Meningeal carcinoma,
Meniere's disease, 223
Menotrophin, 409
Menopur
Menjugate
Menitorix
Meningitis
Meningioma, 367
Meningeal carcinoma,
Meningeal sarcoma, 223
Menotrophin, 409
Menopur
Menaquinone, 57
Menopausal symptoms, 248, 395
Menopon, 409
Menorrhagia, 402, 446
antifibrinolytics, 138
NSAIDS, 559
Menotrophin, 409
Menthol and eucalyptus inhalation, 180
Mepacrine
discoid lupus erythematosus, 565
giardiasis, 362
Mepifropime, 890
Mepiplex products, 892
Mepitsc, 899
Mepitel, 893
Mepivacaine, 703
Mepore products, 890, 891
Mepredac (omeprazole), 49
Meprobamate, 191
muscle spasm, 579
Mepazol, 234, 238
Mepid, 238
Mebetoxy preparations, 41
Mercaptamine (cysteamine), 417, 418
Mercapturiprine, 470, 471
inflammatory bowel disease, 52, 53, 57
Mecysteine, 179
Mecysteine, 179
Mercaptopurine, 470, 471
infusion table, 861
Mesalamine, 52, 54, 55
Mesalazine, 547, 548
Mercaptopurine, 470, 471
inflammatory bowel disease, 52, 53, 57
Mercilon, 442
Merional, 409
Meropenem, 302
Meropenem, 301, 302
infusion table, 861
Mesalazine, 52, 54, 55
Mesoron products, 887, 895
Mesna, 463
infusion fluid, 861
Mesob, 891
Mesorin MR, 55
Mesterolone, 406
Mestinon, 577
Mestranol, norethisterone with, 443
Methadone, 238
cough, 181
lactus, 181
opioid dependence, 279, 280
oral solutions, 280
pain, 234, 238
palliative care, 15
parenteral, 280
poisoning by, 31
Methadone, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone, 280
Methaemoglobinenaemia, 706
Methal, poisoning by, 34
Methadone with, 280
Methadone, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaemia, 706
Methanol, poisoning by, 34
Methadone with, 280
Methaemoglobinenaema
Norgalax—Orgran  966

Norgalax Micro-enema, 61
Norgestimate, ethinylestradiol with, 445
Norgeston, 444
Norgestrel see Levonorgestrel
Noriday, 444
Norimne, 443
Norimode (loperamide), 52
Norigest L, 443
Noristerat, 445
Norvalol preparations, 60
Normal immunoglobulin see Immuno-
globulins, normal, 681, 682
Normal saline see Sodium chloride
Norvasc, 341
NovoNordisk see Prandin, 381
NovoPen products, 375
NovoRapid, 371
NovoSeven, 448
NovoMix 30, 373
NovoNorm see Prandin, 381
NovoMix, 373
NovoSeven, 448
NovoNorm see Prandin, 381
Olsalazine, 52, 54, 55
Omarycin, 147
Oralzidumab, 173
Omega-3 fatty acid compounds, 146
Omega-3-acyl ethyl esters, 146, 147
Omega-3-marine triglycerides, 147
Omeprazole preparations, 529
Omeprazole, 49, 50
infusion table, 862
Ominex, 548
Omontic MR (tamsulosin), 450
Ondansetron, 222, 226, 227
infusion table, 862
Ondetrol (ondansetron), 227
One Touch products, 375, 385
One-Alpha, 541
Onctoceris, 366
OncoTice, 494
Oncovin, 473
Oncor, 444
Oncotrol see Analgesics, opioid
Oncotrol see Analgesics, opioid
Oncotrol, 701
Opioid antagonists, 701
peripheral, 66
poisoning in, 31
Opine, 280
OpSite products, 890
Optichamber, 160
OptiClik, 375
Opticam preparations, 588
OptiFlo preparations, 456
Optil (ditiazem), 114
Optilast, 587
Optimax, 216
OptiPen Pro, 375
Opioid preparations, 385
Optivate (factor VIII and von Wille-
dan factor concentrate), 139
Optive, 595
Optometrist independent prescribing, 872
OPV see Poliomylitis, immunisation
Oraheal, 609
Orahexive, 609
Oral balance see Bisphane Oralbalance
Oral contraceptives, see Contraception, oral
Oral glucose tolerance test, 386
Oral hypoglycaemic drugs see Anti-
diabetic drugs, oral, 375
Oral rehydration, 520
Oral rehydration salts, 520
WHO formula, 521
Oral syringes, 2
Oralidene, 612
Ora morph preparations, 239
Orap, 196
Oreilen (ibuprofen), 558
Orciprenaline, 157
Orexol, 299
Orenic, 570
Orfavin, 548
Orgalutran, 424
Organophosphorus insecticides, pois-
oning by, 35
Orgaran, 127
Orgran, 876

O

Obesity, 220
Obese-cholesterol disorder, 207
Obetastic and gynaecological surgery, 298
Obstructive pulmonary disease see Chronic obstructive pulmonary dis-
ease
Ocumal, 642
Octagon preparations, 682
Octalin preparations (albumin solu-
tion), 524
Octanate (factor VIII fraction), 139
Octaplas (fresh frozen plasma), 139
Octim, 414
Ocologic afia, 139
Octreotide, 503
Oxycodone, 18
Octyl 2-cyanoacrylate, 656
Ocreatin, 597
Oculotect, 56
Ocusan, 596
Oedema
Oedema cerebral, 79
pulmonary, 75
Oesophageal varices, 412
Oesophagos see Gastro-oesophageal reflux disease, 38
Oestradiol see Estradiol
Oestriol see Estriol
Oestropro, 401
Oestrogens
HRT, 394, 397
conjugated, 399
levonorgestrel with, 397
medroxyprogesterone with, 397
malignant disease, 496
oral contraceptives, 438
vasectomy, 435
Oestrone see Estrone, 401
Ofeoxacin, 323, 325, 326
ear, 603
eye, 585
Ofeoxacil, 584
Oflam
cream, 618
Emollient, 619
Fragrance Free, 619
Plus, 620
shower emollient, 618
Olive oil
cradle cap, 645
ear, 603

Normal parenteral, 526

ACBS, 865
zentral, 532, 865
intravenous, 526
oral, 532
total parenteral, 526
Nutients preparations, 70
NutropinAg, 411
Nuvella preparations, 399
Nycogel, 590
Nystaform, 651
Nystaform-HC, 624
mouth, 611

Nystatin, 328, 332, 333
ear, 602
mouth, 610, 611
perianal, 66
skin, 650, 651
chlorhexidine and hydrocorti-
sone with, 624
hydrocortisone with, 624
tolnaftate with, 651
hydrochlorothiazide with, 107
hydrochlorothiazide with, 107
Olmesartan, 106, 107
hydrochlorothiazide with, 107
Omeprazole preparations, 107
Olopatadine, 587, 588
Olsalazine, 52, 54, 55
Omecor, 147
Omalizumab, 173
Omega-3 fatty acid compounds, 146
Omega-3-acyl ethyl esters, 146, 147
Omega-3-marine triglycerides, 147
Omeprazole preparations, 529
Omeprazole, 49, 50
infusion table, 862
Omidex, 891
Ornidex, 891
Ornifax, 899
Oomen, 375
Ometrop, 411
On omap (papaveretum), 241
Onron nebulisers, 162
Onchocerciasis, 366
OncoTice, 494
Oncovy, 473
Ondansetron, 222, 226, 227
infusion table, 862
Ondetrol (ondansetron), 227
One Touch products, 375, 385
One-Alpha, 541
Onkrone, 467
Oxychomycosis see Fungal infections
Opatanol, 588
Opilon, 120
Opioid analogues see Analgesics, opioid
Opioid antagonists, 701
peripheral, 66
poisoning in, 31
Opine, 280
OpSite products, 890
Optichamber, 160
OptiClik, 375
Opticam preparations, 588
OptiFlo preparations, 456
Optil (ditiazem), 114
Optilast, 587
Optimax, 216
OptiPen Pro, 375
Opioid preparations, 385
Optivate (factor VIII and von Wille-
dan factor concentrate), 139
Optive, 595
Optometrist independent prescribing, 872
OPV see Poliomylitis, immunisation
Oraheal, 609
Orahexive, 609
Oral balance see Bisphane Oralbalance
Oral contraceptives, see Contraception, oral
Oral glucose tolerance test, 386
Oral hypoglycaemic drugs see Anti-
diabetic drugs, oral, 375
Oral rehydration, 520
Oral rehydration salts, 520
WHO formula, 521
Oral syringes, 2
Oralidene, 612
Ora morph preparations, 239
Orap, 196
Oreilen (ibuprofen), 558
Orciprenaline, 157
Orexol, 299
Orenic, 570
Orfavin, 548
Orgalutran, 424
Organophosphorus insecticides, pois-
oning by, 35
Orgaran, 127
Orgran, 876
Index

Peptisorb
Pepti
preparations, 870
Peptac
Peppermint oil, 42,
products, 875
Pentostatin,
Pentazocine, 234,
Pentastarch,
Pentasa

Penicillin VK
Penciclovir, 344, 652,
Penbritin
Pentamidine isetionate,
Pentacarinat
Pennsaid
Penlet II
Penicillins, 290
Penicillinases, 291
broad spectrum, 293
antipseudomonal, 296
Penicillin V
Pemetrexed, 469,
Pegzerepoetin alfa
Pegvisomant,
411
Peginterferon alfa, 348,
Pegasys
Pegaptanib, 597,
Peditrace
Pediculosis, 653
Pediacel
Peak flow meters, 159, 160
Pavacol-D
Patient group direction, 3
Patents, 3
see Patents—PK

Phloxine, 565
Phenothiazine, 104
Phenytoin
Phenytoin sodium
Phenobarbital, 255
Phenindione, 128,

Pepcid (famotidine) preparations, 46
Peptic products, 875
Peppermint oil, 42, 43
Peptan, 46
Peptan preparations, 870
Pepti products see Cow & Gate
Peptisorb, 871
Perative, 871
Percotol, 111
Peril, 104
Pergolin, 232
Pefam, 73
Pergolide, 264, 265, 266
Pergoveris, 409
Percactin, 171
Percorontis, 287
Pericyazine, 195, 196
Pentil, 67
Perindopril, 104
indapamide with, 105
see also ACE inhibitors
Periodontitis, 609
antibacterial treatment, 287
Peristat, 609
Peripheral vascular disease, 119
Peritonitis, 285
PermaFoam products, 885, 886
Permethrin, 653, 655
Permitab, 658
Perfox, 613
Perphenazine
depression
amitriptyline with, 208
najuse, 222, 224
psychoses, 196
Perisin preparations, 134
Personal Best, 159
Perniosis
immunisation, 675
vaccines, combined, 666, 675
prophylaxis, 288
Pethidine
anaesthesia, 241
analgesia, 234, 241
promethazine with, 241
Petit mal, 250
Petroleum jelly, 617
Petroleum products, poisoning by, 28
Petroleum products, poisoning by, 33
Petroleum products, poisoning by, 35
Petroleum products, poisoning by, 37
Petroleum products, poisoning by, 46
Petal

Piroxicam,
Piriton
Pirenzepine, 47
Piracetam, 261,

Pituitary
Pitressin
Pityriasis versicolor, 328, 650
Pityriasis versicolor, 328, 650
Phloxine, 565
Phenothiazine, 104
Phenytoin
Phenytoin sodium
Phenobarbital, 255
Phenindione, 128,

Pimozide, 193,
Pipotiazine,
see Pipotiazine
Pittiriasis versicolor, 328, 650
Pityriasis versicolor, 328, 650
Phloxine, 565
Phenothiazine, 104
Phenytoin
Phenytoin sodium
Phenobarbital, 255
Phenindione, 128,

Phosphorus, 535
Phytotermadne, 543, 544
infusion table, 862
Phytotherolaimia, 144
Picolax, 65
Phexar, 651
Phytomonadene, 543, 544
infusion table, 862
Phytotherolaimia, 144
Picolax, 65
Phexar, 651
Phytomonadene, 543, 544
infusion table, 862
Phytotherolaimia, 144
Picolax, 65
Phexar, 651
Phytomonadene, 543, 544
infusion table, 862
Promethazine
allergic disorders, 169, 172
hypnotic, 187, 188
nausea and vertigo, 222, 223
premedication, 172
Promethazine teolate, 224
Promin, 877
Promixin, 314
Promorgan products, 888
Prontoxan, 887
Propafenone, 82, 84
Propamidine isetionate, 583, 585
Propantheline, 42
gastro-intestinal, 41, 42
urinary tract, 451, 453
Propar SFP, 893
Propeca, 647
Propeli, 431
Propylhalaix, antibacterial, 288
Propine, 592
Propionibacterium acnes, 638
Propionic acidemia, 879
Propiverine, 451, 453
Propofol, 688, 689
infusion table, 863
Propropol-Lipuro, 689
Propoven, 689
Propranolol, 86, 87
cardiovascular, 86
migraine, 247
see also Beta-adrenoceptor blocking
drugs thyrotoxicosis, 387
tremor, 273
Proprietary names, symbol, 1
Propylene glycol, presence of, 2
Propylthiouracil, 388
Prozac
Pro-Viron
Provigil
Provide
Provera
Proxatrol
Proxatrol SDP
Proxil
Psoriasis, 630
Psoriasis vulgaris, 629
Pseudomonas aeruginosa infections,
301, 302, 305, 314
Pseudomembranous colitis
antibacterial therapy metronidazole, in, 321
Psoriasis vulgaris, in, 311
clindamycin, in, 309
Pseudoephedrine, 388
Pseudoephedrine (fluoxetine), 214
Prozep
Quietapine, 200, 201
Provera
Proxatrol SDP
Proxil
Psoriasis, 630
Psoriasis vulgaris, 629
Pseudomonas aeruginosa infections,
301, 302, 305, 314
antipseudomonal penicillins, in,
296
cephalosporins, in, 297
eye, 583
Psittacosis, 303
Pulmicort
Pulmicort preparations, 431
Pulmicort LS
Psoriasis, 630
Psoriasis vulgaris, 629
Pulmocare, 272
Pulmonary
embolism, 124, 136, 177
hypertension, 94, 127, 177
oedema, 75
Pulmicort
Pulmicort LS aerosol inhaler—discontinued
Pulmicort preparations, 166
Purine nucleotides, 476
Q fever, 303
Quaternary ammonium compounds, 41
Pyridoxine, 539
Pyrinidine, 540
Q fever, 303
Quaternary ammonium compounds, 41
Pyridoxine, 539
Pyrinidine, 540
maintained, 661
Pyridostigmine, 576, 577
lacative, 60
Pyridoxine, 539, 540
anaemias, 509
status epilepticus, 261
Pyrimethamine, 360
malaria, 352, 360
sulfadoxine with, 353, 360
toxoplasmosis, 362
Pyrithione zinc shampoos, 645
Q fever, 303
Quaternary ammonium compounds, 41
Pyridoxine, 539
Pyrinidine, 540
maintained, 661
Pyridostigmine, 576, 577
lacative, 60
Pyridoxine, 539, 540
anaemias, 509
status epilepticus, 261
Pyrimethamine, 360
malaria, 352, 360
sulfadoxine with, 353, 360
toxoplasmosis, 362
Pyrithione zinc shampoos, 645
Terazosin

cardiovascular, 98, 99

urinary tract, 440, 450

Terbinfine, 328, 329, 332
topical, 650, 652

Terbutaline

asthma, 152, 156

infusion table, 864

premature labour, 435

Teriparide, 415, 416, 417

Teripressin, 414

Terminal care see Palliative care

Terpenes, gall bladder, 69

Tetroxine, 387

Tetinon, 405

Testogel, 405

Testosterone

buccal tablets, 405

enantate, 405, 405

esters, 404
gel, 405

implants, 405

injection, 405

malignant disease, 497

oral, 405

patches, 405

propionate, 404, 405

undecanoate, 404, 405

Tetanus, 290

immunisation, 678

immunoglobulin, 682, 683

vaccines, combined, 666, 667

muscle spasm, 578

travel, 684

wounds, 678

Tetany, hypocalcaemic, 532

Tetranbenzine, 273, 274

Tetracaine, 66, 707
eye, 594

local anaesthetic, 707

lidocaine with, 704

Tetracosactide, 408

Tetracosactrin see Tetracosactide, 408

Tetracycline, 303
anaco, 640
diabetic neuropathy, 383

oral infections, 303

rosacea, 638

Tetracyclines see Tetracycline

Tetralysal-300, 304

Tetrastop preparations, 526

Tetrastarch, 525, 526

Teveten, 106

Textue, 896

T-Gel, 646

Thalassaemia, 513

Thalidomide, 495

lepra reactions, 321

Thalidomide Pharamion, 495

Thelin, 96

Theophylline, 158

poisoning, 33

elimination, 28

see also Aminophylline

Thermometer, fertility, 448

Thiamine, 539, 540

status epilepticus, 261

Thiazides, 74

diabetes insipidus, 412

see also Diuretics

Thiazolidinediones, 379

Thick and Easy, 873

Thioguanine see Thioguanine, 470, 472

Thiopental, 688

Thiopentone see Thiopental, 688

Thiopurine methyltransferase, 486

Thiotepa, 455, 464, 465

Thioxanthene, 193

Thixo-D, 873

Threadworm infections, 364

Throat infections, 287
gonorrhoea, 286

Thrombocythaemia, 515

Thrombocytopenia, 509

Thrombocytopenic purpura, 515

immunoglobulin, 681

Thromboembolism, 128

pulmonary, 124, 136, 177

Thromboelastics, 136

Thrombosis

antiplatelet drugs, 131

dep-vein, 124, 128

prophylaxis, 124

venous, 136

Thrush see Candidiasis

Thymogulbine, 488

Thymol, 613

Thymoxamine see Moxisylyte, 120

Thyron, 412

Thyroid

agonists, 387

carcinoma, 386

function test, 412

hormones, 386

stimulating hormone, 411

storm, 387

Thyroidectomy, 387

Thyroxic crisis, 387

Thyrotoxicosis, 387

beta-blockers, 86, 387

Thyrotophin-releasing hormone see

Protirelin, 412

Thyrotropin alfa, 411, 412

Thyroxine see Levothyroxine, 386

Thyroid stimulating hormone, 411

Thyroid hormones, 386

cancer, 386

antagonists, 387

Ticarcillin, 296

clavulanic acid with, 296

infusion table, 864

Tick-borne encephalitis, 685

immunisation, vaccine, 679

TicoVac, 679

Tics, 273

Tidelle products, 885, 886

Tigecycline, 305

infusion table, 864

Tilade CFC-free Inhaler, 168

Tilase preparations, 114, 115

Tilofyl (fentanyl), 237

Tiloket CR, 559

Tiloron (erythromycin), 308

Tiludronic acid, 420

Timentin, 296

infusion table, 864

Timozone, 624

Timolol, 91

bendrofluamide with, 91

cardiovascular, 91

eye, 590, 591

bimatoprost with, 591

brimonidine with, 592

dorzolamide with, 593

latanoprost with, 591

travoprost with, 591

migraine, 247

see also Beta-adrenoceptor blocking drugs

Timopidel, 590

Timopidel LA, 591

Tinaderm-M, 651

Tinea infections, 328, 649

Tinidazole, 321, 322, 323

amoebiasis, 361

giardiasis, 362

protozoal infections, 361

trichomoniasis, 361

Tinzaparin, 125, 126

Tioconazole, 650, 652

Tioguanine, 470, 472

Tiotropium, 157, 158

Tipranavir, 335, 341

Tirofiban, 109, 132, 134, 135

infusion table, 864

Twept, 657

Tissue adhesive, 656

Titanium dioxide, 620

Tovaloids preparations, 607

Tizanidine, 577, 578, 579

Tobi, 307

Tobradex, 586

Tobramycin, 306, 307

eye, 586

infusion table, 864

Tocopherol, 543

Tocopheryl, 543

Toctino, 630

Toilet preparations, ACBS, 882

Tolbutamide, 376, 377

Tolcapone, 270, 271

Tolfenamic acid, 244, 553

Tolinafate, 650, 651

Tolterodine, 451, 454

Tomudex, 472

Tonic seizures, 250

Tonic-clonic seizures, 250

Tonics, 544

Tonsilitis see Throat infections

Topal, 41

Topamax, 258

Topiramate, 247, 250, 257, 258

Topotecan, 484

 renegotuation tables, 864

Toraol, 695

Torsades, 75, 76

Torem, 76

Toremifene, 498, 500

Torisel, 483

Torsade de pointes, 80, 555

magnesium sulphate, 555

Torsion dystonias, 274

Tostran, 405

Total parenteral nutrition, 526

Touer, 162

Tourette syndrome, 273

Toviaz, 452

TOXBASE, 27

Toxoplasma chorioretinitis, 362

Toxoplasmosis, 362

TPA see Alteplase

TPN, 526

Trabectdin, 485

Trachoma, 303, 583

Tracrer, 94

Traceme, 698

Tractocile, 434

Trade marks, symbol, 1

Trandecor, XL, 242

Tramacert, 242

Tramadol, 234, 241, 242

infusion table, 864

paracetamol with, 242

Tramaked preparations, 242

Tramaque SR, 242

Trandate, 89

Trandolapril, 105, 106

see also ACE inhibitors

verapamil with, 106

Tranexamic acid, 138

infusion table, 864

Trangia XL, (isosorbide mononitrate), 113

Tranquilisers, 183

Transcutaneous electrical nerve stimulation, 16

Transfusion reactions, 509

Transderm-Nitro, 111
Transient ischaemic attacks, 128
Transbornt, 885
Tranzept, 235
Tranylcypromine, 211, 212
Trasicor, 90
Traside, 90
Trastuzumab, 485
Travept-100, 657
Travatan, 591
Travoprost, 591
with timolol, 591
Tuxam preparations, 581
Trzadoline, 207, 210
Treatment cards, anticoagulant, 129
Tree pollen allergy preparations, 172
Tremors, 273
Trental, 120
Trescoflan, 464, 465
Trifaril, 864
Tretinoin
acne, 639
erythrocycin with, 639
leukaemia, 485, 486

TRH see Protirelin, 412

Tri-Acortyl
cream and ointment—contintiued
Otic, 602
Triadene, 443
Triamcinolone
ear, 602
mouth, 609
nose, 606
parenteral
allergic conditions, 394
rheumatic diseases, 563
skin, 628

Triam-Co (co-triamterzide), 78
Triamterene, 77
benzthiazide with, 78
chlorthalidone with, 79
furomeside with, 79
hydrochlorothiazide with, 78
Triapin preparations, 105
Triazole antifungal drugs, 328
Tribarin see Ribvirin
Trichomonacides, 361
Trichomonal infections, 361
Triclofen, 186, 187
Triglucan, 656, 658
Tricox, 892
Tricyclic antidepressants see Anti-
depressants, tricyclic
Tridexa, 399
Trientine, 545
Trifluoperazine
nausea and vertigo, 222, 224
psychoses, 193, 197
Trigeminal neuralgia, 243
Trihexyphenidyl, 271, 272
movement disorders, 273
Tri-iodothyronine, 387
Trilepital, 252
Triosteol, 427
malignant disease, 408
Trimipramine see Alimemazine
Trimethoprim, 315, 316, 326
acne, 640
pneumocystis pneumonia, 363
sulfamethoxazole with, see Co-
trimoxazole
Trimipramine, 207, 210
Trimopan (trimethoprim), 316
Trimovate, 626
TriNovum, 443
Triptolemion, 315, 316
Trimopan (trimethoprim), 316

U

Ultracet, 451
Uceran, 171
Uftoral, 472
Ulceraive colitis, 52

Ulcerative gingivitis
antibacterial treatment, 287, 322
mouthewashes, 612
Ucer Healing drugs, 43
Ulcers
aphthous, 608
corneal, 583, 585
duodenal, 43, 45
gastric, 43, 45
Hunner’s, 555
mouth, 608
NSAID-associated, 44
skin, 658
Ulex Pro, 889
Ultima, 162
Umbra, 897
Ultra bandages, 898, 899
Ultra foods
glut-free, 877
low-protein, 878
Ultra-Neb-2000, 162
Ultrasoebase, 618
Ultrimalum Plain, 628
Ultraproc, 67
Ultrasonic nebulisers, 162
Ultraviolet radiation, 644
Undecenoates, 652
Unguentum M, 618
Unifine products, 375
Unilet products, 375
Uniphyllin Continus, 158
Uniride-HC, 67
Uniset, 657
Unistik products, 375
Unithiol, 34
Unitelle, 892
Univer, 118
Universal, 375
Unresistant dermatofibrosarcoma
protuberans, 480
Uraci, tegafur with, 472
Urdex, 69
Urea, 617, 618
hydrocortisone with, 624
Urea cycle disorders, 548
arginine supplement, 881
essential amino acids supplement, 379
Ureric colic, 454
Urethritis, non-gonococcal, 286, 303
UrgoCell products, 893
Urgosorb products, 885
Urgotul products, 893
Uriben, 325
Uricosuric drugs, 573
Ureflex preparations, 456
Urinary
frequency, 451
incontinence, 451
infections, 286, 326
pH adjustment, 454
retention, 449
Urine tests, 385
Urnatrop-200, 453
Unista, 386
Urofollitropin see Urofollitropin, 408, 409
Urofollitropin, 408, 409
Urokinase, 136, 137
infusion table, 864
Urological procedures
antibacterial prophylaxis, 289
Uromitexan, 463
Uro-Preparation preparations, 456
Urothelial toxicity, 463
Ursohepatic acid, 68, 69
Ursofalk, 69
Urosan, 69
Urticaria, 169
### Index

<table>
<thead>
<tr>
<th>Page</th>
<th>Content</th>
</tr>
</thead>
<tbody>
<tr>
<td>556</td>
<td>Volsaid (diclofenac), 556</td>
</tr>
<tr>
<td>555, 556</td>
<td>Voltarol preparations, 555, 556</td>
</tr>
<tr>
<td>581</td>
<td>Emalgel, 581</td>
</tr>
<tr>
<td>597</td>
<td>Gel patch, 581</td>
</tr>
<tr>
<td>597</td>
<td>Ophtha, 597</td>
</tr>
<tr>
<td>556</td>
<td>Rapid, 556</td>
</tr>
<tr>
<td>526</td>
<td>Wolyte, 526</td>
</tr>
<tr>
<td>160</td>
<td>Volumatic, 160</td>
</tr>
<tr>
<td>524</td>
<td>Volume expansion, 524</td>
</tr>
<tr>
<td>526</td>
<td>Vonellen, 526</td>
</tr>
<tr>
<td>222</td>
<td>Vomiting, 222</td>
</tr>
<tr>
<td>460</td>
<td>cytotoxic drugs, 460</td>
</tr>
<tr>
<td>17</td>
<td>palliative care, 17</td>
</tr>
<tr>
<td>222</td>
<td>postoperative, 222</td>
</tr>
<tr>
<td>413</td>
<td>von Willebrand's disease, 413</td>
</tr>
<tr>
<td>123</td>
<td>Viciparoxazone, 123</td>
</tr>
<tr>
<td>333</td>
<td>infusion table, 333</td>
</tr>
<tr>
<td>334</td>
<td>Vicipara, 334</td>
</tr>
<tr>
<td>864</td>
<td>infusion table, 864</td>
</tr>
<tr>
<td>436</td>
<td>Vulvitis, candidal, 436</td>
</tr>
<tr>
<td>438</td>
<td>Xalacom, 438</td>
</tr>
<tr>
<td>128</td>
<td>Xamplir, 128</td>
</tr>
<tr>
<td>327</td>
<td>Xeloda, 327</td>
</tr>
<tr>
<td>328</td>
<td>Xenazine, 328</td>
</tr>
<tr>
<td>216</td>
<td>Xyloproct, 216</td>
</tr>
<tr>
<td>223</td>
<td>Xylopast, 223</td>
</tr>
<tr>
<td>183</td>
<td>Xytopen, 183</td>
</tr>
<tr>
<td>170</td>
<td>Xyzoal, 170</td>
</tr>
<tr>
<td>139</td>
<td>Yastron, 139</td>
</tr>
<tr>
<td>443</td>
<td>Zacin, 443</td>
</tr>
<tr>
<td>328</td>
<td>Zaye, 328</td>
</tr>
<tr>
<td>139</td>
<td>Zaditen, 139</td>
</tr>
<tr>
<td>350, 351</td>
<td>Zanaflex, 350, 351</td>
</tr>
<tr>
<td>301</td>
<td>Zanamivir, 301</td>
</tr>
<tr>
<td>546</td>
<td>Zanidol, 546</td>
</tr>
<tr>
<td>239</td>
<td>Zanorphine, 239</td>
</tr>
<tr>
<td>260</td>
<td>Zanox, 260</td>
</tr>
<tr>
<td>156</td>
<td>Zantrac, 156</td>
</tr>
<tr>
<td>649</td>
<td>Zargon, 649</td>
</tr>
<tr>
<td>201</td>
<td>Zostefer, 201</td>
</tr>
<tr>
<td>421</td>
<td>Zoster see Herpes infections</td>
</tr>
<tr>
<td>202</td>
<td>Zotepil, 202</td>
</tr>
<tr>
<td>427</td>
<td>Zopiclone, 427</td>
</tr>
<tr>
<td>301</td>
<td>Zopiclone, 301</td>
</tr>
<tr>
<td>126</td>
<td>Zovirax, 126</td>
</tr>
<tr>
<td>574</td>
<td>Zozo, 574</td>
</tr>
<tr>
<td>403</td>
<td>Zozam, 403</td>
</tr>
<tr>
<td>301</td>
<td>Zyban, 301</td>
</tr>
<tr>
<td>301</td>
<td>Zyloprim, 301</td>
</tr>
<tr>
<td>649</td>
<td>Zypem, 649</td>
</tr>
<tr>
<td>200</td>
<td>Zyprex, 200</td>
</tr>
<tr>
<td>313</td>
<td>Zyvox, 313</td>
</tr>
</tbody>
</table>
If you suspect that an adverse reaction may be related to a drug, or a combination of drugs, you should complete this Yellow Card or complete a report on the website at www.yellowcard.gov.uk. For **intensively monitored medicines** (identified by ▼) report all suspected reactions (including any considered not to be serious). For **established drugs and herbal remedies** report **all serious** adverse reactions in adults; report **all serious and minor** adverse reactions in **children** (under 18 years). You do not have to be certain about causality: if in doubt, please report. Do not be put off reporting just because some details are not known. See BNF (page 11) or the MHRA website (www.yellowcard.gov.uk) for additional advice.

### Patient Details

<table>
<thead>
<tr>
<th>Patient Initials</th>
<th>Sex: M / F</th>
<th>Weight if known (kg):</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age (at time of reaction):</th>
<th>Identification (Your Practice / Hospital Ref.)*:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Suspected Drug(s)

<table>
<thead>
<tr>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Suspected Reaction(s)

<table>
<thead>
<tr>
<th>Please describe the reaction(s) and any treatment given:</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date reaction(s) started:</th>
<th>Date reaction(s) stopped:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Do you consider the reaction to be serious?</th>
<th>Yes / No</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

<table>
<thead>
<tr>
<th>Patient died due to reaction</th>
<th>Involved or prolonged inpatient hospitalisation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Life threatening</th>
<th>Involved persistent or significant disability or incapacity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Congenital abnormality</th>
<th>Medically significant; please give details:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This is to enable you to identify the patient in any future correspondence concerning this report.
Please list other drugs taken in the last 3 months prior to the reaction (including self-medication & herbal remedies)

Was the patient on any other medication?  Yes / No  If yes, please give the following information if known:

<table>
<thead>
<tr>
<th>Drug (Brand, if known)</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed), suspected drug interactions. For congenital abnormalities please state all other drugs taken during pregnancy and the date of the last menstrual period.

REPORTER DETAILS
Name and Professional Address: ____________________________

Post code: __________ Tel No: __________
Speciality: __________ Signature: __________ Date: __________

CLINICIAN (if not the reporter)
Name and Professional Address: ____________________________

Tel No: __________ Post code: __________
Speciality: __________

If you report from an area served by a Yellow Card Centre (YCC), MHRA may ask the Centre to communicate with you, on its behalf, about your report. See BNFC (page 21) for further details on YCCs. If you want only MHRA to contact you, please tick this box.

Send to Medicines and Healthcare products Regulatory Agency, CHM FREEPOST, LONDON SW8 5BR
How to use the Cardiovascular Risk Prediction Charts for Primary Prevention

These charts are for estimating cardiovascular disease (CVD) risk (non-fatal myocardial infarction and stroke, coronary and stroke death and new angina pectoris) for individuals who have not already developed coronary heart disease (CHD) or other major atherosclerotic disease. They are an aid to making clinical decisions about how intensively to intervene on lifestyle and whether to use antihypertensive, lipid lowering and anti-platelet medication, but should not replace clinical judgment.

- The use of these charts is not appropriate for patients who have existing diseases which already put them at high risk such as:
  - coronary heart disease or other major atherosclerotic disease;
  - familial hypercholesterolaemia or other inherited dyslipidaemias;
  - renal dysfunction including diabetic nephropathy;
  - type 1 and 2 diabetes mellitus.

- The charts should not be used to decide whether to introduce antihypertensive medication when blood pressure is persistently at or above 160/100 mmHg or when target organ damage due to hypertension is present. In both cases antihypertensive medication is recommended regardless of CVD risk. Similarly the charts should not be used to decide whether to introduce lipid-lowering medication when the ratio of serum total to HDL cholesterol exceeds 6. Such medication is generally then indicated regardless of estimated CVD risk.

- To estimate an individual’s absolute 10-year risk of developing CVD choose the chart for his or her sex, lifetime smoking status and age. Within this square identify the level of risk according to the point where the coordinates for systolic blood pressure and the ratio of total cholesterol to high density lipoprotein (HDL) cholesterol meet. If no HDL cholesterol result is available, then assume this is 1.0 mmol/litre and the lipid scale can be used for total cholesterol alone.

- Higher risk individuals (red areas) are defined as those whose 10-year CVD risk exceeds 20%, which is approximately equivalent to the coronary heart disease risk of >15% over the same period.

- The chart also assists in identifying individuals whose 10-year CVD risk is moderately increased in the range 10–20% (orange areas) and those in whom risk is lower than 10% over 10 years (green areas).

- Smoking status should reflect lifetime exposure to tobacco and not simply tobacco use at the time of assessment. For example, those who have given up smoking within 5 years should be regarded as current smokers for the purposes of the charts.

- The initial blood pressure and the first random (non-fasting) total cholesterol and HDL cholesterol can be used to estimate an individual’s risk. However, the decision on using drug therapy should generally be based on repeat risk factor measurements over a period of time.

(Continued over)
Men and women do not reach the level of risk predicted by the charts for the three age bands until they reach the ages 49, 59, and 69 years respectively. The charts will overestimate current risk most in the under 40s. Clinical judgement must be exercised in deciding on treatment in younger patients. However, it should be recognised that blood pressure and cholesterol tend to rise most and HDL cholesterol to decline most in younger people already with adverse levels. Left untreated, their risk at the age 49 years is likely to be higher than the projected risk shown on the age-under-50-years chart. From age 70 years the CVD risk, especially for men, is usually ≥ 20% over 10 years and the charts will underestimate true total CVD risk.

These charts (and all other currently available methods of CVD risk prediction) are based on groups of people with untreated levels of blood pressure, total cholesterol and HDL cholesterol. In patients already receiving antihypertensive therapy in whom the decision is to be made about whether to introduce lipid-lowering medication, or vice versa, the charts can only act as a guide. Unless recent pre-treatment risk factor values are available it is generally safest to assume that CVD risk is higher than that predicted by current levels of blood pressure or lipids on treatment.

CVD risk is also higher than indicated in the charts for:
- those with a family history of premature CVD (male first-degree relatives aged < 55 years and female first-degree relatives aged < 65 years) which increases the risk by a factor of approximately 1.3;
- men with HDL cholesterol < 1 mmol/litre or women with HDL cholesterol < 1.2 mmol/litre;
- those with raised triglyceride levels (> 1.7 mmol/litre);
- those with BMI ≥ 30 kg/m²;
- women with premature menopause;
- those who are not yet diabetic, but have impaired fasting glycaemia (6.1–6.9 mmol/litre) or impaired glucose tolerance (2 hour glucose ≥ 7.8 mmol/litre but < 11.1 mmol/litre in an oral glucose tolerance test).

The charts have not been validated in ethnic minorities and in some may underestimate CVD risk. For example, in people originating from the Indian subcontinent it is safest to assume that the CVD risk is higher than predicted from the charts (1.4 times).

An individual can be shown on the chart the direction in which his or her risk of CVD can be reduced by changing smoking status, blood pressure, or cholesterol, but it should be borne in mind that the estimate of risk is for a group of people with similar risk factors and that within that group there will be considerable variation in risk. It should also be pointed out in younger people that the estimated risk will generally not be reached before the age of 50, if their current blood pressure and lipid levels remain unchanged. The charts are primarily to assist in directing intervention to those who typically stand to benefit most.

The estimation of CVD risk in NICE clinical guideline 67 (May 2008): Lipid modification—Cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease (available at www.nice.org.uk) differs from that shown here as follows:

- estimated CVD risk increases by a factor of 1.5 in those with a family history of premature CHD (male first-degree relatives aged < 55 years and female first-degree relatives aged < 65 years)
- estimated CVD risk increases by a factor of 1.5–2 if more than one first-degree relative has a history of premature CHD
- estimated CVD risk for South Asian men is increased by a factor of 1.4
- CVD risk is higher than estimated in those with BMI > 40 kg/m²

The NICE guideline does not include the recommendation to treat all patients with a serum total to HDL cholesterol ratio of greater than 6 with lipid-lowering drugs.

The NICE guideline advises that the following factor is also taken into account when calculating CVD risk:
- presence of left ventricular hypertrophy

In addition, NICE advises that all patients over the age of 75 years should be considered at increased risk of CVD, and are likely to benefit from treatment.
Nondiabetic Men

Non-smoker

Smoker

Age under 50 years

Age 50–59 years

Age 60 years and over

CVD risk over next 10 years

SBP = systolic blood pressure mmHg

TC : HDL = serum total cholesterol to HDL cholesterol ratio

CVD risk <10% over next 10 years
CVD risk 10–20% over next 10 years
CVD risk >20% over next 10 years

(Continued over)
Nondiabetic Women

- **Non-smoker**
  - Age under 50 years
  - Age 50–59 years
  - Age 60 years and over

- **Smoker**
  - Age under 50 years
  - Age 50–59 years
  - Age 60 years and over

SBP = systolic blood pressure mmHg
TC : HDL = serum total cholesterol to HDL cholesterol ratio

© Central Manchester and Manchester Children’s University Hospitals NHS Trust
CPR 30:2
Until def brillator/monitor attached

1 Shock
150-360 J biphasic
or 360 J monophasic
Immediately resume CPR 30:2 for 2 min

Assess rhythm

Shockable (VF/pulseless VT)

1 Shock
150-360 J biphasic
or 360 J monophasic
Immediately resume CPR 30:2 for 2 min

Non-shockable (PEA/Asystole)

During CPR
• Correct reversible causes*
• Check electrode position and contact
• Attempt/verify: IV access, airway, and oxygen
• Give uninterrupted compressions when airway secure
• Give adrenaline every 3-5 min
• Consider: amiodarone, atropine, magnesium

*Reversible causes
Hyperoxia
Hypoxaemia
Hypoglycaemia/metabolic
Hypothermia
Tension pneumothorax
Tamponade, cardiac
Toxins
Thrombosis (coronary or pulmonary)

Open airway. Look for signs of life
Call Resuscitation Team

Unresponsive?

European Resuscitation Council
Reprinted from Resuscitation, E1(Suppl. 1): S45, © 2005, with permission from the European Resuscitation Council and Elsevier Ireland Ltd
Medical emergencies in the community

Drug treatment outlined below is intended for use by community healthcare professionals. Only drugs that are used for immediate relief are shown; advice on supporting care is not given. Where the patient’s condition requires investigation and further treatment, the patient should be transferred to hospital promptly.

Anaphylaxis
(section 3.4.3)

Adrenaline injection 1 mg/mL (1 in 1000)
- By intramuscular injection
  - CHILD UNDER 6 YEARS: 150 micrograms (0.15 mL), repeated every 5 minutes if necessary
  - CHILD 6–12 YEARS: 300 micrograms (0.3 mL), repeated every 5 minutes if necessary
  - CHILD 12–18 YEARS: 500 micrograms (0.5 mL), repeated every 5 minutes if necessary
  - ADULT: 500 micrograms (0.5 mL), repeated every 5 minutes if necessary

Chlorphenamine injection 10 mg/mL
- By intravenous injection over 1 minute or by intramuscular injection
  - CHILD 1–6 MONTHS: 250 micrograms/kg up to 4 times in 24 hours
  - CHILD 6 MONTHS–6 YEARS: 2.5 mg up to 4 times in 24 hours
  - CHILD 6–12 YEARS: 5 mg up to 4 times in 24 hours
  - CHILD 12–18 YEARS: 10 mg up to 4 times in 24 hours
  - ADULT: 10 mg up to 4 times in 24 hours

High-flow oxygen (section 3.6) should be given if required.

Hydrocortisone (preferably as sodium succinate) by intravenous injection (section 6.3.2) has delayed action but should be given to severely affected patients to prevent further deterioration.

Asthma: acute
(section 3.1)

Regard each emergency consultation as being for acute severe asthma until shown otherwise; failure to respond adequately at any time requires immediate referral to hospital

Either salbutamol aerosol inhaler 100 micrograms/metered inhalation
- By aerosol inhalation via large-volume spacer (and face mask in young children)
  - ADULT: 4–10 puffs each inhaled separately, repeated every 10–20 minutes if necessary
  - CHILD: 4–10 puffs each inhaled separately, repeated every 10–20 minutes if necessary

or salbutamol nebuliser solution 1 mg/mL, 2 mg/mL
- By inhalation of nebulised solution (via oxygen-driven nebuliser)
  - CHILD UNDER 5 YEARS: 2.5 mg every 10–20 minutes if necessary
  - CHILD 5–12 YEARS: 2.5–5 mg every 10–20 minutes if necessary
  - ADULT and CHILD OVER 12 YEARS: 2.5–5 mg every 10–20 minutes if necessary

or terbutaline nebuliser solution 2.5 mg/mL
- By inhalation of nebulised solution (via oxygen-driven nebuliser)
  - CHILD UNDER 5 YEARS: 2.5 mg every 10–20 minutes if necessary
  - CHILD 5–12 YEARS: 5–10 mg every 10–20 minutes if necessary
  - ADULT and CHILD OVER 12 YEARS: 10 mg every 10–20 minutes if necessary

Plus (in all cases)
either prednisolone soluble tablets 5 mg
- By mouth
  - CHILD UNDER 18 YEARS: 1–2 mg/kg (max. 40 mg) once daily for 3 days; if child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (CHILD UNDER 2 YEARS max. 40 mg, OVER 2 YEARS max. 50 mg) once daily
  - ADULT and CHILD OVER 12 YEARS: 10 mg every 10–20 minutes if necessary

or hydrocortisone (preferably as sodium succinate)
- By intravenous injection
  - CHILD UNDER 1 YEAR: 25 mg
  - CHILD 1–5 YEARS: 50 mg
  - CHILD 6–12 YEARS: 100 mg
  - ADULT: 100 mg

High-flow oxygen (section 3.6) if available (via face mask in children)

Monitor response 15 to 30 minutes after nebulisation; if any signs of acute asthma persist, arrange hospital admission. While awaiting ambulance, repeat nebulised beta2 agonist (as above) and give with ipratropium nebuliser solution 250 micrograms/mL
- By inhalation of nebulised solution (via oxygen-driven nebuliser)
  - CHILD UNDER 12 YEARS: 250 micrograms, repeated as necessary
  - ADULT and CHILD OVER 12 YEARS: 500 micrograms, repeated as necessary

Angina: unstable
(section 2.6)

Aspirin dispersible tablets 75 mg, 300 mg
- By mouth (dispersed in water or chewed)
  - ADULT: 300 mg

Plus
either Glyceryl trinitrate aerosol spray 400 micrograms/metered dose
- Sublingually
  - ADULT: 1–2 sprays, repeated as required

or Glyceryl trinitrate tablets 300 micrograms, 500 micrograms, 600 micrograms
- Sublingually
  - ADULT: 0.3–1 mg, repeated as required
Croup (section 3.1)

**Dexamethasone** oral solution 2 mg/5 mL.

- **By mouth**
  - **CHILD 1 MONTH–2 YEARS** 150 micrograms/kg as a single dose

Convulsions (section 4.8.2)

**Either diazepam** rectal solution 2 mg/mL, 4 mg/mL.

- **By rectum**, repeated after 10 minutes if necessary
  - **NEONATE** 1.25–2.5 mg
  - **CHILD 1–2 YEARS** 5–10 mg
  - **ADULT and CHILD OVER 12 YEARS** up to max. 30 mg

**or midazolam** buccal liquid 10 mg/mL or injection solution given by buccal route

- **By buccal administration**
  - **NEONATE** 300 micrograms/kg, repeated once if necessary
  - **CHILD 1–6 MONTHS** 300 micrograms/kg (max. 2.5 mg), repeated once if necessary
  - **CHILD 6 MONTHS–1 YEAR** 2.5 mg, repeated once if necessary
  - **CHILD 1–5 YEARS** 5 mg, repeated once if necessary
  - **CHILD 5–10 YEARS** 7.5 mg, repeated once if necessary
  - **CHILD 10–18 YEARS** 10 mg, repeated once if necessary
  - **ADULT** 10 mg, repeated once if necessary

Diabetic hypoglycaemia (section 6.1.4)

**Glucose** or **sucrose**

- **By mouth**
  - **CHILD 2–18 YEARS** approx. 10–20 g (2–4 teaspoonfuls of sugar or 3–6 sugar lumps or 55–110 mL *Lucozade® Energy Original* or 90–180 mL *Coca-Cola®*—both non-diet versions or *GlucoGet®* one or two 25-g tubes (containing glucose 10 g/25-g tube)) repeated after 10–15 minutes if necessary
  - **ADULT** approx. 10–20 g (2–4 teaspoonfuls of sugar or 3–6 sugar lumps or 55–110 mL *Lucozade® Energy Original* or 90–180 mL *Coca-Cola®*—both non-diet versions or *GlucoGet®* one or two 25-g tubes (containing glucose 10 g/25-g tube)) repeated after 10–15 minutes if necessary

**or if hypoglycaemia unresponsive or if oral route cannot be used**

**Glucagon** injection 1 mg/mL

- **By subcutaneous, intramuscular, or intravenous injection**
  - **CHILD BODY-WEIGHT UNDER 25 KG** 500 micrograms (0.5 mL)
  - **CHILD BODY-WEIGHT OVER 25 KG** 1 mg (1 mL)
  - **ADULT** 1 mg (1 mL)
  - **or if hypoglycaemia prolonged or unresponsive to glucagon after 10 minutes**

**Glucose** intravenous infusion 10%

- **By intravenous injection into large vein**
  - **CHILD 1 MONTH–18 YEARS** 5 mL/kg (glucose 500 mg/kg)

**Glucose** intravenous infusion 20%

- **By intravenous injection into large vein**
  - **ADULT** 50 mL

Febrile convulsions lasting longer than 15 minutes (section 4.8.3)

**Diazepam** rectal solution 2 mg/mL, 4 mg/mL

- **By rectum**
  - **CHILD BODY-WEIGHT OVER 10 KG** up to max. 30 mg, repeated after 15 minutes if necessary

Meningococcal disease (Table 1, section 5.1)

**Benzylpenicillin sodium** injection 600 mg, 1.2 g

- **By intravenous injection** (or by intramuscular injection if venous access not available)
  - **NEONATE** 300 mg
  - **CHILD 1 MONTH–1 YEAR** 300 mg
  - **CHILD 1–10 YEARS** 600 mg
  - **CHILD 10–18 YEARS** 1.2 g
  - **ADULT** 1.2 g

**Note** Give single dose and transfer urgently to hospital

**or if history of allergy to penicillin**

**Cefotaxime** injection 1 g

- **By intravenous injection** (or by intramuscular injection if venous access not available)
  - **NEONATE** 50 mg/kg
  - **CHILD 1 MONTH–12 YEARS** 50 mg/kg (max. 1 g)
  - **CHILD 12–18 YEARS** 1 g
  - **ADULT** 1 g

**Note** Give single dose and transfer urgently to hospital

**or if history of immediate hypersensitivity reaction (including anaphylaxis, angioedema, or urticarial reaction) to penicillin or to cephalosporins**

**Chloramphenicol** injection 1 g

- **By intravenous injection**
  - **CHILD 1 MONTH–18 YEARS** 12.5–25 mg/kg
  - **ADULT** 12.5–25 mg/kg

**Note** Give single dose and transfer urgently to hospital
**Myocardial infarction**  
*(section 2.10.1)*

**Aspirin** dispersible tablets 75 mg, 300 mg  
- By mouth (dispersed in water or chewed)  
  **ADULT** 300 mg

**Glyceryl trinitrate** aerosol spray 400 micrograms/ 
metered dose  
- Sublingually  
  **ADULT** 1–2 sprays, repeated as required

*or* **Glyceryl trinitrate** tablets 300 micrograms, 
500 micrograms, 600 micrograms  
- Sublingually  
  **ADULT** 0.3–1 mg, repeated as required

**Metoclopramide** injection 5 mg/mL  
- By intravenous injection  
  **ADULT (UNDER 60 KG) 18–19 YEARS** 5 mg  
  **ADULT (OVER 60 KG) 18–19 YEARS** 10 mg  
  **ADULT OVER 19 YEARS** 10 mg

**Diamorphine** injection (5 mg powder for reconstitution)  
- By slow intravenous injection (1 mg/minute)  
  **ADULT** 5 mg followed by a further 2.5–5 mg if necessary; **ELDERLY** or **FRAIL** patients, reduce dose by half

**Oxygen**, if appropriate

---

**Pneumonia: uncomplicated**  
*(Table 1, section 5.1)*

**Amoxicillin** oral suspension 125 mg/5 mL, 250 mg/ 
5 mL; capsules 250 mg  
- By mouth  
  **CHILD 6 MONTHS–1 YEAR** 125 mg 3 times daily  
  **CHILD 1–5 YEARS** 250 mg 3 times daily  
  **CHILD 5–18 YEARS** 500 mg 3 times daily  
  **ADULT** 0.5–1 g 3 times daily

*or if allergic to penicillin or atypical organism sus- 
pected*

**Erythromycin** oral suspension 125 mg/5 mL, 250 mg/ 
5 mL; tablets 250 mg  
- By mouth  
  **CHILD 6 MONTHS–2 YEARS** 125 mg 4 times daily  
  **CHILD 2–8 YEARS** 250 mg 4 times daily  
  **CHILD 8–18 YEARS** 250–500 mg 4 times daily  
  **ADULT** 500 mg 4 times daily
Approximate conversions and units

<table>
<thead>
<tr>
<th>lb</th>
<th>kg</th>
<th>stones</th>
<th>kg</th>
<th>mL</th>
<th>fl oz</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.45</td>
<td>1</td>
<td>6.35</td>
<td>50</td>
<td>1.8</td>
</tr>
<tr>
<td>2</td>
<td>0.91</td>
<td>2</td>
<td>12.70</td>
<td>100</td>
<td>3.5</td>
</tr>
<tr>
<td>3</td>
<td>1.36</td>
<td>3</td>
<td>19.05</td>
<td>150</td>
<td>5.3</td>
</tr>
<tr>
<td>4</td>
<td>1.81</td>
<td>4</td>
<td>25.40</td>
<td>200</td>
<td>7.0</td>
</tr>
<tr>
<td>5</td>
<td>2.27</td>
<td>5</td>
<td>31.75</td>
<td>500</td>
<td>17.6</td>
</tr>
<tr>
<td>6</td>
<td>2.72</td>
<td>6</td>
<td>38.10</td>
<td>1000</td>
<td>35.2</td>
</tr>
<tr>
<td>7</td>
<td>3.18</td>
<td>7</td>
<td>44.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3.63</td>
<td>8</td>
<td>50.80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4.08</td>
<td>9</td>
<td>57.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>4.54</td>
<td>10</td>
<td>63.50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>4.99</td>
<td>11</td>
<td>69.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5.44</td>
<td>12</td>
<td>76.20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>5.90</td>
<td>13</td>
<td>82.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>6.35</td>
<td>14</td>
<td>88.90</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>15</td>
<td>95.25</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Length

1 metre (m) = 1000 millimetres (mm)
1 centimetre (cm) = 10 mm
1 inch (in) = 25.4 mm
1 foot (ft) = 12 inches = 304.8 mm

Mass

1 kilogram (kg) = 1000 grams (g)
1 gram (g) = 1000 milligrams (mg)
1 milligram (mg) = 1000 micrograms
1 microgram = 1000 nanograms
1 nanogram = 1000 picograms

Volume

1 litre = 1000 millilitres (mL)
1 millilitre (1 mL) = 1000 microlitres
1 pint = 568 mL

Other units

1 kilocalorie (kcal) = 4186.8 joules (J)
1000 kilocalories (kcal) = 4.1868 megajoules (MJ)
1 megajoule (MJ) = 238.8 kilocalories (kcal)
1 millimetre of mercury (mmHg) = 133.3 pascals (Pa)
1 kilopascal (kPa) = 7.5 mmHg (pressure)

Plasma-drug concentrations in the BNF are expressed in mass units per litre (e.g. mg/litre). The approximate equivalent in terms of amount of substance units (e.g. micromol/litre) is given in brackets.

Prescribing for children

Weight, height and body surface area

The table below shows the mean values for weight, height and body surface area by age; these values may be used to calculate doses in the absence of actual measurements. However, an individual's actual weight and height might vary considerably from the values in the table and it is important to ensure that the value chosen is appropriate. In most cases the actual measurement should be obtained as soon as possible and the dose re-calculated.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight</th>
<th>Height</th>
<th>Body surface</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>kg</td>
<td>cm</td>
<td>m²</td>
</tr>
<tr>
<td>Full-term neonate</td>
<td>3.5</td>
<td>50</td>
<td>0.24</td>
</tr>
<tr>
<td>1 month</td>
<td>4.2</td>
<td>55</td>
<td>0.27</td>
</tr>
<tr>
<td>2 months</td>
<td>4.5</td>
<td>57</td>
<td>0.28</td>
</tr>
<tr>
<td>3 months</td>
<td>5.6</td>
<td>59</td>
<td>0.33</td>
</tr>
<tr>
<td>4 months</td>
<td>6.5</td>
<td>62</td>
<td>0.36</td>
</tr>
<tr>
<td>6 months</td>
<td>7.7</td>
<td>67</td>
<td>0.41</td>
</tr>
<tr>
<td>1 year</td>
<td>10</td>
<td>76</td>
<td>0.49</td>
</tr>
<tr>
<td>3 years</td>
<td>15</td>
<td>94</td>
<td>0.65</td>
</tr>
<tr>
<td>5 years</td>
<td>18</td>
<td>108</td>
<td>0.74</td>
</tr>
<tr>
<td>7 years</td>
<td>23</td>
<td>120</td>
<td>0.87</td>
</tr>
<tr>
<td>10 years</td>
<td>30</td>
<td>132</td>
<td>1.10</td>
</tr>
<tr>
<td>12 years</td>
<td>39</td>
<td>148</td>
<td>1.30</td>
</tr>
<tr>
<td>14 years</td>
<td>50</td>
<td>163</td>
<td>1.50</td>
</tr>
<tr>
<td>Adult male</td>
<td>68</td>
<td>173</td>
<td>1.80</td>
</tr>
<tr>
<td>Adult female</td>
<td>56</td>
<td>163</td>
<td>1.60</td>
</tr>
</tbody>
</table>
Recommended wording of cautionary and advisory labels

For details see Appendix 9

1 Warning. May cause drowsiness
2 Warning. May cause drowsiness. If affected do not drive or operate machinery. Avoid alcoholic drink
3 Warning. May cause drowsiness. If affected do not drive or operate machinery
4 Warning. Avoid alcoholic drink
5 Do not take indigestion remedies at the same time of day as this medicine
6 Do not take indigestion remedies or medicines containing iron or zinc at the same time of day as this medicine
7 Do not take milk, indigestion remedies, or medicines containing iron or zinc at the same time of day as this medicine
8 Do not stop taking this medicine except on your doctor's advice
9 Take at regular intervals. Complete the prescribed course unless otherwise directed
10 Warning. Follow the printed instructions you have been given with this medicine
11 Avoid exposure of skin to direct sunlight or sun lamps
12 Do not take anything containing aspirin while taking this medicine
13 Dissolve or mix with water before taking
14 This medicine may colour the urine
15 Caution flammable: keep away from fire or flames
16 Allow to dissolve under the tongue. Do not transfer from this container. Keep tightly closed. Discard 8 weeks after opening
17 Do not take more than ... in 24 hours
18 Do not take more than ... in 24 hours or ... in any one week
19 Warning. Causes drowsiness which may continue the next day. If affected do not drive or operate machinery. Avoid alcoholic drink
21 ... with or after food
22 ... half to one hour before food
23 ... an hour before food or on an empty stomach
24 ... sucked or chewed
25 ... swallowed whole, not chewed
26 ... dissolved under the tongue
27 ... with plenty of water
28 To be spread thinly ...
29 Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
30 Do not take with any other paracetamol products
31 Contains aspirin and paracetamol. Do not take with any other paracetamol products
32 Contains aspirin
33 Contains an aspirin-like medicine
Abbreviations and symbols

Internationally recognised units and symbols are used in the BNF where possible.

ACBS Advisory Committee on Borderline Substances, see Appendix 7
ACE Angiotensin-converting enzyme
ADHD Attention deficit hyperactivity disorder
AIDS Acquired immunodeficiency syndrome
approx. approximately
AV atrioventricular
BAN British Approved Name
BMI body mass index
BP British Pharmacopoeia 2009, unless otherwise stated
BPC British Pharmaceutical Codex 1973 and Supplement 1976, unless otherwise stated
CHM Commission on Human Medicines
CHMP Committee for Medicinal Products for Human Use
CNS central nervous system
CPMP Committee on Proprietary Medicinal Products
CRM Committee on the Review of Medicines
CSM Committee on Safety of Medicines (now subsumed under Commission on Human Medicines)
d. c. direct current
DPF Dental Practitioners’ Formulary
e/c enteric-coated (termed gastro-resistant in BP)
ECG electrocardiogram
EEG electro-encephalogram
EMEA European Medicines Agency
f/c film-coated
G6PD glucose 6-phosphate dehydrogenase
HIV Human immunodeficiency virus
HRT Hormone replacement therapy
i/m intramuscular
i/v intravenous
INR international normalised ratio
MAOI Monoamine-oxidase inhibitor
max. maximum
MCA Medicines Control Agency, now MHRA
MHRA Medicines and Healthcare products Regulatory Agency
m/r modified-release
NCL no cautionary labels, see Appendix 9
NHS National Health Service
NICE National Institute for Health and Clinical Excellence
NPF Nurse Prescribers’ Formulary
NSAID Non-steroidal anti-inflammatory drug
PGD patient group direction
rINN Recommended International Non-proprietary Name
RSV respiratory syncytial virus
s/c sugar-coated
SLS Selected List Scheme
SMAC Standing Medical Advisory Committee
SMC Scottish Medicines Consortium
SPC Summary of Product Characteristics
spp. species
SSRI Selective serotonin reuptake inhibitor
UK United Kingdom
Units for SI units see Prescription Writing, p. 4
USP United States Pharmacopoeia 31 (2008), unless otherwise stated
WHO World Health Organization

Latin abbreviations

Directions should be in English without abbreviation. However, Latin abbreviations have been used when prescribing.

The following is a list of appropriate abbreviations. It should be noted that the English version is not always an exact translation.

a. c. = ante cibum (before food)

b. d. = bis die (twice daily)
o. d. = omni die (every day)
o. m. = omni mane (every morning)
o. n. = omni nocte (every night)
p. c. = post cibum (after food)
p. r. n. = pro re nata (when required)
q. d. s. = quater die sumendum (to be taken four times daily)
q. q. h. = quarta quaque hora (every four hours)
stat = immediately
t. d. s. = ter die sumendum (to be taken three times daily)
t.i.d. = ter in die (three times daily)

E numbers

<table>
<thead>
<tr>
<th>E102</th>
<th>Tartrazine</th>
<th>E223</th>
<th>Sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>E104</td>
<td>Quinoline Yellow</td>
<td>E320</td>
<td>Butylated</td>
</tr>
<tr>
<td>E110</td>
<td>Sunset Yellow FCF</td>
<td>E321</td>
<td>Butylated</td>
</tr>
<tr>
<td>E123</td>
<td>Amanthranthine</td>
<td>E420</td>
<td>Hydroxyanisole</td>
</tr>
<tr>
<td>E124</td>
<td>Ponceau 4R</td>
<td>E421</td>
<td>Hydroxytoluene</td>
</tr>
<tr>
<td>E127</td>
<td>Erythrosine BS</td>
<td>E422</td>
<td>Lecithins</td>
</tr>
<tr>
<td>E132</td>
<td>Indigo Carmine</td>
<td>E423</td>
<td>Sorbitol</td>
</tr>
<tr>
<td>E142</td>
<td>Green S</td>
<td>E424</td>
<td>Mannitol</td>
</tr>
<tr>
<td>E171</td>
<td>Titanium Dioxide</td>
<td>E425</td>
<td>Glycerol</td>
</tr>
<tr>
<td>E172</td>
<td>Iron oxides, Iron hydroxides</td>
<td>E901</td>
<td>Beeswax</td>
</tr>
<tr>
<td>E200</td>
<td>Sorbic Acid</td>
<td>E1520</td>
<td>Propylene Glycol (white and yellow)</td>
</tr>
<tr>
<td>E211</td>
<td>Sodium Benzoate</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

not prescribable under National Health Service (NHS)

prescription-only medicine, see How to use the BNF, p. ix

considered by the Joint Formulary Committee to be less suitable for prescribing, see How to use the BNF, p. ix