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) 424 7298
- 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 (020) 7188 3849 (020) 7188 3855
- Northwick Park Hospital (020) 8869 2761 (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

**DIAL: Paediatric Drug (Medicine) Information Advisory Line**
Paediatric and neonatal drug information resource provided by Alder Hey Royal Liverpool Children’s NHS Trust
Tel: (0151) 252 5837
Fax: (0151) 220 3885
info@dial.org.uk
www.dial.org.uk

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

**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 1130 (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)

**Information on drug therapy relating to dental treatment can be obtained by telephoning:**
Liverpool (0151) 794 8117

**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

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

**Medicines for Children information leaflets**
Medicines information for parents and carers.
www.medicinesforchildren.org.uk

**Patient Information Lines**
NHS Direct 0845 4647

**Addresses, telephone and fax numbers and email addresses of manufacturers listed in BNF Publications are shown in the Index of Manufacturers**
BNF for children

2009

The essential resource for clinical use of medicines in children

bnfc.org
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RG21 6XS
UK
Tel: +44 (0) 1256 302 692
Fax: +44 (0) 1256 812 558
E-mail: orders@macmillan.co.uk
www.pharmpress.com

RPS Publishing also supplies BNF for Children in digital formats suitable for standalone use and for use on a personal digital assistant (PDA).
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- Medical emergencies in the community ................................................................ Inside back cover
BNF for Children aims to provide prescribers, pharmacists and other healthcare professionals with sound up-to-date information on the use of medicines for treating children.

A joint publication of the British Medical Association, the Royal Pharmaceutical Society of Great Britain, the Royal College of Paediatrics and Child Health, and the Neonatal and Paediatric Pharmacists Group, BNF for Children (‘BNFC’) is published under the authority of a Paediatric Formulary Committee.

Many areas of paediatric practice have suffered from inadequate information on effective medicines. BNFC addresses this significant knowledge gap by providing practical information on the use of medicines in children of all ages from birth to adolescence. Medicines for Children (RCPCH Publications Ltd) and the British National Formulary itself form the basis for BNFC. Information in BNFC has been validated against emerging evidence, best-practice guidelines, and crucially, advice from a network of clinical experts.

Drawing information from manufacturers’ literature where appropriate, BNFC also includes a great deal of advice that goes beyond marketing authorisations (product licences). This is necessary because licensed indications frequently do not cover the clinical needs of children; in some cases, products for use in children need to be specially manufactured or imported. Careful consideration has been given to establishing the clinical need for unlicensed interventions with respect to the evidence and experience of their safety and efficacy; local paediatric formularies, clinical literature and national information resources have been invaluable in this process.

BNFC has been designed for rapid reference and the information presented has been carefully selected to aid decisions on prescribing, dispensing and administration of medicines. Less detail is given on areas such as malignant disease and the very specialist use of medicines generally undertaken in tertiary centres. BNFC should be interpreted in the light of professional knowledge and it should be supplemented as necessary by specialised publications. Information is also available from medicines information services (see inside front cover).

The website (bnfc.org) includes additional information of relevance to healthcare professionals. BNFC is also available on other digital platforms.

BNFC aims to provide information suited to the needs of the clinician and recognises that, although this edition represents a considerable advance in the content and presentation of information on the paediatric use of medicines, further changes will be necessary. Comments from healthcare professionals are therefore very welcome and should be sent to:

British National Formulary Publications,
Royal Pharmaceutical Society of Great Britain, 1 Lambeth High Street, London SE1 7JN.
bafc@bnf.org
The Paediatric Formulary Committee is grateful to individuals and organisations that have provided advice and information to the *BNF for Children*.


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The *BNF for Children* has valuable access to the Martindale data banks by courtesy of S. Sweetman and staff.
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How *BNF for Children* is constructed

*BNF for Children* (BNFC) 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 children.

Information in BNFC has been validated against emerging evidence, best-practice guidelines, and advice from a network of clinical experts. BNFC includes a great deal of advice that goes beyond marketing authorisations (product licences or summaries of product characteristics). This is necessary because licensed indications frequently do not cover the clinical needs of children; in some cases, products for use in children need to be specially manufactured or imported. Careful consideration has been given to establishing the clinical need for unlicensed interventions with respect to the evidence and experience of their safety and efficacy.

Hundreds of changes are made between editions, and the most clinically significant changes are listed at the front of each edition (p. xiv).

---

**Paediatric Formulary Committee**

The Paediatric Formulary Committee (PFC) is responsible for the content of BNFC. The PFC includes a neonatologist and paediatricians appointed by the Royal College of Paediatrics and Child Health, paediatric pharmacists appointed by the Royal Pharmaceutical Society of Great Britain and the Neonatal and Paediatric Pharmacists Group, doctors appointed by the BMJ Publishing Group, a GP appointed by the Royal College of General Practitioners, and representatives from the Medicines and Healthcare products Regulatory Agency (MHRA) and the UK health departments. The PFC decides on matters of policy and reviews amendments to BNFC in the light of new evidence and expert advice. The Committee meets every 6 months and each member also receives proofs of all BNFC chapters for review before publication.

**Dental Advisory Group**

The Dental Advisory Group oversees the preparation of advice on the drug management of dental and oral conditions; the group includes representatives from the British Dental Association.

**Editorial team**

BNFC staff editors are pharmacists with a sound understanding of how drugs are used in clinical practice, including paediatrics. Each staff editor is responsible for editing, maintaining, and updating specific chapters of BNFC. During the publication cycle the staff editors review information in BNFC 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 Paediatric 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 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**

BNFC uses about 80 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 BNFC remains reliable by:

- commenting on the relevance of the text in the context of best clinical practice in the UK;
• 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 BNFC diverges from summaries of product characteristics;
• advising on the use of unlicensed medicines or of licensed medicines for unlicensed uses (‘off-label’ use);
• providing independent advice on drug interactions, prescribing in hepatic impairment, renal impairment, pregnancy, breast-feeding, neonatal care, palliative care, and the emergency treatment of poisoning.

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

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

Summaries of product characteristics  BNFC receives summaries of product characteristics (SPCs) of all new products as well as revised SPCs for existing products. The SPCs are a key 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 (BNFC 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 BNFC 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 BNFC 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 BNFC information is discussed above.

Literature  Staff editors monitor core medical, paediatric, and pharmaceutical journals. Research papers and reviews relating to drug therapy are carefully processed. When a difference between the advice in BNFC 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 Paediatric Formulary Committee. BNFC enjoys a close working relationship with a number of national information providers.

Systematic reviews  BNFC 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 BNFC advice.

Consensus guidelines The advice in BNFC is checked against consensus guidelines produced by expert bodies. A number of bodies make drafts or pre-publication copies of the guidelines available to BNFC; it is therefore possible to ensure that a consistent message is disseminated. BNFC 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 Paediatric formularies and reference sources are used to provide background information for the review of existing text or for the construction of new text. The BNFC team works closely with the editorial team that produces *Martindale: The Complete Drug Reference*. BNFC 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 BNFC 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 BNFC complies with the relevant sections of the Medicines Act.

BNFC 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 BNFC as are guidelines from bodies such as the Royal College of Paediatrics and Child Health.

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

Pricing information NHS Prescription Services provide information on prices of medicinal products and appliances in BNFC. BNFC also receives and processes price lists from product suppliers.

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

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

Virtual user groups BNFC has set up virtual user groups across various healthcare professions (e.g. doctors, pharmacists, nurses). 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.
How to use BNF for Children

The BNF for Children provides information on the use of medicines in children ranging from neonates (including preterm neonates) to adolescents. The terms infant, child, and adolescent are not used consistently in the literature; to avoid ambiguity actual ages are used in the dose statements in BNF for Children. The term neonate is used to describe a newborn infant aged 0–28 days. The terms child or children are used generically to describe the entire range from infant to adolescent in BNF for Children.

BNF for Children is divided into the following broad areas.

General Guidance
The section on general guidance includes general advice on the use of medicines for managing childhood conditions. It also includes information on prescribing controlled drugs and the management of palliative care. Advice is given on the reporting of adverse reactions. General principles on the use of medicines in hepatic impairment, renal impairment, pregnancy, and breast-feeding are also included in this section.

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

DRUG NAME

Cautions details of precautions required and also any monitoring required
Hepatic impairment advice for use of drug in these circumstances
Renal impairment
Pregnancy Breast-feeding Counselling verbal explanation to the patient of specific details of the drug treatment (e.g. posture when taking a medicine)
Contra-indications details of any contra-indications to use of drug
Side-effects details of common and more serious side-effects
Licensed use licensing status where this is of clinical relevance
Indication and dose Details of uses and indications
• By route
  Child dose and frequency of administration (max. dose) for specific age group
• By alternative route
  Child dose and frequency
Approved Name (Non-proprietary) 
Pharmaceutical form colour, coating, active ingredient and amount in dosage form, net price, pack size = basic NHS price. Label: (as in Appendix 3)

Proprietary Name (Manufacturer) 
Pharmaceutical form sugar-free, active ingredient mg/mL, net price, pack size = basic NHS price. Label: (as in Appendix 3)
Excipients include clinically important excipients or electrolytes
Note Specific notes about the product e.g. handling

Preparations
Preparations usually follow immediately after the drug which is their main ingredient.

Preparations are included under a non-proprietary title, if they are marketed under such a title, if they are not otherwise prescribable under the NHS, or if they may be prepared extemporaneously.

If proprietary preparations are of a distinctive colour this is stated.

In the case of compound preparations the indications, cautions, contra-indications, side-effects, and interactions of all constituents should be taken into account for prescribing.

When no suitable licensed preparation is available details of preparations that may be imported or formulations available as manufactured specials or extemporaneous preparations are included.

Drugs
The symbol \( \text{\textregistered} \) is used to denote those preparations considered 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 \( \text{\textregistered} \)

This symbol \( \text{\textregistered} \) has been placed against preparations that are available only on a prescription from an appropriate practitioner.

The symbol \( \text{\textregistered} \) indicates that the preparation is subject to the prescription requirements of the Misuse of Drugs Act. For advice on prescribing such preparations see Prescribing Controlled Drugs.

Preparations not available for NHS prescription

This symbol \( \text{\textregistered} \) has been placed against preparations 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 provided that the prescription shows an appropriate non-proprietary name.

Prices
Prices have been calculated from the basic cost used in pricing NHS prescriptions. 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. Since the prices shown in the BNF for Children do not include professional fees and overhead allowances, they are not suitable for quoting to patients seeking private prescriptions or contemplating over-the-counter purchase.
to a particular system of the body or to an aspect of neonatal and paediatric medical care. Each chapter is then divided into sections which begin with notes on the selection and use of medicines. Guidance on dental and oral conditions is identified by means of a relevant heading (e.g. Dental and Orofacial pain) in the appropriate sections. The notes are followed by details of relevant drugs and preparations.

**Drug entries**

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. Information on the properties of each drug is organised as shown in the illustration below; the information on cautions, contraindications, side-effects, dose and indications reflects, as far as possible, the manufacturer's summary of product characteristics.

*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.

For the majority of drugs, *doses* are expressed in terms of body-weight (i.e. standardised by weight). To calculate the dose for a given child the weight-standardised dose is multiplied by the child's weight (or occasionally by the child's ideal body-weight). The calculated dose should not normally exceed the maximum recommended dose for an adult. For example if the dose is 8 mg/kg (max. 300 mg) a child of 10 kg body-weight should receive 80 mg but a child of 40 kg body-weight should receive 300 mg (rather than 320 mg).

Doses are expressed for specific age ranges; neonatal doses are preceded by the word Neonate, all other doses are preceded by the word Child. Age ranges in the BNF for Children are described as follows:

- Child 1 month–4 years refers to a child from 1 month old up to their 4th birthday;
- Child 4–10 years refers to a child from the day of their 4th birthday up to their 10th birthday.

However, a pragmatic approach should be applied to these cut-off points depending on the child's physiological development, condition, and if weight is appropriate for the child's age.

**Emergency treatment of poisoning**

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

**Appendixes and indexes**

The appendixes include information on interactions, borderline substances, 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. xvii).

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 3).

Many medicines are available in manufacturers’ original packs complete with patient information leaflets. Where patient packs are available, the *BNF for Children* 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 this publication 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 for Children, see also General guidance, patient information leaflets.

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 for Children (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 (www.nhsbsa.nhs.uk). This system gives users on-line access through NHSnet to the 3 years’ prescribing data held on the NHS Prescription Services’ database; tools for analysing the data are also provided.

Prices in the BNF for Children

Basic net prices are given in the BNF for Children 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.

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 for Children 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. It should be noted that separate Drug Tariffs are applicable to England and Wales, Scotland, and Northern Ireland. Prices in the different tariffs may vary.
Changes for this edition

Significant changes

The BNF for Children is revised yearly and numerous changes are made between issues. All copies of BNF for Children 2008 should therefore be withdrawn and replaced by BNF for Children 2009. Significant changes have been made in the following sections for BNF for Children 2009:

Adjustment of drug dosages in renal impairment [updated advice and terminology], Prescribing in renal impairment
Salicylate poisoning, Emergency treatment of poisoning
Paracetamol poisoning, Emergency treatment of poisoning
Cyanide poisoning, Emergency treatment of poisoning
Ethylene glycol and methanol poisoning, Emergency treatment of poisoning
Heavy metal poisoning, Emergency treatment of poisoning
Alginate raft-forming oral suspensions, section 1.1.2
Infliximab for subacute manifestations of ulcerative colitis [NICE guidance], section 1.5
 Fistulating Crohn's disease, section 1.5
Irritable Bowel Syndrome, section 1.5
Aminosalicylates [monitoring of renal function], section 1.5.1
Management of acute asthma, section 3.1
Beclomethasone dipropionate CFC-free metered dose inhalers [MHRA/CHM advice], section 3.2
Oxygen, section 3.6
Over-the-counter cough and cold medicines [MHRA/CHM advice], section 3.9.1
Melatonin, section 4.1.1
Attention deficit hyperactivity disorder [updated advice], section 4.4
Fentanyl [risk of severe respiratory depression with transdermal patch], section 4.7.2
Pethidine [restricted indications], section 4.7.2
Clostridium difficile infection, section 5.1, Table 1
Hospital-acquired pneumonia, section 5.1, Table 1
Throat infections, sinusitis, and otitis media, section 5.1, Table 1
Tendon damage with quinolones [updated advice], section 5.1.12
Oseltamivir, zanamivir, and amantadine for the prophylaxis and treatment of influenza [updated NICE guidance], section 5.3.4
Oseltamivir [prophylaxis and treatment of influenza in child under 1 year of age], section 5.3.4
Ascaricides (common round worm infections) [updated advice], section 5.5.2
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
Diabetic ketoacidosis [updated advice], section 6.1.3
Treatment of hypoglycaemia [updated advice on glucose-containing liquids], section 6.1.4
Combined hormonal contraceptives and risk factors for venous thromboembolism [addition of smoking], section 7.3.1
Nocturnal enuresis [updated advice], section 7.4.2
Administration of vinca alkaloids [NPSA advice], section 8.1.4
Tacrolimus [MHRA/CHM advice], section 8.2.2
Management of hyperkalaemia, section 9.8.2
Over-the-counter cough and cold medicines [MHRA/CHM advice], section 12.2.2
Topical oral pain relief products containing salicylates [CHM advice], section 12.3.1
Topical corticosteroids [counselling, application, and labelling requirements], section 13.4
Sunscreen preparations [updated advice on Sun Protection Factor], section 13.8.1
Active immunity [reorganised and updated], section 14.1
Immunisation schedule [table], section 14.1
Vaccines and antisera [reformatted and updated], section 14.4
Risk of neurological and haematological toxic effects with nitrous oxide, section 15.1.2
Enteral feeds and nutritional supplements [new tables], Borderline Substances, Appendix 2
Intravenous infusions for neonatal intensive care, Appendix 4
**Dose changes**

Changes in dose statements introduced into *BNF for Children 2009*:

- Aciclovir [chickenpox and herpes zoster infection], p. 386
- Alpha tocopheryl acetate [malabsorption in cystic fibrosis], p. 582
- Alprostadil, p. 166
- Atomoxetine, p. 234
- Atracurium, p. 780
- Atropine sulphate [control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block], p. 770
- Betaine, p. 594
- Caffeine, p. 202
- Carglumic acid, p. 592
- Chlorphenamine [intramuscular or intravenous injection], p. 194
- Chloroquine [treatment of benign malaria], p. 396 and [prophylaxis of malaria], p. 402
- Ciprofloxacin, p. 358
- Concerta®, p. 236
- Dantrolene, p. 786
- Diazepam [status epilepticus], p. 284
- Digoxin [maintenance doses for 10–18 years], p. 97
- Dobutamine, p. 143
- Doxycycline [late latent syphilis], p. 330
- Epipen®, p. 201
- Eprex®, p. 538
- Equasym XL®, p. 236
- Erythromycin [gastro-intestinal stasis], p. 58
- Etanercept, p. 612
- European viper venom antiserum [text], p. 47
- Folic acid [megaloblastic anaemia], p. 535
- Fentanyl [use in anaesthesia], p. 777
- Fluconazole [vaginal candidiasis and candidal balanitis], p. 366
- Gabapentin [epilepsy], p. 270
- Ganciclovir [congenital cytomegalovirus infection of the CNS], p. 388
- Glycopyronnium [control of upper airways secretion and hypersalivation], p. 770
- Halothane, p. 767
- Hydrocortisone [acute hypersensitivity reactions], p. 451
- Hydroxyurea, p. 330
- Ipratropium bromide [by inhalation of nebulised solution], p. 169
- Lenograstim [mobilisation of peripheral blood progenitor cells following adjunctive myelosuppressive chemotherapy (to improve yield)], p. 545
- Levetiracetam, p. 273
- Levosimendan, p. 438
- Lisinopril, p. 133
- Methotrexate [severe Crohn’s disease], p. 75
- Midazolam [intravenous injection for sedation], p. 774
- Midazolam [status epilepticus], p. 286
- Naloxone, p. 40
- Normacol Plus®, p. 79
- Pancuronium, p. 781
- Pentasa® granules, p. 70
- Pholcodine, p. 209
- Pralidoxime chloride, p. 47
- Propofol [induction of anaesthesia], p. 765
- Pseudoephedrine, p. 210
- Pulmicort® aerosol inhalation, p. 187
- Pyridostigmine, p. 615
- Rifinamide, p. 276
- Salbutamol [by continuous intravenous infusion], p. 174
- Salbutamol [by inhalation of aerosol or nebulised solution], p. 169
- Salofalk® granules, p. 70
- Sevoflurane [induction of anaesthesia], p. 768
- Sodium bicarbonate, p. 550
- Streptomycin, p. 355
- Sucralfate, p. 62
- Thiamine [metabolic disorders], p. 576
- Timentin®, p. 318
- Uniphyllin Continus®, p. 180
- Varilrix®, p. 753
- Varivax®, p. 754
- Vecuronium, p. 782
- Vitamin D, p. 578
- Warfarin, p. 153
- Zanamivir [prevention of influenza], p. 392

**Classification changes**

Classification changes have been made in the following sections of *BNF for Children 2009*:

**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 5.1.2** Cefepime, carbapenems, and other beta-lactams [title change]

**Section 5.1.2.2** Carbapenems [new sub-section]

**Section 5.1.2.3** Other beta-lactam antibiotics [new sub-section]

**Section 6.1.2.3** Other antidiabetic drugs [title change]

**Section 6.1.6** Oral glucose tolerance test [sub-section title change]

**Section 11.8.2** Ocular diagnostic and perioperative preparations [title change]
Deleted preparations
Preparations listed below have been discontinued during the compilation of BNF for Children 2009, or are still available but are not considered suitable for inclusion by the Paediatric Formulary Committee (see footnote):

AeroBec® preparations
Agenerase®
Aquasept®
Ascalix®
Benzatropine
Cardilate MR®
Carylderm®
Cimetidine®
Claforan®
Daclizumab
Efcorelan®
Flagyl® intravenous infusion
Fletchers® Enemas
Graneodin®
Halycitrol®
Hydrocortone®
Idrolax®
Intal® Spincaps
Liquid paraffin®
Locoid C®
Navoban®
Neo-Cortef®
Nifopress® Retard
Paraldehyde injection
Phentolamine mesilate
Pulmicort LS®
Rapolyte®
Senokot® granules
Ster-Zac Bath Concentrate®
Trid-Acordyl® preparations
Tropisetron
Vaseline Dermacare®
Vepesid® infusion
Vibracyn® capsules
Viaform-Hydrocortisone®
Viracept® powder
Viraferon®
Volmax®
Zenapax®

New preparations included in this edition
Preparations included in the relevant sections of BNF for Children 2009:

Advagraf®, p. 524
Apidra®, p. 424
Aptivus®, p. 382
Atripla®, p. 378
Avamys®, p. 650
Bumetanide oral liquid, p. 104
Bridion®, p. 784
Cardioxane®, p. 499
Celsentri®, p. 384
Clasteon®, p. 470
Clinitas®, p. 639
Diacomit®, p. 277
Epilim Chronosphere®, p. 280
Ferinject®, p. 532
Ferriprox®, p. 541
Flexbumin®, p. 557
Geloplasma®, p. 557
Grazax®, p. 197
Humira®, p. 612
Intal® CFC-free inhaler, p. 190
Intelenxe®, p. 383
Isentress®, p. 385
Isoplex®, p. 557
Kavan®, p. 562
Laxido®, p. 83
LMX 4®, p. 789
Maxitram SR®, p. 260
MucoClear®, p. 208
Myacam®, p. 370
Myozyme®, p. 591
Nicorette® Invisi patches, p. 293
NuvaRing®, p. 481
Ocusan®, p. 639
Optive®, p. 637
Oxyal®, p. 639
Prezista®, p. 379
Ratiogranst®, p. 545
Rebetol®, p. 394
Retacrit®, p. 538
Rosicor®, p. 710
Sandocare®+D 600, p. 582
Siklos®, p. 539
Tetraspan®, p. 558
Thymglobuline®, p. 521
Ttramquet SR®, p. 260
Vimpat®, p. 271
Vismed®, p. 639
Vismed® Mult, p. 639
Volulyte®, p. 558
Zavesca®, p. 595

1. Not considered suitable for inclusion by the Paediatric Formulary Committee
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 *BNF for Children*.

### 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; *BNF for Children* has adopted a similar style.

<table>
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<th>Former BAN</th>
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Name changes

*BNF for Children* xvii
Medicines should be given to children only when they are necessary, and in all cases the potential 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).

It is important to discuss treatment options carefully with the child and the child’s carer (see also Taking Medicines to Best Effect, below). In particular, the child and the child’s carer 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, this should be highlighted.

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

- difficulty in taking the medicine (e.g. inability to swallow the medicine);
- unattractive formulation (e.g. unpleasant taste);
- prescription not collected or not dispensed;
- purpose of medicine not clear;
- perceived lack of efficacy;
- real or perceived side-effects;
- carers’ or child’s perception of the risk and severity of side-effects may differ from that of the prescriber;
- ambiguous instructions for administration.

The prescriber, the child’s carer, and the child (if appropriate) should agree on the health outcomes desired and on the strategy for achieving them (‘concordance’). The prescriber should be sensitive to religious, cultural, and personal beliefs of the child’s family that can affect acceptance of medicines.

Taking the time to explain to the child (and carers) the rationale and the potential adverse effects of treatment may improve compliance. Reinforcement and elaboration of the physician’s instructions by the pharmacist and other members of the healthcare team can be important. Giving advice on the management of adverse effects and the possibility of alternative treatments may encourage carers and children 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.

**Administration of medicines to children** Children should be involved in decisions about taking medicines and encouraged to take responsibility for using them correctly. The degree of such involvement will depend on the child’s age, understanding, and personal circumstances.

Occasionally a medicine or its taste has to be disguised or masked with small quantities of food. However, unless specifically permitted (e.g. some formulations of pancreatin), a medicine should **not** be mixed with large quantities of food because the full dose might not be taken and the child might develop an aversion to food if the medicine imparts an unpleasant taste. Medicines should **not** be mixed or administered in a baby’s feeding bottle.

Children under 5 years (and some older children) find a liquid formulation more acceptable than tablets or capsules. However, for long-term treatment it may be possible for a child to be taught to take tablets or capsules.

An oral syringe (see below) should be used for accurate measurement and controlled administration of an oral liquid medicine. The unpleasant taste of an
oral liquid can be disguised by flavouring it or by giving a favourite food or drink immediately afterwards, but the potential for food-drug interactions should be considered.

Advice should be given on dental hygiene to those receiving medicines containing cariogenic sugars for long-term treatment; sugar-free medicines should be provided whenever possible.

Children with nasal feeding tubes in place for prolonged periods should be encouraged to take medicines by mouth if possible; enteral feeding should generally be interrupted before the medicine is given (particularly if enteral feeds reduce the absorption of a particular drug). Oral liquids can be given through the tube provided that precautions are taken to guard against blockage; the dose should be washed down with warm water. When a medicine is given through a nasogastric tube to a neonate, sterile water must be used to accompany the medicine or to wash it down.

The intravenous route is generally chosen when a medicine cannot be given by mouth; reliable access, often a central vein, should be used for children whose treatment involves irritant or inotropic drugs or who need to receive the medicine over a long period or for home therapy. The subcutaneous route is used most commonly for insulin administration. Intramuscular injections should preferably be avoided in children, particularly neonates, infants, and young children. However, the intramuscular route may be advantageous for administration of single doses of medicines when intravenous cannulation would be more problematic or painful to the child. Certain drugs, e.g. some vaccines, are only administered intramuscularly.

The intrathecal, epidural and intraosseous routes should be used only by staff specially trained to administer medicines by these routes. Local protocols for the management of intrathecal injections must be in place (section 8.1).

**Managing medicines in school** Administration of a medicine during schooltime should be avoided if possible; medicines should be prescribed for once or twice-daily administration whenever practicable. If the medicine needs to be taken in school, this should be discussed with parents or carers and the necessary arrangements made in advance; where appropriate, involvement of a school nurse should be sought. Managing Medicines in Schools and Early Years Settings produced by the Department of Health provides guidance on using medicines in schools (www.dh.gov.uk).

**Patient information leaflets** Manufacturers’ patient information leaflets that accompany a medicine cover only the licensed use of the medicine (see BNF for Children and Marketing Authorisation, below). Therefore, when a medicine is used outside its licence, it may be appropriate to advise the child and the child’s parent or carer that some of the information in the leaflet might not apply to the child’s treatment. Where necessary, inappropriate advice in the patient information leaflet should be identified and reassurance provided about the correct use in the context of the child’s condition.

**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 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. 21). 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. Where appropriate, the child and the child’s carers should be asked about the use of their medicines, including dietary supplements and topical products. The scope of BNF
for Children 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.

**BNF for Children and marketing authorisation** Where appropriate the doses, indications, cautions, contra-indications, and side-effects in BNF for Children reflect those in the manufacturers’ Summaries of Product Characteristics (SPCs) which, in turn, reflect those in the corresponding marketing authorisations (formerly known as Product Licences). BNF for Children does not generally include proprietary medicines that are not supported by a valid 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, BNF for Children reflects advice that is the most clinically relevant regardless of any variation in the marketing authorisation. Unlicensed products can be obtained from ‘special-order’ manufacturers or specialist importing companies, see p. 943.

As far as possible, medicines should be prescribed within the terms of the marketing authorisation. However, many children 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.

**BNF for Children** includes advice involving the use of unlicensed medicines or of licensed medicines for unlicensed uses (‘off-label’ use). Such advice reflects careful consideration of the options available to manage a given condition and the weight of evidence and experience of the unlicensed intervention (see also Unlicensed Medicines, p. 7). Where the advice falls outside a drug’s marketing authorisation, BNF for Children shows the licensing status in the drug monograph. However, limitations of the marketing authorisation should not preclude unlicensed use where clinically appropriate.

Prescribing unlicensed medicines or 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.

**Drugs and skilled tasks** Prescribers should advise children and their carers if treatment is likely to affect their ability to perform skilled tasks. This applies especially to drugs with sedative effects; patients should be warned that these effects are increased by alcohol.

**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. It is provided with an adaptor and an instruction leaflet. The 5-mL spoon is used for doses of 5 mL (or multiples thereof). Different sizes of oral syringe are available for the accurate measurement of smaller volumes, although these can not be prescribed.

**Excipients** Branded oral liquid preparations that do not contain fructose, glucose, or sucrose are described as ‘sugar-free’ in BNF for Children. Preparations containing hydrogenated glucose syrup, mannitol, maltitol, sorbitol, or xylitol are also marked ‘sugar-free’ since they do not cause dental caries. Children receiving medicines containing cariogenic sugars, or their carers, should be advised of dental hygiene measures to prevent caries. Sugar-free preparations should be used whenever possible, particularly if treatment is required for a long period.

Where information on the presence of alcohol, aspartame, gluten, sulphites, tartrazine, arachis (peanut) oil or sesame oil is available, this is indicated in BNF for Children 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.

The presence of benzyl alcohol and polyoxyl castor oil (polyethoxylated castor oil) in injections is indicated in BNF for Children. 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 BNF for Children; 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 metronidazole. In the absence of information on excipients in BNF for Children and in the product literature, contact the manufacturer (see Index of Manufacturers) if it is essential to check details.

**Health and safety**  When handling chemical or biological materials particular attention should be given to the possibility of allergy, fire, explosion, radiation, or poisoning. Care is required to avoid sources of heat (including hair dryers) when flammable substances are used on the skin or hair. Substances, such as corticosteroids, some antimicrobials, 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. Healthcare professionals and carers should guard against exposure to sensitising, toxic or irritant substances if it is necessary to crush tablets or open capsules.

**Security 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.

**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 child. However, a Patient Group Direction for supply and administration of medicines by other healthcare professionals can be used where it would benefit the child’s 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 classes of healthcare professionals; the Direction is signed by a doctor (or dentist) and by a pharmacist. Further information on Patient Group Directions is available in Health Service Circular HSC 2000/026 (England), HDL (2001) 7 (Scotland), and WHC (2000) 116 (Wales).

**NICE and Scottish Medicines Consortium**  Advice issued by the National Institute for Health and Clinical Excellence (NICE) and by the Scottish Medicines Consortium (SMC) is included in BNF for Children when relevant. If advice within a NICE Single Technology Appraisal differs from SMC advice, the Scottish Executive expects NHS Boards within NHS Scotland to comply with the SMC advice. Details of the advice together with updates can be obtained from www.nice.org.uk and from www.scottishmedicines.org.
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.

Prescriptions1 should be written legibly in ink or otherwise so as to be indelible2, should be dated, should state the full name and address of the patient, and should be signed in ink by the prescriber3. The age and the date of birth of the child 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.

Wherever appropriate the prescriber should state the current weight of the child to enable the dose prescribed to be checked. Consideration should also be given to including the dose per unit mass e.g. mg/kg or the dose per m² body-surface area e.g. mg/m² where this would reduce error.

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.

Use of the decimal point is acceptable to express a range, e.g. 0.5 to 1 g.

(b) ‘Micrograms’ and ‘nanograms’ should not be abbreviated. Similarly ‘units’ should not be abbreviated.

(c) The term ‘millilitre’ (ml or mL)4 is used in medicine and pharmacy, and cubic centimetre, c.c., or cm³ 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.

Care should be taken to ensure the child receives the correct dose of the active drug. Therefore, the dose should normally be stated in terms of the mass of the active drug (e.g. ‘125 mg 3 times daily’); terms such as ‘5 mL’ or ‘1 tablet’ should be avoided except for compound preparations.

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. 3 (except for preparations intended to be measured with a pipette).

(e) The names of drugs and preparations should be written clearly and not abbreviated, using approved titles only (see also advice in box on p. 6 to avoid creating generic titles for modified-release preparations).

(f) 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.

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

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1. These recommendations are acceptable for prescription-only medicines (p.8). For items marked (C) see also Prescribing Controlled Drugs, p.17.

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 BNF for Children; both ‘mL’ and ‘ml’ are recognised SI abbreviations.
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 for 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 there is a demonstrable difference in clinical effect between different manufacturer’s versions of the formulation, making it important that the child should always receive the same brand; in such cases, the brand name or the manufacturer should be stated.

Non-proprietary names of compound preparations e.g. co-codamol that appear in BNF for Children are those that have been introduced 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 duration of action.

Strengths and quantities  The strength or quantity to be contained in capsules, lozenges, tablets, etc. should be stated by the prescriber. In particular, strengths of liquid preparations should be clearly stated (e.g. 125 mg/5 mL).
Supply of medicines

When supplying a medicine for a child, the pharmacist should ensure that the child and the child’s carer understand the nature and identity of the medicine and how it should be used. The child and the carer should be provided with appropriate information (e.g. how long the medicine should be taken for and what to do if a dose is missed or the child vomits soon after the dose is given).

Safety in the home Carers and relatives of children must be warned to keep all medicines out of the reach and sight of children. Tablets, capsules and 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 child’s carer 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 pharmacy for destruction.

Validity of prescriptions 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.

Strength and quantities If a pharmacist receives an incomplete prescription for a systemically administered preparation1 and considers it would not be appropriate for the patient to return to the prescriber, 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 initialled 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 initialled and dated;

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

Unlicensed medicines A drug or formulation that is not covered by a marketing authorisation (see also BNF for Children and Marketing Authorisation) may be obtained from a pharmaceutical company, imported by a specialist importer, manufactured by a commercial or hospital licensed manufacturing unit, or prepared extemporaneously (see below) against a prescription.

1. With the exception of temazepam, an incomplete prescription is not acceptable for controlled drugs in schedules 2 and 3 of the Misuse of Drugs Regulations 2001.
The safeguards that apply to products with marketing authorisation should be extended, as far as possible, to the use of unlicensed medicines. The safety, efficacy, and quality (including labelling) of unlicensed medicines should be assured by means of clear policies on their prescribing, purchase, supply, and administration. Extra care is required with unlicensed medicines because less information may be available on the drug and any formulation of the drug.

The following should be agreed with the supplier when ordering an unlicensed or extemporaneously prepared medicine:

- the specification of the formulation;
- documentation confirming the specification and quality of the product supplied (e.g. a certificate of conformity or of analysis);
- for imported preparations product and licensing information should be supplied in English.

Extemporaneous preparations A product should be dispensed extemporaneously only when no product with a marketing authorisation is available. Every effort should be made to ensure that an extemporaneously prepared product is stable and that it delivers the requisite dose reliably; the child should be provided with a consistent formulation regardless of where the medicine is supplied to minimise variations in quality. Where there is doubt about the formulation, advice should be sought from a medicines information centre, the pharmacy at a children’s hospital, a hospital production unit, a hospital quality control department, or the manufacturer.

In many cases it is preferable to give a licensed product by an unlicensed route (e.g. an injection solution given by mouth) than to prepare a special formulation. When tablets or capsules are cut, dispersed, or used for preparing liquids immediately before administration, it is important to confirm uniform dispersal of the active ingredient, especially if only a portion of the solid content (e.g. a tablet segment) is used or if only an aliquot of the liquid is to be administered.

In some cases the child’s clinical condition may require a dose to be administered in the absence of full information on the method of administration. It is important to ensure that the appropriate supporting information is available at the earliest opportunity.

Preparation of products that produce harmful dust (e.g. cytotoxic drugs, hormones, or potentially sensitising drugs such as neomycin) should be avoided or undertaken with appropriate precautions to protect staff and carers (see also Safety in the Home, above).

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 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).

Labelling medicines The name of the medicine should appear on the label unless the prescriber indicates otherwise; the name shown on the label should be that written on the prescription. The strength should also be stated on the label in the case of preparations that are available in different strengths.

Labels 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.
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 dentist, 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 name and address of the pharmacy;
   (v) the words ‘Emergency supply’;
   (vi) 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 dentist, 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).
Drug treatment in children

Children, and particularly neonates, differ from adults in their response to drugs. Special care is needed in the neonatal period (first 28 days of life) and doses should always be calculated with care; the risk of toxicity is increased by a reduced rate of drug clearance and differing target organ sensitivity.

Many children’s doses in *BNF for Children* 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) (see also How to Use *BNF for Children*, p. xi). These methods should be used rather than attempting to calculate a child’s dose on the basis of doses used in adults. If a dose is not stated, prescribers should seek advice from a medicines information centre.

For most drugs the adult maximum dose should not be exceeded. For example if the dose is 8 mg/kg (max. 300 mg) a child of 10 kg body-weight should receive 80 mg but a child of 40 kg body-weight should receive 300 mg (rather than 320 mg). For certain drugs, young children may require a higher dose per kilogram than adults because of their higher metabolic rates. Calculation by body-weight in the overweight child may result in much higher doses being administered than necessary; in such cases, the dose should be calculated from an ideal weight, related to height and age.

**Body surface area (BSA) estimates** are often preferable to body-weight for calculating paediatric doses since many physiological phenomena correlate better with body surface area.

Body surface area can be estimated from weight; see inside back cover.

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

**Dose frequency** Most drugs can be administered at slightly irregular intervals during the day. Some drugs, e.g. antimicrobials, are best given at regular intervals. 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 child’s bedtime.
Prescribing in hepatic impairment

Children have a large reserve of hepatic metabolic capacity and modification of the choice and dosage of drugs is usually unnecessary even in apparently severe liver disease. However, special consideration is required in the following situations:

- liver failure characterised by severe derangement of liver enzymes and profound jaundice; the use of sedative drugs, opioids, and drugs such as diuretics and amphotericin which produce hypokalaemia may precipitate hepatic encephalopathy;
- impaired coagulation, which can affect response to oral anticoagulants;
- in cholestatic jaundice elimination may be impaired of drugs such as fusidic acid and rifampicin which are excreted in the bile;
- in hypoproteinaemia, the effect of highly protein-bound drugs such as phenytoin, prednisolone, warfarin, and benzodiazepines may be increased;
- use of hepatotoxic drugs is more likely to cause toxicity in children with liver disease; such drugs should be avoided if possible;
- in neonates, particularly preterm neonates, and also in infants metabolic pathways may differ from older children and adults because liver enzyme pathways may be immature.

Where care is needed in hepatic impairment, this is indicated under the relevant drug in *BNF for Children*. 
Prescribing in renal impairment

The use of drugs in children with reduced renal function can give rise to problems for several reasons:

- reduced renal excretion of a drug or its metabolites may produce toxicity;
- sensitivity to some drugs is increased even if elimination is unimpaired;
- many side-effects are tolerated poorly by children with renal impairment;
- some drugs are not effective when renal function is reduced;
- neonates, particularly preterm, may have immature renal function.

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 dose regimens based on glomerular filtration rate 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.

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 concentration. Because the plasma half-life of drugs excreted by the kidney is prolonged in renal impairment, it can take many doses at the reduced dosage to achieve a therapeutic plasma concentration. The loading dose should usually be the same as the initial dose for a child with normal renal function.

Nephrotoxic drugs should, if possible, be avoided in children with renal disease because the consequences of nephrotoxicity are likely to be more serious when the renal reserve is already reduced.

Glomerular filtration rate is low at birth and increases rapidly during the first 6 months. Thereafter, glomerular filtration rate increases gradually to reach adult levels by 1–2 years of age, when standardised to a typical adult body surface area (1.73 m²). In the first weeks after birth, serum creatinine falls; a single measure of serum creatinine provides only a crude estimate of renal function and observing the change over days is of more use. In the neonate, a sustained rise in serum creatinine or a lack of the expected postnatal decline, is indicative of a reduced glomerular filtration rate.

Dose recommendations are based on the severity of renal impairment. This is expressed in terms of glomerular filtration rate (mL/minute/1.73 m²).

The following equations provide a guide to glomerular filtration rate.

Child over 1 year:
Estimated glomerular filtration rate (mL/minute/1.73 m²)= $40 \frac{1}{2} \times$ height (cm)/serum creatinine (micromol/litre)

Neonate:
Estimated glomerular filtration rate (mL/minute/1.73 m²)= $30 \frac{1}{2} \times$ height (cm)/serum creatinine (micromol/litre)

The serum-creatinine concentration is sometimes used as a measure of renal function but is only a rough guide even when corrected for age, weight, and sex.

1. The values used in these formulas may differ according to locality or laboratory.
Important

The information on dose adjustment in *BNF for Children* is expressed in terms of estimated glomerular filtration rate.

Renal function in adults is increasingly being reported as estimated glomerular filtration rate (eGFR) normalised to a body surface area of 1.73 m$^2$; however, eGFR is derived from the MDRD (Modification of Diet in Renal Disease) formula which is not validated for use in children. eGFR derived from the MDRD formula should not be used to adjust drug doses in children with renal impairment.

In *BNF for Children*, values for measures of renal function are included where possible. However, where such values are not available, the *BNF for Children* reflects the terms used in the published information.

*Chronic kidney disease in adults: UK guidelines for identification, management and referral* (March 2006) defines renal function as follows:

<table>
<thead>
<tr>
<th>Degree of impairment</th>
<th>eGFR$^1$: mL/minute/1.73 m$^2$</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$^2$: 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. Estimated glomerular filtration rate (eGFR) derived from the Modification of Diet in Renal Disease (MDRD) formula for use in patients over 18 years
2. NICE clinical guideline 73 (September 2008)—Chronic kidney disease: Stage 3A eGFR = 45–59, Stage 3B eGFR = 30–44

**Dialysis**

For prescribing in children on renal replacement therapy consult specialist literature.

Drug prescribing should be kept to the minimum in all children 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.

Where care is needed in renal impairment, this is indicated under the relevant drug entry in *BNF for Children*.  

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1 Prescribing in renal impairment BNFC 2009

General guidance
Prescribing in pregnancy

Drugs can have harmful effects on the fetus at any time during pregnancy. It is important to bear this in mind when prescribing for a female of childbearing age or for men trying to father a child.

During the first trimester drugs may 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 may affect the growth and functional development of the fetus or have toxic effects on fetal tissues; and drugs given shortly before term or during labour may have adverse effects on labour or on the neonate after delivery.

BNF for Children identifies drugs which:
- may have harmful effects in pregnancy and indicates the trimester of risk;
- are not known to be harmful in pregnancy.

The information is based on human data but information on animal studies has been included for some drugs when its omission might be misleading. Maternal drug doses may require adjustment during pregnancy due to changes in maternal physiology but this is beyond the scope of BNF for Children.

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 humans but no drug is safe beyond all doubt in early pregnancy. Screening procedures are available where there is a known risk of certain defects.

Absence of a drug from the list does not imply safety. It should be noted that BNF for Children 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:

Tel: (0191) 232 1525
Tel: (0191) 223 1307 (out of hours emergency only)
www.nyrdtc.nhs.uk/Services/teratology/teratology.html
Prescribing in breast-feeding

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).

Most medicines given to a mother cause no harm to breast-fed infants and there are few contra-indications to breast-feeding when maternal medicines are necessary. However, administration of some drugs to nursing mothers can harm the infant. In the first week of life, some such as preterm or jaundiced infants are at a slightly higher risk of toxicity.

Toxicity to the infant can occur if the drug enters the milk in pharmacologically significant quantities. The concentration in milk of some drugs (e.g. fluvastatin) may exceed the concentration in maternal plasma so that therapeutic doses in the mother can cause toxicity to the infant. Some drugs inhibit the infant’s sucking reflex (e.g. phenobarbital) while others can affect lactation (e.g. bromocriptine). Drugs in breast milk may, at least theoretically, cause hypersensitivity in the infant even when concentration is too low for a pharmacological effect. BNF for Children identifies drugs:

- which should be used with caution or which are contra-indicated in breast-feeding for the reasons given above;
- which, on present evidence, may be given to the mother during breast-feeding, because they appear in milk in amounts which are too small to be harmful to the infant;
- which are not known to be harmful to the infant although they are present in milk in significant amounts.

For many drugs insufficient evidence is available to provide guidance and it is advisable to administer only essential drugs to a mother during breast-feeding. Because of the inadequacy of information on drugs in breast milk information in BNF for Children should be used only as a guide; absence of information does not imply safety.
Prescribing Controlled Drugs

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, phencyclidine, remifentanil, and class B substances when prepared for injection.

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

**Class C** includes: certain drugs related to the amphetamines such as benzphetamine and chlorphentermine, buprenorphine, diethylpropion, mazindol, meprobamate, pemoline, pipradol, 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, secobarbital, glutethimide, amfetamine, and cocaine and are subject to the full controlled drug requirements relating to prescriptions, safe custody (except for secobarbital), the need to keep registers, etc. (unless exempted in Schedule 5).

**Schedule 3** includes the barbiturates (except secobarbital, now Schedule 2), buprenorphine, diethylpropion, mazindol, meprobamate, midazolam, pentazocine, phentermine, and temazepam. They are subject to the special prescription requirements (except for temazepam) but not to the safe custody requirements (except for buprenorphine 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 (but see Department of Health Guidance, p. 18) 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 BNF for Children by the symbol [*](Controlled Drug). The principal legal requirements relating to medical prescriptions are listed below (see also Department of Health Guidance, p. 18).
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 carers and delay in supply of the necessary medicine. A prescription for a Controlled Drug in Schedules 2, 3, or 4 is valid for 28 days from the date stated thereon.

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.

For a sample prescription, see p. 19

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 requirement 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.

Dependence and misuse The most serious drugs of addiction are cocaine, diamorphine (heroin), morphine, and the synthetic opioids.

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 mixture should be written in millilitres.
6. The instruction ‘one as directed’ constitutes a dose but ‘as directed’ does not.
7. Implementation date for N. Ireland not confirmed.
8. The prescriber may forward-date the prescription; the start date may also be specified in the body of the prescription.
9. A total of 14 days’ treatment by instalment of any drug listed in Schedule 2 of the Misuse of Drugs Regulations, buprenorphine and diazepam may be prescribed in England. In England, forms FP10(MDA) (blue) and FP10H(MDA) (blue) should be used. In Scotland, forms GP10 (peach), HBP (blue), or HBPA (pink) should be used. In Wales a total of 14 days’ treatment by instalment of any drug listed in Schedules 2–5 of the Misuse of Drugs Regulations may be prescribed. In Wales, forms WP10(MDA) or form WP10HP(AD) should be used.

2 Prescribing Controlled Drugs BNFC 2009

General guidance
Despite marked reduction in the prescribing of amphetamines the 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. The prescriber should keep a close eye on the amount prescribed to prevent patients or their carers 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 and being vigilant to methods for obtaining medicines which 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 doctor. It is sensible to reduce dosages steadily or to issue weekly or even daily prescriptions for small amounts if dependence is suspected.

The stealing and misuse of prescription forms could be minimised by the following precautions:

(a) 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;

(b) draw a diagonal line across the blank part of the form under the prescription;

(c) the quantity should be shown in words and figures when prescribing drugs prone to abuse; this is obligatory for controlled drugs (see Prescriptions, above);

(d) alterations are best avoided but if any are made they should be clear and unambiguous; add initials against altered items;

(e) 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 (020) 7035 0484 or licensing_enquiry.aadu@homeoffice.gsi.gov.uk.

Applications must be supported by a covering letter from the prescriber and should give details of:

- the patient’s name and current address;
- the quantities of drugs to be carried;
- the strength and form in which the drugs will be dispensed;
- the country or countries of destination;
- the dates of travel to and from the United Kingdom.

Applications for licences should be sent to 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 wish to take Controlled Drugs abroad while accompanying patients may similarly be issued with licences. Licences are not normally issued to doctors who wish 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 facilitate passage through UK Customs and Excise control. For clearance in the country to be visited it would be 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—for further advice and contact telephone numbers consult the BNF.
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 unrecognised 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, prepaid Yellow Cards for reporting are available from the address below and are also bound in this book (inside back cover).

Medicines and Healthcare products Regulatory Agency
CHM
Freepost
London, SW8 5BR.
Tel: (0800 731 6789)

The reporting of all suspected adverse drug reactions in children, including those relating to unlicensed or off-label use of medicines, is strongly encouraged through the Yellow Card Scheme 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 may not be extensively tested in children;
- children may be more susceptible to developmental disorders or they may have delayed adverse reactions which do not occur in adults;
- 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.

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.

Spontaneous reporting is particularly valuable for recognising possible new hazards rapidly. 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, or if other drugs have been given at the same time. Reports of overdoses (deliberate or accidental) can complicate the assessment of adverse drug reactions, but provide important information on the potential toxicity of drugs.

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, North West
70 Pembroke Place
Liverpool, L69 3GF.
Tel: (0151) 794 8206

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

Yellow Card Centre, Northern & Yorkshire
Wolfson Unit
Claremont Place
Newcastle upon Tyne, NE2 4HH.
Tel: (0191) 260 6181 (direct line)
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.

Drug Safety Update is a monthly newsletter from the MHRA and the Commission on Human Medicines (CHM); it is available at www.mhra.gov.uk/mhra/drugsafetyupdate.

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 0808 100 3352. Alternatively, patient Yellow Cards are available from pharmacies or can be downloaded from www.mhra.gov.uk, where more detailed information on patient reporting is available.

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.

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.

Side-effects in the BNF for Children The BNF for Children 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 for Children.

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 for Children]: 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

Symptoms Children may be poor at expressing the symptoms of an adverse drug reaction and parental opinion may be required.

Delayed drug effects Some reactions (e.g. cancers, and effects on development) 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.

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.
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 child has had previous reactions to the drug or formulation;
- prescribe as few drugs as possible and give very clear instructions to the child, parent, or carer;
- whenever possible use a familiar drug; with a new drug be particularly alert for adverse reactions or unexpected events;
- consider if excipients (e.g. colouring agents) may be contributing to the adverse reaction. If the reaction is minor, a trial of an alternative formulation of the same drug may be considered before abandoning the drug;
- obtain a full drug history including asking if the child is already taking other drugs including over-the-counter medicines; interactions may occur;
- age and hepatic or renal disease may alter the metabolism or excretion of drugs, particularly in neonates, which can affect the potential for adverse effects. Genetic factors may also be responsible for variations in metabolism, and therefore for the adverse effects of the drug;
- warn the child, parent, or carer if serious adverse reactions are liable to occur.

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
17–157 Market Towers
1 Nine Elms Lane
London SW8 5NQ
(020) 7084 2574 (weekdays 9.00 am–5.00 pm)
or (020) 7210 3000 (urgent calls any other time)
info@mhra.gsi.gov.uk
Prescribing in palliative care

Palliative care is the active total care of children and young adults who have incurable, life-limiting conditions and are not expected to survive beyond young adulthood.

The child may be cared for in a hospice or at home according to the needs of the child and the child’s family. In all cases, children should receive total care of their physical, emotional, social, and spiritual needs, and their families should be supported throughout. In particular, specialist palliative care is essential for end-of-life care of the child and for supporting the family through death and bereavement.

Drug treatment The number of drugs should be as few as possible. Oral medication is usually appropriate 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.

Paracetamol (p. 247) or a NSAID (section 10.1.1) given regularly will often make the use of opioid analgesics unnecessary. A NSAID may also control the pain of bone secondaries. Radiotherapy and bisphosphonates (section 6.6.2) may also be useful for pain due to bone metastases.

An opioid analgesic (section 4.7.2) such as codeine (p. 252), alone or in combination with a non-opioid analgesic at adequate dosage, may be helpful in the control of moderate pain if non-opioid analgesics alone are not sufficient. If these preparations do not control the pain, morphine (p. 255) is the most useful opioid analgesic. Alternatives to morphine, including transdermal fentanyl (see below and p. 253), 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 or physical dependence (addiction).

Equivalent single doses of opioid analgesics

<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 (subcutaneous)</td>
<td>3 mg</td>
</tr>
<tr>
<td>Hydromorphone hydrochloride</td>
<td>1.3 mg</td>
</tr>
<tr>
<td>Oxycodone (oral)</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Oral route Morphine (p. 255) is given by mouth as an oral solution or as standard (‘immediate release’) tablets regularly every 4 hours, the initial dose depending largely on the patient’s previous treatment. If the first dose of morphine is no more effective than the previous analgesic, the next dose should be increased by 30–50%, 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 low doses of morphine are usually adequate there should be no hesitation in increasing the dose stepwise according to response if necessary.

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).

When the pain is controlled and the patient’s 24-hour morphine requirement is established, the daily dose can be given as a single dose or in 2 divided doses as a modified-release preparation. The first dose of the modified-release preparation is given within 4 hours of the last dose of the oral solution.1

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.
MST Continus® tablets or suspension (p. 257) are designed for twice daily administration; MXL® capsules (p. 257) allow administration of the total daily morphine requirement as a single dose.

Alternatively, a modified-release preparation may be commenced immediately and the dose adjusted according to pain control. The starting dose of modified-release preparations designed for twice daily administration is usually 200–800 micrograms/kg every 12 hours if no other analgesic (or only paracetamol) has been taken previously, but to replace a weaker opioid analgesic (such as codeine) the starting dose is usually higher. Increments should be made to the dose, not to the frequency of administration, which should remain at every 12 hours.

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). Children often require a higher dose of morphine in proportion to their body-weight compared to adults. Children are more susceptible to certain adverse effects of opioids such as urinary retention (which can be eased by carbachol or bethanechol), and opioid-induced pruritus.

Oxycodone (p. 257) is used in a child who requires an opioid but cannot tolerate morphine. If the child is already receiving an opioid, oxycodone should be started at a dose equivalent to the current analgesic.

Parenteral route Diamorphine (p. 252) is preferred for injection because, being more soluble, it can be given in a smaller volume. The equivalent subcutaneous dose is approximately a third of the oral dose of morphine. Subcutaneous infusion of diamorphine via a continuous infusion device can be useful (for details, see p. 28).

If the child can resume taking medicines by mouth, then oral morphine may be substituted for subcutaneous infusion of diamorphine. See table of approximate equivalent doses of morphine and diamorphine, p. 29.

Rectal route Morphine (p. 257) is also available for rectal administration as suppositories.

Transdermal route Transdermal preparations of fentanyl (p. 254) are available; they are not suitable for acute pain or in those children whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. Prescribers should ensure that they are familiar with the correct use of transdermal preparations (see under fentanyl, p. 253) because prescribing errors have caused fatalities.

The following 24-hour doses of morphine by mouth are considered to be approximately equivalent to the fentanyl patches shown:

- Morphine salt 45 mg daily ≡ fentanyl ‘12’ patch
- Morphine salt 90 mg daily ≡ fentanyl ‘25’ patch
- Morphine salt 180 mg daily ≡ fentanyl ‘50’ patch
- Morphine salt 270 mg daily ≡ fentanyl ‘75’ patch
- Morphine salt 360 mg daily ≡ fentanyl ‘100’ patch

Morphine (as oral solution or standard formulation tablets) is given for breakthrough pain.

Gastro-intestinal pain The pain of bowel colic may be reduced by loperamide (p. 65). Hyoscine hydrobromide (p. 245) may also be helpful in reducing the frequency of spasms; it is given sublingually at a dose of 10 micrograms/kg (max. 300 micrograms) 3 times daily as Kwells® tablets. For the dose by subcutaneous infusion using a continuous infusion device, see p. 28).

Gastric distension pain due to pressure on the stomach may be helped by a preparation incorporating an antacid with an antiflatulent (p. 51) and a prokinetic such as domperidone (p. 58) before meals.

Muscle spasm The pain of muscle spasm can be helped by a muscle relaxant such as diazepam (p. 618) or baclofen (p. 616).

Neuropathic pain Patients with neuropathic pain (p. 261) may benefit from a trial of a tricyclic antidepressant, most commonly amitriptyline (p. 229), for
several weeks. An anticonvulsant, most commonly carbamazepine (p. 267), may be added or substituted if pain persists; gabapentin is licensed for neuropathic pain in adults.

Pain due to nerve compression may be reduced by a corticosteroid such as dexamethasone, 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.

**Anorexia**  
Anorexia may be helped by prednisolone or dexamethasone.

**Anxiety**  
Anxiety can be treated with a long-acting benzodiazepine such as diazepam, or by continuous infusion of the short-acting benzodiazepine midazolam. Interventions for more acute episodes of anxiety (such as panic attacks) include short-acting benzodiazepines such as lorazepam given sublingually or midazolam given subcutaneously. Temazepam provides useful night-time sedation in some children.

**Capillary bleeding**  
Capillary bleeding can be treated with tranexamic acid (p. 158) by mouth; treatment is usually continued for one week after the bleeding has stopped but it can be continued at a reduced dose if bleeding persists. 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. Vitamin K may be useful in bleeding associated with liver dysfunction.

**Constipation**  
Constipation is a very common cause of distress and is almost invariable after administration of an opioid analgesic. It should be prevented if possible by the regular administration of laxatives. Suitable laxatives include osmotic laxatives (p. 83) (such as lactulose or macrogols), stimulant laxatives (p. 79) (such as co-danthramer and senna) or the combination of lactulose and a senna preparation. Naloxone given by mouth may help relieve opioid-induced constipation; it is poorly absorbed and there is little risk of it reversing opioid analgesia.

**Convulsions**  
Intractable seizures are relatively common in children dying from non-malignant conditions. Phenobarbital by mouth or as a continuous subcutaneous infusion may be beneficial; continuous infusion of midazolam is an alternative. Both cause drowsiness, but this is rarely a concern in the context of intractable seizures. For breakthrough convulsions diazepam (p. 284) given rectally (as a solution), buccal midazolam (p. 286), or paraldehyde (p. 286) as an enema may be appropriate.

For the use of midazolam by subcutaneous infusion using a continuous infusion device, see p. 28.

**Dry mouth**  
Dry mouth may be caused by certain medications including opioid analgesics, antimuscarinic drugs (e.g. hyoscine), antidepressants and some antiepileptics; if possible, an alternative preparation should be considered. Dry mouth may be relieved by good mouth care and measures such as sucking ice or pineapple chunks, chewing gum, or the use of artificial saliva (p. 661); dry mouth associated with candidiasis can be treated by oral preparations of nystatin (p. 658) or miconazole (p. 658); alternatively, fluconazole (p. 366) can be given by mouth.

**Dysphagia**  
A corticosteroid such as dexamethasone may help, temporarily, if there is an obstruction due to tumour. See also Dry Mouth, above.

**Dyspnoea**  
Breathlessness at rest may be relieved by regular oral morphine in carefully titrated doses. Diazepam may be helpful for dyspnoea associated with anxiety. Sublingual lorazepam or subcutaneous or buccal midazolam are alternatives. A nebulised short-acting beta agonist (section 3.1.1.1) or a corticosteroid (section 3.2), such as dexamethasone or prednisolone, may also be helpful for bronchospasm or partial obstruction.
Excessive respiratory secretion  Excessive respiratory secretion (death rattle) may be reduced by hyoscine hydrobromide patches (p. 245) or by subcutaneous or intravenous injection of hyoscine hydrobromide 10 micrograms/kg (max. 600 micrograms) every 4 to 8 hours; however, care must be taken to avoid the discomfort of dry mouth. Alternatively, glycopyrronium (p. 770) may be given. Benzodiazepines such as rectal diazepam or subcutaneous midazolam may be helpful in the final stages.

Fungating tumours  Fungating tumours can be treated by regular dressing and antibacterial drugs; systemic treatment with metronidazole (p. 356) is often required, but topical metronidazole (p. 709) is also used.

Hiccup  Hiccup due to gastric distension may be helped by a preparation incorporating an antacid with an antiflatulent (p. 52).

Hypercalcaemia  See section 9.5.1.2.

Insomnia  Children 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 (p. 212) are used. Benzodiazepines, such as temazepam, may be useful.

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

Mucosal bleeding  Mucosal bleeding from the mouth and nose occurs commonly in the terminal phase, particularly in a child suffering from haemopoietic malignancy. Bleeding from the nose caused by a single bleeding point can be arrested by cauterisation or by dressing it. Tranexamic acid (p. 158) may be effective applied topically or given systemically.

Nausea and vomiting  Nausea and vomiting are common in children with advanced cancer. Ideally, the cause should be determined before treatment with an antiemetic (section 4.6) is started.

Nausea and vomiting with opioid therapy are less common in children than in adults but may occur particularly in the initial stages and can be prevented by giving an antiemetic. 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 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 therefore be used concurrently.

Haloperidol (p. 219) is used by mouth for most metabolic causes of vomiting (e.g. hypercalcaemia, renal failure).

Cyclizine (p. 239) is used for nausea and vomiting due to mechanical bowel obstruction, raised intracranial pressure, and motion sickness.

Ondansetron (p. 244) is most effective when the vomiting is due to damaged or irritated gut mucosa (e.g. after chemotherapy or radiotherapy).

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

Levomepromazine (methotrimeprazine) (p. 219) can be used if first-line antiemetics are inadequate. Dexamethasone 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.

Pruritus  Pruritus, even when associated with obstructive jaundice, often responds to simple measures such as application of emollients (p. 666). Ondansetron may be effective in some children. Where opioid analgesics cause pruritus
it may be appropriate to review the dose or to switch to an alternative opioid analgesic. In the case of obstructive jaundice, further measures include administration of colestyramine (p. 93).

**Raised intracranial pressure**  Headache due to raised intracranial pressure often responds to a high dose of a corticosteroid, such as dexamethasone, for 4 to 5 days, subsequently reduced if possible; dexamethasone should be given before 6 p.m. to reduce the risk of insomnia. Treatment of headache and of associated nausea and vomiting should also be considered.

**Restlessness and confusion**  Restlessness and confusion may require treatment with haloperidol (p. 219) 10–20 micrograms/kg by mouth every 8–12 hours. Levomepromazine (methotrimeprazine) (p. 219) is also used occasionally for restlessness.

**Continuous infusion devices**

Although drugs can usually be administered by mouth to control symptoms in palliative care, the parenteral route may sometimes be necessary. Repeated administration of intramuscular injections should be avoided in children, particularly if cachectic. This has led to the use of portable continuous infusion devices such as syringe drivers 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 medication errors.

Indications for the parenteral route are:

- inability to take medicines by mouth owing to nausea and vomiting, dysphagia, severe weakness, or coma;
- malignant bowel obstruction for which surgery is inappropriate (avoiding the need for an intravenous infusion or for insertion of a nasogastric tube);
- refusal by the child to take regular medication by mouth.

**Bowel colic and excessive respiratory secretions**  Hyoscine hydrobromide (p. 245) effectively reduces respiratory secretions and is sedative (but occasionally causes paradoxical agitation); it is given in a subcutaneous or intravenous infusion dose of 40–60 micrograms/kg/24 hours. Glycopyrronium (p. 770) may also be used.

Hyoscine butylbromide (p. 55) 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 by subcutaneous infusion (important: hyoscine butylbromide must not be confused with hyoscine hydrobromide, above).

**Convulsions**  If a child 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 (p. 286) is the benzodiazepine antiepileptic of choice for continuous subcutaneous infusion.

**Nausea and vomiting**  Levomepromazine (methotrimeprazine) (p. 219) causes sedation in about 50% of patients. Haloperidol (p. 219) has little sedative effect. Cyclizine (p. 239) is particularly likely to precipitate if mixed with diamorphine or other drugs (see under Mixing and Compatibility); it is given by subcutaneous infusion.

**Pain control**  Diamorphine (p. 252) is the preferred opioid since its high solubility permits a large dose to be given in a small volume (see under Mixing and Compatibility). The table on p. 29 shows approximate equivalent doses of morphine and diamorphine.

**Restlessness and confusion**  Haloperidol has little sedative effect. Levomepromazine (methotrimeprazine) (p. 219) has a sedative effect. Midazolam is a sedative and an antiepileptic that may be suitable for a very restless patient.

**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).

The following can be mixed with diamorphine:

- Cyclizine
- Dexamethasone
- Haloperidol
- Hyoscine butylbromide
- Hyoscine hydrobromide
- Levomepromazine
- Metoclopramide
- 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.

### Equivalent doses of morphine sulphate and diamorphine hydrochloride

<table>
<thead>
<tr>
<th>Morphine sulphate by mouth (oral solution or standard tablets)</th>
<th>Morphine sulphate by subcutaneous infusion</th>
<th>Diamorphine hydrochloride by subcutaneous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>every 4 hours</td>
<td>every 24 hours</td>
<td>every 24 hours</td>
</tr>
<tr>
<td>5 mg</td>
<td>15 mg</td>
<td>10 mg</td>
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<tr>
<td>10 mg</td>
<td>30 mg</td>
<td>20 mg</td>
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<td>15 mg</td>
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<td>90 mg</td>
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<td>40 mg</td>
<td>120 mg</td>
<td>80 mg</td>
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<tr>
<td>60 mg</td>
<td>180 mg</td>
<td>120 mg</td>
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<tr>
<td>80 mg</td>
<td>240 mg</td>
<td>160 mg</td>
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<tr>
<td>130 mg</td>
<td>390 mg</td>
<td>260 mg</td>
</tr>
<tr>
<td>160 mg</td>
<td>480 mg</td>
<td>320 mg</td>
</tr>
<tr>
<td>200 mg</td>
<td>600 mg</td>
<td>400 mg</td>
</tr>
</tbody>
</table>

If breakthrough pain occurs give a subcutaneous injection equivalent to one-sixth of the total 24-hour subcutaneous infusion dose. With an intermittent subcutaneous injection 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 subcutaneous infusion solution should be used for longer than 24 hours.

---

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.
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.
Prescribing in dental practice

Advice on the drug management of dental and oral conditions is covered in the main text. 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.

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

**General guidance**

Prescribing by dental surgeons, see BNF
Oral side-effects of drugs, see BNF
Medical emergencies in dental practice, see BNF
Medical problems in dental practice, see BNF

**Drug management of dental and oral conditions**

**Dental and orofacial pain**, p. 246
- Neuropathic pain, p. 261
- Non-opioid analgesics, p. 246
- Opioid analgesics, p. 251
- Non-steroidal anti-inflammatory drugs, p. 600

**Oral infections**

Bacterial infections, p. 297
- Phenoxymethylpenicillin, p. 309
- Broad-spectrum penicillins (amoxicillin and ampicillin), p. 313
- Cephalosporins (cefalexin and cefradine), p. 319
- Tetracyclines, p. 329
- Macrolides (erythromycin and azithromycin), p. 336
- Clindamycin, p. 339
- Metronidazole, p. 355
- Fusidic acid, p. 709

Fungal infections, p. 657
- Local treatment, p. 657
- Systemic treatment, p. 361

Viral infections, p. 657
- Herpetic gingivostomatitis, local treatment, p. 657
- Herpetic gingivostomatitis, systemic treatment, p. 385 and p. 657
- Herpes labialis, p. 715

**Anaesthetics, anxiolytics and hypnotics**

Anaesthesia, sedation, and resuscitation in dental practice, p. 762
Hypnotics, p. 212
Peri-operative anxiolytics, p. 772
Local anaesthesia, p. 787

**Oral ulceration and inflammation**, p. 654

**Mouthwashes and gargles**, p. 659

Dry mouth, p. 661

**Minerals**

Fluorides, p. 571
Aromatic inhalations, p. 208
Nasal decongestants, p. 652

Dental Practitioners’ Formulary, p. 924
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. Alternatively, 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 appropriate management.

Most childhood poisoning is accidental. Other causes include intentional overdose, drug abuse, iatrogenic and deliberate poisoning. The drugs most commonly involved in childhood poisoning are paracetamol, ibuprofen, orally ingested creams, aspirin, iron preparations, cough medicines, and the contraceptive pill.

Hospital admission Children who have features of poisoning should generally be admitted to hospital. Children who have taken poisons with delayed actions 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 children require active removal of the poison. In most children, 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 child and from their carers. However, such information should be interpreted with care because it may not be complete or entirely reliable. Sometimes symptoms arise from other illnesses, and children should be assessed carefully. Accidents may involve a number of 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 children. 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 children with reduced consciousness to
Blood pressure

Hypotension is common in severe poisoning with central nervous system depressants; if severe this 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. Vasoconstrictor 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 may 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 child reaches hospital.

Body temperature

Hypothermia 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. Hypothermia is best treated by wrapping the patient (e.g. in a ‘space blanket’) to conserve body heat.

Hyperthermia can develop in children taking CNS stimulants; children 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 hypothermia 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 100 micrograms/kg (max. 4 mg) or diazepam (preferably as emulsion) 300–400 micrograms/kg (max. 20 mg) should be given by slow intravenous injection into a large vein. 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).

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

Removal and elimination

Prevention of absorption  Given by mouth, activated charcoal can adsorb 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.

A second dose may occasionally be required when blood-drug concentration continues to rise suggesting delayed drug release or delayed gastric emptying. For the use of charcoal in active elimination techniques, see below.

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

- Carbamazepine
- Dapsone
- Theophylline

Activated charcoal may enhance the elimination of some drugs after they have been absorbed; repeated doses are given after overdosage with:

- Quinine
- Phenobarbital

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 but this may compromise efficacy.

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
- alkalinisation of the urine for salicylates.

Removal from the gastro-intestinal tract  Gastric lavage is rarely required as benefit rarely outweighs risk; advice should be sought from the National Poisons Information Service if a significant quantity of iron or lithium has been ingested within the previous hour.

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 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 a poisons information centre.

The administration of laxatives alone has no role in the management of the poisoned child and is not a recommended method of gut decontamination. The routine use of a laxative in combination with activated charcoal has mostly been abandoned. Laxatives should not be administered to young children because of the likelihood of fluid and electrolyte imbalance.

CHARCOAL, ACTIVATED

Cautions  drowsy or comatose child (risk of aspiration); reduced gastro-intestinal motility (risk of obstruction); not for poisoning with petroleum distillates, corrosive substances, alcohols, malathion, and metal salts including iron and lithium salts

Contra-indications  unprotected airway; gastro-intestinal tract not intact

Side-effects  black stools

Indication and dose

<table>
<thead>
<tr>
<th>Reduction of absorption of poisons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td>Neonate 1 g/kg</td>
</tr>
<tr>
<td>Child 1 month–12 years 1 g/kg (max. 50 g)</td>
</tr>
<tr>
<td>Child 12–18 years 50 g</td>
</tr>
</tbody>
</table>
Active elimination of poisons

- By mouth

**Neonate** 1 g/kg every 4 hours

**Child 1 month–12 years** 1 g/kg (max. 50 g) every 4 hours

**Child 12–18 years** 50 g every 4 hours

Administration suspension or reconstituted powder may be mixed with soft drinks (e.g. caffeine-free diet cola) or fruit juices to mask the taste

**Actidose-Aqua Advance** (Cambridge)
- Oral suspension, activated charcoal 1.04 g/5 mL, net price 50-g pack (240 mL) = £8.69

**Carbomix** (Beacon)
- Powder, activated charcoal, net price 25-g pack = £8.50, 50-g pack = £11.90

**Charcodote** (PLIVA)
- Oral suspension, activated charcoal 1 g/5 mL, net price 50-g pack = £11.88

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**Specific drugs**

**Alcohol**

Acute intoxication with alcohol (ethanol) is common in adults but also occurs in children. The features include ataxia, dysarthria, nystagmus, and drowsiness, which may progress to coma, with hypotension and acidosis. Aspiration of vomit is a special hazard and hypoglycaemia may occur in children and some adults. Patients are managed supportively, with particular attention to maintaining a clear airway and measures to reduce the risk of aspiration of gastric contents. The blood glucose is measured and glucose given if indicated.

**Analgesics (non-opioid)**

**Aspirin** The main 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 (particularly potassium) can be measured; absorption of aspirin may be slow and the plasma-salicylate concentration may continue to rise for several hours, requiring repeated measurement. Plasma-salicylate concentration may not correlate with clinical severity in children, 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) unless there is evidence of metabolic acidosis. Activated charcoal should be given within 1 hour of ingesting more than 125 mg/kg aspirin. Fluid losses should be replaced and intravenous sodium bicarbonate may be given (ensuring plasma-potassium concentration is maintained within the reference range) to enhance urinary salicylate excretion (optimum urinary pH 7.5–8.5); treatment should be given in a high dependency unit.

Plasma-potassium concentration should be corrected before giving sodium bicarbonate as hypokalaemia may complicate alkalinisation of the urine.

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, convulsions, renal failure, pulmonary oedema or persistently high plasma-salicylate concentrations unresponsive to urinary alkalinisation.

**NSAIDs** Mefenamic acid has important consequences in overdosage because it can cause convulsions, which if prolonged or recurrent, require treatment with intravenous lorazepam or diazepam.

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 150 mg/kg of paracetamol taken within 24 hours may cause severe hepatocellular necrosis and, much less frequently, renal tubular necrosis. Children 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 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 tenderness, 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 in excess of 75 mg/kg for those considered to be at high-risk, see below) 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 either 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 only if acetylcysteine cannot be given promptly. Once the child reaches hospital the need to continue treatment with the antidote will be assessed from the plasma-paracetamol concentration (related to the time from ingestion). Children 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.38). 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 child is not vomiting). Children at high-risk of liver damage include those:

- taking liver enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, St John’s wort);
- who are malnourished (e.g. in anorexia, cystic fibrosis, in underweight children with ‘failure to thrive’, in alcoholism, or those who are HIV-positive);
- who have a febrile illness;
- who have not eaten for a few days.

These children may develop toxicity at lower plasma-paracetamol concentrations 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 (staggered overdose). If there is doubt about timing or the need for treatment then the child should be treated with acetylcysteine.

See also Co-proxamol, under Analgesics (opioid).
 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). Children at high-risk of liver damage include those:
- taking liver enzyme-inducing drugs (e.g. carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, alcohol, St John’s wort);
- who are malnourished (e.g. in anorexia, cystic fibrosis, in underweight children with failure to thrive, in alcoholism, or those who are HIV-positive);
- who have a febrile illness;
- who have not eaten for a few days.
These children 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

ACETYLCYSTEINE

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 by giving nebulised short-acting beta₂ agonist)
Indication and dose

Paracetamol overdosage see notes above

- By intravenous infusion

Neonate initially 150 mg/kg in 3 mL/kg Glucose 5% and given over 15 minutes, followed by 50 mg/kg in 7 mL/kg Glucose 5% and given over 4 hours, then 100 mg/kg in 14 mL/kg Glucose 5% and given over 16 hours

Child 1 month–5 years (or body-weight under 20 kg) initially 150 mg/kg in 3 mL/kg Glucose 5% and given over 15 minutes, followed by 50 mg/kg in 7 mL/kg Glucose 5% and given over 4 hours, then 100 mg/kg in 14 mL/kg Glucose 5% and given over 16 hours

Child 5–12 years (or body-weight over 20 kg) initially 150 mg/kg in 100 mL Glucose 5% and given over 15 minutes, followed by 50 mg/kg in 250 mL Glucose 5% and given over 4 hours, then 100 mg/kg in 500 mL Glucose 5% and given over 16 hours

Child 12–18 years initially 150 mg/kg (max. 16.5 g) in 200 mL Glucose 5% and given over 15 minutes, followed by 50 mg/kg (max. 5.5 g) in 500 mL Glucose 5% and given over 4 hours, then 100 mg/kg (max.11 g) in 1 litre Glucose 5% and given over 16 hours

Note Manufacturer also recommends other infusion fluids, but Glucose 5% is preferable

Acetylcysteine (Non-proprietary) (®)
Injection, acetylcysteine 200 mg/mL, net price 10-mL amp = £2.50

Parvolex® (UCB Pharma) (®)
Injection, acetylcysteine 200 mg/mL, net price 10-mL amp = £2.50

Methionine

Cautions

Hepatic impairment May precipitate coma in hepatic impairment

Side-effects nausea, vomiting, drowsiness, irritability

Indication and dose

Paracetamol overdosage see notes above

- By mouth

Child under 6 years 1 g every 4 hours for a total of 4 doses

Child 6–18 years 2.5 g every 4 hours for a total of 4 doses

Methionine (Pharma Nord)
Tablets, f/c, methionine 500 mg, net price 20-tab pack = £9.95

Methionine (UCB Pharma)
Tablets, DL-methionine 250 mg, net price 200-tab pack = £87.76

Analgesics (opioid)

Opioids (narcotic analgesics) cause varying degrees of 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 vital signs. All children should be observed for at least 6 hours after the last dose of naloxone. The effects of some opioids, such as buprenorphine, are only partially reversed by naloxone. Dextropropoxyphene and methadone have very long durations of action; patients may need to be monitored for long periods following large overdoses.

Co-proxamol A combination of dextropropoxyphene and paracetamol (co-proxamol) taken in overdose is much more likely to cause death than a combination of other opioids and paracetamol. The initial features are those of acute opioid overdose with coma, respiratory depression, and pinpoint pupils. Patients may die of acute cardiovascular collapse before reaching hospital (particularly if alcohol has also been consumed) unless adequately resuscitated.

Naloxone reverses the opioid effects of dextropropoxyphene; the long duration of action of dextropropoxyphene calls for prolonged monitoring and further doses of naloxone may be required. Norpropoxyphene, a metabolite of dextropropoxyphene, also has cardiotoxic effects which may require treatment with sodium bicarbonate, or magnesium sulphate, or both; arrhythmias may occur for up to 12 hours. Paracetamol hepatotoxicity may develop later and should be anticipated and treated as indicated above.

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

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

Indication and dose

Safe Practice 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

Overdosage with opioids

• By intravenous injection

Neonate 10 micrograms/kg; if no response give subsequent dose of 100 micrograms/kg (then review diagnosis); further doses may be required if respiratory function deteriorates

Child 1 month–12 years 10 micrograms/kg; if no response give subsequent dose of 100 micrograms/kg (then review diagnosis); further doses may be required if respiratory function deteriorates

Child 12–18 years 0.4–2 mg; if no response repeat at intervals of 2–3 minutes to a max. of 10 mg (then review diagnosis); further doses may be required if respiratory function deteriorates

• By subcutaneous or intramuscular injection

As intravenous injection but only if intravenous route not feasible (onset of action slower)

• By continuous intravenous infusion using an infusion pump

Neonate 5–20 micrograms/kg/hour, adjusted according to response

Child 1 month–12 years 5–20 micrograms/kg/hour, adjusted according to response

Child 12–18 years initially 0.24–1.2 mg infused over 1 hour, then using a solution of 4 micrograms/mL infuse at a rate adjusted according to response

Reversal of postoperative respiratory depression, reversal of respiratory and CNS depression in neonate following maternal opioid use during labour section 15.1.7

Administration for continuous intravenous infusion, dilute to a concentration of 4 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% infusion

Naloxone (Non-proprietary) Injection, naloxone hydrochloride 400 micrograms/mL, net price 1-mL amp = £4.10; 1 mg/mL, 2-mL prefilled syringe = £6.61

Minijet® Naloxone (UCB Pharma) Injection, naloxone hydrochloride 400 micrograms/mL, net price 1-mL disposable syringe = £9.00, 2-mL disposable syringe = £11.78, 5-mL disposable syringe = £11.53

Antidepressants

Tricyclic and related antidepressants Tricyclic and related antidepressants cause dry mouth, coma of varying degree, hypotension, hypothermia, hype-reflexia, 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.

Assessment in hospital is strongly advised in case of poisoning by tricyclic and related antidepressants but symptomatic treatment can be given before transfer. Supportive measures to ensure a clear airway and adequate ventilation during transfer are mandatory. Intravenous lorazepam or diazepam (preferably in emulsion form) may be required to treat convulsions. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. 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 children 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 instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.
Management of SSRI poisoning is supportive. Activated charcoal given within 1 hour of the overdose reduces absorption of the drug. Convulsions can be treated with lorazepam, diazepam, or buccal midazolam [unlicensed use] (see p. 34). Contact the National Poisons Information Service for the management of hyperthermia or the serotonin syndrome.

**Antimalarials**

Overdosage 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 children with conduction system disorders or impaired myocardial function. Bradycardia 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 overdosage can vary from one beta-blocker to another; propranolol overdosage in particular may cause coma and convulsions.

**Acute massive overdosage** 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 (40 micrograms/kg, max. 3 mg). Cardiogenic shock unresponsive to atropine is probably best treated with an intravenous injection of glucagon (50–150 micrograms/kg, max. 10 mg) [unlicensed indication and dose] in glucose 5% (with precautions to protect the airway in case of vomiting) followed by an intravenous infusion of 50 micrograms/kg/hour. If glucagon is not available, intravenous isoprenaline (available from ‘special-order’ manufacturers or specialist importing companies, see p. 943) is an alternative. A cardiac pacemaker can be used to increase the heart rate.

**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.

Activated charcoal should be considered if the child presents within 1 hour of overdosage with a calcium-channel blocker; repeated doses of activated charcoal are considered if a modified-release preparation is involved (although activated charcoal may be effective beyond 1 hour with modified-release preparations). In children 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 bradycardia. For the management of hypotension, the choice of inotropic sympathomimetic depends on whether hypotension is secondary to vasodilatation or to myocardial depression and advice should be sought from the National Poisons Information Service.

**Hypnotics and anxiolytics**

**Benzodiazepines** Benzodiazepines taken alone cause drowsiness, ataxia, dysarthria, and occasionally minor and short-lived depression of consciousness. They potentiate the effects of other central nervous system depressants taken concomitantly. Activated charcoal can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the child is awake and the airway is protected. Use of the benzodiazepine antagonist flumazenil can be hazardous,
particularly in mixed overdoses involving tricyclic antidepressants or in benzodiazepine-dependent patients. Flumazenil should be used on expert advice only.

**Iron salts**

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

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.

**DESFERRIOXAMINE MESILATE**

(Deferoxamine Mesilate)

**Cautions** section 9.1.3

**Side-effects** section 9.1.3

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

- **Iron poisoning**
  - By continuous intravenous infusion
  - **Neonate** up to 15 mg/kg/hour, reduced after 4–6 hours; max. 80 mg/kg in 24 hours (in severe cases, higher doses on advice from the National Poisons Information Service)

**Chronic iron overload** section 9.1.3

**Preparations**

Section 9.1.3

**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) due 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 due to the child’s depressive illness. Vomiting, diarrhoea, ataxia, weakness, dysarthria, 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. Whole-bowel irrigation should be considered for significant ingestion, but advice should be sought from the National Poisons Information Service, p. 33.
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 (section 4.2.1) 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 an 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. 33) 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, hypotonia, 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 p. 34); hypertension and cardiac effects require specific treatment and expert advice should be sought.

Ecstasy

Ecstasy (methyleneoxyamphetamine, 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, hyperreflexia, hypotension and intracerebral haemorrhage; hyponatraemia has also been associated with ecstasy use and syndrome of inappropriate antidiuretic hormone secretion (SIADH) can occur.

Treatment of methyleneoxyamphetamine 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). Ondansetron (section 4.6) may be effective for severe vomiting that is resistant
to other antiemetics. Hypokalaemia is corrected by intravenous infusion of potassium chloride in 0.9% sodium chloride and may be so severe as to require high doses under ECG monitoring. Convulsions should be controlled by intravenous administration of diazepam (emulsion preferred). Sedation with lorazepam or diazepam (emulsion preferred) may be necessary in agitated children. Provided the child does not suffer from asthma, a short-acting beta-blocker (section 2.4) can be administered intravenously to reverse severe tachycardia, hypokalaemia, and hyperglycaemia.

Other poisons
Consult either the National Poisons Information Service day and night or TOXBASE, see p. 33.

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 children 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 strong 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 70 mg/kg (max. 5 g) by intravenous infusion (given once or twice according to severity). Cyanokit® provides hydroxocobalamin 2.5 g/bottle (no other preparation of hydroxocobalamin is suitable)—contact the National Poisons Information Service for advice.

DICOBALT EDETATE

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

Indication and dose
Severe poisoning with cyanides

By intravenous injection
Consult the National Poisons Information Service

† Dicobalt Edetate (Cambridge) [THR]
Injection, dicobalt edetate 15 mg/mL, net price 20-mL (300-mg) amp = £13.75
†. [THR] restriction does not apply where administration is for saving life in emergency

SODIUM NITRITE

Side-effects flushing and headache due to vasodilatation

Indication and dose
Poisoning with cyanides (used in conjunction with sodium thiosulphate)
See under preparation

† Sodium Nitrite [THR]
Injection, sodium nitrite 3% (30 mg/mL) in water for injections

Dose
By intravenous injection over 5–20 minutes
Child 1 month–18 years 4–10 mg/kg max. 300 mg (0.13–0.33 mL/kg, max. 10 mL, of 3% solution) followed by sodium thiosulphate injection 400 mg/kg, max. 12.5 g (0.8 mL/kg, max. 25 mL, of 50% solution) over 10 minutes

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
†. [THR] restriction does not apply where administration is for saving life in emergency
**SODIUM THIOSULPHATE**

**Indication and dose**

*Poisoning with cyanides* (used in conjunction with sodium nitrite)

See above under Sodium Nitrite

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**Ethylene glycol and methanol**

Fomepizole (available from ‘special-order’ manufacturers or specialist importing companies, see p. 943) is the treatment of choice for ethylene glycol and methanol (methyl alcohol) poisoning. If necessary, ethanol (by mouth or by intravenous infusion) can be used with caution in children. Advice on the treatment of ethylene glycol and methanol poisoning should be obtained from the National Poisons Information Service. It is important to start antidote treatment promptly in cases of suspected poisoning with these agents.

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**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.

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**DIMERCAPROL**

*(BAL)*

**Cautions**

- hypertension, pregnancy and breastfeeding;
- interactions: Appendix 1 (dimercaprol)

**Renal impairment**

discontinue or use with extreme caution if impairment develops during treatment

**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, lacrimation, sweating, burning sensation (mouth, throat, and eyes), feeling of constriction of throat and chest, headache, muscle spasm, abdominal pain, tingling of extremities; pyrexia; local pain and abscess at injection site

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**SODIUM CALCIUM EDETATE**

*(Sodium Calciumedetate)*

**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, lacrimation, myalgia, nasal congestion, sneezing, malaise, thirst, fever, chills, headache and zinc depletion also reported

**Licensed use**

licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

*Poisoning by antimony, arsenic, bismuth, gold, mercury*

- By intramuscular injection

  **Child 1 month–18 years** 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

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**Administration**

for *intravenous infusion*, dilute to a concentration of not more 30 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over at least 1 hour

**Ledclair** *(Durbin)*

**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 child should be moved to fresh air, the airway cleared, and high-flow oxygen 100% administered as soon as available. 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 child should be admitted to hospital because complications may arise after a delay of hours or days. Cerebral oedema may occur 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 patient 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. Children 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 secre-
tions, hypoxia, 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 child to fresh air, removing soiled clothing, and washing contaminated skin. In severe poisoning it is vital to ensure a clear 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 intravenously in a dose of 20 micrograms/kg (max. 2 mg) as atropine sulphate every 5 to 10 minutes (according to the severity of poisoning) until the skin becomes flushed and dry, the pupils dilate, and bradycardia is abolished.

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. 33).

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**PRALIDOXIME CHLORIDE**

| Cautions | renal impairment, myasthenia gravis |
| Contra-indications | poisoning with carbamates or organophosphorus compounds without anticholinesterase activity |
| Side-effects | drowsiness, dizziness, disturbances of vision, nausea, tachycardia, headache, hyperventilation, and muscular weakness |
| Licensed use | licensed for use in children (age range not specified by manufacturer) |
| Indication and dose |

- **Adjunct to atropine in the treatment of poisoning by organophosphorus insecticide or nerve agent**
  - By intravenous infusion over 20 minutes

  **Child under 18 years** initially 30 mg/kg, 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 may differ from those in product literature

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**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 anaphylactic 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.

Early anaphylactic 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. 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 body-weight). The same dose should be used for adults and children. The dose can be repeated in 1–2 hours if symptoms of systemic envenoming persist. For children who present with clinical features of
severe envenoming (e.g. shock, ECG abnormalities, and rapidly advancing local swelling), an initial dose of 2 vials (20 mL) of the antiserum is recommended. Adrenaline (epinephrine) injection must be immediately to hand for treatment of anaphylactic 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 the National Poisons Information Service (Tel: 0844 892 0111).

**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 (or administered by a carer) intramuscular adrenaline (e.g. EpiPen®) is the best first-aid treatment for children 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 severe anaphylaxis and systemic reactions in children with systemic hypersensitivity to bee or wasp stings (section 3.4.2).

**Marine stings** The severe pain of weeverfish (Trachinus vipera) 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). Children 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.

*The National Poisons Information Service (Tel: 0844 892 0111) will provide specialist advice on all aspects of poisoning day and night*
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- *Clostridium difficile* infection, p. 68
- constipation, p. 77
- Crohn’s disease, p. 66
- food allergy, p. 76
- *Helicobacter pylori* infection, p. 59
- irritable bowel syndrome, p. 68
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## 1.1 Dyspepsia and gastro-oesophageal reflux disease

### 1.1.1 Antacids and simeticone

Dyspepsia covers pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration (section 1.3), gastro-oesophageal reflux disease, gastritis, and upper gastro-intestinal motility disorders, but most commonly it is of uncertain origin.

Children 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.

A compound alginate preparation (section 1.1.2) may provide relief from dyspepsia; persistent dyspepsia requires investigation. Treatment with a H2-receptor antagonist (section 1.3.1) or a proton pump inhibitor (section 1.3.5) should be initiated only on the advice of a hospital specialist.

*Helicobacter pylori* may be present in children with dyspepsia. *H. pylori* eradication therapy (section 1.3) should be considered for persistent dyspepsia if it is ulcer-like. However, most children with functional (investigated, non-ulcer) dyspepsia do not benefit symptomatically from *H. pylori* eradication.

### 1.1.2 Compound alginate preparations

#### Dyspepsia

Dyspepsia covers pain, fullness, early satiety, bloating, and nausea. It can occur with gastric and duodenal ulceration (section 1.3), gastro-oesophageal reflux disease, gastritis, and upper gastro-intestinal motility disorders, but most commonly it is of uncertain origin.

Children 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.

A compound alginate preparation (section 1.1.2) may provide relief from dyspepsia; persistent dyspepsia requires investigation. Treatment with a H2-receptor antagonist (section 1.3.1) or a proton pump inhibitor (section 1.3.5) should be initiated only on the advice of a hospital specialist.

*Helicobacter pylori* may be present in children with dyspepsia. *H. pylori* eradication therapy (section 1.3) should be considered for persistent dyspepsia if it is ulcer-like. However, most children with functional (investigated, non-ulcer) dyspepsia do not benefit symptomatically from *H. pylori* eradication.

#### Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease includes non-erosive gastro-oesophageal reflux and erosive oesophagitis. Uncomplicated gastro-oesophageal reflux is common in infancy and most symptoms, such as intermittent vomiting or repeated, effortless regurgitation, resolve without treatment between 12 and 18 months of age. Older children with gastro-oesophageal reflux disease may have heartburn, acid regurgitation and dysphagia. Oesophageal inflammation (oesophagitis), ulceration or stricture formation may develop in early childhood; gastro-oesophageal reflux disease may also be associated with chronic respiratory disorders including asthma.

Parents and carers of *neonates* and *infants* should be reassured that most symptoms of uncomplicated gastro-oesophageal reflux resolve without treatment. An increase in the frequency and a decrease in the volume of feeds may reduce symptoms. A feed thickener or pre-thickened formula feed (Appendix 2) can be used on the advice of a dietician. If necessary, a suitable alginate-containing preparation (section 1.1.2) can be used instead of thickened feeds.

*Older children* should be advised about lifestyle changes such as weight reduction if overweight, and the avoidance of alcohol and smoking. An alginate-containing antacid (section 1.1.2) can be used to relieve symptoms.

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. On the advice of a paediatrician, a *histamine H2*-receptor antagonist (section 1.3.1) can be used to relieve symptoms of gastro-oesophageal reflux disease,
promote mucosal healing and permit reduction in antacid consumption. A proton pump inhibitor (section 1.3.5) can be used for the treatment of moderate, non-erosive oesophagitis that is unresponsive to an H₂-receptor antagonist. Endoscopically confirmed erosive, ulcerative, or stricturing disease in children is usually treated with a proton pump inhibitor. Reassessment is necessary if symptoms persist despite 4–6 weeks of treatment; long-term use of an H₂-receptor antagonist or proton pump inhibitor should not be undertaken without full assessment of the underlying condition. For endoscopically confirmed erosive, ulcerative, or stricturing disease, the proton pump inhibitor usually needs to be maintained at the minimum effective dose.

Motility stimulants (section 1.2), such as domperidone or erythromycin may improve gastro-oesophageal sphincter contraction and accelerate gastric emptying. Evidence for the long-term efficacy of motility stimulants in the management of gastro-oesophageal reflux in children is unconvincing.

For advice on specialised formula feeds, see section 9.4.2.

Antacids (usually containing aluminium or magnesium compounds) can be used for short-term relief of intermittent symptoms of ulcer dyspepsia and non-erosive gastro-oesophageal reflux (see section 1.1) in children; they are also used in functional (non-ulcer) dyspepsia, but the evidence of benefit is uncertain. Aluminium- and magnesium-containing antacids, being relatively insoluble in water, are long-acting if retained in the stomach. 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-containing antacids should not be used in children with renal impairment, or in neonates and infants because accumulation may lead to increased plasma-aluminium concentrations.

Complexes such as hydrotalcite confer no special advantage.

Calcium-containing antacids can induce rebound acid secretion; with modest doses the clinical significance of this is doubtful, but prolonged high doses also cause hypercalcaemia and alkalosis.

Simeticone (activated dimeticone) is used to treat infantile colic, but the evidence of benefit is uncertain. Simeticone is added to an antacid as an antifoaming agent to relieve flatulence; such preparations may also be useful for the relief of hiccups in palliative care (see Prescribing in Palliative Care, p. 27).

Alginates act as mucosal protectants in gastro-oesophageal reflux disease (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.

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 designed to prevent dissolution in the stomach. See also Appendix 1 (antacids, calcium salts).

The words 'low Na⁺' added after some preparations indicate a sodium content of less than 1 mmol per tablet or 10-mL dose.

**Aluminium- and magnesium-containing antacids**

**Aluminium hydroxide**

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

**Renal impairment** risk of aluminium accumulation and aluminium toxicity. Absorption of aluminium from aluminium salts is increased by citrates, which are contained in many effervescent preparations

**Pregnancy** use with caution especially in first trimester

**Contra-indications** hypophosphataemia; neonates and infants
ALUMINIUM HYDROXIDE (continued)

Side-effects  see notes above
Indication and dose
Dyspepsia for dose see preparations

Hyperphosphataemia  section 9.5.2.2

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
- By mouth
  Child 14–18 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
- By mouth
  Child 12–18 years 10–20 mL 3 times daily, 20–60 minutes after meals and at bedtime, or when required

MAGNESIUM TRISILICATE

Cautions  heart failure, hypertension; metabolic or respiratory alkalosis, hypermagnesaemia; interactions: Appendix 1 (antacids)
Renal impairment  increased risk of toxicity—avoid or reduce dose. Magnesium trisilicate mixture has a high sodium content
Pregnancy  use with caution especially in first trimester; avoid antacid preparations containing high sodium content
Contra-indications  severe renal failure; hyperphosphataemia
Side-effects  see notes above; silica-based renal stones reported on long-term treatment

Indication and dose
Dyspepsia for dose see under preparation

Hydroxide 220 mg/5 mL (low Na+). Net price 500 mL = £1.96
Note The brand name Altacite® is used for hydroxide suspension; for Altacite Plus® suspension, see below

Dose
- By mouth
  Child 5–12 years 5 mL 4 times daily (between meals and at bedtime)
  Child 12–18 years 10 mL 4 times daily (between meals and at bedtime)

Antacid preparations containing simeticone

Altacite Plus® (Peckforton)
Suspension, sugar-free, co-simalcite 125/500 (simeticone 125 mg, hydroxide 500 mg)/5 mL (low Na+). Net price 500 mL = £1.96

Dose
- By mouth
  Child 8–12 years 5 mL 4 times daily (between meals and at bedtime) when required
  Child 12–18 years 10 mL 4 times daily (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
- By mouth
  Child 12–18 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
- By mouth
  Child 2–5 years 5 mL 3 times daily
  Child 5–12 years 5–10 mL 3–4 times daily
  Child 12–18 years 5–10 mL 4 times daily (after meals and at bedtime) or when required

**Simeticone alone**

**Activated dimeticone**

**Indication and dose**

Colic or wind pain for dose see under individual preparations

**Dentinox® (DDD)**

Colic drops (= emulsion), simeticone 21 mg/2.5-mL dose. Net price 100 mL = £1.73

Dose
- By mouth
  Neonate 2.5 mL with or after each feed (max. 6 doses in 24 hours); may be added to bottle feed

**Infacol® (Forest)**

Liquid, sugar-free, simeticone 40 mg/mL (low Na⁺). Net price 50 mL = £2.26. Counselling, use of dropper

Dose
- By mouth
  Neonate 0.5–1 mL before feeds
  Child 1 month–2 years 0.5–1 mL before feeds

**1.1.2 Compound alginate preparations**

Alginate taken in combination with an antacid increases the viscosity of stomach contents and can protect the oesophageal mucosa from acid reﬂux. Some alginate-containing preparations form a viscous gel (raft) that ﬂoats on the surface of the stomach contents, thereby reducing symptoms of reﬂux. Alginate-containing preparations are used in the management of mild symptoms of dyspepsia and gastro-oesophageal reﬂux disease (see section 1.1). Antacids may damage enteric coatings designed to prevent dissolution in the stomach. For interactions, see Appendix 1 (antacids, calcium salts).

Preparations containing aluminium should not be used in children with renal impairment, or in neonates and infants.

**Alginate raft-forming oral suspensions**

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

**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
- By mouth
  Child 6–12 years 5–10 mL after meals and at bedtime
  Child 12–18 years 10–20 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
- By mouth
  Child 6–12 years 5–10 mL after meals and at bedtime
  Child 12–18 years 10–20 mL after meals and at bedtime
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.

The dopamine-receptor antagonist domperidone stimulates transit in the gut.

### Antimuscarinics

Antimuscarinics (formerly termed ‘anticholinergics’) reduce intestinal motility. They are occasionally used for the management of irritable bowel syndrome but the evidence of their value has not been established and response varies. Other
indications for antimuscarinic drugs include asthma and airways disease (section 3.1.2), motion sickness (section 4.6), urinary frequency and enuresis (section 7.4.2), mydriasis and cycloplegia (section 11.5), premedication (section 15.1.3), palliative care (p. 26), and as an antidote to organophosphorus poisoning (p. 47).

Antimuscarinics that are used for gastro-intestinal smooth muscle spasm include the tertiary amine dicycloverine hydrochloride (dicyclomine hydrochloride) and the quaternary ammonium compounds propantheline bromide and hyoscine butylbromide. The quaternary ammonium compounds are less lipid soluble than atropine and so are less likely to cross the blood-brain barrier; they are also less well absorbed from the gastro-intestinal tract.

Dicycloverine hydrochloride 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 may be useful in endoscopy and radiology.

**Cautions** Antimuscarinics should be used with caution in children (especially children with Down’s syndrome) due to increased risk of side-effects; they should also be used with caution in hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), pyrexia, pregnancy, and in children susceptible to angle-closure glaucoma. Antimuscarinics are not used in children with gastro-oesophageal reflux disease, diarrhoea or ulcerative colitis.

**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, and pyloric stenosis.

**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 nausea, vomiting, and giddiness.

### DICYCLOVERINE HYDROCHLORIDE
(Dicyclomine hydrochloride)

**Cautions** see notes above

**Contra-indications** see notes above; child under 6 months

**Breast-feeding** avoid—present in milk; apnoea reported in infant

**Side-effects** see notes above

**Indication and dose** Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

- **By mouth**
  - Child 6 months–2 years 5–10 mg 3–4 times daily 15 minutes before feeds
  - Child 2–12 years 10 mg 3 times daily
  - Child 12–18 years 10–20 mg 3 times daily

**Licensed use** tablets not licensed for use in children under 6 years; injection not licensed for use in children (age range not specified by manufacturer)

**Compound preparations**

**Kolanticon®** (Peckforton)

- **Gel**, sugar-free, dicycloverine hydrochloride 2.5 mg, dried aluminium hydroxide 200 mg, light magnesium oxide 100 mg, simeticone 20 mg/5 mL, net price 200 mL = £2.21, 500 mL = £2.79

**Dose**

- Child 12–18 years 10–20 mL every 4 hours when required

### HYOSCINE BUTYLBROMIDE

**Cautions** see notes above; also intestinal and urinary outlet obstruction

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** amount too small to be harmful

**Contra-indications** see notes above

**Side-effects** see notes above

**Licensed use** tablets not licensed for use in children under 6 years; injection not licensed for use in children (age range not specified by manufacturer)
HYOSCINE BUTYLBROMIDE

**Indication and dose**
Symptomatic relief of gastro-intestinal or genito-urinary disorders characterised by smooth muscle spasm

- **By mouth**
  - Child 6–12 years: 10 mg 3 times daily
  - Child 12–18 years: 20 mg 4 times daily

- **Excessive respiratory secretions and bowel colic in palliative care** (see also p. 28)
  - **By mouth**
    - Child 1 month–2 years: 300–500 micrograms/kg (max. 5 mg) 3–4 times daily
    - Child 2–5 years: 5 mg 3–4 times daily
    - Child 5–12 years: 10 mg 3–4 times daily
    - Child 12–18 years: 10–20 mg 3–4 times daily

- **By intramuscular or intravenous injection**
  - Child 1 month–4 years: 300–500 micrograms/kg (max. 5 mg) 3–4 times daily
  - Child 5–12 years: 5–10 mg 3–4 times daily
  - Child 12–18 years: 10–20 mg 3–4 times daily

**Acute spasm, spasm in diagnostic procedures**
- **By intramuscular or intravenous injection**
  - Child 2–6 years: 5 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 15 mg daily
  - Child 6–12 years: 5–10 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 30 mg daily
  - Child 12–18 years: 20 mg repeated after 30 minutes if necessary (may be repeated more frequently in endoscopy), max. 80 mg daily

**Administration**
- **For intravenous injection**, may be diluted with Glucose 5% or Sodium Chloride 0.9%; give over at least 1 minute.
- For administration **by mouth**, injection solution may be used; content of ampoule may be stored in a refrigerator for up to 24 hours after opening.

**PROPANTHELINE BROMIDE**

**Cautions**
- Hepatic impairment: manufacturer advises caution
- Renal impairment: manufacturer advises caution
- Pregnancy: manufacturer advises caution
- Breast-feeding: may suppress lactation

**Contra-indications**
- See notes above

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

**Licensed use**
- Tablets not licensed for use in children under 12 years

**Indication and dose**
Symptomatic relief of gastro-intestinal disorders characterised by smooth muscle spasm

- **By mouth**
  - Child 1 month–12 years: 300 micrograms/kg (max. 15 mg) 3–4 times daily at least one hour before food
  - Child 12–18 years: 15 mg 3 times daily at least one hour before meals and 30 mg at night (max. 120 mg daily)

**Pro-Banthine®**
- Tablets, pink, s/c, propantheline bromide 15 mg, net price 112-tab pack = £15.32. Label: 23

**ALVERINE CITRATE**

**Cautions**
- Pregnancy: caution
- Breast-feeding: little information available—manufacturer advises avoid

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

**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 primary dysmenorrhea. They have no serious adverse effects; peppermint oil occasionally causes heartburn.
ALVERINE CITRATE (continued)

Indication and dose
Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm, dysmenorrhhea
- By mouth
Child 12–18 years 60–120 mg 1–3 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

MEBEVERINE HYDROCHLORIDE

Cautions
- avoid in acute porphyria (section 9.8.2)
- Pregnancy not known to be harmful—manufacturers advise caution

Contra-indications
- paralytic ileus

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

Licensed use
- tablets and liquid not licensed for use in children under 10 years; granules not licensed for use in children under 12 years; modified-release capsules not licensed for use in children under 18 years

Indication and dose
Adjunct in gastro-intestinal disorders characterised by smooth muscle spasm
- By mouth
Child 3–4 years 25 mg 3 times daily, preferably 20 minutes before meals
Child 4–8 years 50 mg 3 times daily, preferably 20 minutes before meals
Child 8–10 years 100 mg 3 times daily, preferably 20 minutes before meals
Child 10–18 years 135–150 mg 3 times daily, preferably 20 minutes before meals

1 Mebeverine Hydrochloride (Non-proprietary)
- Tablets, mebeverine hydrochloride 135 mg, net price 20 = £2.21

Oral suspension, mebeverine hydrochloride (as mebeverine embonate) 50 mg/5 mL. Contains Na+ 0.87 mmol/5 mL. Net price 300 mL = £107.00

PEPPERMINT OIL

Cautions
- sensitivity to menthol
- Breast-feeding significant levels of menthol in breast milk unlikely

Side-effects
- heartburn, perianal irritation; rarely, allergic reactions (including rash, headache, bradyarrhythmia, muscle tremor, ataxia)
- Local irritation Capsules should not be broken or chewed because peppermint oil may irritate mouth or oesophagus

Indication and dose
Relief of abdominal colic and distension, particularly in irritable bowel syndrome
- By mouth
Child 15–18 years 1–2 capsules, swallowed whole with water, 3 times daily for up to 3 months if necessary

Colpermin® (McNeil)
Capsules, e/c, light blue/dark blue, blue band, peppermint oil 0.2 mL. Net price 100-cap pack = £12.05. Label: 5, 25
Excipients include arachis (peanut) oil
Motility stimulants

Domperidone and metoclopramide (section 4.6) are dopamine receptor antagonists which stimulate gastric emptying and small intestinal transit, and enhance the strength of oesophageal sphincter contraction. Metoclopramide and occasionally domperidone can cause acute dystonic reactions—for further details of this and other side-effects, see section 4.6.

A low dose of erythromycin stimulates gastro-intestinal motility and may be used on the advice of a paediatric gastroenterologist to promote tolerance of enteral feeds; erythromycin may be less effective as a prokinetic drug in preterm neonates than in older children.

### DOMPERIDONE

**Cautions**  see under Domperidone (section 4.6)

**Side-effects**  see under Domperidone (section 4.6); also QT-interval prolongation reported

**Licensed use**  not licensed for use in gastro-intestinal stasis; not licensed for use in children for gastro-oesophageal reflux disease

**Indication and dose**

- **Gastro-oesophageal reflux disease (but efficacy not proven, see section 1.1), gastro-intestinal stasis**
  - By mouth
  - **Neonate** 100–300 micrograms/kg 4–6 times daily before feeds

**Nausea and vomiting**  section 4.6

#### Preparations

- **Child 1 month–12 years** 200–400 micrograms/kg (max. 20 mg) 3–4 times daily before food
- **Child 12–18 years** 10–20 mg, 3–4 times daily before food

### ERYTHROMYCIN

**Cautions**  see section 5.1.5; **interactions:** Appendix 1 (macrolides)

**Side-effects**  see section 5.1.5

**Licensed use**  not licensed for use in gastro-intestinal stasis

**Indication and dose**

- **Gastro-intestinal stasis**
  - By mouth
  - **Neonate** 3 mg/kg 4 times daily
  - **Child 1 month–18 years** 3 mg/kg 4 times daily
  - **By intravenous infusion**
    - **Neonate** 3 mg/kg 4 times daily
    - **Child 1 month–1 year** 3 mg/kg 4 times daily

**Preparations**  Section 5.1.5

### 1.3 Antisecretory drugs and mucosal protectants

#### 1.3.1 H₂-receptor antagonists

Peptic ulceration commonly involves the stomach, duodenum, and lower oesophagus; after gastric surgery it involves the gastro-enterostomy stoma.

Healing can be promoted by general measures, stopping smoking and taking antacids and by antisecretory drug treatment, but relapse is common when treatment ceases. Nearly all duodenal ulcers and most gastric ulcers not associated with NSAIDs are caused by *Helicobacter pylori*. 
The management of *H. pylori* infection and of NSAID-associated ulcers is discussed below.

**Helicobacter pylori infection**

Eradication of *Helicobacter pylori* reduces the recurrence of gastric and duodenal ulcers and the risk of rebleeding. The presence of *H. pylori* should be confirmed before starting eradication treatment. If possible, the antibacterial sensitivity of the organism should be established at the time of endoscopy and biopsy. Acid inhibition combined with antibacterial treatment is highly effective in the eradication of *H. pylori*, reinfection is rare. Antibiotic-associated colitis is an uncommon risk.

Treatment to eradicate *H. pylori* infection in children should be initiated under specialist supervision. One-week triple-therapy regimens that comprise omeprazole, amoxicillin, and either clarithromycin or metronidazole are recommended. Resistance to clarithromycin or to metronidazole is much more common than to amoxicillin and can develop during treatment. A regimen containing amoxicillin and clarithromycin is therefore recommended for initial therapy and one containing amoxicillin and metronidazole for eradication failure. There is usually no need to continue antisecretory treatment (with a proton pump inhibitor or H$_2$-receptor antagonist), however, if the ulcer is large, or complicated by haemorrhage or perforation then antisecretory treatment is continued for a further 3 weeks. Lansoprazole may be considered if omeprazole is unsuitable. Treatment failure usually indicates antibacterial resistance, poor compliance, or familial reinfection.

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 produce low rates of *H. pylori* eradication and are not recommended.

For the role of *H. pylori* eradication therapy in children starting or taking NSAIDs, see NSAID-associated ulcers, below.

### Recommended regimens for *Helicobacter pylori* eradication

<table>
<thead>
<tr>
<th>Eradication therapy</th>
<th>Age range</th>
<th>Oral dose (to be used in combination with omeprazole, section 1.3.5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amoxicillin</strong></td>
<td>1–6 years</td>
<td>250 mg twice daily (with clarithromycin)</td>
</tr>
<tr>
<td></td>
<td>1–6 years</td>
<td>125 mg 3 times daily (with metronidazole)</td>
</tr>
<tr>
<td></td>
<td>6–12 years</td>
<td>500 mg twice daily (with clarithromycin)</td>
</tr>
<tr>
<td></td>
<td>6–12 years</td>
<td>250 mg 3 times daily (with metronidazole)</td>
</tr>
<tr>
<td></td>
<td>12–18 years</td>
<td>1 g twice daily (with clarithromycin)</td>
</tr>
<tr>
<td></td>
<td>12–18 years</td>
<td>500 mg 3 times daily (with metronidazole)</td>
</tr>
<tr>
<td><strong>Clarithromycin</strong></td>
<td>1–12 years</td>
<td>7.5 mg/kg (max. 500 mg) twice daily (with metronidazole or amoxicillin)</td>
</tr>
<tr>
<td></td>
<td>12–18 years</td>
<td>500 mg twice daily (with metronidazole or amoxicillin)</td>
</tr>
<tr>
<td><strong>Metronidazole</strong></td>
<td>1–6 years</td>
<td>100 mg twice daily (with clarithromycin)</td>
</tr>
<tr>
<td></td>
<td>1–6 years</td>
<td>100 mg 3 times daily (with amoxicillin)</td>
</tr>
<tr>
<td></td>
<td>6–12 years</td>
<td>200 mg twice daily (with clarithromycin)</td>
</tr>
<tr>
<td></td>
<td>6–12 years</td>
<td>200 mg 3 times daily (with amoxicillin)</td>
</tr>
<tr>
<td></td>
<td>12–18 years</td>
<td>400 mg twice daily (with clarithromycin)</td>
</tr>
<tr>
<td></td>
<td>12–18 years</td>
<td>400 mg 3 times daily (with amoxicillin)</td>
</tr>
</tbody>
</table>
**Test for Helicobacter pylori**

13C-Urea breath test kits are available for confirming the presence of gastro-duodenal infection with *Helicobacter pylori*. The test involves collection of breath samples before and after ingestion of an oral solution of 13C-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 13C-Urea breath test kit for children is available (*Helicobacter Test INFAI for children of the age 3–11*). However the appropriateness of testing for *H. pylori* infection in children has not been established. Breath, saliva, faecal, and urine tests for *H. pylori* are frequently unreliable in children; the most accurate method of diagnosis is endoscopy with biopsy.

**Helicobacter Test INFAI for children of the age 3–11® (Infai)**

Oral powder, 13C-urea 45 mg, net price 1 kit (including 4 breath sample containers, straws) = £19.20 (spectrometric analysis included)

**Helicobacter Test INFAI® (Infai)**

Oral powder, 13C-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)

**NSAID-associated ulcers**

Gastro-intestinal bleeding and ulceration can occur with NSAID use (section 10.1.1). In adults, the risk of serious upper gastro-intestinal side-effects varies between individual NSAIDs (see Gastro-intestinal side-effects, p. 602). Whenever possible, NSAIDs should be withdrawn if an ulcer occurs.

Children at high risk of developing gastro-intestinal complications include those with a history of peptic ulcer disease or serious upper gastro-intestinal complication, those taking other medicines that increase the risk of upper gastro-intestinal side-effects, or those with serious co-morbidity. In children at risk of ulceration, a proton pump inhibitor (section 1.3.5) or an H2-receptor antagonist, such as ranitidine, may be considered for protection against gastric and duodenal ulcers associated with non-selective NSAIDs.

NSAID use and *H. pylori* infection are independent risk factors for gastro-intestinal bleeding and ulceration. In children already taking a NSAID, eradication of *H. pylori* is unlikely to reduce the risk of NSAID-induced bleeding or ulceration. However, in children about to start long-term NSAID treatment who are *H. pylori* positive and have dyspepsia or a history of gastric or duodenal ulcer, eradication of *H. pylori* may reduce the overall risk of ulceration.

If the NSAID can be discontinued in a child who has developed an ulcer, a proton pump inhibitor usually produces the most rapid healing, alternatively the ulcer can be treated with an H2-receptor antagonist.

If NSAID treatment needs to continue, the ulcer is treated with a proton pump inhibitor (section 1.3.5).

**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 dyspepsia and 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 has largely been replaced in *Helicobacter pylori* positive children by eradication regimens (section 1.3).

H2-receptor antagonist therapy can promote healing of NSAID-associated ulcers (section 1.3).

Treatment with a H2-receptor antagonist has not been shown to be beneficial in haematemesis and melaena, but prophylactic use reduces the frequency of bleeding from gastro-duodenal erosions in hepatic coma, and possibly in other
conditions requiring intensive care. Treatment also reduces the risk of \textit{acid aspiration} in obstetric patients at delivery (Mendelson’s syndrome).

\textbf{H$_2$-receptor antagonists} are also used to reduce the degradation of pancreatic enzyme supplements (section 1.9.4) in children with cystic fibrosis.

\textbf{Side-effects} Side-effects of the H$_2$-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 very ill, hypersensitivity reactions (including fever, arthralgia, myalgia, anaphylaxis), blood disorders (including agranulocytosis, leucopenia, pancytopenia, thrombocytopenia), and skin reactions (including erythema multiforme and toxic epidermal necrolysis). There have been occasional reports of gynaecomastia and impotence.

\textbf{RANITIDINE}

\textbf{Cautions} acute porphyria; \textbf{interactions}: Appendix 1 (histamine H$_2$-antagonists)

\textbf{Renal impairment} use half normal dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m$^2$

\textbf{Pregnancy} manufacturer advises avoid unless essential, but not known to be harmful

\textbf{Breast-feeding} significant amount present in milk, but not known to be harmful

\textbf{Side-effects} see notes above; also rarely tachycardia, agitation, visual disturbances, alopecia; very rarely interstitial nephritis

\textbf{Licensed use} oral preparations not licensed for use in children under 3 years; \textit{injection} not licensed for use in children under 6 months

\textbf{Indication and dose}

\textbf{Reflux oesophagitis, benign gastric and duodenal ulceration, prophylaxis of stress ulceration, other conditions where gastric acid reduction is beneficial} (see notes above and section 1.9.4)

- \textbf{By mouth}
  - \textbf{Neonate} 2 mg/kg 3 times daily but absorption unreliable; max. 3 mg/kg 3 times daily
  - \textbf{Child 1–6 months} 1 mg/kg 3 times daily; max. 3 mg/kg 3 times daily
  - \textbf{Child 6 months–3 years} 2–4 mg/kg twice daily
  - \textbf{Child 3–12 years} 2–4 mg/kg (max. 150 mg) twice daily; increased up to 5 mg/kg (max. 300 mg) twice daily in severe gastro-oesophageal reflux disease
  - \textbf{Child 12–18 years} 150 mg twice daily or 300 mg at night; increased if necessary, to 300 mg twice daily or 150 mg 4 times daily for up to 12 weeks in moderate to severe gastro-oesophageal reflux disease
  - \textbf{Note} In fat malabsorption syndrome, give 1–2 hours before food to enhance effects of pancreatic enzyme replacement

- \textbf{By slow intravenous injection}
  - \textbf{Neonate} 0.5–1 mg/kg every 6–8 hours
  - \textbf{Child 1 month–18 years} 1 mg/kg (max. 50 mg) every 6–8 hours (may be given as an intermittent infusion at a rate of 25 mg/hour)

\textbf{Zollinger–Ellison syndrome (but see notes above)}

- \textbf{By mouth}
  - \textbf{Child 12–18 years} 150 mg 3 times daily (doses up to 6 g daily in divided doses have been used)

\textbf{Administration} For slow \textit{intravenous injection} dilute to a concentration of 2.5 mg/mL with Glucose 5%, Sodium Chloride 0.9%, or Compound Sodium Lactate. Give over at least 3 minutes

1 Ranitidine \textbf{(Non-proprietary) \textregistered}

- \textbf{Tablets}, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £1.27; 300 mg, 30-tab pack = £1.32
- \textbf{Brands include} Ranitic\textregistered

\textbf{Effervescent tablets}, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £10.74; 300 mg, 30-tab pack = £11.25

\textbf{Excipients} may include sodium (check with supplier)

\textbf{Oral solution}, ranitidine (as hydrochloride) 75 mg/5 mL, 100 mL = £7.44, 300 mL = £21.43

\textbf{Excipients} may include alcohol (check with supplier)

1. Ranitidine can be sold to the public for 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 (max. single dose 75 mg, max. daily dose 300 mg)

\textbf{Zantac\textregistered (GSK) \textregistered}

- \textbf{Tablets}, f/c, ranitidine (as hydrochloride) 150 mg, net price 60-tab pack = £1.30; 300 mg, 30-tab pack = £1.30

\textbf{Effervescent tablets}, pale yellow, ranitidine (as hydrochloride) 150 mg (contains 14.3 mmol Na+)/tablet, net price 60-tab pack = £25.94; 300 mg (contains 20.8 mmol Na+)/tablet, 30-tab pack = £25.51. Label: 13

\textbf{Excipients} include aspartame (section 9.4.1)

\textbf{Syrup}, sugar-free, ranitidine (as hydrochloride) 75 mg/5 mL. Net price 300 mL = £20.76

\textbf{Excipients} include alcohol 8%

\textbf{Injection}, ranitidine (as hydrochloride) 25 mg/mL. Net price 2-mL amp = 60p
1.3.2 Selective antimuscarinics
Classification not used in BNF for Children.

1.3.3 Chelates and complexes
Sucralfate is a complex of aluminium hydroxide and sulphated sucrose that appears to act by protecting the mucosa from acid-pepsin attack; it has minimal antacid properties. Sucralfate can be used to prevent stress ulceration in children receiving intensive care. It should be used with caution in this situation (important: reports of bezoar formation, see CSM advice below).

**SUCRALFATE**

**Cautions** administration of sucralfate and enteral feeds should be separated by 1 hour; interactions: Appendix 1 (sucralfate)

Renal impairment use with caution; aluminium is absorbed and may accumulate

Breast-feeding amount probably too small to be harmful

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

**Licensed use** not licensed for use in children under 15 years; tablets not licensed for prophylaxis of stress ulceration

**Indication and dose**

- **Prophylaxis of stress ulceration in child under intensive care**
  - By mouth
    - Child 1 month–2 years 250 mg 4–6 times daily
    - Child 2–12 years 500 mg 4–6 times daily

- **Benign gastric and duodenal ulceration**
  - By mouth
    - Child 1 month–2 years 250 mg 4–6 times daily
    - Child 2–12 years 500 mg 4–6 times daily
    - Child 12–15 years 1 g 4–6 times daily
    - Child 15–18 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

**Administration** for administration **by mouth**, sucralfate should be given 1 hour before meals, see also Cautions, above; **oral suspension** blocks fine-bore feeding tubes; crushed tablets may be dispersed in water.

**Antepsin®** (Chugai)

- Tablets, scored, sucralfate 1 g, net price 50-tab pack = £4.81. Label: 5
- Suspension, sucralfate, 1 g/5 mL, net price 250 mL (aniseed- and caramel-flavoured) = £4.81. Label: 5

1.3.4 Prostaglandin analogues
Classification not used in BNF for Children.

1.3.5 Proton pump inhibitors
The proton pump inhibitors omeprazole and lansoprazole inhibit gastric acid secretion by blocking the hydrogen-potassium adenosine triphosphatase enzyme system (the ‘proton pump’) of the gastric parietal cell. Omeprazole is currently only licensed in children for the treatment of gastro-oesophageal reflux disease with severe symptoms. Lansoprazole is not licensed for use in children, but may be considered when the available formulations of omeprazole are unsuitable. Proton pump inhibitors are effective short-term treatments for gastric and duodenal ulcers; they are also used in combination with antibacterials for the eradication of Helicobacter pylori (see p. 59 for specific regimens). An initial short course of a proton pump inhibitor is the treatment of choice in gastro-oesophageal reflux disease with severe symptoms; children with endoscopically confirmed erosive, ulcerative, or stricturing oesophagitis usually need to be maintained on a proton pump inhibitor.

Proton pump inhibitors are also used for the prevention and treatment of NSAID-associated ulcers (see p. 60). In children who need to continue NSAID treatment after an ulcer has healed, the dose of proton pump inhibitor should not normally be reduced because asymptomatic ulcer deterioration may occur.

Proton pump inhibitors are effective in the treatment of the Zollinger-Ellison syndrome (including cases resistant to other treatment). They are also used to
reduce the degradation of pancreatic enzyme supplements (section 1.9.4) in children with cystic fibrosis.

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, bronchospasmy, fever, depression, hallucinations, confusion, gynaecomastia, interstitial nephritis, hyponatraemia, blood disorders (including leucopenia, leucocytopenia, 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).

**LANSOPRAZOLE**

**Cautions** interactions: Appendix 1 (proton pump inhibitors)

Hepatic impairment may accumulate in severe impairment

Pregnancy manufacturer advises avoid

Breast-feeding present in milk in animal studies—manufacturer advises avoid

**Side-effects** see notes above; also glossitis, pancreatitis, anorexia, restlessness, tremor, impotence, petechiae, and purpura; very rarely colitis, raised serum cholesterol or triglycerides

**Licensed use** not licensed for use in children

**Indication and dose**

Gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcer including those complicating NSAID therapy, fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis

- By mouth
  - Child body-weight under 30 kg 0.5–1 mg/kg (max. 15 mg) once daily in the morning

**OMEPRAZOLE**

**Cautions** interactions: Appendix 1 (proton pump inhibitors)

Hepatic impairment no more than 700 micromg/kg (max. 20 mg) once daily

Pregnancy not known to be harmful

Breast-feeding present in milk but not known to be harmful

**Side-effects** see notes above; also agitation and impotence

**Licensed use** capsules and tablets not licensed for use in children except for severe ulcerating reflux oesophagitis in children over 1 year; injection not licensed for use in children under 12 years

**Indication and dose**

Gastro-oesophageal reflux disease, acid-related dyspepsia, treatment of duodenal and benign gastric ulcers including those complicating NSAID therapy, prophylaxis of acid aspiration, Zollinger-Ellison syndrome, fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis

- By mouth
  - Neonate 700 micrograms/kg once daily, increased if necessary after 7–14 days to 1.4 mg/kg; some neonates may require up to 2.8 mg/kg once daily
  - Child 1 month–2 years 700 micrograms/kg once daily, increased if necessary to 3 mg/kg (max. 20 mg) once daily
  - Child body-weight 10–20 kg 10 mg once daily increased if necessary to 20 mg once daily (in severe ulcerating reflux oesophagitis, max. 12 weeks at higher dose)
Child body-weight over 20 kg
20 mg once daily
increased if necessary to 40 mg once daily (in severe ulcerating reflux oesophagitis, max. 12 weeks at higher dose)

- By intravenous injection over 5 minutes or by intravenous infusion

Child 1 month–12 years initially 500 micromg/kg (max. 20 mg) once daily, increased to 2 mg/kg (max. 40 mg) once daily if necessary
Child 12–18 years 40 mg once daily

Helicobacter pylori eradication (in combination with antibacterials see p. 59)
- By mouth
  Child 1–12 years 1–2 mg/kg (max. 40 mg) once daily
  Child 12–18 years 40 mg once daily

Administration for administration by mouth, swallow whole, or disperse Losec MUPS tablets in water, or mix capsule contents or Losec MUPS tablets with fruit juice or yoghurt. Preparations consisting of an e/c tablet within a capsule should not be opened.
For administration through an enteral feeding tube, use Losec MUPS or the contents of a capsule containing omeprazole dispersed in a large volume of water, or in 10 mL Sodium Bicarbonate 8.4% (1 mmol Na+/mL) (allow to stand for 10 minutes before administration).
For intermittent intravenous infusion, dilute reconstituted solution to a concentration of 400 micromg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 20–30 minutes

Omeprazole (Non-proprietary)
Capsules, enclosing e/c granules, 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 = £58.00. 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 = £6.13; 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

Losec® (AstraZeneca)
MUPS® (multiple-unit pellet system = dispersible tablets), e/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 Acute diarrhoea

1.4.1 Adsorbents and bulk-forming 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. For details of oral rehydration preparations, see section 9.2.1.2. Severe dehydration requires immediate admission to hospital and urgent replacement of fluid and electrolytes.

Antimotility drugs (section 1.4.2) relieve symptoms of diarrhoea. They are used in the management of uncomplicated acute diarrhoea in adults, but are not recommended for use in children under 12 years. Fluid and electrolyte replacement (section 9.2.1.2) are of prime importance in the treatment of acute diarrhoea.

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 since 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 such treatment, 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 p 298

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 diarrhoeas. Bulk-forming drugs, such as ispaghula, methylcellulose, and sterculia (section 1.6.1) are rarely effective in controlling faecal consistency in ileostomy and colostomy.

1.4.2 Antimotility drugs

Antimotility drugs have a role in the management of uncomplicated acute diarrhoea in adults but not in children under 12 years; see also section 1.4. However, in the case of dehydration, fluid and electrolyte replacement (section 9.2.1.2) are of primary importance.

For comments on their role in chronic bowel disorders see section 1.5. Antimotility drugs are also used in children with stoma (section 1.8).

**CODEINE PHOSPHATE**

- **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 distention develops, or in acute diarrhoeal conditions such as acute ulcerative colitis or antibiotic-associated colitis
- **Side-effects** see section 4.7.2

- **Indication and dose**
  - **Diarrhoea** (but see notes above)
    - By mouth
    - Child 12–18 years 30 mg (range 15–60 mg) 3–4 times daily

- **Pain** section 4.7.2

**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

- **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

- **Cautions** see under Codeine Phosphate (section 4.7.2); also young children are particularly susceptible to overdose 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 overdose (section 1.2); interactions: Appendix 1 (antimuscarinics, opioid analgesics)
- **Pregnancy** may depress neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
- **Breast-feeding** may be present in milk

- **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

- **Licensed use** not licensed for use in children under 4 years

- **Indication and dose**
  - See preparations

- **Administration** for administration by mouth tablets may be crushed

**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**
  - Control of faecal consistency after colostomy or ileostomy, adjunct to rehydration in acute diarrhoea (but see notes above)
    - By mouth
    - Child 2–4 years half tablet 3 times daily
    - Child 4–9 years 1 tablet 3 times daily
    - Child 9–12 years 1 tablet 4 times daily
    - Child 12–16 years 2 tablets 3 times daily
    - Child 16–18 years initially 4 tablets then 2 tablets 4 times daily

- **Note** Co-phenotrope 2.5/0.025 can be sold to the public for 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**

- **Cautions** see notes above; interactions: Appendix 1 (loperamide)
- **Hepatic impairment** risk of accumulation—manufacturer advises avoid

- **Pregnancy** manufacturer advises avoid—no information available
- **Breast-feeding** amount probably too small to be harmful
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

Licensed use  capsules not licensed for use in children under 8 years; syrup not licensed for use in children under 4 years; not licensed for use in children for chronic diarrhoea

Indication and dose

<table>
<thead>
<tr>
<th>Condition</th>
<th>Age Range</th>
<th>Dose Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic diarrhoea</td>
<td>Child 1 month–1 year</td>
<td>100–200 micrograms/kg twice daily, 30 minutes before feeds; up to 2 mg/kg daily in divided doses occasionally required</td>
</tr>
<tr>
<td></td>
<td>Child 1–12 years</td>
<td>100–200 micrograms/kg (max. 2 mg) 3–4 times daily; up to 1.25 mg/kg daily in divided doses may be required (max. 16 mg daily)</td>
</tr>
<tr>
<td></td>
<td>Child 12–18 years</td>
<td>2–4 mg 2–4 times daily (max. 16 mg daily)</td>
</tr>
<tr>
<td>Acute diarrhoea (but see notes above)</td>
<td>By mouth</td>
<td>Child 4–8 years  1 mg 3–4 times daily for up to 3 days only</td>
</tr>
</tbody>
</table>

Loperamide

Loperamide (Non-proprietary) (TM)

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 use in children over 12 years, provided it is licensed and labelled for the treatment of acute diarrhoea

Imodium® (Janssen-Cilag) (TM)

Capsules, green/grey, loperamide hydrochloride 2 mg. Net price 30-cap pack = £1.13

Syrup, sugar-free, red, 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
Child 12–18 years initially 1 caplet, then 1 caplet after each loose stool; max. 4 caplets daily for up to 2 days

1.5 Chronic bowel disorders

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*. The treatment of inflammatory bowel disease in children should be initiated and supervised by a paediatric gastroenterologist. Effective management requires drug therapy, attention to nutrition, and in severe or chronic active disease, surgery.

Aminosalicylates (balsalazide, mesalazine, 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 (section 1.5.1); alternatively a local corticosteroid (section 1.5.2) can be used but it is less effective. Foam preparations and suppositories are useful for children who 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 upper colon can be treated with an oral aminosalicylate alone; a combination of a local and an oral aminosalicylate can 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 used for children with Crohn’s disease affecting the ileum and the ascending colon; it
causes fewer systemic side-effects than oral prednisolone but may be less effective.

Active Crohn’s disease affecting the small intestine may be treated with enteral nutrition (Appendix 2) for 6–8 weeks. Alternatively, an oral corticosteroid may be used but at the expense of side-effects; the dose of the corticosteroid is reduced gradually over 8–10 weeks.

Severe inflammatory bowel disease calls for hospital admission and treatment with an intravenous corticosteroid such as hydrocortisone (p. 451) or methylprednisolone (p. 452); other therapy may include intravenous fluid and electrolyte replacement, and possibly parenteral nutrition. Children with ulcerative colitis that fails to respond adequately to these measures may benefit from a short course of ciclosporin. Children with unresponsive or chronically active Crohn’s disease may benefit from azathioprine, mercaptopurine, or once-weekly methotrexate.

Infliximab (section 1.5.3) is used in specialist centres for children with severe active Crohn’s disease whose condition has not responded adequately to treatment with a corticosteroid and a conventional immunosuppressant or who are intolerant of them. Infliximab has also been used for the treatment of severe, refractory ulcerative colitis. There are concerns about the long-term safety of infliximab in children; hepatosplenic T-cell lymphoma has been reported.

Crohn’s disease of the mouth or of the perineum is more common in children than in adults and it is difficult to treat; elimination diets and the use of a topical corticosteroid (section 13.4) may be beneficial, but a systemic corticosteroid (section 6.3.2) and occasionally azathioprine may be required in severe cases.

**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.

**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 and should be encouraged. 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 available 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) or mercaptopurine (section 1.5.3) may be helpful. Methotrexate (section 1.5.3) is used in Crohn’s disease when azathioprine or mercaptopurine are ineffective or not tolerated. Infliximab (p. 75) can be used for maintenance therapy in Crohn’s disease or ulcerative colitis in children who respond to the initial induction course of this drug. There are concerns about the long-term safety of infliximab in children.

**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 [both unlicensed for this indication]. Metronidazole by mouth is usually used at a dose of 7.5 mg/kg 3 times daily 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 5 mg/kg twice daily. Other antibacterials should be given if specifically indicated (e.g. sepsis 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. Infliximab is used for fistulating Crohn’s disease refractory to conventional treatments and it can be continued as maintenance therapy.

**Adjunctive treatment of inflammatory bowel disease**  
Due attention should be paid to diet; high-fibre or low-residue diets should be used as appropriate.

Antimotility drugs such as codeine phosphate 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.

**Irritable bowel syndrome**  
Irritable bowel syndrome can present with pain, constipation, or diarrhoea. Some children have important psychological aggravating factors which respond to reassurance. The fibre intake of children with irritable bowel syndrome should be reviewed. If an increase in dietary fibre is required, soluble fibre (e.g. oats, ispaghula husk, or sterculia) 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.

**Clostridium difficile infection**  
Antibiotic-associated colitis is caused by colonisation of the colon with *Clostridium difficile* which may follow antibacterial therapy. It is usually of acute onset, but may run a chronic course; it is a particular hazard of clindamycin but few antibacterials are free of this side-effect. Oral metronidazole (section 5.1.11) or oral vancomycin (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.

**Malabsorption syndromes**  
Individual conditions need specific management and also general nutritional consideration. Coeliac disease (gluten enteropathy) usually needs a gluten-free diet (Appendix 2) and pancreatic insufficiency needs pancreatin supplements (section 1.9.4).

For further information on foods for special diets (ACBS), see Appendix 2.

**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 sulphonamide-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). Blood disorders can occur with aminosalicylates (see recommendation below).
Blood disorders

Children receiving aminosalicylates and their carers 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

Cautions

see notes above; also history of asthma; interactions: Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Renal impairment manufacturer advises avoid in moderate to severe impairment

Pregnancy manufacturer advises avoid

Breast-feeding manufacturer advises avoid

Contra-indications see notes above

Hepatic impairment avoid in severe impairment

Side-effects see notes above; also cholelithiasis

Licensed use not licensed for use in children under 18 years

Indication and dose

Treatment of mild to moderate ulcerative colitis and maintenance of remission

• By mouth

Child 12–18 years 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. 3 g twice daily)

Colazide® (Shire) Capsules, beige, balsalazide sodium 750 mg. Net price 130-cap pack = £39.00. Label: 21, 25, counselling, blood disorder symptoms (see recommendation above)

MESALAZINE

Cautions

see notes above; interactions: Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Renal impairment use with caution; avoid if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy negligible quantity crosses placenta

Breast-feeding diarrhoea reported but manufacturers advise negligible amounts detected in breast milk

Contra-indications see notes above; blood clotting abnormalities

Hepatic impairment avoid in severe impairment

Side-effects see notes above

Licensed use Asacol® (all preparations), Ipocol®, Salofalk® rectal enema, not licensed for use in children under 18 years; Pentasa® tablets and suppositories, Salofalk® tablets and suppositories, not licensed for use in children under 15 years; Mesren MR®, Pentasa® granules, Salofalk® rectal foam, not licensed for use in children under 12 years; Salofalk® granules not licensed for use in children under 6 years; Pentasa® retention enema, no dose recommendation for children (age range not specified by manufacturer)

Indication and dose

Treatment of mild to moderate ulcerative colitis and maintenance of remission for dose see 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

• By rectum

Child 12–18 years 1 metered application (mesalazine 1 g) into the rectum daily for 4–6 weeks

Acute attack affecting the descending colon

• By rectum

Child 12–18 years 2 metered applications (mesalazine 2 g) once daily for 4–6 weeks
Mesoril (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
Acute attack
Child 12–18 years 400–800 mg 3–4 times daily
Maintenance of remission
Child 12–18 years 400–800 mg 2–3 times daily
Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine
Ipocol (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
Child 12–18 years 800 mg 3 times daily
Maintenance of remission
Child 12–18 years 400–800 mg 3 times daily
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
Acute attack
Child 12–18 years 800 mg 3 times daily
Maintenance of remission
Child 12–18 years 400–800 mg 3 times 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
Acute attack
Child 5–15 years 15–20 mg/kg (max. 1 g) 3 times daily
Child 15–18 years 1 g daily
Maintenance of remission
Child 12–18 years 500 mg 3 times daily; total daily dose may alternatively be given in 3 divided doses
Administration tablets may be halved, quartered, or dispersed in water, but should not be chewed
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
Child 5–12 years 15–20 mg/kg (max. 1 g) 3 times daily
Child 12–18 years 1–2 g twice daily; total daily dose may alternatively be given in 3–4 divided doses
Administration contents of one sachet should be weighed and divided immediately before use; discard any remaining granules. Granules should be placed on tongue and washed down with water or orange juice without chewing
Retention enema, mesalazine 1 g in 100-mL pack. Net price 7 enemas = £18.09. Counselling, blood disorder symptoms (see recommendation above)
Dose
Acute attack affecting the rectosigmoid region
Child 12–18 years 1 g at bedtime
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
Acute attack, ulcerative proctitis
Child 12–18 years 1 g daily for 2–4 weeks
Maintenance, ulcerative proctitis
Child 12–18 years 1 g daily
Notes:
- 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)
- Treatment and maintenance of remission of ulcerative colitis affecting the rectosigmoid region
  - By rectum
  - Child 12–18 years 250–500 mg 3 times daily, with last dose at bedtime
  - Asacol (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
    - Acute attack
      - Child 12–18 years 800 mg 3 times daily
    - Maintenance of remission
      - Child 12–18 years 400–800 mg 2–3 times daily
  - Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine
  - Ipocol (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
      - Child 12–18 years 800 mg 3 times daily
    - Maintenance of remission
      - Child 12–18 years 400–800 mg 3 times daily
  - 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
    - Acute attack
      - Child 12–18 years 800 mg 3 times daily
    - Maintenance of remission
      - Child 12–18 years 400–800 mg 3 times 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
    - Acute attack
      - Child 5–15 years 15–20 mg/kg (max. 1 g) 3 times daily
      - Child 15–18 years 1–2 g twice daily; total daily dose may alternatively be given in 3 divided doses
  - Administration tablets may be halved, quartered, or dispersed in water, but should not be chewed
  - 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
      - Child 5–12 years 15–20 mg/kg (max. 1 g) 3 times daily
      - Child 12–18 years 1–2 g twice daily; total daily dose may alternatively be given in 3–4 divided doses
  - Administration contents of one sachet should be weighed and divided immediately before use; discard any remaining granules. Granules should be placed on tongue and washed down with water or orange juice without chewing
  - Retention enema, mesalazine 1 g in 100-mL pack. Net price 7 enemas = £18.09. Counselling, blood disorder symptoms (see recommendation above)
  - Dose
    - Acute attack affecting the rectosigmoid region
      - Child 12–18 years 1 g at bedtime
  - 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
    - Acute attack
      - Child 12–18 years 500 mg 3 times daily
    - Maintenance, ulcerative proctitis
      - Child 12–18 years 1 g daily
  - Maintenance of remission
    - Child 5–15 years 1 g/kg (max. 1 g) 2–3 times daily
    - Child 15–18 years 500 mg 3 times daily; total daily dose may alternatively be given in 2 divided doses
  - Administration tablets may be halved, quartered, or dispersed in water, but should not be chewed
  - 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)
MESALAZINE (continued)

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. Counselling, administration (see dose), blood disorder symptoms (see recommendation above)

Excipients include aspartame (section 9.4.1)

Dosage

Acute attack
- By mouth
  - Child 6–15 years and body-weight under 40 kg 10–15 mg/kg 3 times daily
  - Child 6–15 years and body-weight over 40 kg 1.5–3 g once daily (preferably in the morning) or 0.5–1 g 3 times daily
  - Child 15–18 years 1.5–3 g once daily (preferably in the morning) or 0.5–1 g 3 times daily

Maintenance of remission
- By mouth
  - Child 6–15 years and body-weight under 40 kg 7.5–15 mg/kg twice daily or 250 mg 3 times daily
  - Child 6–15 years and body-weight over 40 kg 500 mg 3 times daily
  - Child 15–18 years 500 mg 3 times daily

Administration Granules should be placed on tongue and washed down with water without chewing

Note Preparations that lower stool pH (e.g. lactulose) may prevent release of mesalazine

Suppositories, mesalazine 500 mg. Net price 30-suppos pack = £15.90. Counselling, blood disorder symptoms (see recommendation above)

Dose
- Acute attack or maintenance
  - By rectum
    - Child 12–18 years 0.5–1 g 2–3 times daily adjusted according to response

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
    - Child 12–18 years 2 g once daily at bedtime

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 metabisulphite

Dose
- Mild ulcerative colitis affecting sigmoid colon and rectum
  - By rectum
    - Child 12–18 years 2 metered applications (mesalazine 2 g) into the rectum at bedtime increased if necessary to 2 metered applications (mesalazine 2 g) twice daily

OLASALAZINE SODIUM

Cautions see notes above; interactions: Appendix 1 (aminosalycylates)

Blood disorders see recommendation above

Renal impairment use with caution; manufacturer advises avoid in significant impairment

Pregnancy manufacturer advises avoid unless potential benefit outweighs risks

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risks—may cause diarrhoea in infant

Contra-indications see notes above

Side-effects see notes above; watery diarrhoea common; also reported, tachycardia, palpitation, pyrexia, blurred vision, and photosensitivity

Licensed use not licensed for use in children under 12 years

Indication and dose

Treatment of acute attack of mild ulcerative colitis
- By mouth
  - Child 2–18 years 500 mg twice daily after food increased if necessary over 1 week to max. 1 g 3 times daily

Maintenance of remission of mild ulcerative colitis
- By mouth
  - Child 2–18 years 250–500 mg twice daily after food

Administration Capsules can be opened and contents sprinkled on food

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)

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 with doses over 4 g daily; acute porphyria (section 4.4.5); use with caution in renal impairment

Contra-indications see notes above

Side-effects see notes above; watery diarrhoea common; also reported, tachycardia, palpitation, pyrexia, blurred vision, and photosensitivity

Licensed use not licensed for use in children under 12 years

Indication and dose

Treatment of acute attack of mild ulcerative colitis
- By mouth
  - Child 2–18 years 500 mg twice daily after food increased if necessary over 1 week to max. 1 g 3 times daily

Maintenance of remission of mild ulcerative colitis
- By mouth
  - Child 2–18 years 250–500 mg twice daily after food

Administration Capsules can be opened and contents sprinkled on food

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 (continued)

9.8.2); interactions: Appendix 1 (aminosalicylates)

Blood disorders see recommendation above

Renal impairment risk of toxicity including crystalluria—ensure high fluid intake; avoid in severe impairment

Pregnancy theoretical risk of neonatal haemolysis in third trimester; adequate folate supplements should be given to mother

Breast-feeding small amount in milk (1 report of bloody diarrhoea and rashes); theoretical risk of neonatal haemolysis especially in G6PD-deficient infants

Contra-indications see notes above; also sulphonamide hypersensitivity; child under 2 years of age

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 periorbital oedema); stomatitis, parotitis; ataxia, aseptic meningitis, vertigo, tinnitus, insomnia, depression, hallucinations; kidney reactions (including proteinuria, crystalluria, haematuria); oligospermia; urine may be coloured orange; some soft contact lenses may be stained

Indication and dose

Treatment of acute attack of mild to moderate and severe ulcerative colitis, active Crohn’s disease

• By mouth
  - Child 2–12 years 10–15 mg/kg (max. 1 g) 4–6 times daily until remission occurs; increased to max. 60 mg/kg daily in divided doses, if necessary
  - Child 12–18 years 1–2 g 4 times daily until remission occurs

Maintenance of remission of mild to moderate and severe ulcerative colitis

• By mouth
  - Child 2–12 years 5–7.5 mg/kg (max. 500 mg) 4 times daily

CHILD 12–18 years 500 mg 4 times daily

Treatment of mild to moderate or severe ulcerative colitis and maintenance of remission, active Crohn’s disease

• By rectum as suppositories
  - Child 5–8 years 500 mg twice daily
  - Child 8–12 years 500 mg in the morning and 1 g at night
  - Child 12–18 years 0.5–1 g twice daily

Juvenile idiopathic arthritis section 10.1.3

Sulfasalazine (Non-proprietary) (UK)

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 Sulazine EC*, Salazopyrin® (Pharmacia)®

Tablets, yellow, scored, sulfasalazine 500 mg. Net price 112-tab pack = £6.97. 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

Cautions section 6.3.2; interactions: Appendix 1 (corticosteroids)

Hepatic impairment plasma-budesonide concentration may increase

Contra-indications section 6.3.2

Side-effects section 6.3.2

Licensed use not licensed for use in children

Indication and dose

See preparations

Administration Capsules can be opened and the contents mixed with apple or orange juice

1.5.2 Corticosteroids

For the role of corticosteroids in acute ulcerative colitis and Crohn’s disease, see Inflammatory Bowel Disease, p. 66.
BUDESONIDE (continued)

Budenofalk® (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
- By mouth
  Child 12–18 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

Entocort® (AstraZeneca) CR Capsules, grey/pink, enclosing e/c, m/r granules, budesonide 3 mg, net price 100-cap pack = £99.00. Label: 5, 10, steroid card, 22, 25

Note Dispense in original container (contains desiccant)

Dose Mild to moderate Crohn’s disease affecting the ileum or ascending colon
- By mouth
  Child 12–18 years 9 mg once daily in the morning before breakfast for up to 8 weeks; reduce dose for the last 2–4 weeks of treatment. See also section 6.3.2

Hydrocortisone

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

Indication and dose

Inflammatory bowel disease
- By intravenous administration
  See p. 451
- By rectum
  See preparations

Prednisonolone

Cautions section 6.3.2; systemic absorption may occur; 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

Licensed use Predfoam®, Predsol® retention enema not licensed for use in children (age range not specified by manufacturer)

Indication and dose

Ulcerative colitis, Crohn’s disease see also under preparations, below
- By mouth
  Child 2–18 years 2 mg/kg (max. 60 mg) once daily until remission occurs, followed by reducing doses
- By rectum
  See under 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) = 71p, 1 (long tube) = £1.21

Dose Ulcerative colitis
- By rectum
  Child 12–18 years initially 20 mg at bedtime for 2–4 weeks, continued if good response
1.5.3 Drugs affecting the immune response

Predfoam® (Forest) Foam in aerosol pack, prednisolone 20 mg (as metasulphobenzoate sodium)/metered application, net price 14-application cannister with disposable applicators = £6.32

Dose

Proctitis and distal ulcerative colitis
- By rectum
  Child 12–18 years 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.

Predsol® (UCB Pharma) Suppositories, prednisolone 5 mg (as sodium phosphate). Net price 10 = £1.40

Dose

Proctitis and rectal complications of Crohn’s disease
- By rectum
  Child 2–18 years 5 mg inserted night and morning after a bowel movement

1.5.3 Drugs affecting the immune response

Azathioprine, mercaptopurine, or once weekly methotrexate are used to induce remission in unresponsive or chronically active Crohn’s disease. Azathioprine or mercaptopurine may also be helpful for retaining remission in frequently relapsing inflammatory bowel disease; once weekly methotrexate is used in Crohn’s disease when azathioprine or mercaptopurine are ineffective or not tolerated. Response to azathioprine or mercaptopurine may not become apparent for several months. Folic acid (section 9.1.2) should be given to reduce the possibility of methotrexate toxicity. Folic acid can be given at a dose of 5 mg weekly; alternative regimens may be used in some settings.

Ciclosporin (cyclosporin) is a potent immunosuppressant and is markedly nephrotoxic. In children with severe ulcerative colitis unresponsive to other treatment, ciclosporin may reduce the need for urgent colorectal surgery.

1.5.3 Drugs affecting the immune response

AZATHIOPRINE

Cautions see section 8.2.1; interactions: Appendix 1 (azathioprine)

Contra-indications see section 8.2.1

Side-effects see section 8.2.1

Licensed use not licensed for use in ulcerative colitis or Crohn’s disease

Indication and dose

Severe ulcerative colitis and Crohn’s disease
- By mouth
  Child 2–18 years initially 2 mg/kg (if necessary up to 3 mg/kg) once daily, then reduced according to response to lowest effective dose; total daily dose may alternatively be given in 2 divided doses

Licensed use not licensed for use in ulcerative colitis

Indication and dose

Refractory ulcerative colitis
- By mouth
  Child 2–18 years initially 2 mg/kg twice daily, dose adjusted according to blood-ciclosporin concentration and response; max. 5 mg/kg twice daily

Important For advice on counselling and conversion between preparations, see section 8.2.2

- By intravenous infusion
  Child 3–18 years initially 0.5–1 mg/kg twice daily, dose adjusted according to blood-ciclosporin concentration and response

Administration for intermittent intravenous infusion, dilute to a concentration of 0.5–2.5 mg/mL with Glucose 5% or Sodium Chloride 0.9% and give over 2–6 hours; not to be used with PVC equipment; observe for at least 30 minutes after starting infusion and at frequent intervals thereafter.

Preparations

Section 8.2.2

Preparations

Section 8.2.2

Preparations

Section 8.2.2

Nephrotic syndrome section 8.2.2

Transplantation rejection and auto-immune conditions section 8.2.2

Atopic dermatitis and psoriasis section 13.5.3
**MERCAPTOPURINE**

**Cautions** see section 8.1.3; see also Azathioprine, section 8.2.1

**Contra-indications** see section 8.1.3

**Side-effects** see section 8.1.3

**Licensed use** not licensed for use in severe ulcerative colitis and Crohn’s disease; for other indications, see section 8.1.3

**Indication and dose**

**Severe ulcerative colitis and Crohn’s disease**

- **By mouth**
  - Child 2–18 years 1–1.5 mg/kg once daily (initial max. 50 mg; may be increased to 75 mg once daily)

**Acute leukaemias** section 8.1.3

**METHOTREXATE**

**Cautions** section 10.1.3

**Contra-indications** section 10.1.3

**Side-effects** section 10.1.3

**Licensed use** not licensed for use in children for non-malignant conditions

**Indication and dose**

**Severe acute Crohn’s disease**

- **By subcutaneous or intramuscular injection**
  - Child 7–18 years 15 mg/m² (max. 25 mg) once weekly

**Maintenance of remission of severe Crohn’s disease**

- **By mouth or by subcutaneous or intramuscular injection**
  - Child 7–18 years 15 mg/m² (max. 25 mg) once weekly; dose reduced according to response to lowest effective dose

**Safe Practice**

Note that the above dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:

- the child or their carer 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 child or their carer 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

**INFLIXIMAB**

**Cytokine modulators**

**Infliximab** is a monoclonal antibody which inhibits the pro-inflammatory cytokine, tumour necrosis factor alpha. It should be administered under specialist supervision where adequate resuscitation facilities are available and is used in the treatment of severe refractory or fistulating Crohn’s disease in children. Infliximab should be used only when treatment with other immunomodulating drugs has failed or is not tolerated and for children in whom surgery is inappropriate.

**Cautions** hepatic impairment; renal impairment; monitor for infections before, during, and for 6 months after treatment (see also Tuberculosis below); 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; interactions: Appendix 1 (infl iximab)

**Tuberculosis** Children 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. Children who have previously received adequate treatment for tuberculosis can start infliximab but should be monitored every 3 months for possible recurrence. In those without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting infliximab. Children and their carers 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 children who discontinue other immunosuppressants. All children should be observed carefully for 1–2 hours after infusion and resuscitation equipment should be available for immediate use. Prophylactic antipyretics, antihistamines, or hydrocortisone may be administered. Readministration not recommended after infliximab-free interval of more than 16 weeks—risk of delayed hypersensitivity reactions. Children and carers 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 avoid; manufacturer advises adequate contraception during and for at least 6 months after last dose
Breast-feeding avoid; manufacturer advises avoid for at least 6 months after last dose

Side-effects see under Cytokine Modulators (section 10.1.3) and Cautions above; also diarrhoea, dyspepsia; flushing, chest pain; dyspnoea; dizziness, fatigue; sinusitis; rash, increased sweating, dry skin; less commonly constipation, gastro-oesophageal reflux, cholecystitis, palpitation, arrhythmia, hypertension, hypotension, vasospasm, cyanosis, bradycardia, syncope, oedema, thombophlebitis, epistaxis, pleurisy, confusion, agitation, nervousness, amnesia, sleep disturbances, vaginitis, demyelinating disorders, antibody formation, pyelonephritis, myalgia, arthralgia, eye disorders, abnormal skin pigmentation, ecchymosis, cheilitis, and alopecia; rarely hepatitis, intestinal stenosis, intestinal perforation, gastro-intestinal haemorrhage, pancreatitis, hepatosplenic T-cell lymphoma, circulatory failure, meningitis, seizure, neuropathy, paraesthesia, and lymphoma; very rarely pericardial effusion, and skin reactions (including Stevens-Johnson syndrome and toxic epidermal necrolysis); also reported interstitial lung disease and transverse myelitis.

Licensed use not licensed for fistulating Crohn’s disease in children

Indication and dose

Severe active Crohn’s disease
• By intravenous infusion
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
• By intravenous infusion
Child 6–18 years initially 5 mg/kg, then 5 mg/kg 2 weeks and 6 weeks after initial dose, then if condition has responded, consult literature for guidance on further doses

Administration for intravenous infusion reconstitute each 100-mg vial of powder with 10 mL Water for Injections; to dissolve, gently swirl vial without shaking; allow to stand for 5 minutes; dilute required dose with Sodium Chloride 0.9% 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; start infusion within 3 hours of reconstitution

Remicade® (Schering-Plough)▼ (PA)
Intravenous infusion, powder for reconstitution, infliximab, net price 100-mg vial = £419.62.
Label: 10, alert card, counselling, tuberculosis and hypersensitivity reactions

1.5.4 Food allergy

Allergy with classical symptoms of vomiting, colic and diarrhoea caused by specific foods such as cow’s milk should be managed by strict avoidance. The condition should be distinguished from symptoms of occasional food intolerance in children with irritable bowel syndrome. Sodium cromoglicate (sodium cromoglycate) may be helpful as an adjunct to dietary avoidance.

SODIUM CROMOGLICATE
(Sodium cromoglycate)

Side-effects occasional nausea, rashes, and joint pain

Indication and dose

Food allergy (in conjunction with dietary restriction)
• By mouth
Child 2–14 years 100 mg 4 times daily before meals, dose may be increased after 2–3 weeks to a max. 40 mg/kg daily and then reduced according to response
Child 14–18 years 200 mg 4 times daily before meals, dose may be increased after 2–3 weeks to max. 40 mg/kg daily and then reduced according to response

Asthma section 3.3
Allergic conjunctivitis section 11.4.2
Allergic rhinitis section 12.2.1

Administration capsules may be swallowed whole or the contents dissolved in hot water and diluted with cold water before taking

Nalcrom® (Sanofi-Aventis)▼ (PA)
Capsules, sodium cromoglicate 100 mg. Net price 100-cap pack = £62.17. Label: 22, counselling, administration
### 1.6 Laxatives

#### 1.6.1 Bulk-forming laxatives

#### 1.6.2 Stimulant laxatives

#### 1.6.3 Faecal softeners

#### 1.6.4 Osmotic laxatives

#### 1.6.5 Bowel cleansing solutions

#### 1.6.6 Peripheral opioid-receptor antagonists

Before prescribing laxatives it is important to be sure that the child is constipated and that the constipation is not secondary to an underlying undiagnosed complaint.

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.

In infants, increased intake of fluids, particularly fruit juice containing sorbitol (e.g. prune, pear, or apple), may be sufficient to soften the stool. In infants under 1 year with mild constipation, lactulose (section 1.6.4) can be used to soften the stool; glycerol suppositories may be used to clear faecal impaction. The infant should be referred to a hospital paediatric specialist if these measures fail.

In children over 1 year with infrequent bowel motion or hard stools, if increased fluid and fibre intake is insufficient, an osmotic laxative containing macrogols 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 macrogols (section 1.6.4) 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 a persistence of withholding. If the impacted mass is not expelled following treatment with macrogols, 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, 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. Laxatives are also of value in drug-induced constipation (see Prescribing in Palliative Care, p. 26), in distal intestinal obstruction syndrome in children with cystic fibrosis, for the expulsion of parasites after anthelmintic treatment, and to clear the alimentary tract before surgery and radiological procedures (section 1.6.5).

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 are of value if the diet is deficient in fibre. They relieve constipation by increasing faecal mass which stimulates peristalsis; children and their carers should be advised that the full effect may take some days to develop.

During treatment with bulk-forming laxatives, adequate fluid intake must be maintained to avoid intestinal obstruction. Proprietary preparations containing a bulking agent such as ispaghula husk are often difficult to administer to children; 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.

Bulk-forming laxatives may be used in the management of children with haemorrhoids, anal fissure, and irritable bowel syndrome.

### ISPAGHULA HUSK

**Cautions** adequate fluid intake should be maintained to avoid intestinal obstruction

**Contra-indications** difficulty in swallowing, intestinal obstruction, colonic atony, faecal impaction

**Side-effects** flatulence and abdominal distension (especially during the first few days of treatment), gastro-intestinal obstruction or impaction; hypersensitivity reported

**Licensed use** Regular® not licensed for use in children under 6 years; Fybogel® and Ispagel Orange® not licensed for use in children under 6 years (unless on specialist practitioner’s advice); Isonel® licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

**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

**Fibrelief®** (Manx)

Granules, sugar- and gluten-free, ispaghula husk 3.5 g/sachet (natural or orange flavour), net price 10 sachets = £1.23, 30 sachets = £2.07. Label: 13, counselling, see above

**Excipients** include aspartame (section 9.4.1)

**Dose**

**Constitution**

- By mouth
  - Child 12–18 years 1–6 sachets daily in water in 1–3 divided doses

**Fybogel®** (R&C)

Granules, effervescent, sugar- and gluten-free, ispaghula husk 3.5 g/sachet (low Na+), net price 30 sachets (plain, lemon, or orange flavour) = £3.84. Label: 13, counselling, see above

**Excipients** include aspartame 16 mg/sachet (see section 9.4.1)

**Dose**

**Constitution**

- By mouth
  - Child 2–12 years ½–1 level 5-mL spoonful in water twice daily preferably after meals
  - Child 12–18 years 1 sachet (or 2 level 5-mL spoonfuls) in water 1–3 times daily preferably after meals

**Isogel®** (Potters)

Granules, brown, sugar- and gluten-free, ispaghula husk 90%. Net price 200 g = £2.67. Label: 13, counselling, see above

**Dose**

**Constitution**

- By mouth
  - Child 2–12 years 1 level 5-mL spoonful in water once or twice daily, preferably at mealtimes
  - Child 12–18 years 2 level 5-mL spoonfuls in water once or twice daily, preferably at mealtimes

**Note** May be difficult to obtain

**Ispagel Orange®** (LPC)

Granules, beige, effervescent, sugar- and gluten-free, ispaghula husk 3.5 g/sachet, net price 30 sachets = £2.10. Label: 13, counselling, see above

**Excipients** include aspartame (section 9.4.1)

**Dose**

**Constitution**

- By mouth
  - Child 2–12 years ½–1 level 5-mL spoonful in water twice daily preferably after meals
  - Child 12–18 years 1 sachet (or 2 level 5-mL spoonfuls) in water 1–3 times daily preferably after meals

**Regulan®** (Procter & Gamble)

Powder, beige, sugar- and gluten-free, ispaghula husk 3.4 g/5.85-g sachet (orange or lemon/lime flavour). Net price 30 sachets = £2.54. Label: 13, counselling, see above

**Excipients** include aspartame (section 9.4.1)

**Dose**

**Constitution**

- By mouth
  - Child 2–12 years ½–1 level 5-mL spoonful in water 1–3 times daily
  - Child 12–18 years 1 sachet in 150 mL water 1–3 times daily

### METHYLCELLULOSE

**Cautions** see under Ispaghula Husk

**Contra-indications** see under Ispaghula Husk; also infective bowel disease
1.6.2 Stimulant laxatives

Stimulant laxatives include bisacodyl, sodium picosulphate, and members of the anthraquinone group, senna and dantron (danthron). 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. Stools should be softened by increasing dietary fibre and liquid or with an osmotic laxative (section 1.6.4) before giving a stimulant laxative. In chronic constipation, especially where withholding of stool occurs, additional doses of a stimulant laxative may be required. Long-term use of stimulant laxatives is sometimes necessary (see section 1.6), but excessive use can cause diarrhoea and related effects such as hypokalaemia.

Glycerol suppositories act as a lubricant and as a rectal stimulant by virtue of the mildly irritant action of glycerol.

**BISACODYL**

**Cautions** prolonged use (risk of electrolyte imbalance)

**Pregnancy** see p. 77

**Contra-indications** ileus, intestinal obstruction, acute abdominal conditions, acute inflammatory bowel disease, severe dehydration

**Side-effects** see notes above; nausea and vomiting; colitis also reported; suppositories local irritation

**1.6.2 Stimulant laxatives (continued)**

**Side-effects** see under Ispaghula Husk

**Licensed use** no age limit specified by manufacturer

**Indication and dose**

See under preparation 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

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**STERCULIA**

**Cautions** see under Ispaghula Husk

**Contra-indications** see under Ispaghula Husk

**Side-effects** see under Ispaghula Husk

**Indication and dose**

**Constipation** for dose see under preparation

**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

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**Bisacodyl**

**Cautions** prolonged use (risk of electrolyte imbalance)

**Pregnancy** see p. 77

**Contra-indications** ileus, intestinal obstruction, acute abdominal conditions, acute inflammatory bowel disease, severe dehydration

**Side-effects** see notes above; nausea and vomiting; colitis also reported; suppositories local irritation

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**METHYLCELLULOSE (continued)**

**Side-effects** see under Ispaghula Husk

**Licensed use** no age limit specified by manufacturer

**Indication and dose**

See under preparation 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

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**Celevac** (Amdipharm)

Tablets, pink, scored, methylcellulose ‘450’ 500 mg. Net price 112-tab pack = £2.69. Counselling, see above and dose

**Dose**

**Constipation, diarrhoea** (see notes above)

- **By mouth**
  - Child 7–12 years 2 tablets twice daily
  - Child 12–18 years 3–6 tablets twice daily.

**Administration** In constipation the dose should be taken with at least 300 mL liquid. In diarrhoea, ileostomy, and colostomy control, minimise liquid intake for 30 minutes before and after dose

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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**Normacol** (Norgine)

Granules, coated, gluten-free, sterculia 62%. Net price 500 g = £6.60; 60 x 7-g sachets = £5.56. Label: 25, 27, counselling, see above

**Dose**

- **By mouth**
  - Child 6–12 years ½–1 heaped 5-mL spoonful or the contents of ½–1 sachet, washed down without chewing with plenty of liquid once or twice daily after meals
  - Child 12–18 years 1–2 heaped 5-mL spoonfuls or the contents of 1–2 sachets, washed down without chewing with plenty of liquid once or twice daily after meals

**Administration** May be mixed with soft food (e.g. yoghurt) before swallowing, followed by plenty of liquid.

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**Normacol Plus** (Norgine)

Granules, brown, coated, gluten-free, sterculia 62%, frangula (standardised) 8%. Net price 500 g = £6.60; 60 x 7-g sachets = £5.56. Label: 25, 27, counselling, see above

**Dose**

- **By mouth**
  - Child 6–12 years ½–1 heaped 5-mL spoonful or the contents of ½–1 sachet, washed down without chewing with plenty of liquid, once or twice daily after meals
  - Child 12–18 years 1–2 heaped 5-mL spoonfuls or the contents of 1–2 sachets, washed down without chewing with plenty of liquid, once or twice daily after meals
### Indication and dose

**Constipation** (tablets act in 10–12 hours; suppositories act in 20–60 minutes)

- **By mouth**
  - Child 4–10 years: 5 mg at night
  - Child 10–18 years: 5–10 mg at night; increased if necessary (max. 20 mg)

- **By rectum (suppository)**
  - Child 2–10 years: 5 mg in the morning
  - Child 10–18 years: 10 mg in the morning

**Bowel clearance before radiological procedures and surgery**

- **By mouth and by rectum**
  - Child 4–10 years: 5 mg at bedtime for 2 days before procedure and, if necessary, by rectum.
  - Child 10–18 years: 10 mg at bedtime for 2 days before procedure and, if necessary, by rectum.

### Bisacodyl (Non-proprietary)

- **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)

**Cautions**  
Avoid prolonged contact with skin (as in incontinent patients or infants wearing nappies)—risk of irritation and excoriation; rodent studies indicate potential carcinogenic risk

**Pregnancy**  
Manufacturer advises avoid—no information available

**Breast-feeding**  
Manufacturer advises avoid—limited information available

**Contra-indications**  
See Bisacodyl above

**Side-effects**  
See notes above; also urine may be coloured red

### Indication and dose

**Constipation in terminally ill children** for 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**

- **By mouth**
  - Child 6–12 years: 1 capsule at night (restricted indications, see notes above)
  - Child 12–18 years: 1–2 capsules at night (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**

- **By mouth**
  - Child 6–12 years: 1 capsule at night (restricted indications, see notes above)
  - Child 12–18 years: 1–2 capsules at night (restricted indications, see notes above)

**Suspension**, yellow, co-danthrusate 50/60 (dantron 50 mg, docusate sodium 60 mg). Net price 200 mL = £8.75. Label: 14, (urine red)

**Dose**

- **By mouth**
  - Child 6–12 years: 5 mL at night (restricted indications, see notes above)
  - Child 12–18 years: 5–15 mL at night (restricted indications, see notes above)
**DOCUSATE SODIUM**  
(Dioctyl sodium sulphosuccinate)

**Cautions** see notes above; do not give with liquid paraffin

**Pregnancy** not known to be harmful—manufacturer advises caution

**Breast-feeding** present in milk following oral administration—manufacturer advises caution

**Contra-indications** see notes above; also for rectal preparations, haemorrhoids or anal fissure

**Side-effects** see notes above

**Licensed use** adult oral solution and capsules not licensed for use in children under 12 years

**Indication and dose**

**Constipation**

- **By mouth**
  - **Child 6 months–2 years** 12.5 mg 3 times daily (use paediatric oral solution)
  - **Child 2–12 years** 12.5–25 mg 3 times daily (use paediatric oral solution)
  - **Child 12–18 years** up to 500 mg daily in divided doses

**Note** Oral preparations act within 1–2 days; response to rectal administration usually occurs within 20 minutes; recommended doses may be exceeded on specialist advice

**Adjunct in abdominal radiological procedures**

- **By mouth**
  - **Child 12–18 years** 400 mg with barium meal

**Administration** for administration by mouth, solution may be mixed with milk or squash

**Diocyl** (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**

- **By rectum**
  - **Child 12–18 years** 1 enema as a single dose

**Glyceryl Suppositories, BP**  
(Glycerin Suppositories)

- **Suppositories**, gelatin 140 mg, glycerol 700 mg, purified water to 1 g. Net price 12 = £1.07 (infant, 1-g mould), £1.03 (child, 2-g mould), £1.54 (adult, 4-g mould)

**Administration** Moisten with water before insertion

**GLYCEROL**  
(Glycerin)

**Indication and dose**

**Constipation**

- **By rectum**
  - **Child 1 month–1 year** 1-g suppository as required
  - **Child 1–12 years** 2-g suppository as required
  - **Child 12–18 years** 4-g suppository as required

**Senning (Non-proprietary)**

- **Tablets**, total sennosides (calculated as sennoside B) 7.5 mg. Net price 60 = £1.70

**Dose**

- **By mouth**
  - **Child 6–12 years** 1–2 tablets at night (or in the morning if preferred)
  - **Child 12–18 years** 2–4 tablets at night (or in the morning if preferred)

**Senna** (Non-proprietary)

- **Tablets**, total sennosides (calculated as sennoside B) 7.5 mg. Net price 60 = £1.70

**Brands include Senokot®**

**Note** Onset of action 8–12 hours; initial dose should be low; recommended doses may be exceeded on specialist advice
**Manevac** (Galen)  
Granules, coated, senna fruit 12.4%, ispaghula 54.2%, net price 400 g = £7.45. Label: 25, 27, counselling, see below  

**Dose**  
- **By mouth**  
  - **Child 5–12 years**: 1 level 5-mL spoonful once daily  
  - **Child 12–18 years**: 1–2 level 5-mL spoonfuls after evening meal and, if necessary, before breakfast or every 6 hours in resistant cases for 1–3 days  

**Administration** granules can be taken mixed with a cold or warm drink or be sprinkled on food  
**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

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**Senokot** (R&C)  
- **Tablets**: see above  
- **Syrup**: sugar-free, brown, total sennosides (calculated as sennoside B) 7.5 mg/5 mL. Net price 500 mL = £2.69  

**Dose**  
- **By mouth**  
  - **Child 1 month–2 years**: 0.5 mL/kg (max. 2.5 mL) once daily  
  - **Child 2–6 years**: 2.5–5 mL once daily in the morning  
  - **Child 6–12 years**: 5–10 mL at night or in the morning  
  - **Child 12–18 years**: 10–20 mL once daily, usually at bedtime

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**1.6.3 Faecal softeners**

Enemas containing **arachis oil** (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement.

Bulk laxatives (section 1.6.1) and non-ionic surfactant ‘wetting’ agents e.g. docucate sodium (section 1.6.2) also have softening properties. Such drugs are useful for oral administration in the management of anal fissure; glycerol suppositories (section 1.6.2) are useful for rectal use.

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**ARACHIS OIL**

**Cautions** intestinal obstruction; hypersensitivity to soya

**Contra-indications** inflammatory bowel disease, hypersensitivity to arachis oil or peanuts

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**  
- **Impacted faeces**  
  - **By rectum**  
    - **Child 3–7 years**: 45–65 mL as required

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**Bowel evacuation before abdominal radiological and endoscopic procedures on the colon, and surgery** section 1.6.5

**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  

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**Bowel cleansing solutions**  
Section 1.6.5

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**Enemas containing arachis oil** (ground-nut oil, peanut oil) lubricate and soften impacted faeces and promote a bowel movement.

Bulk laxatives (section 1.6.1) and non-ionic surfactant ‘wetting’ agents e.g. docucate sodium (section 1.6.2) also have softening properties. Such drugs are useful for oral administration in the management of anal fissure; glycerol suppositories (section 1.6.2) are useful for rectal use.
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. Macrogols are an effective non-traumatic means of evacuation in children with faecal impaction and can be used in the long-term management of chronic constipation.

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. Enemas containing phosphate or sodium citrate, and oral bowel cleansing solutions (section 1.6.5) should only be used on the advice of a specialist practitioner.

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**LACTULOSE**

**Cautions** lactose intolerance; interactions:

Appendix 1 (lactulose)

**Contra-indications** galactosaemia, intestinal obstruction

**Side-effects** flatulence, cramps, and abdominal discomfort

**Licensed use** not licensed for use in children for hepatic encephalopathy

**Indication and dose**

- **Constipation** (may take up to 48 hours to act)
  - **Child 1 month–1 year** 2.5 mL twice daily, adjusted according to response
  - **Child 1–5 years** 5 mL twice daily, adjusted according to response
  - **Child 5–10 years** 10 mL twice daily, adjusted according to response
  - **Child 10–18 years** initially 15 mL twice daily, adjusted according to response

- **Hepatic encephalopathy**
  - **Child 12–18 years** 30–50 mL 3 times daily; adjust dose to produce 2–3 soft stools per day

**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

Brands include *Duphalac*®, *Lactugal*®, *Regulose*®

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**MACROGOLS** (Polyethylene glycols)

**Cautions** discontinue if symptoms of fluid and electrolyte disturbance; see also preparations below

- **Pregnancy** manufacturer advises use only if essential—no information available
- **Breast-feeding** no information available, but absorption from gastro-intestinal tract negligible

**Contra-indications** intestinal perforation or obstruction, paralytic ileus, severe inflammatory conditions of the intestinal tract (such as Crohn’s disease, ulcerative colitis, and toxic megacolon); see also preparations below

**Side-effects** abdominal distension and pain, nausea

**Licensed use** Movicol® Paediatric Plain not licensed for use in faecal impaction in children under 5 years, or for chronic constipation in children under 2 years

**Indication and dose**

- **See under 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 46.6 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

**Dose**

- **Chronic constipation**
  - **By mouth**
    - **Child 12–18 years** 1–3 sachets daily in divided doses usually for up to 2 weeks; maintenance, 1–2 sachets daily
    - **Administration** Mix contents of each sachet in half a glass (approx. 125 mL) of water

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1.6.4 Osmotic laxatives

1 Gastro-intestinal system
Faecal impaction
• By mouth
Child 12–18 years 8 sachets daily, usually for max. 3 days
Administration Mix contents of 8 sachets in 1 litre of water. 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 46.6 mg/sachet, net price 20-sachet pack (lime- and lemon- flavoured) = £4.63, 30-sachet pack (lime- and lemon- or chocolate- or plain- flavoured) = £6.95, 50-sachet pack (lime- and lemon- or plain-flavoured) = £11.58. Label: 13

Cautions patients with impaired cardiovascular function should not take more than 4 sachets in any 1 hour

Dose
Chronic constipation
• By mouth
Child 12–18 years 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance, 2–4 sachets daily
Administration Mix content of each sachet dissolved in quarter of a glass (approx. 60–65 mL) of water

Faecal impaction
• By mouth
Child 12–18 years 16 sachets daily, usually for max. 3 days
Administration Mix contents of 16 sachets in 1 litre of water. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 6 hours

Movicol® Paediatric Plain (Norgine)
Oral powder, macrogol ‘3350’ (polyethylene glycol ‘3350’) 6.563 g, sodium bicarbonate 89.3 mg, sodium chloride 175.4 mg, potassium chloride 25.1 mg/sachet, net price 30-sachet pack = £4.63. Label: 13

Cautions with high doses, impaired gag reflex, reflux oesophagitis, impaired consciousness

Contra-indications cardiovascular impairment, renal impairment—no information available

Dose
Chronic constipation, prevention of faecal impaction
• By mouth
Child 1–6 years 1 sachet daily; adjust dose to produce regular soft stools (max. 4 sachets daily)
Child 6–12 years 2 sachets daily; adjust dose to produce regular soft stools (max. 4 sachets daily)
Administration Mix content of each sachet in quarter of a glass (approx. 60–65 mL) of water

MAGNESIUM SALTS

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

Hepatic impairment avoid in hepatic coma if risk of renal impairment
Renal impairment avoid or reduce dose; increased risk of toxicity

Contra-indications acute gastro-intestinal conditions

Side-effects colic

Indication and dose Constipation see under preparations below

lemon flavour) = £2.78, 30-sachet pack = £4.17. Label: 13

Cautions patients with impaired cardiovascular function should not take more than 4 sachets in any 1 hour

Dose
Chronic constipation
• By mouth
Child 12–18 years 2–6 sachets daily in divided doses usually for up to 2 weeks; maintenance, 2–4 sachets daily
Administration Mix content of each sachet dissolved in quarter of a glass (approx. 60–65 mL) of water

Faecal impaction
• By mouth
Child 12–18 years 16 sachets daily, usually for max. 3 days
Administration Mix contents of 16 sachets in 1 litre of water. 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 (lime and lemon flavour) = £2.78, 30-sachet pack = £4.17. Label: 13

Cautions patients with impaired cardiovascular function should not take more than 2 sachets in any 1 hour

Dose
Chronic constipation
• By mouth
Child 1–6 years 1 sachet daily; adjust dose to produce regular soft stools (max. 4 sachets daily)
Child 6–12 years 2 sachets daily; adjust dose to produce regular soft stools (max. 4 sachets daily)
Administration Mix content of each sachet in quarter of a glass (approx. 60–65 mL) of water

Faecal impaction
• By mouth
Child 1–5 years (treat until impaction resolves or for max. 7 days) 2 sachets on first day, then 4 sachets daily for 2 days, then 6 sachets daily for 2 days, then 8 sachets daily for 2 days
Child 5–12 years (treat until impaction resolves or for max. 7 days) 4 sachets on first day, then increased in steps of 2 sachets daily to max. 12 sachets daily
Administration Mix each sachet in quarter of a glass (approx. 60–65 mL) of water; total daily dose to be taken over a 12-hour period

Magnesium hydroxide

Magnesium Hydroxide Mixture, BP
Aqueous suspension containing about 8% hydrated magnesium oxide. Do not store in cold place

Dose
• By mouth
Child 3–12 years 5–10 mL with water at bedtime when required
Child 12–18 years 30–45 mL with water at bedtime when required

Bowel cleansing solutions

Section 1.6.5
PHOSPHATES (RECTAL)

Cautions see also notes above; 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

Indication and dose Constipation, bowel evacuation before abdominal radiological procedures, endoscopy, and surgery

For dose see preparations

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 = £2.98, with long rectal tube = £3.98

Dose

- By rectum
  - Child 3–7 years 40–60 mL once daily
  - Child 7–12 years 60–90 mL once daily
  - Child 12–18 years 90–118 mL once daily

Phosphates Enema BP Formula B
Enema, sodium dihydrogen phosphate dihydrate 12.8 g, disodium 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

- By rectum
  - Child 3–7 years 45–65 mL once daily
  - Child 7–12 years 65–100 mL once daily
  - Child 12–18 years 100–128 mL once daily

SODIUM CITRATE (RECTAL)

Cautions see notes above

Contra-indications acute gastro-intestinal conditions

Indication and dose Constipation for 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

- By rectum
  - Child 12–18 years 1 suppository, inserted 30 minutes before evacuation required; moisten with water before use

SODIUM CITRATE (RECTAL)

Cautions see notes above

Contra-indications acute gastro-intestinal conditions

Indication and dose Constipation for 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

- By rectum
  - Child 12–18 years 1 suppository, inserted 30 minutes before evacuation required; moisten with water before use

Micolette Micro-enema® (Pinewood)
Enema, sodium citrate 450 mg, sodium laurel sulphoacetate 45 mg, glycerol 625 mg, together with citric acid, potassium sorbate, and sorbitol in a viscous solution, in 5-mL single-dose disposable packs with nozzle. Net price 5 mL = 31p

Dose

- By rectum
  - Child 3–18 years 5–10 mL as a single dose

Mircalax 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

- By rectum
  - Child 3–18 years 5 mL as a single dose

Relaxit Micro-enema® (Crawford)
Enema, sodium citrate 450 mg, sodium laurel 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

- By rectum
  - Child 1 month–18 years 5 mL as a single dose (insert only half nozzle length in child under 3 years)

1.6.5 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.

Gastrografin® is an amidotrizoate radiological contrast medium with high osmolality; it is used in the treatment of meconium ileus in neonates and in the management of distal intestinal obstruction syndrome in children with cystic fibrosis.

BOWEL CLEANSING SOLUTIONS

Cautions recent gastro-intestinal surgery; heart disease; inflammatory bowel disease; reflux oesophagitis; impaired gag reflex; administer solution via nasogastric tube in semi-conscious or unconscious patients

Renal impairment avoid Citramag® and Picolax® if estimated glomerular filtration rate less than
30 mL/minute/1.73 m² (risk of hypermagnesaemia); manufacturer of Fleet Phospho-soda® advises avoid in significant renal impairment

Pregnancy no evidence of harm in animal studies; manufacturer advises caution especially in first trimester

Breast-feeding not excreted in breast milk

Contra-indications gastro-intestinal obstruction, gastric retention, gastro-intestinal ulceration, perforated bowel, congestive cardiac failure; toxic colitis, toxic megacolon or ileus

Side-effects nausea, vomiting, abdominal pain (usually transient—reduced by taking more slowly), abdominal distension, anal discomfort; less frequently headache, rash, and electrolyte disturbances

Licensed use Klean-Prep® not licensed for use in children

Indication and dose

Clearance of bowel prior to radiological examination, colonoscopy, or surgery

For dose see under preparations

Citramag® (Sanochemia)

Oral powder, sugar-free, effervescent, magnesium carbonate 11.57 g, anhydrous citric acid 17.79 g/sachet, net price 10-sachet pack (lemon and lime flavour) = £14.90. Label: 10, patient information leaflet, counselling, see below

Dose

• By mouth
  Child 5–10 years on day before procedure, one-third of a sachet at 8 a.m. and one-third of a sachet between 2 and 4 p.m.
  Child 10–18 years on day before procedure, ½–1 sachet at 8 a.m. and ½–1 sachet between 2 and 4 p.m.

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+/45 mL. Net price 2 × 45 mL bottles = £4.79. Label: 10, patient information leaflet, counselling

Dose

• By mouth
  Child 15–18 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’) 59 g, anhydrous sodium sulphate 5.685 g, sodium bicarbonate 1.685 g, sodium chloride 1.465 g, potassium chloride 743 mg/sachet, net price 4 sachets = £8.56. Label: 10, patient information leaflet, counselling

Excipients include aspartame (section 9.4.1)

Note Allergic reactions reported. 1 sachet when reconstituted with 1 litre water provides Na+ 125 mmol, K+ 10 mmol

Dose

Clearance of bowel prior to radiological examination, colonoscopy or surgery

• By mouth
  Child 12–18 years a glass (approx. 250 mL) of reconstituted solution every 10–15 minutes, or by nasogastic tube 20–30 mL/minute, until 4 litres have been consumed or watery stools are free of solid matter. The solution from all 4 sachets should be drunk within 4–6 hours (250 mL drunk rapidly every 10–15 minutes)

Alternatively total volume for administration given in 2 divided doses, first dose taken on the evening before examination and second dose on the morning of the examination

Distal intestinal obstruction syndrome

• By mouth, nasogastric or gastrostomy tube
  Child 1–18 years 10 mL/kg/hour for 30 minutes, then 20 mL/kg/hour if tolerated; max. 100 mL/kg (or 4 litres) over 4 hours; repeat 4-hour treatment if necessary.

Administration Each sachet should be made up to 1 litre with water; flavouring such as clear fruit cordials may be added if required; to facilitate gastric emptying domperidone (section 1.2) may be given 30 minutes before starting. After reconstitution the solution should be kept in a refrigerator and discarded if unused after 24 hours.

Picolax® (Ferring)

Oral powder, sugar-free, sodium picosulfate 10 mg/sachet, with magnesium citrate. Contains 87 mmol Mg²⁺ 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

• By mouth
  Child 1–2 years ¼ sachet before 8 a.m. then ¼ sachet 6–8 hours later
  Child 2–4 years ½ sachet before 8 a.m. then ½ sachet 6–8 hours later
  Child 4–9 years 1 sachet before 8 a.m. then ½ sachet 6–8 hours later
  Child 9–18 years 1 sachet before 8 a.m. then 1 sachet 6–8 hours later

Note Acts within 3 hours of first dose. 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; children and carers should be warned that heat is generated during reconstitution and that the solution should be allowed to cool before drinking
AMIDOTRIZOATES
Diatrizoates

Cautions  asthma or history of allergy, latent hyperthyroidism, dehydration and electrolyte disturbance (correct first); in children with oesophageal fistulae (aspiration may lead to pulmonary oedema); benign nodular goitre; enteritis; risk of anaphylactoid reactions increased by concomitant administration of beta-blockers

Pregnancy  manufacturer advises caution

Contra-indications  hypersensitivity to iodine, hyperthyroidism

Side-effects  diarrhoea, nausea, vomiting; also reported, abdominal pain, intestinal perforation, bowel necrosis, oral mucosal blistering, hypersensitivity reactions, pyrexia, headache, dizziness, disturbances in consciousness, hyperthyroidism, electrolyte disturbances, and skin reactions (including toxic epidermal necrolysis)

Licensed use  not licensed for use in distal intestinal obstruction syndrome

Indication and dose

Uncomplicated meconium ileus
- By rectum

Neonate 15–30 mL as a single dose

Distal intestinal obstruction syndrome
- By mouth or by rectum

Child 1 month–2 years 15–30 mL as a single dose

Administration  Intravenous prehydration is essential in neonates and infants. Fluid intake should be encouraged for 3 hours after administration. By mouth, for child bodyweight under 25 kg, dilute Gastrografin® with 3 times its volume of water or fruit juice; for child bodyweight over 25 kg, dilute Gastrografin® with twice its volume of water or fruit juice. By rectum, administration must be carried out slowly under radiological supervision to ensure required site is reached. For child under 5 years, dilute Gastrografin® with 5 times its volume of water; for child over 5 years dilute Gastrografin® with 4 times its volume of water. Administer using a large syringe and soft rubber catheter (No.8 French); the buttocks may be taped tightly together to minimise leakage, but a balloon catheter should not be used.

Radiological investigations  dose to be recommended by radiologist

Gastrografin® (Bayer)
Solution, sodium amidotrizoate 100 mg, meglumine amidotrizoate 660 mg/mL, net price 100-mL bottle = £15.58
Excipients include disodium edetate

1.6.6 Peripheral opioid-receptor antagonists
Classification not used in BNF for Children.

1.7 Local preparations for anal and rectal disorders

1.7.1 Soothing anal and rectal preparations
1.7.2 Compound anal and rectal preparations with corticosteroids
1.7.3 Rectal sclerosants
1.7.4 Management of anal fissures

In children with perianal soreness or pruritus ani, good toilet hygiene is essential; the use of alcohol-free ‘wet-wipes’ after each bowel motion, regular bathing and the avoidance of local irritants such as bath additives is recommended. Excoriated skin is best treated with a protective barrier emollient (section 13.2.2); in children over 1 month, hydrocortisone ointment or cream (section 13.4) or a compound rectal preparation (section 1.7.2) may be used for a short period of time, up to a maximum of 7 days.

Pruritus ani  caused by threadworm infection requires treatment with an anthelminetic (section 5.5.1). Topical application of white soft paraffin or other bland emollient (section 13.2.1) may reduce anal irritation caused by threadworms.

Perianal erythema  caused by streptococcal infection should be treated initially with an oral antibacterial such as phenoxymethylpenicillin (section 5.1.1.1) or erythromycin (section 5.1.5), while awaiting results of culture and sensitivity testing.

Perianal candidiasis (thrush) requires treatment with a topical antifungal preparation (section 13.10.2). For treatment of vulvovaginal candidiasis, see section 7.2.2.

Proctitis  associated with inflammatory bowel disease in children is treated with corticosteroids and aminosalicylates (section 1.5).

For the management of anal fissures, see section 1.7.4.
1.7.1 Soothing anal and rectal preparations

Haemorrhoids in children are rare, but may occur in infants with portal hypertension. Soothing rectal preparations containing mild astringents such as bismuth subgallate, zinc oxide, and hamamelis may provide symptomatic relief, but proprietary preparations which also contain lubricants, vasoconstrictors, or mild antiseptics may cause further perianal irritation.

Local anaesthetics may be used to relieve pain in children with anal fissures or pruritus ani, but local anaesthetics are absorbed through the rectal mucosa and may cause sensitisation of the anal skin. Excessive use of local anaesthetics may result in systemic effects, see section 15.2. Preparations containing local anaesthetics should be used for no longer than 2–3 days.

Lidocaine (lignocaine) ointment (section 15.2) may be applied before defaecation to relieve pain associated with anal fissure, but local anaesthetics can cause stinging initially and this may aggravate the child’s fear of pain.

Other local anaesthetics such as tetracaine (amethocaine), cinchocaine (dibucaine), and pramocaine (pramoxine) may be included in rectal preparations, but these are more irritant than lidocaine.

Corticosteroids are often combined with local anaesthetics and soothing agents in topical preparations for haemorrhoids and proctitis. Topical preparations containing corticosteroids (section 1.7.2) should not be used long-term or if infection (such as herpes simplex) is present. For further information on the use of topical corticosteroids, see section 13.4.

1.7.2 Compound anal and rectal preparations with corticosteroids

Anugesic-HC® (Pfizer) (Mw)

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

- Haemorrhoids, pruritus ani
  - By rectum
  - Child 12–18 years apply night and morning and after a bowel movement; do not use for longer than 7 days

Suppositories, buff, benzyl benzoate 33 mg, bismuth oxide 24 mg, bismuth subgallate 59 mg, hydrocortisone acetate 5 mg, Peru balsam 49 mg, pramocaine hydrochloride 27 mg, zinc oxide 296 mg, net price 12 = £2.69

Dose

- Haemorrhoids, pruritus ani
  - By rectum
  - Child 12–18 years insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days

Anusol-HC® (McNeil) (Mw)

Ointment, benzyl benzoate 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

- Haemorrhoids, pruritus ani
  - By rectum
  - Child 12–18 years apply night and morning and after a bowel movement; do not use for longer than 7 days

Suppositories, benzyl benzoate 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

- Haemorrhoids, pruritus ani
  - By rectum
  - Child 12–18 years insert 1 suppository night and morning and after a bowel movement; do not use for longer than 7 days

Perinal® (Dermal)

Spray application, hydrocortisone 0.2%, lidocaine hydrochloride 1%. Net price 30-mL pack = £6.39

Dose

- Haemorrhoids, pruritus ani
  - By rectum
  - Child 2–18 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)

Proctofoam HC® (Meda) (Mw)

Foam in aerosol pack, hydrocortisone acetate 1%, pramocaine hydrochloride 1%. Net price 21.2-g pack (approx. 40 applications) with applicator = £5.06

Dose

- Pain and irritation associated with local, non-infected anal or perianal conditions
  - By rectum
  - Child 12–18 years 1 applicatorful (4–6 mg hydrocortisone acetate, 4–6 mg pramocaine hydrochloride) by rectum 2–3 times daily and after a bowel movement (max. 4 times daily); do not use for longer than 7 days
**Rectal sclerosants**

Classification not used in *BNF for Children*.

### 1.7.4 Management of anal fissures

The management of anal fissures includes stool softening (section 1.6) and the short-term use of a topical preparation containing a local anaesthetic (section 1.7.1). If these measures are inadequate, children with chronic anal fissures should be referred for specialist treatment in hospital. Topical glyceryl trinitrate, 0.05% or 0.1% ointment, may be used in children to relax the anal sphincter, relieve pain and aid healing of anal fissures. Excessive application of topical nitrates causes side-effects such as headache, flushing, dizziness, and postural hypotension.

Before considering surgery, diltiazem 2% ointment may be used in children with chronic anal fissures resistant to topical nitrates.
Ointments containing glyceryl trinitrate in a range of strengths or diltiazem 2% are available as manufactured specials (see Special-order Manufacturers, p. 943).

## 1.8 Stoma and enteral feeding tubes

### Stoma

Prescribing for children with stoma calls for special care. The following is a brief account of some of the main points to be borne in mind.

When a solid-dose formulation such as a capsule or a tablet is given the contents of the ostomy bag should be checked for any remnants; response to treatment should be carefully monitored because of the possibility of incomplete absorption. **Enteric-coated and modified-release preparations are unsuitable,** particularly in children with an ileostomy, as there may not be sufficient release of the active ingredient.

**Laxatives** Enemas and washouts should not be used in children with stoma only under specialist supervision; they should not be prescribed for those with an ileostomy as they may cause rapid and severe loss of water and electrolytes. Children with colostomy may suffer from constipation and whenever possible it should be treated by increasing fluid intake or dietary fibre. If a laxative (section 1.6) is required, it should generally be used for short periods only.

**Antidiarrhoeals** Loperamide, codeine phosphate, and co-phenotrope (section 1.4.2) are effective for controlling excessive stool losses. 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 children with stoma.

**Diuretics** Diuretics should be used with caution in children with an ileostomy because they may become excessively dehydrated and potassium depletion may easily occur. It is usually advisable to use a **potassium-sparing** diuretic (section 2.2.3).

**Digoxin** Children with stoma are particularly susceptible to hypokalaemia. This predisposes children on digoxin to digoxin toxicity; potassium supplements (section 9.2.1.1) or a potassium-sparing diuretic (section 2.2.3) may be advisable.

**Analgesics** Opioid analgesics (section 4.7.2) may cause troublesome constipation in children with colostomy. When a non-opioid analgesic is required paracetamol is usually suitable; anti-inflammatory analgesics may cause gastric irritation and bleeding.

**Iron preparations** Iron supplements may cause loose stools and sore skin at the stoma site. If this is troublesome and if iron is definitely indicated a parenteral iron preparation (section 9.1.1.2) should be used. Modified-release iron preparations should be avoided.

**Care of stoma** Children and carers 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 a stoma-care nurse. Voluntary organisations offer help and support to patients with stoma.

### Enteral feeding tubes

Care is required in choosing an appropriate formulation of a drug for administration through a nasogastric narrow-bore feeding tube or through a percutaneous endoscopic gastrostomy (PEG) or jejunostomy tube. Liquid preparations (or soluble tablets) are preferred; injection solutions may also be suitable for administration through an enteral tube.

If a solid formulation of a medicine needs to be given, it should be given as a suspension of particles fine enough to pass through the tube. It is possible to crush many immediate-release tablets but enteric-coated or modified-release preparations should not be crushed.
Enteral feeds may affect the absorption of drugs and it is therefore important to consider the timing of drug administration in relation to feeds. If more than one drug needs to be given, they should be given separately and the tube should be flushed with water after each drug has been given.

Clearing blockages  Carbonated (sugar-free) drinks may be marginally more effective than water in unblocking feeding tubes, but mildly acidic liquids (such as pineapple juice or cola-based drinks) can coagulate protein in feeds, causing further blockage. If these measures fail to clear the enteral feeding tube, an alkaline solution containing pancreatic enzymes may be introduced into the tube (followed after at least 5 minutes by water). Specific products designed to break up blockages caused by formula feeds are also available.

1.9 Drugs affecting intestinal secretions

1.9.1 Drugs affecting biliary composition and flow

Bile acids (ursodeoxycholic and chenodeoxycholic acid) may be used as dietary supplements in children with inborn errors of bile acid synthesis. Ursodeoxycholic acid is used to improve the flow of bile in children with cholestatic conditions such as familial intrahepatic cholestasis, biliary atresia in infants, cystic-fibrosis-related liver disease, and cholestasis caused by total parenteral nutrition or following liver transplantation. Ursodeoxycholic acid may also relieve the severe itching associated with cholestasis.

In sclerosing cholangitis, ursodeoxycholic acid is used to lower liver enzyme and serum-bilirubin concentrations.

Ursodeoxycholic acid is also used in the treatment of intrahepatic cholestasis in pregnancy.

Smith-Lemli-Opitz syndrome  Chenodeoxycholic and ursodeoxycholic acid have been used with cholesterol in children with Smith-Lemli-Opitz syndrome. Chenodeoxycholic acid is also used in combination with cholic acid to treat bile acid synthesis defects but cholic acid is difficult to obtain. Chenodeoxycholic acid and cholesterol are available from ‘special-order’ manufacturers or specialist importing companies, see p. 943.

### URSODEOXYCHOLIC ACID

**Cautions**

**interactions:** Appendix 1 (ursodeoxycholic acid)

**Hepatic impairment**  avoid in chronic liver disease (but used in primary biliary cirrhosis)

**Pregnancy**  no evidence of harm but manufacturer advises avoid

**Breast-feeding**  not known to be harmful but manufacturer advises avoid

**Contra-indications**  radio-opaque stones; non-functioning gall bladder (in patients with radiolucent gallstones)

**Side-effects**  rarely, diarrhoea

**Licensed use**  not licensed for use in children for indications shown below

**Indication and dose**

**Cholestasis**

- **By mouth**

**Neonate**  5 mg/kg 3 times daily, adjust dose and frequency according to response, max. 10 mg/kg 3 times daily

**Child 1 month–2 years**  5 mg/kg 3 times daily, adjust dose and frequency according to response, max. 10 mg/kg 3 times daily

**Improvement of hepatic metabolism of essential fatty acids and bile flow, in children with cystic fibrosis**

- **By mouth**

**Child 1 month–18 years**  10–15 mg/kg twice daily; total daily dose may alternatively be given in 3 divided doses

**Cholestasis associated with total parenteral nutrition**

- **By mouth**

**Neonate**  10 mg/kg 3 times daily

**Child 1 month–18 years**  10 mg/kg 3 times daily
Sclerosing cholangitis

- By mouth
  
  Child 1 month–18 years 5–10 mg/kg 2–3 times daily, adjusted according to response, max. 15 mg/kg 3 times daily

Ursodeoxycholic Acid (Non-proprietary)

- Tablets, ursodeoxycholic acid 150 mg, net price 60-tab pack = £18.51. Label: 21
- Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £35.11. Label: 21

- Destolit® (Norgine) (Non-proprietary)
  - Tablets, scored, ursodeoxycholic acid 150 mg, net price 60-tab pack = £18.39. Label: 21

- Urdox® (CP) (Non-proprietary)
  - Tablets, f/c, ursodeoxycholic acid 300 mg, net price 60-tab pack = £26.50. Label: 21

- Ursofalk® (Dr Falk) (Non-proprietary)
  - Capsules, ursodeoxycholic acid 250 mg, net price 60-cap pack = £31.10, 100-cap pack = £32.85. Label: 21
  - Suspension, sugar-free, ursodeoxycholic acid 250 mg/5 mL, net price 250 mL = £28.50. Label: 21

- UrsoGal® (Galen) (Non-proprietary)
  - Tablets, scored, ursodeoxycholic acid 150 mg, net price 60-cap pack = £30.50. Label: 21

Other preparations for bile synthesis defects

CHENODEOXYCHOLIC ACID

- Cautions see under Ursodeoxycholic Acid
- Pregnancy avoid—fetotoxicity reported in animal studies
- Contra-indications see under Ursodeoxycholic Acid
- Side-effects see under Ursodeoxycholic Acid
- Licensed use not licensed

Indication and dose

- Cerebrotendinous xanthomatosis
  - By mouth
  
  Neonate 5 mg/kg 3 times daily
  
  Child 1 month–18 years 5 mg/kg 3 times daily

- Defective synthesis of bile acid
  - By mouth
  
  Neonate initially 5 mg/kg 3 times daily, reduced to 2.5 mg/kg 3 times daily

- Smith-Lemli-Opitz syndrome see notes above

- Administration for administration by mouth, add the contents of a 250-mg capsule to 25 mL of sodium bicarbonate solution 8.4% (1 mmol/mL) to produce a suspension containing chenodeoxycholic acid 10 mg/mL; use immediately after preparation, discard any remaining suspension

- Chenofalk (Non-proprietary)
  - Capsules, chenodeoxycholic acid 250mg
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

CHOLESEROLOL

- Cautions consult product literature
- Contra-indications consult product literature
- Licensed use not licensed

Indication and dose

- Smith-Lemli-Opitz syndrome
  - By mouth
  
  Neonate 7 mg/kg once daily or in divided doses

- Child 1 month–18 years 7 mg/kg once daily or in divided doses

- Administration cholesterol powder can be mixed with a vegetable oil before administration

- Cholesterol Powder (Non-proprietary)
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

1.9.2 Bile acid sequestrants

Colestyramine (cholestyramine) is an anion-exchange resin that forms an insoluble complex with bile acids in the gastro-intestinal tract; it is used to relieve diarrhoea associated with surgical procedures such as ileal resection, or following radiation therapy. Colestyramine is also used in the treatment of familial hypercholesterolaemia (see section 2.12), and to relieve pruritus in children with partial biliary obstruction, (for treatment of pruritus, see section 3.4.1). Colestyramine is
not absorbed from the gastro-intestinal tract, but will interfere with the absorption of a number of drugs, so timing of administration is important.

**COLESTYRAMINE**
(Cholestyramine)

**Cautions** see section 2.12

**Contra-indications** see section 2.12

**Side-effects** see section 2.12

**Licensed use** not licensed for use in children under 6 years

**Indication and dose**
Pruritus associated with partial biliary obstruction and primary biliary cirrhosis, diarrhoea associated with Crohn’s disease, ileal resection, vagotomy, diabetic vagal neuropathy, and radiation

- By mouth
  - **Child 1 month–1 year**: 1 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 9 g daily)
  - **Child 1–6 years**: 2 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 18 g daily)
  - **Child 6–12 years**: 4 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 24 g daily)
  - **Child 12–18 years**: 4–8 g once daily in a suitable liquid, adjusted according to response; total daily dose may alternatively be given in 2–4 divided doses (max. 36 g daily)

**Counselling**
Other drugs should be taken at least 1 hour before or 4–6 hours after colestyramine to reduce possible interference with absorption

**Note**
For treatment of diarrhoea induced by bile acid malabsorption, if no response within 3 days an alternative therapy should be initiated

**Hypercholesterolaemia** section 2.12

**Administration**
The contents of one sachet should be mixed with at least 150 mL of water or other suitable liquid such as fruit juice, skimmed milk, thin soups, or pulpy fruits with a high moisture content

- **Preparations**
  - Section 2.12

1.9.3 Aprotinin
Classification not used in BNF for Children.

1.9.4 Pancreatin
Pancreatin containing a mixture of protease, lipase and amylase in varying proportions aids the digestion of starch, fat, and protein. Supplements of pancreatin are given by mouth to compensate for reduced or absent exocrine secretion in cystic fibrosis, and following pancreatectomy, total gastrectomy, or chronic pancreatitis.

The dose of pancreatin is adjusted according to size, number, and consistency of stools, and the nutritional status of the child; extra allowance will be needed if snacks are taken between meals. Daily dose should not exceed 10 000 lipase units per kg body-weight per day. (important: see CSM advice on Higher-strength preparations below).

### Pancreatin preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Protease units</th>
<th>Amylase units</th>
<th>Lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon® 10 000 capsule, e/c granules</td>
<td>600</td>
<td>8000</td>
<td>10 000</td>
</tr>
<tr>
<td>Creon® Micro e/c granules (per 100 mg)</td>
<td>200</td>
<td>3600</td>
<td>5000</td>
</tr>
<tr>
<td>Nutrizym 10® capsule, e/c minitablets</td>
<td>500</td>
<td>9000</td>
<td>10 000</td>
</tr>
<tr>
<td>Pancrex® granules (per gram)</td>
<td>300</td>
<td>4000</td>
<td>5000</td>
</tr>
<tr>
<td>Pancrex V® capsule, powder</td>
<td>430</td>
<td>9000</td>
<td>8000</td>
</tr>
<tr>
<td>Pancrex V®125® capsule, powder</td>
<td>160</td>
<td>3300</td>
<td>2950</td>
</tr>
<tr>
<td>Pancrex V® e/c tablet</td>
<td>110</td>
<td>1700</td>
<td>1900</td>
</tr>
<tr>
<td>Pancrex V® Forte e/c tablet</td>
<td>330</td>
<td>5000</td>
<td>5600</td>
</tr>
<tr>
<td>Pancrex V® powder (per gram)</td>
<td>1400</td>
<td>30 000</td>
<td>25 000</td>
</tr>
</tbody>
</table>

**Higher-strength pancreatin preparations**
Pancrease HL® and Nutrizym 22® have been associated with the development of large bowel strictures (fibrosing
colonopathy) in children with cystic fibrosis aged between 2 and 13 years. The CSM (1995) has recommended the following:

- *Pancrease HL*, *Nutrizym 22* should not be used in children under 16 years 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.

### Higher-strength pancreatin preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Protease units</th>
<th>Amylase units</th>
<th>Lipase units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creon® 25 000 capsule, e/c pellets</td>
<td>1000</td>
<td>18 000</td>
<td>25 000</td>
</tr>
<tr>
<td>Creon® 40 000 capsule, e/c granules</td>
<td>1600</td>
<td>25 000</td>
<td>40 000</td>
</tr>
<tr>
<td>Nutrizym 22* capsule, e/c minitablets</td>
<td>1100</td>
<td>19 800</td>
<td>22 000</td>
</tr>
<tr>
<td>Pancrease HL® capsule, e/c minitablets</td>
<td>1250</td>
<td>22 500</td>
<td>25 000</td>
</tr>
</tbody>
</table>

Pancreatin is inactivated by gastric acid therefore pancreatin preparations are best taken with food (or immediately before or after food). In children with cystic fibrosis with persistent fat malabsorption despite optimal use of enzyme replacement, an *H₂-receptor antagonist* (section 1.3.1), or a *proton pump inhibitor* (section 1.3.5) may improve fat digestion and absorption. Enteric-coated preparations are designed to deliver a higher enzyme concentration in the duodenum (provided the capsule contents are swallowed whole without chewing). If the capsules are opened the enteric-coated granules should be mixed with milk, slightly acidic soft food or liquid such as apple juice, and then swallowed immediately without chewing. Any left-over food or liquid containing pancreatin should be discarded. Since pancreatin is also inactivated by heat, excessive heat should be avoided if preparations are mixed with liquids or food.

Pancreatin can irritate the perioral skin and buccal mucosa if retained in the mouth, and excessive doses can cause perianal irritation. Hypersensitivity reactions may occur particularly if the powder is handled.

### PANCREATIN

**Cautions** see CSM advice above; hyperuricaemia and hyperuricosuria have been associated with very high doses; **interactions**: Appendix 1 (pancreatin)

**Side-effects** nausea, vomiting, abdominal discomfort; skin and mucosal irritation (see notes above)

**Indication and dose**

**Pancreatic insufficiency** for dose see individual preparations, below

**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. Counseling, see dose

**Dose**

- By mouth

  **Child 1 month–18 years** initially 1–2 capsules with each meal either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing), see notes above
**Nutrizym 10**<sup>®</sup> (Merck)
Capsules, red/yellow, enclosing e/c minitablets of pancreatin (pork) providing minimum of: protease 500 units, lipase 10 000 units, amylase 9000 units. Net price 100 = £14.47. Counselling, see dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–18 years</td>
<td>1–2 capsules with meals and 1 capsule with snacks, swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing, see notes above); higher doses may be required according to response</td>
</tr>
</tbody>
</table>

**Pancrease®** (Paines & Byrne)
Granules, pancreatin (pork), providing minimum of: protease 300 units, lipase 8000 units, amylase 4000 units/g. Net price 300 g = £20.39. Label: 25, counselling, see dose

**Excipients** include lactose (7 g per 10 g dose)

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 2–18 years</td>
<td>5–10 g just before meals washed down or mixed with milk or water</td>
</tr>
</tbody>
</table>

**Pancrease V®** (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

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–1 year</td>
<td>contents of 1–2 capsules mixed with feeds</td>
</tr>
<tr>
<td>Child 1–18 years</td>
<td>2–6 capsules with meals, swallowed whole or sprinkled on food</td>
</tr>
</tbody>
</table>

**Capsules ‘125’,** pancreatin (pork), providing minimum of: protease 160 units, lipase 2950 units, amylase 3300 units. Net price 300-cap pack = £9.72. Counselling, see dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>contents of 1–2 capsules mixed with feeds</td>
</tr>
<tr>
<td>Child 2–18 years</td>
<td>initially 1 capsule with meals either taken whole or contents mixed with fluid or soft food (then swallowed immediately without chewing), see notes above</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 2–18 years</td>
<td>1–2 capsules during each meal and 1 capsule with snacks, swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing), see notes above</td>
</tr>
</tbody>
</table>

**Nutrizym 22**<sup>®</sup> (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-cap pack = £33.33. Counselling, see above and under dose

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 15–18 years</td>
<td>1–2 capsules with meals and 1 capsule with snacks swallowed whole or contents mixed with slightly acidic liquid or soft food (then swallowed immediately without chewing), see notes above</td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Dose</th>
<th>By mouth</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 15–18 years</td>
<td>1–2 capsules during each meal and 1 capsule with snacks swallowed whole or contents taken with water or mixed with soft food (then swallowed immediately without chewing), see notes above</td>
</tr>
</tbody>
</table>
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- arrhythmias, p. 107
- heart failure, p. 100
- hypertension, p. 119
- pulmonary hypertension, p. 123

## Positive inotropic drugs

### 2.1 Positive inotropic drugs

#### 2.1.1 Cardiac glycosides

The cardiac glycoside digoxin increases the force of myocardial contraction and reduces conductivity within the atrioventricular (AV) node.

Digoxin is most useful in the treatment of supraventricular tachycardias, especially for controlling ventricular response in persistent atrial fibrillation (section 2.3.1). Digoxin has a limited role in children with chronic heart failure; for reference to the role of digoxin in heart failure, see section 2.2.

For the management of atrial fibrillation, the maintenance dose of digoxin is determined on the basis of the ventricular rate at rest, which should not be allowed to fall below an acceptable level for the child.

Digoxin is now rarely used for rapid control of heart rate (see section 2.3.2), 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.

Unwanted effects depend both on the concentration of digoxin 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 the symptoms of both are similar. Also, the plasma-digoxin concentration alone cannot indicate toxicity reliably but the likelihood of toxicity increases progressively through the range 1.5 to 3 micrograms/litre for digoxin. Renal function is very important in determining digoxin dosage.

Hypokalaemia predisposes the child to digitalis toxicity and should be avoided; it is managed by giving a potassium-sparing diuretic or, if necessary, potassium supplements (or foods rich in potassium).

Toxicity can often be managed by discontinuing digoxin and correcting hypokalaemia if appropriate; serious manifestations require urgent specialist management. **Digoxin-specific antibody fragments** are available for reversal of life-threatening overdosage (see below).

### 2.1.2 Phosphodiesterase inhibitors

Positive inotropic drugs increase the force of contraction of the myocardium. Drugs which produce inotropic effects include cardiac glycosides, phosphodiesterase inhibitors, and some sympathomimetics (section 2.7.1).

#### DIGOXIN

**Cautions** sick sinus syndrome; thyroid disease; hypoxia; severe respiratory disease; avoid hypokalaemia, hypomagnesaemia, hypercalcaemia, and hypoxia (risk of digitalis toxicity); monitor serum electrolytes and renal function; avoid rapid intravenous administration (risk of hypotension and reduced coronary flow); **interactions:** Appendix 1 (cardiac glycosides)

**Renal impairment** reduce dose; toxicity increased by electrolyte disturbances, adjust dose according to plasma-digoxin concentration

**Pregnancy** may need dosage adjustment

**Breast-feeding** amount too small to be harmful

**Contra-indications** intermittent complete heart block, second degree AV block; supraventricular arrhythmias associated with accessory conducting pathways e.g. Wolff-Parkinson-White syndrome (although can be used in infancy); ventricular tachycardia or fibrillation; hypertrophic cardiomyopathy (unless concomitant atrial fibrillation and heart failure—but 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,
eosiophilia; less commonly depression; very rarely anorexia, intestinal ischaemia and necrosis, psychosis, apathy, confusion, headache, fatigue, weakness, gynaecomastia on long-term use, and thrombocytopenia

Pharmacokinetics For plasma-digoxin concentration assay, blood should ideally be taken at least 6 hours after a dose; plasma-digoxin concentration should be maintained in the range 0.8–2 micrograms/litre (see also notes above)

Licensed use heart failure, supraventricular arrhythmias

Indication and dose

Supraventricular arrhythmias and chronic heart failure (see also notes above) consult product literature for details

By mouth

Child under 1.5 kg initially 25 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg daily in 1–2 divided doses
Child 1.5–2.5 kg initially 30 micrograms/kg in 3 divided doses for 24 hours then 4–6 micrograms/kg daily in 1–2 divided doses
Child over 2.5 kg initially 45 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses

Child 1 month–2 years initially 45 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses
Child 2–5 years initially 35 micrograms/kg in 3 divided doses for 24 hours then 10 micrograms/kg daily in 1–2 divided doses
Child 5–10 years initially 25 micrograms/kg (max. 750 micrograms) in 3 divided doses for 24 hours then 6 micrograms/kg daily (max. 250 micrograms daily) in 1–2 divided doses

Child 10–18 years initially 0.75–1.5 mg in 3 divided doses for 24 hours then 62.5–250 micrograms daily in 1–2 divided doses (higher doses may be necessary)

Less urgent digitalisation

• By mouth
  Rapid digitalisation may not always be required.
  Child 10–18 years 250–500 micrograms daily (higher dose may be divided) for 5–7 days followed by maintenance dose

Note The above doses may need to be reduced if digoxin (or another cardiac glycoside) has been given in the preceding 2 weeks. When switching from intravenous to oral route may need to increase dose by 20–30% to maintain the same plasma digoxin concentration. Plasma monitoring may be required when changing formulation to take account of varying bioavailabilities. For plasma concentration monitoring, blood should ideally be taken at least 6 hours after a dose

Administration For intravenous infusion, dilute with sodium chloride 0.9% intravenous infusion or glucose 5% to a max. concentration of 62.5 micrograms/mL; loading doses should be given over 30–60 minutes and maintenance dose over 10–20 minutes. Protect from light. For oral administration, oral solution must not be diluted

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
Excipients include alcohol, propylene glycol (see excipients) Available from Antigen
Paediatric injection, digoxin 100 micrograms/mL Available from ‘special-order’ manufacturers or specialist importing companies, see p.943

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

Digoxin-specific antibody

Digoxin-specific antibody fragments are indicated for the treatment of known or strongly suspected digoxin or digitoxin overdosage, in situations where mea-
sures beyond the withdrawal of the cardiac glycoside and correction of any electrolyte abnormalities are felt to be necessary (see also notes above).

Digibind® (GSK) [H53] 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 or Poisons Information Centre

2.1.2 Phosphodiesterase inhibitors

Enoximone and milrinone are selective phosphodiesterase inhibitors which exert most of their effect on the myocardium. They possess positive inotropic and vasodilator activity and are useful in infants and children with low cardiac output especially after cardiac surgery. Phosphodiesterase inhibitors should be limited to short-term use because long-term oral administration has been associated with increased mortality in adults with congestive heart failure.

**ENOXIMONE**

**Cautions** heart failure associated with hypertrophic cardiomyopathy, stenotic or obstructive valvular disease or other outlet obstruction; monitor blood pressure, heart rate, ECG, central venous pressure, fluid and electrolyte status, renal function, platelet count, hepatic enzymes; avoid extravasation; **interactions:** Appendix 1 (phosphodiesterase inhibitors)

**Hepatic impairment** dose reduction may be required

**Renal impairment** consider dose reduction

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** manufacturer advises caution—no information available

**Side-effects** ectopic beats; less frequently ventricular tachycardia or supraventricular arrhythmias (more likely in children with pre-existing arrhythmias); hypotension; also headache, insomnia, nausea and vomiting, diarrhoea; occasionally, chills, oliguria, fever, urinary retention; upper and lower limb pain

**Licensed use** not licensed for use in children

**Indication and dose**

Congestive heart failure, low cardiac output following cardiac surgery
- By intravenous injection and continuous intravenous infusion

**Neonate** initial loading dose of 500 micrograms/kg by slow intravenous injection, followed by 5–20 micrograms/kg/minute by continuous intravenous infusion over 24 hours adjusted according to response; max 24 mg/kg over 24 hours

**Child 1 month–18 years** initial loading dose of 500 micrograms/kg by slow intravenous injection, followed by 5–20 micrograms/kg/minute by continuous intravenous infusion over 24 hours adjusted according to response; max. 24 mg/kg over 24 hours

**Administration** for intravenous administration dilute to concentration of 2.5mg/mL with sodium chloride 0.9% intravenous infusion or water for injections; the initial loading dose should be given by slow intravenous injection over at least 15 minutes. Use plastic apparatus—crystal formation if glass used

Perfan® (INCA-Pharm) [H53] Injection, enoximone 5 mg/mL. For dilution before use. Net price 20-mL amp = £15.02

**Excipients** include alcohol, propylene glycol

**MILRINONE**

**Cautions** see under Enoximone; also correct hypokalaemia; monitor renal function; **interactions:** Appendix 1 (phosphodiesterase inhibitors)

**Renal impairment** reduce dose and monitor response

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** manufacturer advises caution—no information available

**Side-effects** ectopic beats, ventricular tachycardia, supraventricular arrhythmias (more likely in children with pre-existing arrhythmias), hypotension; headache; **less commonly** ventricular fibrillation, chest pain, tremor, hypokalaemia, thrombocytopenia; **very rarely** bronchospasm, anaphylaxis, and rash

**Licensed use** not licensed for use in children under 18 years

**Indication and dose**

Congestive heart failure, low cardiac output following cardiac surgery, shock
- By intravenous infusion

**Neonate** initially 50–75 micrograms/kg over 30–60 minutes (reduce or omit initial dose if at risk of hypotension) then 30–45 micrograms/kg/hour by continuous intravenous infusion for 2–3 days (usually for 12 hours after cardiac surgery)
Diuretics are used for a variety of conditions in children including pulmonary oedema (caused by conditions such as respiratory distress syndrome and bronchopulmonary dysplasia), congestive heart failure, and hypertension. Hypertension in children is often resistant to therapy and may require the use of several drugs in combination (see section 2.5). Maintenance of fluid and electrolyte balance can be difficult in children on diuretics, particularly neonates whose renal function may be immature.

Loop diuretics (section 2.2.2) are used for pulmonary oedema, congestive heart failure, and in renal disease.

Thiazides (section 2.2.1) are used less commonly than loop diuretics but are often used in combination with loop diuretics or spironolactone in the management of pulmonary oedema and, in lower doses, for hypertension associated with cardiac disease.

Aminophylline infusion has been used with intravenous furosemide to relieve fluid overload in critically ill children.

Heart failure is less common in children than in adults; it can occur as a result of congenital heart disease (e.g. septal defects), dilated cardiomyopathy, myocarditis, or cardiac surgery. 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.

Acute heart failure can occur after cardiac surgery or as a complication in severe acute infections with or without myocarditis. Therapy consists of volume loading, vasodilator or inotropic drugs.

Chronic heart failure is initially treated with a loop diuretic (section 2.2.2), usually furosemide supplemented with spironolactone, amiloride, or potassium. If diuresis with furosemide is insufficient, the addition of metolazone or a thiazide diuretic (section 2.2.1) can be considered. With metolazone, the resulting diuresis can be profound and care is needed to avoid potentially dangerous electrolyte disturbance.

If diuretics are insufficient an ACE inhibitor, titrated to the maximum tolerated dose, can be used. ACE inhibitors (section 2.5.5.1) are used for the treatment of all grades of heart failure in adults and can also be useful for children with heart failure. Addition of digoxin can be considered in children who remain symptomatic despite treatment with a diuretic and an ACE inhibitor.

Some beta-blockers improve outcome in adults with heart failure, but data on beta-blockers in children are limited. Carvedilol (section 2.4) has vasodilatory properties and therefore (like ACE inhibitors) also lowers afterload.

In children receiving specialist cardiology care, the selective phosphodiesterase inhibitor enoximone is sometimes used by mouth for its inotropic and vasodilator effects. Spironolactone (section 2.2.3) is usually used as a potassium-sparing drug with a loop diuretic; in adults low doses of spironolactone are effective in the treatment of heart failure. Careful monitoring of serum potassium is necessary if spironolactone is used in combination with an ACE inhibitor.

Potassium loss Hypokalaemia can 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.
Hypokalaemia is particularly dangerous in children being treated with cardiac glycosides. In hepatic failure hypokalaemia caused by diuretics can precipitate encephalopathy.

The use of potassium-sparing diuretics (section 2.2.3) avoids the need to take potassium supplements.

### 2.2.1 Thiazides and related diuretics

Thiazides and related compounds are moderately potent diuretics; they inhibit sodium reabsorption at the beginning of the distal convoluted tubule. 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 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 2.2.

Bendroflumethiazide is licensed for use in children; chlorothiazide is also used. Chlortalidone (chlorthalidone), a thiazide-related compound, has a longer duration of action than the thiazides and may be given on alternate days in younger children.

Metholazone is particularly effective when combined with a loop diuretic (even in renal failure) and is most effective when given 30–60 minutes before furosemide; profound diuresis can occur and the child should therefore be monitored carefully.

**Cautions** See also section 2.2. Thiazides and related diuretics can exacerbate diabetes, gout, and systemic lupus erythematosus. Electrolytes should be monitored particularly with high doses, long-term use, or in renal impairment. Thiazides and related diuretics should also be used with caution in nephrotic syndrome, hyperaldosteronism, malnourishment, hepatic impairment (avoid if severe), renal impairment, pregnancy, and breast-feeding; interactions: Appendix 1 (diuretics).

**Contra-indications** Thiazides and related diuretics should be avoided in refractory hypokalaemia, hyperonatraemia, and hypercalcaemia, symptomatic hyperuricaemia, and Addison’s disease.

**Side-effects** Side-effects of thiazides and related diuretics include mild gastrointestinal disturbances, postural hypotension, altered plasma-lipid concentrations, metabolic and electrolyte disturbances including hypokalaemia (see also notes above), hyperonatraemia, hypomagnesaemia, hypercalcaemia, hyperglycaemia, hypochloraemic alkalosis, and hyperuricaemia, and gout. Less common side-effects include blood disorders including 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.

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**BENDROFLUMETHIAZIDE**

*(Bendrofluazide)*

**Cautions** see notes above

**Hepatic impairment** use with caution in mild to moderate impairment; avoid in severe impairment; hypokalaemia may precipitate coma (potassium-sparing diuretics can prevent)

**Renal impairment** use with caution; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—ineffective

**Pregnancy** not used to treat gestational hypertension; may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may be reduced; stimulation of labour, uterine inertia, and meconium staining also reported

**Breast-feeding** amount too small to be harmful; large doses may suppress lactation

**Contra-indications** see notes above

**Side-effects** see notes above

**Indication and dose**

<table>
<thead>
<tr>
<th>Oedema and hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Child 1 month–2 years</strong> 50–100 micrograms/kg daily adjusted according to response</td>
</tr>
<tr>
<td><strong>Child 2–12 years</strong> initially 50–400 micrograms/kg daily (max. 10 mg daily) then 50–100 micrograms/kg daily adjusted according to response</td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> initially 5–10 mg daily or on alternate days (2.5 mg in hypertension) as a single morning dose, adjusted according to response</td>
</tr>
</tbody>
</table>
Bendroflumethiazide (Non-proprietary) Tablets, bendroflumethiazide 2.5 mg, net price 28 = 83p; 5 mg, 28 = 86p. Brands include Aprinox®, Neo-NaClex®.

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

CHLOROTHIAZIDE

Cautions see notes above; also neonate (theoretical risk of kernicterus if very jaundiced)

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment; hypokalaemia may precipitate coma (potassium-sparing diuretics can prevent)

Renal impairment use with caution; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—ineffective

Pregnancy not used to treat gestational hypertension; may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may be reduced; stimulation of labour, uterine inertia, and meconium staining also reported

Breast-feeding amount too small to be harmful; large doses may suppress lactation

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed

Indication and dose

Heart failure, hypertension, ascites

- By mouth

Neonate 10–20 mg/kg twice daily

Child 1–6 months 10–20 mg/kg twice daily

Child 6 months–12 years 10 mg/kg twice daily (max. 1 g daily)

Child 12–18 years 0.25–1 g once daily or 125–500 mg twice daily

Chronic hypoglycaemia section 6.1.4

Diabetes insipidus section 6.5.2

Preparations

Chlorothiazide oral suspension 250 mg/5 mL is available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

CHLORTALIDONE

(Chlorthalidone)

Cautions see notes above

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment; hypokalaemia may precipitate coma (potassium-sparing diuretics can prevent)

Renal impairment avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—ineffective

Pregnancy not used to treat gestational hypertension; may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfusion may be reduced; stimulation of labour, uterine inertia, and meconium staining also reported

Breast-feeding amount too small to be harmful; large doses may suppress lactation

Contra-indications see notes above

Side-effects see notes above; also rarely jaundice

Indication and dose

Hypertension

- By mouth

Child 5–12 years 0.5–1 mg/kg in the morning every 48 hours; max. 1.7 mg/kg every 48 hours

Stable heart failure

- By mouth

Child 5–12 years 0.5–1 mg/kg in the morning every 48 hours; max. 1.7 mg/kg every 48 hours

Child 12–18 years 25–50 mg daily in the morning, increased if necessary to 100–200 mg daily (reduce to lowest effective dose for maintenance)

Ascites, oedema in nephrotic syndrome

- By mouth

Child 5–12 years 0.5–1 mg/kg in the morning every 48 hours; max. 1.7 mg/kg every 48 hours

Child 12–18 years up to 50 mg daily

Preparations

Hygroton® (Alliance) Tablets, yellow, scored, chlortalidone 50 mg, net price 28-tab pack = £1.64

METOLAZONE

Cautions see notes above; also acute porphyria (section 9.8.2)

Hepatic impairment use with caution in mild to moderate impairment; avoid in severe impairment; hypokalaemia may precipitate coma (potassium-sparing diuretics can prevent)

Renal impairment remains effective in moderate impairment but risk of excessive diuresis

Pregnancy not used to treat gestational hypertension; may cause neonatal thrombocytopenia, bone marrow suppression, jaundice, electrolyte disturbances, and hypoglycaemia; placental perfu-
METOLAZONE (continued)

- sion may be reduced; stimulation of labour, uterine inertia, and meconium staining also reported.
- Breast-feeding amount too small to be harmful; large doses may suppress lactation.
- Contra-indications see notes above.
- Side-effects see notes above; also chills, chest pain.
- Licensed use not licensed for use in children.

**Indication and dose**

- Oedema resistant to loop diuretics; adjunct to loop diuretics to induce diuresis.
  - By mouth
  - Child 1 month–12 years 100–200 micrograms/kg once or twice daily

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**2.2.2 Loop diuretics**

Loop diuretics inhibit reabsorption of sodium, potassium, and chloride from the ascending limb of the loop of Henlé in the renal tubule and are powerful diuretics. Hypokalaemia may develop, and care is needed to avoid hypotension.

**Furosemide** (frusemide) and **bumetanide** are similar in activity; they produce dose-related diuresis. In children with impaired renal function very large doses may occasionally be needed; in such doses both drugs can cause deafness and bumetanide can cause myalgia. Furosemide is used extensively in children. It can be used for pulmonary oedema (e.g. in respiratory distress syndrome and bronchopulmonary dysplasia), congestive heart failure, and in renal disease. Furosemide may occasionally cause ototoxicity but the risk can be reduced by giving large oral doses in 2 or more divided doses. Long-term use of furosemide in neonates can lead to nephrocalcinosis because it increases urinary calcium excretion; a thiazide diuretic may be an alternative in this case.

**FUROSEMIDE** (Frusemide)

- Cautions see section 2.2; also monitor electrolytes; hypotension; correct hypovolaemia before using in oliguria.
- Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this)
- Renal impairment may need high doses; deafness and tinnitus may follow rapid intravenous injection.
- Pregnancy not to be used to treat hypertension in pregnancy.
- Breast-feeding amount too small to be harmful; may inhibit lactation.
- Contra-indications hypovolaemia, dehydration, severe hypokalaemia, severe hyponatraemia; renal failure due to nephrotoxic or hepatotoxic drugs, anuria.
- Side-effects mild gastro-intestinal disturbances; hypotension; hyperglycaemia (less common than with thiazides), hyperuricaemia and gout; electrolyte disturbances including hyponatraemia, hypokalaemia (see also section 2.2), increased calcium excretion (nephrocalcinosis and nephrolithiasis reported in preterm infants), and hypomagnesaemia, metabolic alkalosis; rarely paraesthesia, blood disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia), bone marrow depression (withdraw 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, intrahepatic cholestasis.

**Indication and dose**

- Oedema
  - By mouth
  - Neonate 0.5–2 mg/kg every 12–24 hours (every 24 hours if postmenstrual age under 31 weeks)
  - Child 1 month–12 years 0.5–2 mg/kg 2–3 times daily (every 24 hours if postmenstrual age under 31 weeks); higher doses may be required in resistant oedema; max. 12 mg/kg daily, not to exceed 80 mg daily
  - Child 12–18 years 20–40 mg daily, increased in resistant oedema to 80–120 mg daily
  - By slow intravenous injection
  - Neonate 0.5–1 mg/kg every 12–24 hours (every 24 hours after post-menstrual age under 31 weeks)
  - Child 1 month–12 years 0.5–1 mg/kg (max. 4 mg/kg) repeated every 8 hours as necessary
Oliguria

- By mouth
  Child 12–18 years initially 250 mg daily; if necessary, dose increased in steps of 250 mg given every 4–6 hours; max. single dose 2 g (rarely used)

- By intravenous infusion
  Child 1 month–12 years 2–5 mg/kg up to 4 times daily (max. 1 g daily)
  Child 12–18 years initially 250 mg over 1 hour (rate not exceeding 4 mg/minute), increase to 500 mg over 2 hours if satisfactory urine output not obtained, then give a further 1 g over 4 hours if no satisfactory response within subsequent hour, if no response obtained dialysis probably required; effective dose (up to 1 g) can be repeated every 24 hours

Administration

- For administration by mouth tablets may be crushed and mixed with water or injection solution diluted and given by mouth; for intravenous injection give over 5–10 minutes at a usual rate of 100 micrograms/kg/minute (not exceeding 500 micrograms/kg/minute), max. 4 mg/minute; for intravenous infusion dilute with sodium chloride 0.9% intravenous infusion to a concentration of 1–2 mg/mL—glucose solutions unsuitable (infusion pH must be above 5.5)

Furosemide (Non-proprietary)

- Tablets, furosemide 20 mg, net price 28 = 81p; 40 mg, 28-tab pack = 86p; 500 mg, 28 = £4.37

- 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

Cautions

- Hepatic impairment hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this)

- Renal impairment may need high doses

- Pregnancy not to be used for treating hypertension in pregnancy

- Breast-feeding manufacturer advises avoid if possible—no information available

Contra-indications

see under Furosemide

Side-effects

see under Furosemide; also headache, dizziness, fatigue, gynaecomastia, myalgia

Licensed use not licensed for use in children under 12 years

Indication and dose

Oedema

- By mouth
  Child 1 month–12 years 15–50 micrograms/kg 1–4 times daily (max. single dose 2 mg); do not exceed 5 mg daily

- Child 12–18 years 1 mg in the morning, repeated after 6–8 hours if necessary; severe cases up to 5 mg daily

Administration

For intravenous injection give over 20 minutes if necessary

By intravenous infusion over 30–60 minutes

- Child 1 month–12 years 25–50 micrograms/kg

- Child 12–18 years 1–5 mg

Bumetanide (Non-proprietary)

- Tablets, bumetanide 1 mg, net price 28-tab pack = £1.22; 5 mg, 28-tab pack = £2.53

- Oral liquid, 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-tab pack = £9.67

Note

Large-volume bumetanide injections also available; brands include Minijet®

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

2.2.3 Potassium-sparing diuretics and aldosterone antagonists

Spironolactone is the most commonly used potassium-sparing diuretic in children; it is an aldosterone antagonist and enhances potassium retention and sodium excretion in the distal tubule. Spironolactone is combined with other diuretics to reduce urinary potassium loss. It is also used in the long-term management of Bartter’s syndrome and high doses can help to control ascites
in babies with chronic neonatal hepatitis. The clinical value of spironolactone in the management of pulmonary oedema in preterm neonates with chronic lung disease is uncertain.

**Potassium canrenoate**, given intravenously, is an alternative aldosterone antagonist that may be useful if a potassium-sparing diuretic is required and the child is unable to take oral medication. It is metabolised to canrenone, which is also a metabolite of spironolactone.

**Amiloride** on its own is a weak diuretic. It causes retention of potassium and is therefore given with thiazide or loop diuretics as an alternative to giving potassium supplements (see section 2.2.4 for compound preparations with thiazides or loop diuretics).

A potassium-sparing diuretic such as spironolactone or amiloride may also be used in the management of amphotericin-induced hypokalaemia.

Potassium supplements must **not** be given with potassium-sparing diuretics. Administration of a potassium-sparing diuretic to a child receiving an ACE inhibitor or an angiotensin-II receptor antagonist (section 2.5.5) can also cause severe hyperkalaemia.

### AMILORIDE HYDROCHLORIDE

**Cautions** monitor electrolytes; diabetes mellitus; interactions: Appendix 1 (diuretics)

Renal impairment monitor plasma-potassium concentration (high risk of hyperkalaemia in renal impairment); manufacturers advise avoid in severe impairment

Pregnancy not to be used for treating hypertension in pregnancy

Breast-feeding manufacturer advises avoid—no information available

Contra-indications hyperkalaemia; anuria; Addison’s disease

Side-effects include gastro-intestinal disturbances, dry mouth, rashes, confusion, postural hypotension, hyperkalaemia, hyponatraemia

Licensed use Not licensed for use in children

**Indication and dose**

Adjunct to thiazide or loop diuretics in oedema or congestive heart failure (where potassium conservation desirable)

- By mouth

  **Neonate** 100–200 micrograms/kg twice daily

### SPIRONOLACTONE

**Cautions** potential metabolic products carcinogenic in rodents; monitor electrolytes (discontinue if hyperkalaemia); acute porphyria (section 9.8.2); interactions: Appendix 1 (diuretics)

Renal impairment monitor plasma-potassium concentration; high risk of hyperkalaemia in renal impairment; manufacturer advises avoid if rapidly deteriorating or severe impairment

Pregnancy feminisation of male fetus in animal studies

Breast-feeding metabolites present in milk but unlikely to be harmful; manufacturer advises avoid

Contra-indications hyperkalaemia, hyponatraemia; Addison’s disease

**Side-effects** gastro-intestinal disturbances; impotence, gynaecomastia; menstrual irregularities; lethargy, headache, confusion; rashes; hyperkalaemia (discontinue); hyponatraemia; hepatotoxicity; osteomalacia, and blood disorders reported

**Licensed use** Not licensed for reduction of hypokalaemia induced by diuretics or amphotericin

**Indication and dose**

Diuresis in congestive heart failure, ascites and oedema, reduction of hypokalaemia induced by diuretics or amphotericin

- By mouth

  **Neonate** 1–2 mg/kg daily in 1–2 divided doses; up to 7 mg/kg daily in resistant ascites


2.2.4 Potassium-sparing diuretics with other diuretics

Although it is preferable to prescribe diuretics separately in children, the use of fixed combinations may be justified in older children if compliance is a problem. The most commonly used preparations are listed below (but they may not be licensed for use in children—consult product literature), for other preparations see the BNF. For interactions, see Appendix 1 (diuretics).

### Amiloride with thiazides

**Amiloride with thiazides**

**Co-amilozide** (Non-proprietary) [\[\]

Tablets, co-amilozide 2.5/25 (amiloride hydrochloride 2.5 mg, hydrochlorothiazide 25 mg), net price 28-tab pack = £2.57

Brands include Moduret 25

**Amiloride with loop diuretics**

**Co-amilofruse** (Non-proprietary) [\[\]

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

**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

**Tablets, co-amilofruse 10/80 (amiloride hydrochloride 10 mg, furosemide 80 mg), net price 28-tab pack = £9.33**

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**POTASSIUM CANRENOATE**

**Cautions** potential metabolic products carcino-
genic in rodents; monitor electrolytes (discontinue if hyperkalaemia); hypertension; acute porphyria (section 9.8.2); interactions: Appendix 1 (diur-

**Renal impairment** use with caution and monitor plasma-potassium concentration if estimated glomerular filtration rate 30–60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

**Contra-indications** hyperkalaemia; hyponatraemia

**Pregnancy** crosses placenta; feminisation and undescended testes in male fetus in animal studies—manufacturer advises avoid

**Breast-feeding** present in breast milk—manufacturer advises avoid

**Side-effects** drowsiness, headache, ataxia; men-

**Short-term diuresis in congestive heart failure, oedema, and ascites**

*By intravenous injection over at least 3 minutes or intravenous infusion*

**Neonate** 1–2 mg/kg twice daily

**Child 1 month–12 years** 1–2 mg/kg twice daily

**Child 12–18 years** 1–2 mg/kg (max. 200 mg) twice daily

**Note** To convert to equivalent oral spironolactone dose, multiply potassium canrenoate dose by 0.7

**Administration** consult product literature

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2.2.4 Potassium-sparing diuretics with other diuretics BNFC 2009
2.2.5 Osmotic diuretics

Mannitol is used to treat cerebral oedema, raised intra-ocular pressure, peripheral oedema, and ascites.

**MANNITOL**

**Cautions** extravasation causes inflammation and thrombophlebitis; monitor fluid and electrolyte balance, serum osmolality, and pulmonary and renal function; assess cardiac function before and during treatment; **interactions:** Appendix 1 (mannitol)

**Renal impairment** caution in severe impairment

**Pregnancy** manufacturer advises avoid unless essential—no information available

**Breast-feeding** manufacturer advises avoid unless essential—no information available

**Contra-indications** severe heart failure; severe pulmonary oedema; intracranial bleeding (except during craniotomy); anuria; severe dehydration

**Side-effects** less commonly hypotension, thrombophlebitis, fluid and electrolyte imbalance; rarely dry mouth, thirst, nausea, vomiting, oedema, raised intracranial pressure, arrhythmia, hypertension, pulmonary oedema, chest pain, headache, convulsions, dizziness, chills, fever, urinary retention, focal osmotic nephrosis, dehydration, cramp, blurred vision, rhinitis, skin necrosis, and hypersensitivity reactions (including urticaria and anaphylaxis); very rarely congestive heart failure and acute renal failure

**Licensed use** not licensed for use in children under 12 years

### Indication and dose

**Cerebral oedema, raised intra-ocular pressure**

- **By intravenous infusion over 30–60 minutes**
  - **Child 1 month–12 years** 0.25–1.5 g/kg repeated if necessary 1–2 times after 4–8 hours
  - **Child 12–18 years** 0.25–2 g/kg repeated if necessary 1–2 times after 4–8 hours

**Peripheral oedema and ascites**

- **By intravenous infusion over 2–6 hours**
  - **Child 1 month–18 years** 1–2 g/kg

**Administration** examine infusion for crystals; if crystals present, dissolve by warming infusion fluid (allow to cool to body temperature before administration); for mannitol 20%, an in-line filter is recommended (15-micron filters have been used)

Mannitol (Baxter) **Intravenous infusion**, mannitol 10%, net price 500-mL Viaflex® bag = £1.87, 500-mL Viaflo® bag = £2.15; 250-mL Viaflex® bag = £2.70, 250-mL Viaflo® bag = £3.10, 500-mL Viaflex® bag = £2.72, 500-mL Viaflo® bag = £3.12

2.2.6 Mercurial diuretics

Classification not used in **BNF for Children**.

2.2.7 Carbonic anhydrase inhibitors

The carbonic anhydrase inhibitor acetazolamide is a weak diuretic although it is little used for its diuretic effect. Acetazolamide and eye drops of dorzolamide and brinzolamide inhibit the formation of aqueous humour and are used in glaucoma (section 11.6). In children, acetazolamide is also used in the treatment of epilepsy (section 4.8.1), and raised intracranial pressure (section 11.6).

2.2.8 Diuretics with potassium

Diuretics and potassium supplements should be prescribed separately for children.

2.3 Anti-arrhythmic drugs

2.3.1 Management of arrhythmias

2.3.2 Drugs for arrhythmias

**Management of arrhythmias**

Management of an arrhythmia requires precise diagnosis of the type of arrhythmia; electrocardiography and referral to a paediatric cardiologist is essential; underlying causes such as heart failure require appropriate treatment.
Arrhythmias may be broadly divided into bradycardias, supraventricular tachycardias, and ventricular arrhythmias.

**Bradycardia** Adrenaline (epinephrine) is useful in the treatment of symptomatic bradycardia in an infant or child.

### Supraventricular tachycardias

In supraventricular tachycardia adenosine is given by rapid intravenous injection. If adenosine is ineffective, intravenous amiodarone, flecainide, or a beta-blocker (such as esmolol, see section 2.4) can be tried; verapamil can also be considered in children over 1 year. Atenolol, sotalol (section 2.4), and flecainide are used for the prophylaxis of paroxysmal supraventricular tachycardias.

The use of d.c. shock and vagal stimulation also have a role in the treatment of supraventricular tachycardia.

### Syndromes associated with accessory conducting pathways

Amiodarone, flecainide, or a beta-blocker is used to prevent recurrence of supraventricular tachycardia in infants and young children with these syndromes (e.g. Wolff-Parkinson-White syndrome).

### Atrial flutter

In atrial flutter without structural heart defects, sinus rhythm is restored with d.c. shock or cardiac pacing; drug treatment is usually not necessary. Amiodarone is used in atrial flutter when structural heart defects are present or after heart surgery. Sotalol (section 2.4) may also be considered.

### Atrial fibrillation

Atrial fibrillation is very rare in children. To restore sinus rhythm d.c. shock is used; beta-blockers, alone or together with digoxin, may be useful for ventricular rate control.

### Ectopic tachycardia

Intravenous amiodarone is used in conjunction with body cooling and synchronised pacing in postoperative junctional ectopic tachycardia. Oral amiodarone or flecainide are used in congenital junctional ectopic tachycardia.

Amiodarone, flecainide, or a beta-blocker are used in atrial ectopic tachycardia; amiodarone is preferred in those with poor ventricular function.

### Ventricular tachycardia and ventricular fibrillation

Pulseless ventricular tachycardia or ventricular fibrillation require resuscitation, see Paediatric Advanced Life Support algorithm (inside back cover). Amiodarone is used in resuscitation for pulseless ventricular tachycardia or ventricular fibrillation unresponsive to d.c. shock; lidocaine can be used as an alternative only if amiodarone is not available.

Amiodarone is also used in a haemodynamically stable child where drug treatment is required; lidocaine can be used as an alternative only if amiodarone is not available.

### Torsade de pointes

Torsade de pointes is a form of ventricular tachycardia associated with long QT syndrome, which may be congenital or drug induced. Episodes may be 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 magnesium sulphate (section 9.5.1.3) can be used to treat torsade de pointes (dose recommendations vary—consult local guidelines). 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 as those acting on supraventricular arrhythmias (adenosine, digoxin, and verapamil), those acting on both supraventricular and ventricular arrhythmias (amiodarone, beta-blockers, flecainide and procainamide), and those acting on ventricular arrhythmias (lidocaine (lignocaine)). For the treatment of bradycardia, see section 2.3.1.
Anti-arrhythmic drugs can also be classified according to their effects on the electrical behaviour of myocardial cells during activity (the Vaughan Williams classification) although this classification is of less clinical significance:

- **Class I**: membrane stabilising drugs (e.g. lidocaine, flecainide)
- **Class II**: beta-blockers
- **Class III**: amiodarone and sotalol (also Class II)
- **Class IV**: calcium-channel blockers (includes verapamil but not dihydropyridines)

**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.

**Adenosine** is the treatment of choice for terminating supraventricular tachycardias, including those associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome). It is also used in the diagnosis of supraventricular arrhythmias. It is not negatively inotropic and does not cause significant hypotension; it can be used safely in children with impaired cardiac function or postoperative arrhythmias. The injection should be administered by rapid intravenous injection into a central or large peripheral vein.

**Amiodarone** is useful in the management of both supraventricular and ventricular tachyarrhythmias. It may be given by intravenous infusion and by mouth and causes little or no myocardial depression. Unlike oral amiodarone, intravenous amiodarone acts relatively rapidly. Intravenous amiodarone is also used in cardiopulmonary resuscitation for ventricular fibrillation or pulseless ventricular tachycardia unresponsive to d.c. shock (see algorithm, inside back cover). 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, children and carers should be advised to shield the child’s skin from light during treatment and for several months after discontinuing amiodarone; a wide-spectrum sunscreen (section 13.8.1) should be used to protect against both long-wave ultraviolet and visible light.

Amiodarone contains iodine and can cause disorders of thyroid function; both hypothyroidism and hyperthyroidism can 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 progressive shortness of breath or cough develops in a patient taking amiodarone. Fresh neurological symptoms should raise the possibility of peripheral neuropathy. Amiodarone is also associated with hepatotoxicity (see under amiodarone, below).

**Beta-blockers** act as anti-arrhythmic drugs principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart, for details see section 2.4. For special reference to the role of sotalol in ventricular arrhythmias, see section 2.4.
Oral administration of digoxin (section 2.1.1) slows the ventricular rate in atrial fibrillation and in atrial flutter. However, intravenous infusion of digoxin is rarely effective for rapid control of ventricular rate.

Flecainide is useful for the treatment of resistant re-entry supraventricular tachycardia, ventricular tachycardia, ventricular ectopic beats, arrhythmias associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome), and paroxysmal atrial fibrillation. Flecainide crosses the placenta and can be used to control fetal supraventricular arrhythmias.

Lidocaine (lignocaine) can be used in cardiopulmonary resuscitation in children with ventricular fibrillation or pulseless ventricular tachycardia unresponsive to d.c. shock, but only if amiodarone is not available. Doses may need to be reduced in children with persistently poor cardiac output and hepatic or renal failure (see under lidocaine, below).

Verapamil (section 2.6.2) can cause severe haemodynamic compromise (refractory hypotension and cardiac arrest) when used for the acute treatment of arrhythmias in neonates and infants; it is contra-indicated in children under 1 year. It is also contra-indicated in those with congestive heart failure, syndromes associated with accessory conducting pathways (e.g. Wolff-Parkinson-White syndrome) and in most receiving concomitant beta-blockers. It can be useful in older children with supraventricular tachycardia.

### Adenosine

**Cautions** atrial fibrillation or flutter with accessory pathway (conduction down anomalous pathway may increase); asthma; ECG monitoring should be carried out and resuscitation facilities should be available during administration; **interactions:** Appendix 1 (adenosine)

**Pregnancy** no evidence of harm

**Breast-feeding** no information available—unlikely to be present in milk owing to short half-life

**Contra-indications** second- or third-degree AV block and sick sinus syndrome (unless pacemaker fitted)

**Side-effects** include transient facial flush, chest pain, dizziness, bronchospasm, choking sensation, nausea, light-headedness; severe bradycardia reported (requiring temporary pacing); ECG may show transient rhythm disturbances

**Licensed use** not licensed for use in children

#### Indication and dose

**Arrhythmias (see also section 2.3.1), diagnosis of arrhythmias**

- **By intravenous injection**

  **Neonates** 150 micrograms/kg; if necessary repeat injection every 1–2 minutes increasing dose by 50–100 micrograms/kg until tachycardia terminated or max. single dose of 300 micrograms/kg given

  **Child 1 month–1 year** 150 micrograms/kg; if necessary repeat injection every 1–2 minutes increasing the dose by 50–100 micrograms/kg until tachycardia terminated or max. single dose of 500 micrograms/kg given

#### Administration

**Child 1–12 years** 100 micrograms/kg; if necessary repeat injection every 1–2 minutes increasing dose by 50–100 micrograms/kg until tachycardia terminated or max. single dose of 500 micrograms/kg given

**Child 12–18 years** initially 3 mg; if necessary followed by 6 mg after 1–2 minutes, and then by 12 mg after a further 1–2 minutes

**Note** In some children over 12 years 3-mg dose ineffective (e.g. if a small peripheral vein is used for administration) and higher initial dose sometimes used; however, those with heart transplant are very sensitive to the effects of adenosine, and should not receive higher initial doses. In children receiving dipyridamole reduce dose to a quarter of usual dose of adenosine

#### Adenoscan®

**Injection** adenosine 3 mg/mL in physiological saline, net price 2-mL vial = £4.45 (hosp. only)

**Note** Intravenous infusion of adenosine (Adenoscan®, 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

### Amiodarone Hydrochloride

**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); pulmonary function tests and chest x-ray required before treatment; heart failure; 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); ECG monitoring and resuscitation facilities must be available during...
AMIODARONE HYDROCHLORIDE (continued)

intravenous use; acute porphyria (section 9.8.2); avoid benzyl alcohol containing injections in neonates (see Excipients, p. 3); 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 cardio-myopathy

Pregnancy possible risk of neonatal goitre if amiodarone used in second or third trimester; use only if no alternative

Breast-feeding avoid; significant amount present in milk—theroretical risk of neonatal thyroid dysfunction

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; hypothyroidism, hyperthyroidism; reversible corneal microdeposits (sometimes with night glare); phototoxicity, persistent slate-grey skin discolouration (see also notes above); 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

Licensed use Not licensed for use in children under 3 years

Indication and dose

Supraventricular and ventricular arrhythmias see notes above (initiated in hospital or under specialist supervision)

• By mouth

Neonate initially 5–10 mg/kg twice daily for 7–10 days, then reduced to maintenance dose of 5–10 mg/kg once daily

Child 1 month–12 years initially 5–10 mg/kg (max. 200 mg) twice daily for 7–10 days, then reduced to maintenance dose of 5–10 mg/kg once daily (max. 200 mg daily)

FLECAINIDE ACETATE

Cautions children with pacemakers (especially those who may be pacemaker dependent because stimulation threshold may rise appreciably); atrial fibrillation following heart surgery; monitor ECG
and have resuscitation facilities available during intravenous use; **interactions**: Appendix 1 (flecainide)

**Hepatic impairment** avoid or reduce dose in severe impairment; monitor plasma concentration (see pharmacokinetics below)

**Renal impairment** reduce dose by 25–50% if estimated glomerular filtration rate less than 35 mL/minute/1.73 m² and monitor plasma-flecainide concentration

**Pregnancy** used in pregnancy to treat maternal and fetal arrhythmias in specialist centres; toxicity reported in animal studies; infant hyperbilirubinaemia also reported

**Breast-feeding** significant amount present in milk but not known to be harmful

**Contra-indications** heart failure; abnormal left ventricular function; 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, amnesia, dyskinesia, convulsions, peripheral neuropathy; also reported gastrointestinal disturbances, anorexia, hepatic dysfunction, flushing, syncope, drowsiness, tremor, vertigo, headache, anxiety, insomnia, ataxia, paraesthesia, hypoesthesia, anaemia, leucopenia, thrombocytopения, corneal deposits, tinnitus, increased antinuclear antibodies, hypersensitivity reactions (including rash, urticaria, and photosensitivity), increased sweating

**Pharmacokinetics** plasma-flecainide concentration for optimal response 200–800 micrograms/litre; blood sample should be taken immediately before next dose

**Licensed use** Not licensed for use in children under 12 years

**Indication and dose**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate</strong></td>
<td>2 mg/kg 2–3 times daily adjusted according to response and plasma-flecainide</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong></td>
<td>2 mg/kg 2–3 times daily adjusted according to response and plasma-flecainide concentration (max. 8 mg/kg/day or 300 mg daily)</td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong></td>
<td>initially 50–100 mg twice daily; max. 300 mg daily (max. 400 mg daily for ventricular arrhythmias in heavily built children)</td>
</tr>
</tbody>
</table>

**By slow intravenous injection or intravenous infusion**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate</strong></td>
<td>1–2 mg/kg over 10–30 minutes; if necessary followed by continuous infusion at a rate of 100–250 micrograms/kg/hour until arrhythmia controlled; transfer to oral treatment as above</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong></td>
<td>2 mg/kg over 10–30 minutes; if necessary followed by continuous infusion at a rate of 100–250 micrograms/kg/hour until arrhythmia controlled (max. cumulative dose 600 mg in 24 hours); transfer to oral treatment as above</td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong></td>
<td>2 mg/kg (max. 150 mg) over 10–30 minutes; if necessary followed by continuous infusion at a rate of 1.5 mg/kg/hour for 1 hour, then reduced to 100–250 micrograms/kg/hour until arrhythmia controlled (max. cumulative dose 600 mg in first 24 hours); transfer to oral treatment as above</td>
</tr>
</tbody>
</table>

**Administration** for administration by mouth, milk, infant formula, and dairy products may reduce absorption of flecainide—separate doses from feeds. Liquid has a local anaesthetic effect and should be given at least 30 minutes before or after food. Do not store liquid in refrigerator as precipitation occurs.

For intravenous administration, give initial dose over 30 minutes in children with sustained ventricular tachycardia or cardiac failure. Dilute injection using Glucose 5%; concentrations of more than 300 micrograms/mL are unstable in chloride containing solutions

**Flecainide** (Non-proprietary) tablets, flecainide acetate 50 mg, net price 60-tab pack = £9.81; 100 mg, 60-tab pack = £15.04

**Liquid**, available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**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**

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dose Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong></td>
<td>200 mg once daily</td>
</tr>
</tbody>
</table>

**Note** Not to be used to control arrhythmias in acute situations; children stabilised on 200 mg daily of immediate-release flecainide may be transferred to Tambocor® XL
LIDOCAINE HYDROCHLORIDE
(Lignocaine hydrochloride)

**Cautions** lower doses in congestive heart failure and following cardiac surgery; monitor ECG; resuscitation facilities should be available; interactions: Appendix 1 (lidocaine)

**Hepatic impairment** manufacturer advises caution—increased risk of side-effects

**Renal impairment** possible accumulation of lidocaine and active metabolite; manufacturers advise caution in severe impairment

**Pregnancy** crosses the placenta but not known to be harmful in animal studies—use if benefit outweighs risk

**Breast-feeding** present in milk but amount too small to be harmful

**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

**Licensed use** not licensed for use in children under 1 year

**Indication and dose**

- **Ventricular arrhythmias, pulseless ventricular tachycardia or ventricular fibrillation**
  - By intravenous or intraosseous injection, and intravenous infusion

- **Neonate** 0.5–1 mg/kg by injection followed by infusion of 0.6–3 mg/kg/hour; if infusion not immediately available following initial injection, injection of 0.5–1 mg/kg may be repeated at intervals of not less than 5 minutes (to max. total dose 3 mg/kg)

- **Child 1 month–12 years** 0.5–1 mg/kg by injection followed by infusion of 0.6–3 mg/kg/hour; if infusion not immediately available following initial injection, injection of 0.5–1 mg/kg may be repeated at intervals of not less than 5 minutes (to max. total dose 3 mg/kg)

- **Child 12–18 years** 50–100 mg by injection followed by infusion of 120 mg over 30 minutes then 240 mg over 2 hours then 60 mg/hour; reduce dose further if infusion continued beyond 24 hours; if infusion not immediately available following initial injection, injection of 50–100 mg may be repeated at intervals of not less than 5 minutes (to max. 300 mg in 1 hour)

**Administration** For intravenous infusion dilute with glucose 5% intravenous infusion or sodium chloride 0.9%

**Lidocaine** (Non-proprietary) (HN)

- **Injection** 2%, lidocaine hydrochloride 20 mg/mL, net price 2-mL amp = 28p; 5-mL amp = 26p; 10-mL amp = 60p; 20-mL amp = 61p
  - Available from Braun

- **Infusion** lidocaine hydrochloride 0.1% (1 mg/mL) and 0.2% (2 mg/mL) in glucose intravenous infusion 5%, 500-mL containers
  - Available from Baxter

**Minijet® Lignocaine** (UCB Pharma) (HN)

- **Injection** lidocaine hydrochloride 1% (10 mg/mL), net price 10-mL disposable syringe = £4.85; 2% (20 mg/mL), 5-mL disposable syringe = £4.73

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**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 available but experience in children is limited to the use of only a few.

Differences between beta-blockers may affect choice. The water-soluble beta-blockers, atenolol and sotalol, 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.

Some beta-blockers, such as atenolol, have an intrinsically longer duration of action and need to be given only once daily. Carvedilol and labetalol are beta-blockers which have, in addition, an arteriolar vasodilating action and thus lower peripheral resistance. Although carvedilol and labetalol possess both alpha- and beta-blocking properties, these drugs have no important advantages over other beta-blockers in the treatment of hypertension.

Beta-blockers slow the heart and can depress the myocardium; they are contra-indicated in children with second- or third-degree heart block. Sotalol may prolong the QT interval, and it occasionally causes life-threatening ventricular arrhythmias (important: particular care is required to avoid hypokalaemia in children taking sotalol).
Beta-blockers can precipitate asthma and they should be avoided in children 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 and metoprolol 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, 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. The cardioselective beta-blockers (e.g. atenolol and metoprolol) may be preferable in diabetes but beta-blockers should be avoided altogether in those with frequent episodes of hypoglycaemia.

**Hypertension** Beta-blockers are effective for reducing blood pressure (section 2.5), but their mode of action is not understood; 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. Blood pressure can usually be controlled with relatively few side-effects. In general the dose of beta-blocker does not have to be high.

Labetalol may be given intravenously for hypertensive emergencies in children (section 2.5); however, care is needed to avoid dangerous hypotension or beta-blockade, particularly in neonates. Esmolol is also used intravenously for the treatment of hypertension particularly in the peri-operative period.

Beta-blockers can be used to control the pulse rate in children 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; phenoxybenzamine should always be used together with the beta-blocker.

**Arrhythmias** In arrhythmias (section 2.3), beta-blockers act principally by attenuating the effects of the sympathetic system on automaticity and conductivity within the heart. They can be used alone or in conjunction with digoxin to control the ventricular rate in atrial fibrillation. Beta-blockers are also useful in the management of supraventricular tachycardias and ventricular tachycardias particularly to prevent recurrence of the tachycardia.

Esmolol is a relatively cardioselective beta-blocker with a very short duration of action, used intravenously for the short-term treatment of supraventricular arrhythmias and sinus tachycardia, particularly in the peri-operative period.

Sotalol is a non-cardioselective beta-blocker with additional class III anti-arrhythmic activity. Atenolol and sotalol suppress ventricular ectopic beats and non-sustained ventricular tachycardia (section 2.3.1). However, the pro-arrhythmic effects of sotalol, particularly in children with sick sinus syndrome, may prolong the QT interval and induce torsade de pointes.

**Heart failure** Beta-blockers may produce benefit in heart failure by blocking sympathetic activity and the addition of a beta-blocker such as carvedilol to other treatment for heart failure may be beneficial. Treatment should be initiated by those experienced in the management of heart failure (see section 2.2 for details on heart failure).

**Thyrotoxicosis** Beta-blockers are used in the management of thyrotoxicosis including neonatal thyrotoxicosis; propranolol can reverse clinical symptoms within 4 days. Beta-blockers are also used for the pre-operative preparation for thyroidectomy; the thyroid gland is rendered less vascular, thus facilitating surgery (section 6.2.2).

Other uses In tetralogy of Fallot, esmolol or propranolol may be given intravenously in the initial management of cyanotic spells; propranolol is given by mouth for preventing cyanotic spells. If a severe cyanotic spell in a child with congenital heart disease persists despite optimal use of 100% oxygen, propranolol is given by intravenous infusion (for dose, see below). If cyanosis is still present after 10 minutes, sodium bicarbonate intravenous infusion is given in a dose of 1 mmol/kg to correct acidosis (or dose calculated according to arterial blood gas
**PROPRANOLOL HYDROCHLORIDE**

**Cautions** see notes above; also avoid abrupt withdrawal; first-degree AV block; portal hypertension (risk of deterioration in liver function); diabetes (see also notes above); history of obstructive airways disease (introduce cautiously and monitor lung function—see also Bronchospasm below); myasthenia gravis; symptoms of thyrotoxicosis may be masked (see also 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); interactions: Appendix 1 (beta-blockers), important: verapamil interaction, see also p. 140

**Hepatic impairment** reduce oral dose in liver disease

**Renal impairment** manufacturer advises caution—dose reduction may be required

**Pregnancy** may cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension

**Breast-feeding** present in milk but amount probably too small to be harmful; monitor infant for symptoms of beta-blockade

**Contra-indications** asthma (important: see Bronchospasm below), uncontrolled heart failure, 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, periastris, dizziness, psychoses; sexual dysfunction; purpura, thrombocytopenia; visual disturbances; exacerbation of psoriasis, alopecia; rarely rashes and dry eyes (reversible on withdrawal); over-dosage: see Emergency Treatment of Poisoning, p. 41

**Licensed use** not licensed for treatment of hypertension in children under 12 years

<table>
<thead>
<tr>
<th>Indication and dose</th>
<th>Arrhythmias</th>
</tr>
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<tbody>
<tr>
<td></td>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong></td>
<td>250–500 micrograms/kg 3 times daily, adjusted according to response</td>
</tr>
<tr>
<td><strong>Child 1 month–18 years</strong></td>
<td>250–500 micrograms/kg 3–4 times daily, adjusted according to response; max. 1 mg/kg/4 times daily, total daily dose not to exceed 160 mg daily</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td><strong>By slow intravenous injection, with ECG monitoring</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong></td>
<td>20–50 micrograms/kg repeated if necessary every 6–8 hours</td>
</tr>
<tr>
<td><strong>Child 1 month–18 years</strong></td>
<td>25–50 micrograms/kg repeated every 6–8 hours if necessary</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong> initially, 250 micrograms/kg 3 times daily, increased if necessary to max. 2 mg/kg 3 times daily</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong> 0.25–1 mg/kg 3 times daily, increased at weekly intervals to max. 5 mg/kg daily</td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> initially 80 mg twice daily; increased at weekly intervals as required; maintenance 160–320 mg daily; slow-release preparations may be used for once daily administration</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Tetralogy of Fallot</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong> 0.25–1 mg/kg 2–3 times daily, max. 2 mg/kg 3 times daily</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong> 0.25–1 mg/kg 3–4 times daily, max. 5 mg/kg daily</td>
</tr>
<tr>
<td><strong>By slow intravenous injection with ECG monitoring</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong> initially 15–20 micrograms/kg (max. 100 micrograms/kg), repeated every 12 hours if necessary</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong> initially 15–20 micrograms/kg (max. 100 micrograms/kg), repeated every 6–8 hours if necessary; higher doses rarely necessary</td>
</tr>
</tbody>
</table>

results); sodium bicarbonate 4.2% intravenous infusion is appropriate for a child under 1 year and sodium bicarbonate 8.4% intravenous infusion in children over 1 year. If blood-glucose concentration is less than 3 mmol/litre, glucose 10% intravenous infusion is given in a dose of 2 mL/kg (glucose 200 mg/kg) over 10 minutes, followed by morphine in a dose of 100 micrograms/kg by intravenous or intramuscular injection.

Beta-blockers are also used in the prophylaxis of migraine (section 4.7.4.2). Betaxolol, carteolol, levobunolol, and timolol are used topically in glaucoma (section 11.6).
Migraine prophylaxis

- By mouth
  - Child 2–12 years: 200–500 micrograms/kg 3 times daily; max. 4 mg/kg daily, usual dose 10–20 mg 2–3 times daily
  - Child 12–18 years: 20–40 mg 2–3 times daily; maintenance 80–160 mg daily

Administration
Give by slow intravenous injection over at least 3–5 minutes. Rate of administration should not exceed 1 mg/minute. May be diluted with Sodium Chloride 0.9% or Glucose 5%. Incompatible with bicarbonate.

Note
Excessive bradycardia can be countered with intravenous injection of atropine sulphate; for **overdosage** see Emergency Treatment of Poisoning, p. 41

**Propranolol (Non-proprietary)**

Tablets, propranolol hydrochloride 10 mg, net price 28 = £1.68; 160 mg, 56 = £3.29. Label: 8

Brands include Angilol®

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** (AstraZeneca)

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** (AstraZeneca)

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®

**ATENOLOL**

Cautions
see under Propranolol Hydrochloride

Renal impairment
initially use 50% of usual dose if estimated glomerular filtration rate 10–35 mL/minute/1.73 m²; initially use 30–50% of usual dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Pregnancy
may cause intra-uterine growth restriction, neonatal hypoglycaemia, and bradycardia; risk greater in severe hypertension

Breast-feeding
present in milk in greater amounts than some other beta-blockers; possible toxicity due to beta-blockade—monitor infant and use with caution

Contra-indications
see under Propranolol Hydrochloride

Side-effects
see under Propranolol Hydrochloride

Licensed use
not licensed for use in children under 12 years

Indication and dose

**Hypertension**

- By mouth
  - Neonate: 0.5–2 mg/kg once daily; may be given in 2 divided doses
  - Child 1 month–12 years: 0.5–2 mg/kg once daily (max. 100 mg daily); may be given in 2 divided doses
  - Child 12–18 years: 50–100 mg once daily; may be given in 2 divided doses

**Arrhythmias**

- By mouth
  - Neonate: 0.5–2 mg/kg once daily; may be given in 2 divided doses
  - Child 1 month–12 years: 0.5–2 mg/kg once daily (max. 100 mg daily); may be given in 2 divided doses
  - Child 12–18 years: 50–100 mg once daily; may be given in 2 divided doses

**Atenolol (Non-proprietary)**

Tablets, atenolol 25 mg, net price 28-tab pack = £4.41. Label: 8

Brands include Atenix®

**Tenormin** (AstraZeneca)

‘25’ tablets, f/c, atenolol 25 mg, net price 28-tab pack = £6.50. 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/5 mL, net price 300 mL = £8.55. Label: 8
CARVEDILOL

Cautions see under Propranolol Hydrochloride; monitor renal function during dose titration in children with heart failure who also have low blood pressure, renal impairment, ischaemic heart disease, or diffuse vascular disease.

Pregnancy see under Propranolol Hydrochloride; also lack of experience in human pregnancy limits any assessment of fetal risk.

Breast-feeding present in milk in animal studies but amount probably too small to be harmful; monitor infant for symptoms of alpha- and beta-blockade.

Contra-indications see under Propranolol Hydrochloride; acute or decompensated heart failure requiring intravenous inotropes.

Hepatic impairment avoid.

Side-effects postural hypotension, dizziness, headache, fatigue, gastro-intestinal disturbances, bradycardia; occasionally diminished peripheral circulation, peripheral oedema and painful extremities, dry mouth, dry eyes, 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.

Licensed use not licensed for use in children under 18 years.

Indication and dose

Adjunct in heart failure (limited information available)

- By mouth
  - Child 2–18 years initially 50 micrograms/kg (max. 3.125 mg) twice daily, double dose at intervals of at least 2 weeks up to 350 micrograms/kg (max. 25 mg) twice daily.

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 = £1.54; 25 mg, 28-tab pack = £2.14.

Label: 8

Eucardic® (Roche) Tablets, scored, carvedilol 3.125 mg (pink), net price 28-tab pack = £7.57; 6.25 mg (yellow), 28-tab pack = £8.41; 12.5 mg (peach), 28-tab pack = £9.35; 25 mg, 28-tab pack = £11.68. Label: 8

ESMOLOL HYDROCHLORIDE

Cautions see under Propranolol Hydrochloride

Renal impairment manufacturer advises caution

Contra-indications see under Propranolol Hydrochloride.

Side-effects see under Propranolol Hydrochloride; infusion causes venous irritation and thrombophlebitis.

Licensed use not licensed for use in children.

Indication and dose

Arrhythmias, hypertensive emergencies (see also notes above and section 2.5)

- By intravenous administration
  - Child 1 month–18 years initially by intravenous injection over 1 minute 500 micrograms/kg then by intravenous infusion 50 micrograms/kg/minute for 4 minutes (rate reduced if low blood pressure or low heart rate); if inadequate response, repeat loading dose and increase maintenance infusion by 50 micrograms/kg/minute increments; repeat until effective or max. infusion of 200 micrograms/kg/minute reached; doses over 300 micrograms/kg/minute not recommended.

Administration Dilute injection solution (with Glucose 5% or Sodium Chloride 0.9%) to a concentration of 10 mg/mL (20 mg/mL if fluid restricted) and give through central venous catheter; incompatible with bicarbonate.

Brevibloc® (Baxter) Injection, esmolol hydrochloride 10 mg/mL, net price 10-mL vial = £7.79, 250-mL infusion bag = £89.69.

LABETALOL HYDROCHLORIDE

Cautions see under Propranolol Hydrochloride; interferes with laboratory tests for catecholamines; liver damage (see below).

Liver damage Severe hepatocellular 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.

Renal impairment dose reduction may be required.


Breast-feeding present in milk but amount probably too small to be harmful—monitor infant for possible symptoms of alpha- and beta-blockade.

Contra-indications see under Propranolol Hydrochloride.
LABETALOL HYDROCHLORIDE (continued)

Side-effects postural hypotension (avoid upright position during and for 3 hours after intravenous administration), tiredness, weakness, headache, rashes, scalp tingling, difficulty in micturition, epigastic pain, nausea, vomiting; liver damage (see above); rarely lichenoid rash

Licensed use not licensed for use in children

Indication and dose

Hypertensive emergencies see also section 2.5

• By intravenous infusion

Neonate 500 micrograms/kg/hour adjusted at intervals of at least 15 minutes according to response; max. 4 mg/kg/hour

Child 1 month–12 years initially 0.5–1 mg/kg/hour adjusted at intervals of at least 15 minutes according to response; max. 3 mg/kg/hour

Child 12–18 years 30–120 mg/hour adjusted at intervals of at least 15 minutes according to response

Note Consult local guidelines. In hypertensive encephalopathy reduce blood pressure to normotensive level over 24–48 hours (more rapid reduction may lead to cerebral infarction, blindness, and death). If child fitting, reduce blood pressure rapidly, but not to normal levels

Hypertension

• By mouth

Child 1 month–12 years 1–2 mg/kg 3–4 times a day

Child 12–18 years initially 50–100 mg daily increased if required at intervals of 3–14 days to usual dose of 200–400 mg twice daily (3–4 divided doses if higher); max. 2.4 g daily

Administration Injection may be given orally with squash or juice

• By intravenous injection

Child 1 month–12 years 250–500 micrograms/kg as a single dose; max. 20 mg

Child 12–18 years 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; for overdosage see p. 41

Administration for intravenous infusion, dilute to a concentration of 1 mg/mL in Glucose 5% or Sodium Chloride and Glucose 5%; if fluid restricted may be given undiluted, preferably through a central venous catheter

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

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

METOPROLOL TARTRATE

Cautions see under Propranolol Hydrochloride

Hepatic impairment reduce dose in severe impairment

Pregnancy see under Propranolol Hydrochloride

Breast-feeding present in milk but amount probably too small to be harmful—monitor infant for possible symptoms of beta-blockade

Contra-indications see under Propranolol Hydrochloride

Side-effects see under Propranolol Hydrochloride

Licensed use not licensed for use in children

Indication and dose

Hypertension

• By mouth

Child 1 month–12 years 1 mg/kg twice daily, increased to necessary to max. 8 mg/kg daily in 2–4 divided doses

Child 12–18 years initially 50–100 mg daily increased if necessary to 200 mg daily in 1–2 divided doses; max. 400 mg daily (but high doses rarely necessary)

Arrhythmias

• By mouth

Child 12–18 years usually 50 mg 2–3 times daily; up to 300 mg daily in divided doses if necessary

Metoprolol Tartrate (Non-proprietary) Tablets, metoprolol tartrate 50 mg, net price 28 = £1.39, 56 = £1.54; 100 mg, 28 = £1.88, 56 = £2.24. Label: 8

Lopresor® (Novartis) Tablets, f/c, scored, metoprolol tartrate 50 mg (pink), net price 56-tab pack = £2.57; 100 mg (blue), 56-tab pack = £6.68. Label: 8

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

SOTALOL HYDROCHLORIDE

Cautions see under Propranolol Hydrochloride; correct hypokalaemia, hypomagnesaemia, or other electrolyte disturbances; severe or pro-longed diarrhoea; reduce dose or discontinue if corrected QT interval exceeds 550 msec; inter-
1 SOTALOL HYDROCHLORIDE (continued)

actions: Appendix 1 (beta-blockers), important: verapamil interaction see also p. 140
Renal impairment halve normal dose if estimated glomerular filtration rate 30–60 mL/min–
ute/1.73 m²; use one-quarter normal dose if estimated glomerular filtration rate 10–30 mL/min–
ute/1.73 m²; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²
Pregnancy see under Propranolol Hydrochloride
Breast-feeding present in milk; possible toxicity due to beta-blockade—monitor infant
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
Contra-indications see under Propranolol Hydrochloride
Side-effects see under Propranolol Hydrochloride; arrhythmogenic (pro-arrhythmic) effect (torsade de pointes—increased risk in females)
Licensed use not licensed for use in children under 12 years
Indication and dose

Ventricular arrhythmias, life-threatening ventricular tachyarrhythmia and supraventricular arrhythmias initiated under specialist supervision and ECG monitoring and measurement of corrected QT interval
• By mouth

Neonate initially 1 mg/kg twice daily, increased as necessary every 3–4 days to max. 4 mg/kg twice daily

2.5 Hypertension

2.5.1 Vasodilator antihypertensive drugs and pulmonary hypertension
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

Hypertension in children and adolescents can have a substantial effect on long-
term health. Possible causes of hypertension (e.g. congenital heart disease, renal disease and endocrine disorders) and the presence of any complications (e.g. left ventricular hypertrophy) should be established. Treatment should take account of contributory factors and any factors that increase the risk of cardiovascular complications.

Serious hypertension is rare in neonates but it can present with signs of congestive heart failure; the cause is often renal and can follow embolic arterial damage.

Children (or their parents or carers) should be given advice on lifestyle changes to reduce blood pressure or cardiovascular risk; these include weight reduction (in obese children), reduction of dietary salt, reduction of total and saturated fat,
increasing exercise, increasing fruit and vegetable intake, and smoking cessation
in children who smoke).

Indications for antihypertensive therapy in children include symptomatic hyper-
tension, secondary hypertension, hypertensive target-organ damage, diabetes
mellitus, persistent hypertension despite lifestyle measures (see above), and
pulmonary hypertension (section 2.5.1.2). The effect of antihypertensive treat-
ment on growth and development is not known; treatment should be started only
if benefits are clear.

Antihypertensive therapy should be initiated with a single drug at the lowest
recommended dose; the dose can be increased until the target blood pressure is
achieved. Once the highest recommended dose is reached, or sooner if the patient
begins to experience side-effects, a second drug may be added if blood pressure is
not controlled. If more than one drug is required, these should be given as
separate products because there is little paediatric experience in using fixed-
dose combination products.

Acceptable drug classes for use in children with hypertension include ACE
inhibitors (section 2.5.5.1), alpha-blockers (section 2.4), beta-blockers (sec-
tion 2.4), calcium-channel blockers (section 2.6.2), and thiazide diuretics
(section 2.2.1). There is limited information on the use of angiotensin-II receptor
antagonists (section 2.5.5.2) in children. Diuretics and beta-blockers have a long
history of safety and efficacy in children. The newer classes of antihypertensive
drugs, including ACE inhibitors and calcium-channel blockers have been shown
to be safe and effective in short-term studies in children. Refractory hypertension
may require additional treatment with agents such as minoxidil (section 2.5.1.1)
or clonidine (section 2.5.2).

Other measures to reduce cardiovascular risk Aspirin (section 2.9) may be
used to reduce the risk of cardiovascular events; however, concerns about an
increased risk of bleeding and Reye’s syndrome need to be considered.

A statin can be of benefit in older children who have a high risk of cardiovascular
disease and have hypercholesterolaemia (see section 2.12).

Hypertension in diabetes Hypertension can occur in type 2 diabetes and
treatment prevents both macrovascular and microvascular complications. ACE
inhibitors (section 2.5.5.1) may be considered in children with diabetes and
microalbuminuria or proteinuric renal disease (see also section 6.1.5). Beta-
blockers are best avoided in children with, or at a high risk of developing, diabetes,
especially when combined with a thiazide diuretic.

Hypertension in renal disease ACE inhibitors may be considered in children
with micro-albuminuria or proteinuric renal disease (see also section 6.1.5). High
doses of loop diuretics may be required. Specific cautions apply to the use of ACE
inhibitors in renal impairment, see section 2.5.5.1, but ACE inhibitors may be
effective. Dihydropyridine calcium-channel blockers may be added.

Hypertension in pregnancy High blood pressure in pregnancy may usually be
due to pre-existing essential hypertension or to pre-eclampsia. Methyldopa
(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 2.5.1.1) may be used by the intravenous route.

Hypertensive emergencies Hypertensive emergencies in children may be
accompanied by signs of hypertensive encephalopathy, including seizures. Con-
trolled reduction in blood pressure over 72–96 hours is essential; rapid reduction
can reduce perfusion leading to organ damage. It may be necessary to infuse
fluids particularly during the first 12 hours to expand plasma volume should the
blood pressure drop too rapidly. Once blood pressure is controlled oral therapy
should be started.

Controlled reduction of blood pressure is achieved by sodium nitroprusside
(section 2.5.1.1). Esmolol (section 2.4) is useful for short-term use and has a short
duration of action. Nicardipine (section 2.6.2) may be administered as a con-
tinuous intravenous infusion but it is not licensed for this use. In less severe cases,
nifedipine capsules (section 2.6.2) can be used.
In resistant cases, diazoxide (section 2.5.1.1) is given intravenously, but it can cause sudden hypotension. Other antihypertensive drugs which may be given intravenously include hydralazine (section 2.5.1.1) and clonidine (section 2.5.2). Hypertension in acute nephritis occurs as a result of sodium and water retention; it should be treated with sodium and fluid restriction, and with furosemide (section 2.2.2); antihypertensive drugs may be added if necessary.

For advice on short-term management of hypertensive episodes in phaeochromocytoma, see under Phaeochromocytoma, section 2.5.4.

### 2.5.1 Vasodilator antihypertensive drugs and pulmonary hypertension

#### 2.5.1.1 Vasodilator antihypertensives

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 Hypertensive Emergencies, p. 120.

**Sodium nitroprusside** is given by intravenous infusion to control severe hypertensive crisis when parenteral treatment is necessary. At low doses it reduces systemic vascular resistance and increases cardiac output; at high doses it can produce profound systemic hypotension—continuous blood pressure monitoring is therefore essential. Sodium nitroprusside may also be used to control paradoxical hypertension after surgery for coarctation of the aorta.

**Diazoxide** has also been used by intravenous injection in hypertensive emergencies; however it is not first-line therapy.

**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 low, but systemic lupus erythematosus should be suspected if there is unexplained weight loss, arthritis, or any other unexplained ill health.

**Minoxidil** should be reserved for the treatment of severe hypertension resistant to other drugs. Vasodilatation is accompanied by increased cardiac output and tachycardia and children 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 females.

Prazosin and doxazosin (section 2.5.4) have alpha-blocking and vasodilator properties.

### DIAZOXIDE

**Cautions** during prolonged use monitor white cell and platelet count, and regularly assess growth, bone, and psychological development; **interactions:** Appendix 1 (diazoxide)

**Renal impairment** dose reduction may be required

**Contra-indications**

- **Pregnancy** prolonged use may produce alopecia, hypertrichosis, and impaired glucose tolerance in neonate; inhibits uterine activity during labour
- **Breast-feeding** manufacturer advises avoid—no information available

**Side-effects** tachycardia, hypotension, hyperglycaemia, sodium and water retention; rarely cardiomegaly, hyperosmolar non-ketotic coma, leucopenia, thrombocytopenia, and hirsutism

**Licensed use** intractable hypoglycaemia (section 6.1.4)

#### Indication and dose

**Hypertensive emergencies** initiated on specialist advice

- **By intravenous injection**
  - **Child 1 month–18 years** 1–3 mg/kg (max. 150 mg) as a single dose, repeat dose after 5–15 minutes until blood pressure controlled; max. 4 doses in 24 hours

**Administration** intravenous injection over 30 seconds. Do not dilute

**Resistant hypertension**

- **By mouth**
  - **Neonate** initially 1.7 mg/kg 3 times daily, adjusted according to response; usual max. 15 mg/kg daily
  - **Child 1 month–18 years** initially 1.7 mg/kg 3 times daily, adjusted according to response; usual max. 15 mg/kg daily

**Intractable hypoglycaemia** section 6.1.4
## DIAZOXIDE (continued)

### Eudemine® (Goldshield) (£50.10)
- **Injection**, diazoxide 15 mg/mL, net price 20-mL amp = £30.00
- **Tablets**, section 6.1.4

### HYDRAZINE HYDROCHLORIDE

#### Cautions
- Cerebrovascular disease; occasionally blood pressure reduction too rapid even with low parenteral doses; manufacturer advises test for antinuclear factor and for proteinuria every 6 months and check acetylator status before increasing dose, but evidence of clinical value unsatisfactory; **interactions**: Appendix 1 (hydralazine)
- Hepatic impairment: reduce dose
- Renal impairment: reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²
- Pregnancy: manufacturer advises avoid before third trimester; no reports of serious harm following use in third trimester
- Breast-feeding: present in milk but not known to be harmful; monitor infant

#### Contra-indications
- Idiopathic systemic lupus erythematosus, severe tachycardia, high output heart failure, myocardial insufficiency due to mechanical obstruction, cor pulmonale; 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 (especially in slow acetylator individuals); rarely rashes, fever, peripheral neuritis, polyneuritis, paraesthesia, arthralgia, myalgia, increased lacrimation, nasal congestion, dyspnœa, agitation, anxiety, anorexia; blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia), abnormal liver function, jaundice, raised plasma creatinine, proteinuria and haematuria reported

#### Licensed use
- Not licensed for use in children

#### Indication and dose

<table>
<thead>
<tr>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong> 250–500 micrograms/kg every 8–12 hours increased as necessary to max. 2–3 mg/kg every 8 hours</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong> 250–500 micrograms/kg every 8–12 hours increased as necessary to max. 7.5 mg/kg daily (not exceeding 200 mg daily)</td>
</tr>
</tbody>
</table>

#### Administration
- For **intravenous injection** initially reconstitute 20 mg with 1 mL water for injections, then dilute to a concentration of 0.5–1 mg/mL with sodium chloride 0.9% intravenous infusion and administer over 5–20 minutes. For administration by **mouth** diluted injection may be given orally. For **continuous intravenous infusion** initially reconstitute 20 mg with 1 mL water for injections, then dilute with sodium chloride 0.9% or Ringer’s solution. Incompatible with glucose intravenous infusion

#### Hydralazine (Non-proprietary) (£50.10)
- **Tablets**, hydralazine hydrochloride 25 mg, net price 56 = £11.79; 50 mg, 56 = £18.54

#### Apresoline® (Amdipharm) (£50.10)
- **Tablets**, yellow, s/c, hydralazine hydrochloride 25 mg, net price 84-tab pack = £2.82
- Excipients include gluten

#### Injection, powder for reconstitution, hydralazine hydrochloride, net price 20-mg amp = £1.84

#### Minoxidil

#### Cautions
- See notes above; acute porphyria (section 9.8.2); **interactions**: Appendix 1 (vasodilator antihypertensives)
- Renal impairment: use with caution in significant impairment
- Pregnancy: neonatal hirsutism reported

#### Contra-indications
- Phaeochromocytoma

#### Side-effects
- Sodium and water retention; weight gain, peripheral oedema, tachycardia, hypertrichosis; reversible rise in creatinine and blood
SODIUM NITROPRUSSIDE

Cautions hypothyroidism, hyponatraemia, impaired cerebral circulation, 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; interactions: Appendix 1 (nitroprusside)

Hepatic impairment avoid in severe liver impairment

Renal impairment cyanide or thiocyanate metabolites may accumulate—avoid prolonged use

Pregnancy potential for accumulation of cyanide in fetus—avoid prolonged use

Breast-feeding no information available; caution advised due to thiocyanate metabolite

Contra-indications severe vitamin B₁₂ 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 phlebitis

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. 44)

Licensed use not licensed for use in the UK

Indication and dose

Hypertensive emergencies

By continuous infusion

Neonate 500 nanograms/kg/minute then increased in steps of 200 nanograms/kg/minute as necessary to max. 8 micrograms/kg/minute (max. 4 micrograms/kg/minute if used for longer than 24 hours)

Child 1 month–18 years 500 nanograms/kg/minute then increased in steps of 200 nanograms/kg/minute as necessary to max. 8 micrograms/kg/minute (max. 4 micrograms/kg/minute if used for longer than 24 hours)

Administration For continuous intravenous infusion in glucose 5%, infuse via infusion device to allow precise control; protect infusion from light. For further details, consult product literature

Sodium Nitroprusside (Non-proprietary) Intravenous infusion, powder for reconstitution, sodium nitroprusside 10 mg/mL. For dilution and use as an infusion. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

2.5.1.2 Pulmonary hypertension

Only pulmonary arterial hypertension is currently suitable for drug treatment. Pulmonary arterial hypertension includes persistent pulmonary hypertension of the newborn, idiopathic pulmonary arterial hypertension in children, and pulmonary hypertension related to congenital heart disease and cardiac surgery.

Some types of pulmonary hypertension are treated with vasodilator antihypertensive therapy and oxygen. Diuretics (section 2.2) may also have a role in children with right-sided heart failure.

Initial treatment of persistent pulmonary hypertension of the newborn involves the administration of nitric oxide; epoprostenol can be used until nitric oxide is available. Oral sildenafil may be helpful in less severe cases. Epoprostenol and sildenafil can cause profound systemic hypotension. In rare circumstances either tolazoline or magnesium sulphate can be given by intravenous infusion when nitric oxide and epoprostenol have failed.

Treatment of idiopathic pulmonary arterial hypertension is determined by acute vasodilator testing; drugs used for treatment include calcium-channel blockers (usually nifedipine, section 2.6.2), long-term intravenous epoprostenol, nebulised iloprost, bosentan, or sildenafil. Anticoagulation (usually with warfarin) may also be required to prevent secondary thrombosis.
Inhaled nitric oxide is a potent and selective pulmonary vasodilator. It acts on cyclic guanosine monophosphate (cGMP) resulting in smooth muscle relaxation. Inhaled nitric oxide is used in the treatment of persistent pulmonary hypertension of the newborn, and may also be useful in other forms of arterial pulmonary hypertension. Dependency can occur with high doses and prolonged use; to avoid rebound pulmonary hypertension the drug should be withdrawn gradually, often with the aid of sildenafil.

Excess nitric oxide can cause methaemoglobinaemia; therefore, methaemoglobin concentration should be measured regularly, particularly in neonates.

Nitric oxide increases the risk of haemorrhage by inhibiting platelet aggregation, but it does not usually cause bleeding.

Epoprostenol (prostacyclin) is a prostaglandin and a potent vasodilator. It is used in the treatment of persistent pulmonary hypertension of the newborn, idiopathic pulmonary arterial hypertension, and in the acute phase following cardiac surgery. It is given by continuous 24-hour intravenous infusion.

Epoprostenol is a powerful inhibitor of platelet aggregation and there is a possible risk of haemorrhage. It is sometimes used as an antiplatelet in renal dialysis either alone or with heparin (see section 2.8.1). It can also cause serious systemic hypotension and, if withdrawn suddenly, can cause pulmonary hypertensive crisis.

Children on prolonged treatment can become tolerant to epoprostenol, and therefore require an increase in dose.

Iloprost is a synthetic analogue of epoprostenol and is efficacious when nebulised in adults with pulmonary arterial hypertension, but experience in children is limited. It is more stable than epoprostenol and has a longer half-life.

Bosentan is a dual endothelin receptor antagonist used orally in the treatment of idiopathic pulmonary arterial hypertension. The concentration of endothelin, a potent vasoconstrictor, is raised in sustained pulmonary hypertension.

Sildenafil, a vasodilator developed for the treatment of erectile dysfunction, is also used for pulmonary arterial hypertension. It is used either alone or as an adjunct to other drugs and has relatively few side-effects.

Sildenafil is a selective phosphodiesterase type-5 inhibitor. Inhibition of this enzyme in the lungs enhances the vasodilatory effects of nitric oxide and promotes relaxation of vascular smooth muscle.

Sildenafil has also been used in pulmonary hypertension for weaning children off inhaled nitric oxide following cardiac surgery, and less successfully in idiopathic pulmonary arterial hypertension.

Tolazoline is now rarely used to correct pulmonary artery vasospasm in pulmonary hypertension of the newborn as better alternatives are available (see above). Tolazoline is an alpha-blocker and produces both pulmonary and systemic vasodilation.

**BOSENTAN**

**Cautions** not to be initiated if systemic systolic blood pressure is below 85 mmHg; monitor liver function before and 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 (see Contra-indications below); monitor haemoglobin before and during treatment (monthly for first 4 months, then 3-monthly thereafter), withdraw treatment gradually; **interactions:** Appendix 1 (bosentan)

**Contra-indications** acute porphyria (section 9.8.2)

**Hepatic impairment** avoid in moderate and severe hepatic impairment

**Pregnancy** 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

**Breast-feeding** manufacturer advises avoid—no information available

**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)

**Licensed use** not licensed for use in children under 12 years
**Indication and dose**

**Idiopathic pulmonary arterial hypertension**

- **By mouth**
  - Child 3–18 years and body-weight 10–20 kg:
    - Initially 31.25 mg once daily increased after 4 weeks to 31.25 mg twice daily
  - Child 3–18 years and body-weight 20–40 kg:
    - Initially 31.25 mg twice daily increased after 4 weeks to 62.5 mg twice daily
  - Child 12–18 years and body-weight over 40 kg:
    - Initially 62.5 mg twice daily increased after 4 weeks to 125 mg twice daily; max. 250 mg twice daily

**Administration**

Tablets may be cut, or suspended in water or non-acidic liquid. Suspension is stable at room-temperature (max. 25°C) for 24 hours.

**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

**Epoprostenol**

**Cautions**

- Anticoagulant monitoring required when given with heparin; haemorrhagic diathesis; avoid abrupt withdrawal (see notes above); monitor blood pressure; concomitant use of drugs that increase risk of bleeding

**Pregnancy**

- Manufacturer advises use with caution—no information available

**Contra-indications**

- Severe left ventricular dysfunction; pulmonary veno-occlusive disease

**Side-effects**

- See notes above; gastro-intestinal disturbances, hypotension, bradycardia, tachycardia, pallor, flushing, sweating with higher doses; headache; lassitude, anxiety, agitation; dry mouth, jaw pain, chest pain; also reported, hyperglycaemia and injection-site reactions

**Licensed use**

- Not licensed for use in children

**Indication and dose**

** Persistent pulmonary hypertension of the newborn**

- **By continuous intravenous infusion**
  - Neonate:
    - Initially 2 nanograms/kg/minute
    - Adjusted according to response
    - Usual max. 20 nanograms/kg/minute (rarely up to 40 nanograms/kg/minute)

**Flolan (GSK)**

Infusion, powder for reconstitution, epoprostenol (as sodium salt)
- 500-microgram vial (with diluent) = £64.57; 1.5-mg vial (T) (with diluent) = £130.07

**Iloprost**

**Cautions**

- Unstable pulmonary hypertension with advanced right heart failure; hypotension (do not initiate if systolic blood pressure below 85 mmHg); acute pulmonary infection; severe asthma; interactions: Appendix 1 (iloprost)

- Hepatic impairment:
  - Dose may need to be halved in liver cirrhosis—initially 2.5 micrograms at intervals of at least 3 hours (max. 6 times daily), adjusted according to response

**Contra-indications**

- Decompensated cardiac failure (unless under medical supervision); severe coronary heart disease; severe arrhythmias; congenital or acquired valvular defects of the myocardium; pulmonary veno-occlusive disease; conditions which increase risk of haemorrhage

**Pregnancy**

- Manufacturer advises avoid (toxicity in animal studies); effective contraception must be used during treatment

**Breast-feeding**

- Manufacturer advises avoid—no information available

**Side-effects**

- Vasodilatation, hypotension, syncope, cough, headache, throat or jaw pain; nausea, vomiting, diarrhoea, chest pain, dyspnoea, bronchospasm, and wheezing also reported

**Licensed use**

- Not licensed for use in children under 18 years

**Indication and dose**

**Idiopathic or familial pulmonary arterial hypertension**

- **By inhalation of nebulised solution**
  - Child 8–18 years:
    - 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

**Raynaud’s syndrome** section 2.6.4.1

**Ventavis (Schering Health)**

Nebuliser solution, iloprost (as trometamol)
- 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
MAGNESIUM SULPHATE

Cautions  see section 9.5.1.3
Side-effects  see section 9.5.1.3
Licensed use  see section 9.5.1.3

Indication and dose
Persistent pulmonary hypertension of the newborn
• By intravenous infusion
Neonate initially 200 mg/kg over 20–30 minutes; if response occurs, then by continuous intravenous infusion of 20–75 mg/kg/hour to maintain plasma-magnesium concentration between 3.5–5.5 mmol/litre) given for up to 5 days

Neonatal hypocalcaemia  see section 9.5.1.3
Hypomagnesaemia  see section 9.5.1.3

Administration  For intravenous infusion dilute with glucose 5% or sodium chloride 0.9% intravenous infusion to a max. concentration of 100 mg/mL (200 mg/mL if fluid restricted)

Magnesium Sulphate (Non-proprietary) [FW]
Injection, magnesium sulphate 50% (Mg²⁺ approx. 2 mmol/mL), net price 2-mL (1-g) amp= £3.80, 5-mL (2.5-g) amp = £3.00, 10-mL (5-g) amp = £3.35; prefilled 10-mL (5-g) syringe = £4.95

SILDENAFIL

Cautions  hypotension (avoid if severe); intravascular volume depletion; left ventricular outflow obstruction; autonomic dysfunction; avoid abrupt withdrawal; other cardiovascular disease; pulmonary veno-occlusive disease; predisposition to priapism; anatomical deformation of the penis; bleeding disorders or active peptic ulceration; ocular disorders; initiate cautiously if child also on epoprostenol, iloprost, bosentan or nitric oxide; interactions: Appendix 1 (sildenafil)

Hepatic impairment  reduce dose if not tolerated in mild to moderate impairment; manufacturer advises avoid in severe impairment

Renal impairment  reduce dose if not tolerated

Contra-indications  recent history of stroke; history of non-arteritic anterior ischaemic 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 gynaecomastia, priapism; also reported rash, retinal vascular occlusion, non-arteritic anterior ischaemic optic neuropathy (discontinue if sudden visual impairment occurs), and sudden hearing loss (advise patient to seek medical help)

Licensed use  not licensed for use in children under 18 years

Indication and dose
Pulmonary hypertension after cardiac surgery, weaning from nitric oxide, idiopathic pulmonary arterial hypertension, persistent pulmonary hypertension of the newborn
• By mouth

Neonate initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; max. 2 mg/kg every 4 hours; start with lower dose and frequency especially if used with other vasodilators (see Cautions above); withdraw gradually

Child 1 month–18 years initially 250–500 micrograms/kg every 4–8 hours, adjusted according to response; max. 2 mg/kg every 4 hours; start with lower dose and frequency especially if used with other vasodilators (see Cautions above)

Administration  tablet may be dissolved in water or blackcurrant drink and given by mouth or through a nasogastric tube

Viagra® (Pfizer) [FW and]
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) ▼ [FW]
Tablets, f/c, sildenafil (as citrate), 20 mg, net price 90-tab pack = £373.50

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

TOLAZOLINE

Cautions  mitral stenosis; cardiotoxic accumulation may occur with continuous infusion, particularly in renal impairment—monitor blood pressure regularly for sustained systemic hypotension; interactions: Appendix 1 (alpha-blockers)

Renal impairment  accumulates in renal impairment; risk of cardiotoxicity; lower doses may be necessary

Contra-indications  peptic ulcer disease

Side-effects  nausea, vomiting, diarrhoea, epigastric pain; flushing, tachycardia, cardiac arrhythmias; headache, shivering, sweating; oliguria, metabolic alkalosis, haematuria, blood dyscrasias (including thrombocytopenia); blotchy skin; at high doses severe hypotension, marked hypertension, renal failure, and haemorrhage reported

Licensed use  not licensed for use in children
Indication and dose

**Correction of pulmonary vasospasm in neonates**
- By intravenous injection and continuous intravenous infusion (maintenance)
  
  **Neonate** initially 1 mg/kg by intravenous injection over 2–5 minutes, followed if necessary by continuous intravenous infusion of 200 micrograms/kg/hour with careful blood pressure monitoring; doses above 300 micrograms/kg/hour associated with cardiotoxicity and renal failure

- By endotracheal administration
  
  **Neonate** 200 micrograms/kg

Administration

For **continuous intravenous infusion** dilute with glucose 5% or sodium chloride 0.9% intravenous infusion. Prepare a fresh solution every 24 hours.

For **endotracheal administration** dilute with 0.5–1 mL of sodium chloride 0.9% solution for injection

Tolazoline (Non-proprietary)

**Injection**, tolazoline 25 mg/mL

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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### 2.5.2 Centrally acting antihypertensive drugs

**Methyldopa**, a centrally acting antihypertensive, is of little value in the management of refractory sustained hypertension in infants and children. On prolonged use it is associated with fluid retention (which may be alleviated by concomitant use of diuretics).

Methyldopa is effective for the management of hypertension in pregnancy.

**Clonidine** is also a centrally acting antihypertensive but has the disadvantage that sudden withdrawal may cause a hypertensive crisis. Clonidine is also used under specialist supervision for pain management, sedation, and opioid withdrawal, attention deficit hyperactivity disorder, and Tourette syndrome.

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### Clonidine Hydrochloride

**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); interactions: Appendix 1 (clonidine)

**Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

**Pregnancy** may lower fetal heart rate, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension; avoid intravenous injection

**Breast-feeding** present in milk—manufacturer advises avoid

**Side-effects** dry mouth, sedation, depression, fluid retention, bradycardia. Raynaud’s phenomenon, headache, dizziness, euphoria, nocturnal unrest, rash, nausea, constipation, rarely impotence

**Licensed use** not licensed for use in children

**Indication and dose**

**Severe hypertension**
- By mouth
  
  **Child 2–18 years** initially 0.5–1 microgram/kg 3 times daily, increased gradually if necessary;

- **max. 25 micrograms/kg daily in divided doses** (not exceeding 1.2 mg daily)

- **By slow intravenous injection**
  
  **Child 2–18 years** 2–6 micrograms/kg (max. 300 micrograms) as a single dose

**Administration** For **intravenous injection** give over 10–15 minutes; compatible with sodium chloride 0.9% or glucose 5% intravenous infusion. For administration by **mouth** tablets may be crushed and dissolved in water

**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

**Extemporaneous formulations available see Extemporaneous Preparations, p. 8**

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### Methyldopa

**Cautions** withdraw treatment gradually; 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); inter-
ference with laboratory tests; **interactions:** Appendix 1 (methyldopa)

**Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol may be enhanced

**Hepatic impairment** manufacturer advises caution in history of liver disease; avoid in active liver disease

**Renal impairment** start with small dose; increased sensitivity to hypotensive and sedative effect

**Pregnancy** not known to be harmful

**Breast-feeding** amount too small to be harmful

**Contra-indications** depression, active liver disease, phaeochromocytoma; acute porphyria (section 9.8.2)

**Side-effects** gastro-intestinal disturbances, dry mouth, stomatitis, sialadenitis; bradycardia, postural hypotension, oedema; sedation, headache, dizziness, asthenia, myalgia, arthralgia, paraesthesia, nightmares, mild psychosis, depression, impaired mental acuity, parkinsonism, Bell’s palsy; 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

**Indication and dose**

- **Refractory hypertension** (but see notes above)
  - **By mouth**
    - Child 1 month–12 years initially 2.5 mg/kg 3 times daily, increased as necessary at intervals of at least 2 days to max. 65 mg/kg daily (not exceeding 3 g daily)
    - Child 12–18 years initially 250 mg 2–3 times daily increased as necessary at intervals of at least 2 days to max. 3 g daily

**Methyldopa**

| Tablets, coated, methyldopa (anhydrous) 125 mg, net price 56 tab pack = £13.60 | 56 tab pack = £12.78. Label: 3, 8
| Tablets, yellow, f/c, methyldopa (anhydrous) 250 mg, net price 60 = £1.88 | 30 = £1.90. Label: 3, 8
| Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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### 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 in adults and are rarely used in children.

### 2.5.4 Alpha-adrenoceptor blocking drugs

**DOXAZOSIN**

**Cautions** care with initial dose (postural hypotension); cataract surgery (risk of intra-operative floppy iris syndrome); susceptibility to heart failure; **interactions:** Appendix 1 (alpha-blockers)

**Driving** May affect performance of skilled tasks e.g. driving

**Hepatic impairment** no information available—manufacturer advises caution

**Pregnancy** no evidence of teratogenicity, manufacturer advises use only when potential benefit outweighs risk

**Breast-feeding** accumulates in milk in animal studies—manufacturer advises avoid

**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, hypoaesthesia, syncope, tremor, agitation, micturition disturbances, impotence, epistaxis, arthralgia, tinnitus, hypersensitivity reactions (including pruritus, purpura, rash), alopecia; very rarely cholestasis, hepatitis, jaundice, bronchospasm, gynaecomastia, priapism, abnormal ejaculation, leucopenia, thrombocytopenia, blurred vision

**Licensed use** not licensed for use in children

**Indication and dose**

- **Hypertension** (see notes above)
  - **By mouth**
    - Child 6–12 years 500 micrograms once daily, increased at 1-week intervals to 2–4 mg daily
    - Child 12–18 years 1 mg daily, increased after 1–2 weeks to 2 mg once daily, and thereafter to 4 mg once daily if necessary; usual max. 4 mg daily (rarely up to 16 mg daily may be required)

**Dysfunctional voiding** section 7.4.1
DOXAZOSIN (continued)

Doxazosin (Non-proprietary)  
Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = £1.42. Counselling, driving  
Brands include Doxadura®

Cardura® (Pfizer)  
Tablets, doxazosin (as mesilate) 1 mg, net price 28-tab pack = £10.56; 2 mg, 28-tab pack = £14.08. Counselling, driving

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

MODIFIED-RELEASE

Note  
Children stabilised on immediate-release doxazosin can be transferred to the equivalent dose of modified-release doxazosin

Doxazosin (Non-proprietary)  
Tablets, m/r, doxazosin (as mesilate) 4 mg, net price 28-tab pack = £6.33. Label: 25, counselling, driving  
Brands include Doxadura® XL, Slocisn® XL

Cardura® XL (Pfizer)  
Tablets, m/r, doxazosin (as mesilate) 4 mg, net price 28-tab pack = £6.33; 8 mg, 28-tab pack = £12.67. Label: 25, counselling, driving

PRAZOSIN

Cautions  
first dose may cause collapse due to hypotension (therefore should be taken on retiring to bed); interactions: Appendix 1 (alpha-blockers)

Hepatic impairment  
start with low doses and adjust according to response

Renal impairment  
start with low doses in moderate to severe impairment; increase with caution

Pregnancy  
no evidence of teratogenicity; manufacturer advises use only when potential benefit outweighs risk

Breast-feeding  
present in milk; manufacturer advises use with caution

Contra-indications  
not recommended for congestive heart failure due to mechanical obstruction (e.g. aortic stenosis)

Side-effects  
gastro-intestinal disturbances; postural hypotension, oedema, palpitation; dyspnoea, nasal congestion; drowsiness, headache, depression, nervousness, vertigo; urinary frequency; weakness; less commonly tachycardia, insomnia, paraesthesia, sweating, vasculitis, allergic reactions including rash, pruritus, and urticaria; rarely pancreatitis, flushing, vasculitis, bladder calculus, hallucinations, worsening of narcolepsy, gynaecomastia, priapism, urinary incontinence, and alopecia

Licensed use  
not licensed for use in children under 12 years

Indication and dose

Hypertension  
(see notes above)

• By mouth

Child 1 month–12 years 10–15 micrograms/kg 2–4 times daily (initial dose at bedtime) increased gradually to max. 500 micrograms/kg daily in divided doses (not exceeding 20 mg daily)

Child 12–18 years 500 micrograms 2–4 times daily (initial dose at bedtime), increased after 3–7 days to 1 mg 2–3 times daily for a further 3–7 days; further increased gradually if necessary to max. 20 mg daily in divided doses

Congestive heart failure (but rarely used, see section 2.2)

• By mouth

Child 1 month–12 years 5 micrograms/kg twice daily (initial dose at bedtime), increased gradually to max. 100 micrograms/kg daily in divided doses

Child 12–18 years 500 micrograms 2–4 times daily (initial dose at bedtime), increasing to 4 mg daily in divided doses; maintenance 4–20 mg daily in divided doses

Administration  
For oral administration tablets may be dispersed in water

Prazosin (Non-proprietary)  
Tablets, prazosin (as hydrochloride) 500 micrograms, net price 56-tab pack = £2.51; 1 mg, 56-tab pack = £3.23; 2 mg, 56-tab pack = £4.39; 5 mg, 56-tab pack = £8.75. Label: 3, counselling, initial dose

Phaeochromocytoma

Long-term management of phaeochromocytoma involves surgery. However, surgery should not take place until there is adequate blockade of both alpha- and beta-adrenoceptors. 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. There is no nationwide
Phenoxybenzamine, a powerful alpha-blocker, is effective in the management of phaeochromocytoma but it has many side-effects. Phenoxybenzamine has also been used to treat severe shock in the presence of adequate circulating blood volume, and to lower systemic vascular resistance after cardiac surgery.

**PHENOXYBENZAMINE HYDROCHLORIDE**

**Cautions**
- congestive heart failure; severe heart disease (see also Contra-indications);
cerebrovascular disease (avoid if history of cerebrovascular accident);
carcinogenic in animals; avoid in acute porphyria (section 9.8.2);
- avoid infusion in hypovolaemia; avoid extravasation (irritant to tissues);
avoid contact with skin (risk of contact sensitisation)
- Renal impairment use with caution
- Pregnancy hypotension in newborn may occur—use with caution
- Breast-feeding may be present in milk

**Contra-indications**
- history of cerebrovascular accident

**Side-effects**
- postural hypotension with dizziness and marked compensatory tachycardia, lassitude, nasal congestion, miosis, inhibition of ejaculation;
rarely gastro-intestinal disturbances;
dehydration and dry mouth after intravenous infusion;
idiosyncratic profound hypotension within five minutes of starting infusion

**Licensed use**
- not licensed for use in children

### Indication and dose

**Hypertension in phaeochromocytoma**
- **Child 1 month–18 years**
  - 0.5–1 mg/kg twice daily adjusted according to response

**Severe shock following cardiac surgery**
- **Child 1 month–18 years**
  - Initially 1 mg/kg then if necessary 500 micrograms/kg every 8–12 hours adjusted according to response

**Administration**
- for administration by mouth, capsules may be opened;
- for intravenous infusion, dilute with Sodium Chloride 0.9% and give over at least 2 hours; max. 4 hours between dilution and completion of infusion

**Phenoxybenzamine (Goldshield)**
- Injection concentrate, phenoxybenzamine hydrochloride 50 mg/mL. To be diluted before use. Net price 2-mL amp = £57.14 (hosp. only)

**Dibenzyline® (Goldshield)**
- Capsules, red/white, phenoxybenzamine hydrochloride 10 mg. Net price 30-cap pack = £10.84

**Note**
- May be difficult to obtain

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### 2.5.5 Drugs affecting the renin-angiotensin system

#### 2.5.5.1 Angiotensin-converting enzyme inhibitors

Angiotensin-converting enzyme inhibitors (ACE inhibitors) inhibit the conversion of angiotensin I to angiotensin II. The main indications of ACE inhibitors in children are shown below. In infants and young children, captopril is often considered first.

**Initiation under specialist supervision**
- Treatment with ACE inhibitors should be initiated under specialist supervision and with careful clinical monitoring in children.

**Heart failure**
- ACE inhibitors have a valuable role in all grades of heart failure, usually combined with a loop diuretic (section 2.2). Potassium supplements and potassium-sparing diuretics should be discontinued before introducing an ACE inhibitor because of the risk of hyperkalaemia. In adults, a low dose of spironolactone may be beneficial in severe heart failure and can be used with an ACE inhibitor provided serum potassium is monitored carefully. Profound first-dose hypotension can occur when ACE inhibitors are introduced to children with heart failure who are already taking a high dose of a loop diuretic (see Cautions below). Temporary withdrawal of the loop diuretic reduces the risk, but can cause severe rebound pulmonary oedema.
ACE inhibitors may be considered for hypertension when thiazides and beta-blockers are contra-indicated, not tolerated, or fail to control blood pressure; they may be considered for hypertension in children with type 1 diabetes with nephropathy (see also section 6.1.5). ACE inhibitors can 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.

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 are present). Hyperkalaemia and other side-effects of ACE inhibitors are more common in children with impaired renal function and the dose may need to be reduced (see under individual drugs).

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 children 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 contra-indicated in children known to have these forms of critical renovascular disease.

ACE inhibitor treatment is unlikely to have an adverse effect on overall renal function in children 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 those with known or suspected renovascular disease, unless the blood pressure cannot be controlled by other drugs. If they are used in these circumstances renal function needs to be monitored.

ACE inhibitors should also be used with particular caution in children who may have undiagnosed and clinically silent renovascular disease. ACE inhibitors are useful for the management of hypertension and proteinuria in children with nephritis. They are thought to have a beneficial effect by reducing intra-glomerular hypertension and protecting the glomerular capillaries and membrane.

Cautions ACE inhibitors need to be initiated with care in children receiving diuretics (important: see Concomitant diuretics, below); first doses can cause hypotension especially in children taking high doses of diuretics, on a low-sodium diet, on dialysis, dehydrated or with heart failure (see above). Discontinue if marked elevation of hepatic enzymes or jaundice (risk of hepatic necrosis). Renal function should be monitored before and during treatment, and the dose reduced in renal impairment (see also above and under individual drugs). 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 children with severe or symptomatic aortic stenosis (risk of hypotension) and in hypertrophic cardiomyopathy. They should be used with care (or avoided) in those with a history of idiopathic or hereditary angioedema. Children with primary aldosteronism and Afro-Caribbean children may respond less well to ACE inhibitors.

Interactions: Appendix 1 (ACE inhibitors).

Anaphylactoid reactions To prevent anaphylactoid reactions, ACE inhibitors should be avoided during dialysis with high-flux polyacrylonitrile 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 children; treatment should therefore be initiated with very low doses. In some children 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 children with hypersensitivity to ACE inhibitors (including angioedema) and in bilateral renovascular disease (see also above). ACE inhibitors should not be used in pregnancy unless essential—they may adversely affect fetal and neonatal blood pressure control and renal function, and possibly cause skull defects and oligohydramnios; toxicity in animal studies has been reported.

Side-effects  ACE inhibitors can cause profound hypotension (see Cautions), 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, cholestatic jaundice, hepatitis, fulminant hepatic necrosis, and hepatic failure have been reported—discontinue if marked elevation of hepatic enzymes or jaundice. 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, serosis, vasculitis, myalgia, arthralgia, positive antinuclear antibody, raised erythrocyte sedimentation rate, eosinophilia, leucocytosis, and photosensitivity.

Neonates  The neonatal response to treatment with ACE inhibitors is very variable, and some neonates develop profound hypotension with even small doses; a test-dose should be used initially and increased cautiously. Adverse effects such as apnoea, seizures, renal failure, and severe unpredictable hypotension are very common in the first month of life and it is therefore recommended that ACE inhibitors are avoided whenever possible, particularly in preterm neonates.

### CAPTOPRIL

**Cautions**  see notes above; acute porphyria (section 9.8.2)

**Renal impairment**  see notes above; start with low dose and adjust according to response

**Breast-feeding**  avoid in first few weeks after delivery—risk of profound neonatal hypotension; can be used in older infant if essential but monitor infant’s blood pressure

**Contra-indications**  see notes above

**Pregnancy**  avoid unless essential (see notes above)

**Side-effects**  see notes above; tachycardia, serum sickness, weight loss, stomatitis, maculopapular rash, photosensitivity, flushing and acidosis

**Licensed use**  not licensed for use in children under 18 years

**Indication and dose**

**Hypertension, heart failure, proteinuria in nephritis** (under specialist supervision)

- **By mouth**

**Neonate** (caution, see neonatal information above) test dose, 10–50 micrograms/kg (10 micrograms/kg in neonate less than 37 weeks post-menstrual age), monitor blood pressure carefully for 1–2 hours; if tolerated give 10–50 micrograms/kg 2–3 times daily increased as necessary to max. 2 mg/kg daily in divided doses (max. 300 micrograms/kg daily in divided doses in neonate less than 37 weeks post-menstrual age)

**Child 1 month–12 years** test dose, 100 micrograms/kg (max. 6.25 mg), monitor blood pressure carefully for 1–2 hours; if tolerated give 100–300 micrograms/kg 2–3 times a day, increased as necessary to max. 6 mg/kg daily in divided doses (max. 4 mg/kg daily in divided doses for child 1 month–1 year)

**Child 12–18 years** test dose, 100 micrograms/kg or 6.25 mg, monitor blood pressure carefully for 1–2 hours; if tolerated give 12.5–25 mg 2–3 times a day, increased as necessary to max. 150 mg daily in divided doses

**Diabetic nephropathy** (under specialist supervision)

- **By mouth**

**Child 12–18 years** test dose, 100 micrograms/kg or 6.25 mg, monitor blood pressure carefully for 1–2 hours; if tolerated, give 12.5–25 mg 2–3 times a day, increased as necessary to max. 150 mg daily in divided doses

**Administration**  Administer under close supervision, see notes above. Give test dose whilst child supine. Tablets can be dispersed in water

**Captopril** (Non-proprietary)  

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®, Tensopril®

**Liquid**  various strengths available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
ENALAPRIL MALEATE

Cautions  see notes above

Hepatic impairment  monitor closely
Renal impairment  see notes above; start with low dose and adjust according to response
Breast-feeding  avoid in first few weeks after delivery—risk of profound neonatal hypotension; can be used in older infant if essential but monitor infant’s blood pressure

Contra-indications  see notes above

Pregnancy  avoid unless essential (see notes above)

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, Raynaud’s syndrome, pulmonary infiltrates, allergic alveolitis, abnormal dreams, gynaecomastia, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, pemphigus; very rarely gastro-intestinal angioedema

Licensed use  not licensed for use in children for congestive heart failure, proteinuria in nephritis or diabetic nephropathy; not licensed for use in children less than 20 kg for hypertension

Indication and dose

Hypertension, congestive heart failure, proteinuria in nephritis (under specialist supervision)

• By mouth

Neonate (limited information) initially 10 micrograms/kg once daily, monitor blood pressure carefully for 1–2 hours, increased as necessary up to 500 micrograms/kg daily in 1–3 divided doses

Child 1 month–12 years initially 100 micrograms/kg once daily, monitor blood pressure carefully for 1–2 hours, increased as necessary up to max. 1 mg/kg daily in 1–2 divided doses

Child 12–18 years initially 2.5 mg once daily, monitor blood pressure carefully for 1–2 hours, usual maintenance dose 10–20 mg daily in 1–2 divided doses; max. 40 mg daily in 1–2 divided doses if body-weight over 50 kg

Diabetic nephropathy (under specialist supervision)

• By mouth

Child 12–18 years initially 2.5 mg once daily, monitor blood pressure carefully for 1–2 hours, usual maintenance dose 10–20 mg daily in 1–2 divided doses; max. 40 mg daily in 1–2 divided doses if body-weight over 50 kg

Administration  Tablets may be crushed and suspended in water immediately before use

Enalapril Maleate (Non-proprietary)

Tablets, enalapril maleate 2.5 mg, net price 28-tab pack = £1.31; 5 mg, 28-tab pack = £1.10; 10 mg, 28-tab pack = £1.12; 20 mg, 28-tab pack = £1.22

Brands include Ednyt

Liquid, various strengths available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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

Lisinopril

Cautions  see notes above

Renal impairment  see notes above; start with low dose and adjust according to response
Breast-feeding  avoid—no information available

Contra-indications  see notes above

Pregnancy  avoid unless essential (see notes above)

Side-effects  see notes above; also less commonly tachycardia, palpitation, cerebrovascular accident, 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

Licensed use  not licensed for use in children

Indication and dose

Hypertension (under specialist supervision)

Child 6–12 years initially 70 micrograms/kg (max. 5 mg) once daily, increased in intervals of 1–2 weeks to max. 600 micrograms/kg (or 40 mg) once daily

Child 12–18 years initially 2.5 mg once daily; usual maintenance dose 10–20 mg once daily; max. 80 mg once daily
### 2.5.5.2 Angiotensin-II receptor antagonists

**Losartan** is a specific angiotensin-II receptor antagonist with many properties similar to those of the ACE inhibitors. However, unlike ACE inhibitors, losartan does not inhibit the breakdown of bradykinin and other kinins, and therefore does not appear to cause the persistent dry cough which commonly complicates ACE inhibitor therapy. It is therefore an alternative for children who have to discontinue an ACE inhibitor because of persistent cough.

Losartan can be used as an alternative to an ACE inhibitor in the management of hypertension; however, evidence for its use in children is very limited.

#### LOSARTAN POTASSIUM

**Cautions** renal artery stenosis (see also Renal Effects under ACE inhibitors, section 2.5.5.1); monitor plasma-potassium concentration (particularly in children with renal impairment); aortic or mitral valve stenosis; hypertrophic cardiomyopathy; children with primary aldosteronism and Afro-Caribbean children, particularly those with left ventricular hypertrophy, may not benefit from losartan; **interactions**: Appendix 1 (angiotensin-II receptor antagonists)

**Hepatic impairment** manufacturer advises avoid in children 6–16 years—no information available; child 17–18 years consider dose reduction in mild to moderate impairment, avoid in severe impairment (no information available)

**Renal impairment** manufacturer advises avoid in children 6–16 years with estimated glomerular filtration rate less than 30 mL/minute/1.73m²—no information available

**Contra-indications**

**Pregnancy** avoid unless essential—may adversely affect fetal and neonatal blood pressure control and renal function; also possible skull defects and oligohydramnios; toxicity in animal studies

**Breast-feeding** avoid—no information available

**Side-effects** diarrhoea, symptomatic hypotension including dizziness (particularly in children with intravascular volume depletion e.g. those taking high-dose diuretics); cough, asthenia, vertigo, migraine, hyperkalaemia; arthralgia, myalgia; urticaria, pruritus, rash; rarely hepatitis, anaemia (in severe renal disease or following renal transplant), thrombocytopenia, vasculitis (including Henoch-Schönlein purpura), anaphylaxis, and angioedema

**Licensed use** not licensed for use in children

**Indication and dose**

**Hypertension** (under specialist supervision)

- By mouth
  - **Child 6–16 years**
    - Body-weight 20–50 kg initially 25 mg once daily; adjusted according to response to max. 50 mg once daily
    - Body-weight 50 kg and over initially 50 mg once daily adjusted according to response to max. 100 mg once daily
  - **Child 16–18 years** initially 50 mg once daily (intravascular volume depletion, initially 25 mg once daily); if necessary increased after several weeks to 100 mg once daily

**Cozaar®** (MSD) Tablets, lisinopril 25 mg, net price 28-tab pack = £16.18; 50 mg (scored), 28-tab pack = £12.80; 100 mg, 28-tab pack = £16.18
Nitrates, calcium-channel blockers, and other antianginal drugs

2.6.1 Nitrates

Nitrates are potent coronary vasodilators, but 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 if the child is unusually sensitive to the effects of nitrates or is hypovolaemic.

For the use of glyceryl trinitrate in extravasation, see section 10.3.

Children receiving nitrates continuously throughout the day can 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.

GLYCERYL TRINITRATE

Cautions hypothyroidism, malnutrition, hypothermia; head trauma, cerebral haemorrhage; hypoxaemia or other ventilation and perfusion abnormalities; metal-containing transdermal systems should be removed before cardioversion or diathermy; avoid abrupt withdrawal; tolerance (see notes above); interactions: Appendix 1 (nitrates)

Hepatic impairment caution in severe hepatic impairment

Renal impairment use with caution in severe impairment

Pregnancy not known to be harmful but most manufacturers advise avoid unless potential benefit outweighs risk

Breast-feeding no information available—manufacturers advise use only if potential benefit outweighs risk

Contra-indications hypersensitivity to nitrates; hypotensive conditions and hypovolaemia; hypertrophic cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis; marked anaemia, closed-angle glaucoma

Side-effects postural hypotension, tachycardia (but paradoxical bradycardia also reported); throbbing headache, dizziness, less commonly nausea, vomiting, heartburn; flushing

Injection Specific side-effects following injection (particularly if given too rapidly) include severe hypotension, diaphoresis, apprehension, restlessness, muscle twitching, retrosternal discomfort, palpitation, abdominal pain, syncope; prolonged administration has been associated with methaemoglobinemia

Licensed use not licensed for use in children

Indication and dose

Hypertension during and after cardiac surgery, cardiac failure after cardiac surgery, coronary vasoconstriction in myocardial ischaemia, vasoconstriction in shock

- By continuous intravenous infusion

Neonate 0.2–0.5 micrograms/kg/minute, dose adjusted according to response; usual dose 1–3 micrograms/kg/minute; max. 10 micrograms/kg/minute

Child 1 month–18 years initially 0.2–0.5 micrograms/kg/minute, dose adjusted according to response, usual dose 1–3 micrograms/kg/minute; max. 10 micrograms/kg/minute (do not exceed 200 micrograms/minute)

Administration for continuous intravenous infusion dilute to max. concentration of 400 micrograms/mL (but concentration of 1 mg/mL has been used via a central venous catheter) with Glucose 5% or Sodium Chloride 0.9%.

Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used.

Neonatal intensive care, dilute 3 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 1 mL/hour provides a dose of 1 microgram/kg/minute

Glyceryl Trinitrate (Non-proprietary)

Injection, glyceryl trinitrate 5 mg/mL. To be diluted before use. Net price 5-mL amp = £6.49; 10-mL amp = £12.98

Excipients include ethanol, propylene glycol
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, 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 hypertension (section 2.5) and arrhythmias (section 2.3.2). However, it is no longer first-line treatment for arrhythmias in children because it has been associated with fatal collapse especially in infants under 1 year; adenosine is now recommended for first-line use.

Verapamil 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.140). 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 long-term management of hypertension; their use may be associated with large variations in blood pressure and reflex tachycardia. However, they may be used if a modified-release preparation delivering the appropriate dose is not available or if a child is unable to swallow (a liquid preparation may be prepared using capsules). Nifedipine may also be used for the management of angina due to coronary artery disease in Kawasaki disease or progeria and in the management of Raynaud’s syndrome.

**Nicardipine** has similar effects to those of nifedipine and may produce less reduction of myocardial contractility; it is used to treat hypertensive crisis.

**Amlodipine** also resembles nifedipine and nicardipine in its effects and does not reduce myocardial contractility or produce clinical deterioration in heart failure. It has a longer duration of action and can be given once daily. Nifedipine and amlodipine are used for the treatment of hypertension. 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.

**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 a peripheral vasodilator and also has mild depressor effects on the myocardium. It is used in the treatment of Raynaud’s syndrome.

**Withdrawal** There is some evidence that sudden withdrawal of calcium-channel blockers may be associated with an exacerbation of myocardial ischaemia.
AMLODIPINE

Cautions interactions: Appendix 1 (calcium-channel blockers)

Hepatic impairment half-life prolonged—may need dose reduction

Pregnancy no information available—manufacturer advises avoid, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension

Breast-feeding no information available—manufacturer advises avoid

Contra-indications cardiogenic shock, significant aortic stenosis, acute porphyria (section 9.8.2)

Side-effects abdominal pain, nausea; palpitation, flushing, oedema; headache, dizziness, sleep disturbances, fatigue; less commonly gastro-intestinal 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, pruritus, rash (including isolated reports of erythema multiforme), sweating, alopecia, purpura, and skin discoloration; rarely rashes (including isolated reports of erythema multiforme), photographs, anaphylaxis, peripheral neuropathy, hyperglycaemia, thrombocytopenia, angioedema, and urticaria

Licensed use not licensed for use in children

Indication and dose

Hypertension

• By mouth

Child 1 month–12 years initially 100–200 micrograms/kg once daily; if necessary increase at intervals of 1–2 weeks up to 400 micrograms/kg once daily; max. 10 mg once daily

Child 12–18 years initially 5 mg once daily; if necessary increase at intervals of 1–2 weeks to max. 10 mg once daily

Administration Tablets may be dispersed in water

Note Tablets from various suppliers may contain different salts (e.g. amlodipine besilate, amlodipine maleate, and amlodipine mesilate) but the strength is expressed in terms of amlodipine (base); tablets containing different salts are considered interchangeable

Amlodipine (Non-proprietary)

Tablets, amlodipine (as maleate or as mesilate) 5 mg, net price 28-tab pack = £1.12; 10 mg, 28-tab pack = £1.29

Brands include Amlostin®

Istin® (Pfizer)

Tablets, amlodipine (as besilate) 5 mg, net price 28-tab pack = £13.04; 10 mg, 28-tab pack = £19.47

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

DILTIAZEM HYDROCHLORIDE

Cautions 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)

Hepatic impairment reduce dose

Renal impairment start with smaller dose

Breast-feeding significant amount present in milk—no evidence of harm but avoid unless no safer alternative

Contra-indications severe bradycardia, left ventricular failure with pulmonary congestion, second- or third-degree AV block (unless pacemaker fitted), sick sinus syndrome, acute porphyria (but see section 9.8.2)

Pregnancy avoid

Side-effects bradycardia, sino-atrial block, AV block, palpitation, dizziness, hypotension, malaise, asthenia, headache, hot flushes, gastrointestinal disturbances, oedema (notably of ankles); rarely rashes (including erythema multiforme and exfoliative dermatitis), photosensitivity; hepatitis, gynaecomastia, gum hyperplasia, extrapyramidal symptoms, depression reported

Licensed use not licensed for use in children

Indication and dose

Raynaud’s syndrome

• By mouth

Child 12–18 years 30–60 mg 2–3 times daily

Standard formulations

Note These formulations are licensed as generics and there is no requirement for brand name dispensing. Although their means of formulation has called for the strict designation ‘modified-release’ their duration of action corresponds to that of tablets requiring administration more frequently

Diltiazem (Non-proprietary)

Tablets, m/r (but see note above), diltiazem hydrochloride 60 mg, net price 84 = £3.34.

Label: 25

Brands include Opti®

Tildiem® (Sanofi-Synthelabo)

Tablets, m/r (but see note above), off-white, diltiazem hydrochloride 60 mg, net price 90-tab pack = £8.28. Label: 25

NICARDIPINE HYDROCHLORIDE

Cautions congestive heart failure or significantly impaired left ventricular function; avoid grapefruit juice (may affect metabolism); interactions: Appendix 1 (calcium-channel blockers)

Hepatic impairment reduce dose

Renal impairment start with smaller dose

Pregnancy may inhibit labour; toxicity in animal studies; manufacturer advises avoid, but risk to
fetus should be balanced against risk of uncontrolled maternal hypertension.

Contra-indications: cardiogenic shock; advanced aortic stenosis; acute porphyria (section 9.8.2).

Breast-feeding: no information available—manufacturer advises avoid.

Side-effects: dizziness, headache, peripheral oedema, flushing, palpitation, nausea; also gastrointestinal disturbances, drowsiness, insomnia, tinnitus, hypotension, rashes, dyspnoea, paraesthesia, frequency of micturition; thrombocytopenia, depression and impotence reported.

Licensed use: not licensed for use in children.

**Indication and dose**

**Hypertensive crisis**

- By continuous intravenous infusion

**Neonate** initially 500 nanograms/kg/minute, adjusted according to response; usual maintenance of 1–4 micrograms/kg/minute.

**NIFEDIPINE**

Cautions: see notes above; also poor cardiac reserve; heart failure or significantly impaired left ventricular function (heart failure deterioration observed); severe hypotension; diabetes mellitus; avoid grapefruit juice (may affect metabolism); interactions: Appendix 1 (calcium-channel blockers).

Hepatic impairment: dose reduction may be required in severe liver disease.

Pregnancy: may inhibit labour; manufacturer advises avoid before week 20, but risk to fetus should be balanced against risk of uncontrolled maternal hypertension; use only if other treatment options are not indicated or have failed.

Breast-feeding: amount too small to be harmful but manufacturer advises avoid.

Contra-indications: cardiogenic shock; advanced aortic stenosis; acute porphyria (section 9.8.2).

Side-effects: gastro-intestinal disturbance; hypotension, oedema, vasodilatation, palpitation; headache, dizziness, lethargy, asthenia; less commonly: tachycardia, hypotension, syncope, chills, nasal congestion, dyspnoea, anxiety, sleep disturbance, vertigo, migraine, paraesthesia, tremor, polyuria, dysuria, nocturia, erectile dysfunction, epistaxis, myalgia, joint swelling, visual disturbance, sweating, and hypersensitivity reactions (including angioedema, jaundice, pruritus, urticaria, and rash); rarely: anorexia, gum hyperplasia, mood disturbances, hyperglycaemia, male infertility, purpura, and photosensitivity reactions; also reported dysphagia, intestinal obstruction, intestinal ulcer, bezoar formation, gynaecomastia, agranulocytosis, and anaphylaxis.

Licensed use: not licensed for use in children.

**Indication and dose**

**Hypertension, angina in Kawasaki disease or progeria**

- By mouth

**Child 1 month–12 years** 200–300 micrograms/kg 3 times daily; max. 3 mg/kg daily or 90 mg daily.

**Child 12–18 years** 5–20 mg 3 times daily; max. 90 mg daily.

**Raynaud’s syndrome**

- By mouth

**Child 2–18 years** 2.5–10 mg 2–4 times daily; start with low doses at night and increase gradually to avoid postural hypotension.

**Persistent hyperinsulinaemic hypoglycaemia**

see also section 6.1.4.

- By mouth

**Neonates** 100–200 micrograms/kg (max. 600 micrograms/kg) 4 times daily.

**Administration** for rapid effect in hypertensive crisis or acute angina, use capsules or use liquid if 5- or 10-mg dose inappropriate; if liquid unavailable, extract contents of capsule via a syringe and use immediately—cover syringe with foil to protect contents from light; capsule contents may be diluted with water if necessary.

Modified-release tablets may be crushed—this may alter the release profile; crushed tablets should be administered within 30–60 seconds to avoid significant loss of potency of drug.

**Nifedipine** (Non-proprietary)

Capsules, nifedipine 5 mg. net price 84-cap pack = £2.84; 10 mg. 84-cap pack = £3.94.

**Dose**

Give 3 times daily.
### 1 NIFEDIPINE (continued)

Oral liquid, available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Adalat**<sup>(Bayer)</sup><br> Capsules, orange, nifedipine 5 mg, net price 90-cap pack = £6.08; 10 mg, 90-cap pack = £7.74

**Dose**<br> Give 3 times daily

**Coracten SR**<sup>(UCB Pharma)</sup><br> 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**<br> Give twice daily

**Coracten XL**<sup>(UCB Pharma)</sup><br> 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**<br> Give once daily

**Adalat LA**<sup>(Bayer)</sup><br> LA 20 tablets, m/r, f/c, pink, nifedipine 20 mg, net price 28-tab pack = £5.27. Label: 25<br> LA 30 tablets, m/r, f/c, pink, nifedipine 30 mg, net price 28-tab pack = £7.59. Label: 25<br> LA 60 tablets, m/r, f/c, pink, nifedipine 60 mg, net price 28-tab pack = £9.69. Label: 25

**Counselling**<br> Tablet membrane may pass through gastrointestinal tract unchanged, but being porous has no effect on efficacy

**Cautions**<br> 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**<sup>(Bayer)</sup><br> Retard 10 tablets, m/r, f/c, grey-pink, nifedipine 10 mg, net price 56-tab pack = £8.50. Label: 25<br> Retard 20 tablets, m/r, f/c, grey-pink, nifedipine 20 mg, net price 56-tab pack = £10.20. Label: 25

**Dose**<br> Give twice daily

**Fortipine LA 40**<sup>(Goldshield)</sup><br> Tablets, m/r, red, nifedipine 40 mg, net price 30-tab pack = £9.60. Label: 21, 25

**Dose**<br> Give 1–2 times daily

**Hypolar Retard 20**<sup>(Sandoz)</sup><br> Tablets, m/r, red, f/c, nifedipine 20 mg, net price 56-tab pack = £5.75. Label: 25

**Dose**<br> Give twice daily

**Nifedipress MR**<sup>(Dexcel)</sup><br> Tablets, m/r, pink, nifedipine 10 mg, net price 56-tab pack = £9.23; 20 mg, 56–tab pack = £10.06. Label: 25

**Dose**<br> Give twice daily

**Nifedipine MR**<sup>(Chiesi)</sup><br> 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**<br> Give twice daily

**Tensipine MR**<sup>(Genus)</sup><br> 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**<br> Give twice daily

**Valni XL**<sup>(Winthrop)</sup><br> Tablets, m/r, red, nifedipine 30 mg, net price 28-tab pack = £9.89; 60 mg, 28-tab pack = £14.71. Label: 25

**Cautions**<br> 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, inflammatory bowel disease, or ileostomy after proctocolectomy

**Dose**<br> Give once daily

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**BNFC 2009**

2.6.2 Calcium-channel blockers 139

### Cardiovascular system
NIMODIPINE

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); inter-actions: Appendix 1 (calcium-channel blockers, alcohol (infusion only))

Hepatic impairment elimination reduced in cirrhosis—monitor blood pressure; reduce oral dose by 50% in children with severe cirrhosis
Renal impairment manufacturer advises monitor renal function closely
Pregnancy manufacturer advises use only if potential benefit outweighs risks

Contra- indications acute porphyria (section 9.8.2)

Side-effects hypotension, variation in heart-rate, flushing, headache, gastro-intestinal disorders, nausea, sweating and feeling of warmth; thrombocytopenia and ileus reported

Licensed use not licensed for use in children

Indication and dose Treatment of vasospasm following subarachnoid haemorrhage under specialist advice only

- By intravenous infusion
  Child 1 month–12 years initially 15 micrograms/kg/hour (max. 500 micrograms/hour) or initially 7.5 micrograms/kg/hour if blood pressure unstable; increase after 2 hours to 30 micrograms/kg/hour (max. 2 mg/hour) if no severe decrease in blood pressure; continue for at least 5 days (max. 14 days)

Child 12–18 years initially 500 micrograms/hour (up to 1 mg/hour if body-weight over 70 kg and blood pressure stable), increase after 2 hours to 1–2 mg/hour if no severe fall in blood pressure; continue for at least 5 days (max. 14 days)

Prevention of vasospasm following subarachnoid haemorrhage
- By mouth
  Child 1 month–18 years 0.9–1.2 mg/kg (max. 60 mg) 6 times daily, starting within 4 days of haemorrhage and continued for 21 days

Administration for continuous intravenous infusion, administer undiluted via a Y-piece on a central venous catheter connected to a running infusion of Glucose 5%, Sodium Chloride 0.9%, or Compound Sodium Lactate; not to be added to an infusion container; incompatible with polyvinyl chloride giving sets or containers; protect infusion from light.

For administration by mouth, tablets may be crushed or halved but are light sensitive—administer immediately

Nimotop® (Bayef) Tablets, yellow, f/c, nimodipine 30 mg, net price 100-tab pack = £38.85

Intravenous infusion, 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, polypropylene, or glass apparatus should be used; PVC should be avoided

VERAPAMIL HYDROCHLORIDE

Cautions first-degree AV block; patients taking beta-blockers (important: see below); avoid grapefruit juice (may affect metabolism); inter-actions: 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).

Hepatic impairment oral dose may need to be reduced
Pregnancy may reduce uterine blood flow with fetal hypoxia; manufacturer advises avoid during first trimester unless absolutely necessary; may inhibit labour
Breast-feeding amount too small to be harmful

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); myalgia, arthralgia, paraesthesia, erythromelalgia; increased prolactin concentration; gynaecomastia and gingival hyperplasia after long-term treatment; after intravenous administration or high doses, hypotension, heart failure, bradycardia, heart block, and asystole; hypersensitivity reactions involving reversibly raised liver function tests

Licensed use Modified release preparation not licensed for use in children

Indication and dose

Hypertension, prophylaxis of supraventricular arrhythmias under specialist advice only
- By mouth
  Child 1–2 years 20 mg 2–3 times daily
  Child 2–18 years 40–120 mg 2–3 times daily
Treatment of supraventricular arrhythmias

- By intravenous injection over 2–3 minutes (with ECG and blood-pressure monitoring and under specialist advice)

**Child 1–18 years** 100–300 micrograms/kg (max. 5 mg) as a single dose, repeated after 30 minutes if necessary

**Administration** for intravenous injection, may be diluted with Glucose 5% or Sodium Chloride 0.9%; incompatible with solutions of pH greater than 6

**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 = £38.90
- **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

**Extemporaneous formulations available** see Extemporaneous Preparations, p. 8

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**2.6.3 Other antianginal drugs**

Classification not used in BNF for Children.

**2.6.4 Peripheral vasodilators and related drugs**

Raynaud’s syndrome consists of recurrent, long-lasting, and episodic vasospasm of the fingers and toes often associated with exposure to cold. Management includes avoidance of exposure to cold and stopping smoking (if appropriate). More severe symptoms may require vasodilator treatment, which is most often successful in primary Raynaud’s syndrome. **Nifedipine** and **diltiazem** (section 2.6.2) are useful for reducing the frequency and severity of vasospastic attacks. In very severe cases, where digital infarction is likely, intravenous infusion of the prostacyclin analogue **iloprost** may be helpful.

Vasodilator therapy is not established as being effective for **chilblains** (section 13.13).

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**ILOPROST**

**Cautions** see section 2.5.1.2

**Contra-indications** see section 2.5.1.2

**Side-effects** see section 2.5.1.2

**Licensed use** not licensed for use in children

**Indication and dose**

- **Pulmonary hypertension** section 2.5.1.2

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**Raynaud’s syndrome** see notes above

- By intravenous infusion

**Child 12–18 years** initially 30 nanograms/kg/hour, increased gradually to 60–120 nanograms/kg/hour given over 6 hours daily for 3–5 days
### 2.7 Sympathomimetics

#### 2.7.1 Inotropic sympathomimetics

The cardiac stimulants **dobutamine** and **dopamine** act on beta\(_1\) receptors in cardiac muscle and increase contractility with little effect on rate.

Dopamine has a variable, unpredictable, and dose dependent impact on vascular tone. Low dose infusion (2 micrograms/kg/minute) normally causes vasodilation, but there is little evidence that this is clinically beneficial; moderate doses increase myocardial contractility and cardiac output in older children, but in neonates moderate doses may cause a reduction in cardiac output. High doses cause vasoconstriction and increase vascular resistance, and should therefore be used with caution following cardiac surgery, or where there is co-existing neonatal pulmonary hypertension.

In neonates the response to inotropic sympathomimetics varies considerably, particularly in those born prematurely; careful dose titration and monitoring are necessary.

**Isoprenaline** injection is available from ‘special-order’ manufacturers or specialist importing companies, see p. 943.

#### 2.7.2 Vasoconstrictor sympathomimetics

**Shock**

Shock is a medical emergency associated with a high mortality. The underlying causes of shock such as haemorrhage, sepsis or myocardial insufficiency should be corrected. Additional treatment is dependent on the type of shock.

**Septic shock** is associated with severe hypovolaemia (due to vasodilation and capillary leak) which should be corrected with crystalloids or colloids (section 9.2.2). If hypotension persists despite volume replacement, **dopamine** should be started. For shock refractory to treatment with dopamine, if cardiac output is high and peripheral vascular resistance is low (warm shock), **noradrenaline** (norepinephrine) (section 2.7.2) should be added or if cardiac output is low and peripheral vascular resistance is high (cold shock), **adrenaline** (epinephrine) (section 2.7.2) should be added. Additionally, in cold shock, a vasodilator such as **milrinone** (section 2.1.2), **glyceryl trinitrate** (section 2.6.1), or **sodium nitroprusside** (on specialist advice only) (section 2.5.1.1) can be used to reduce vascular resistance.

If the shock is resistant to volume expansion and catecholamines, and there is suspected or proven adrenal insufficiency, low dose **hydrocortisone** (section 6.3.2) can be used. ACTH-stimulated plasma-cortisol concentration should be measured; however, hydrocortisone can be started without such information.

Alternatively, if the child is resistant to catecholamines, and vascular resistance is low, **vasopressin** (section 6.5.2) can be added.

**Neonatal septic shock** can be complicated by the transition from fetal to neonatal circulation. Treatment to reverse right ventricular failure, by decreasing pulmonary artery pressures, is commonly needed in neonates with fluid-refractory...
shock and persistent pulmonary hypertension of the newborn (section 2.5.1.2). Rapid administration of fluid in neonates with patent ductus arteriosus may cause left-to-right shunting and congestive heart failure induced by ventricular overload.

In **cardiogenic shock**, the aim is to improve cardiac output and to reduce the afterload on the heart. If central venous pressure is low, cautious volume expansion with a colloid or crystalloid can be used. An inotrope such as **adrenaline** (epinephrine) (section 2.7.2) or **dopamine** should be given to increase cardiac output. **Dobutamine** is a peripheral vasodilator and is an alternative if hypotension is not significant.

**Milrinone** (section 2.1.2) has both inotropic and vasodilatory effects and can be used when vascular resistance is high. Alternatively, **glyceryl trinitrate** (2.6.1) or **sodium nitroprusside** (on specialist advice only) (section 2.5.1.1) can be used to reduce vasoconstriction.

**Hypovolaemic shock** should be treated with a crystalloid or colloid solution (or whole or reconstituted blood if source of hypovolaemia is haemorrhage) and further steps to improve cardiac output and decrease vascular resistance can be taken, as in cardiogenic shock.

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.

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**DOBUTAMINE**

**Cautions** hyperthyroidism; **interactions**: Appendix 1 (sympathomimetics)

**Pregnancy** no information available

**Contra-indications** marked obstruction of cardiac ejection, such as idiopathic hypertrophic subaortic stenosis

**Side-effects** tachycardia and marked increase in systolic blood pressure indicate overdosage; phlebitis; rarely thrombocytopenia

**Licensed use** not licensed for use in children

**Indication and dose**

- **Inotropic support in low cardiac output states, after cardiac surgery, cardiomyopathies, shock**
  - **By continuous intravenous infusion**
  - **Neonate** initially 5 micrograms/kg/minute, adjusted according to response to 2–15 micrograms/kg/minute; max. 20 micrograms/kg/minute
  - **Child 1 month–18 years** initially 5 micrograms/kg/minute adjusted according to response to 2–20 micrograms/kg/minute

**Administration** for **continuous intravenous infusion**, using infusion pump, dilute to a concentration of 0.5–1 mg/mL (max. 5 mg/mL if fluid restricted) with Glucose 5% or Sodium Chloride 0.9%; infuse higher concentration solutions through central venous catheter only. Incompatible with bicarbonate and other strong alkaline solutions.

**Dobutamine** (Non-proprietary) \(^{3W}\)

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

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**DOPAMINE HYDROCHLORIDE**

**Cautions** correct hypovolaemia; hyperthyroidism; **interactions**: Appendix 1 (sympathomimetics)

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Contra-indications** tachyarrhythmia, phaeochromocytoma

**Side-effects** nausea and vomiting, peripheral vasoconstriction, hypotension, hypertension, tachycardia

**Licensed use** not licensed for use in children under 12 years

**Indication and dose**

To correct the haemodynamic imbalance due to acute hypotension, shock, cardiac failure, adjunct following cardiac surgery
  - **By continuous intravenous infusion**
  - **Neonate** initially 3 micrograms/kg/minute, adjusted according to response (max. 20 micrograms/kg/minute)

**Child 1 month–18 years** initially 5 micrograms/kg/minute adjusted according to response (max. 20 micrograms/kg/minute)

**Administration** for continuous intravenous infusion, dilute to a max. concentration of 3.2 mg/mL with Glucose 5% or Sodium Chloride 0.9%. Infuse higher concentrations through central venous catheter using a syringe pump to avoid extravas-
sation and fluid overload. Incompatible with bicarbonate and other alkaline solutions. Neonatal intensive care, dilute 30 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.3 mL/hour provides a dose of 3 micrograms/kg/minute

Dopamine (Non-proprietary)  
Sterile concentrate, dopamine hydrochloride 40 mg/mL, net price 5-mL amp = £3.98; 160 mg/mL, net price 5-mL amp = £14.75. For dilution and use as an intravenous infusion

DOPAMINE HYDROCHLORIDE (continued)  
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. For dilution and use as an intravenous infusion. Net price 5-mL vial = £5.01; 10-mL vial = £8.05

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.

Ephedrine is used to reverse hypotension caused by spinal and epidural anaesthesia.

Metaraminol is used as a vasopressor during cardiopulmonary bypass.

Phenylephrine causes peripheral vasoconstriction and increases arterial pressure.

Ephedrine, metaraminol and phenylephrine are rarely needed in children and should be used under specialist supervision.

Noradrenaline (norepinephrine) is reserved for children with low systemic vascular resistance that is unresponsive to fluid resuscitation following septic shock, spinal shock, and anaphylaxis.

Adrenaline (epinephrine) is mainly used for its inotropic action. Low doses (acting on beta receptors) cause systemic and pulmonary vasodilation, with some increase in heart rate and stroke volume and also an increase in contractility; high doses act predominantly on alpha receptors causing intense systemic vasoconstriction.

EPHEDRINE HYDROCHLORIDE

Cautions  hyperthyroidism, diabetes mellitus, hypertension, susceptibility to angle-closure glaucoma, interactions: Appendix 1 (sympathomimetics)
Renal impairment  use with caution
Pregnancy  increased fetal heart rate reported

Contra-indications  
Breast-feeding  irritability and disturbed sleep reported in breast-fed infants
Side-effects  nausea, vomiting, anorexia; tachycardia (sometimes bradycardia), arrhythmias, anginal pain, vasoconstriction with hypertension, vasodilation with hypotension, dizziness and flushing; dyspnoea; headache, anxiety, restless-ness, confusion, psychoses, insomnia, tremor; difficulty in micturition, urine retention; sweating, hypersalivation; changes in blood-glucose concentration

Indication and dose  
Reversal of hypotension from epidural and spinal anaesthesia
- By slow intravenous injection of a solution containing ephedrine hydrochloride 3 mg/mL
Child 1–12 years  500–750 micrograms/kg or 17–25 mg/m² every 3–4 minutes according to response; max. 30 mg during episode
Child 12–18 years  3–7.5 mg (max. 9 mg) repeated every 3–4 minutes according to response, max. 30 mg during episode

Nasal congestion section 12.2.2

Administration  By slow intravenous injection, via central line.

Ephedrine Hydrochloride (Non-proprietary)  
Injection, ephedrine hydrochloride 3 mg/mL, net price 10-mL amp = £2.83; 30 mg/mL, net price 1-mL amp = £1.70
METARAMINOL

Cautions  see under Noradrenaline; longer duration of action than noradrenaline (norepinephrine), see below; cirrhosis; interactions: Appendix 1 (sympathomimetics)

Hypertensive response  Metaraminol has a longer duration of action than noradrenaline, and an excessive vasopressor response may cause a prolonged rise in blood pressure

Breast-feeding  manufacturer advises caution—no information available

Contra-indications  see under Noradrenaline

Pregnancy  may reduce placental perfusion—manufacturer advises only if potential benefit outweighs risks

Side-effects  see under Noradrenaline; tachycardia; fatal ventricular arrhythmia reported in Laennec’s cirrhosis

Licensed use  Not licensed for use in children

Indication and dose

Acute hypotension

- By intravenous infusion

Child 12–18 years  15–100 mg adjusted according to response

Emergency treatment of acute hypotension

- By intravenous administration

Child 12–18 years  initially by intravenous injection 0.5–5 mg, then by intravenous infusion 15–100 mg adjusted according to response

Administration  for intravenous infusion dilute to a concentration of 30–200 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% and give through a central venous catheter

Metaraminol (Non-proprietary)  [\textregistered]

Injection, metaraminol 10 mg (as tartrate)/mL. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

NORADRENALINE/NOREPINEPHRINE

Cautions  coronary, mesenteric, or peripheral vascular thrombosis; Prinzmetal’s variant angina, hyperthyroidism, diabetes mellitus; hypoxia or hypercapnia; uncorrected hypovolaemia; extravasation at injection site may cause necrosis; interactions: Appendix 1 (sympathomimetics)

Contra-indications  hypertension (monitor blood pressure and rate of flow frequently)

Pregnancy  avoid—if possible; malformations reported following use in first trimester; fetal hypoxia and bradycardia reported in late pregnancy and labour

Side-effects  see under Noradrenaline; tachycardia; fatal ventricular arrhythmia reported in Laennec’s cirrhosis

Licensed use  not licensed for use in children

Indication and dose

Acute hypotension (septic shock) or shock secondary to excessive vasodilation (as noradrenaline)

- By continuous intravenous infusion

Child 1 month–18 years  20–100 nanograms(base)/kg/minute adjusted according to response; max. 1 microgram(base)/kg/minute

Note  1 mg of noradrenaline acid tartrate is equivalent to 500 micrograms of the base. Dose expressed as the base

Administration  for continuous intravenous infusion, dilute to a max. concentration of noradrenaline (base) 40 micrograms/mL (higher concentrations can be used if fluid-restricted) with Glucose 5% or Sodium Chloride and Glucose. Infuse through central venous catheter; discard if discoloured.

Neonatal intensive care, dilute 600 micrograms (base)/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 20 nanograms (base)/kg/minute

Noradrenaline/Norepinephrine (Non-proprietary)  [\textregistered]

Injection, noradrenaline acid tartrate 2 mg/mL (equivalent to noradrenaline base 1 mg/mL). For dilution before use. Net price 2-mL amp = £1.01, 4-mL amp = £1.50, 20-mL amp = £6.35

Excipients may include sodium metabisulphite

PHENYLEPHRINE HYDROCHLORIDE

Cautions  see under Noradrenaline; longer duration of action than noradrenaline (norepinephrine), see below; coronary disease

Hypertensive response  Phenylephrine 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; severe hyperthyroidism

Pregnancy  avoid if possible; malformations reported following use in first trimester; fetal hypoxia and bradycardia reported in late pregnancy and labour

Side-effects  see under Noradrenaline; tachycardia or reflex bradycardia

Licensed use  not licensed for use in children by intravenous infusion or injection

Indication and dose

Acute hypotension

- By subcutaneous or intramuscular injection (but intravenous injection preferred, see below)

Child 1–12 years  100 micrograms/kg every 1–2 hours as needed (max. 5 mg)
**PHENYLEPHRINE HYDROCHLORIDE (continued)**

**Child 12–18 years** 2–5 mg, followed if necessary by further doses of 1–10 mg (max. initial dose 5 mg)

- **By slow intravenous injection**
  - **Child 1–12 years** 5–20 micrograms/kg (max. 500 micrograms) repeated as necessary after at least 15 minutes
  - **Child 12–18 years** 100–500 micrograms repeated as necessary after at least 15 minutes

- **By intravenous infusion**
  - **Child 1–16 years** 100–500 nanograms/kg/minute, adjusted according to response
  - **Child 16–18 years** initially up to 180 micrograms/minute reduced to 30–60 micrograms/minute according to response

**Administration** for **intravenous injection** dilute to a concentration of 1 mg/mL with Water for Injections and administer slowly.

For **intravenous infusion** dilute to a concentration of 20 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% and administer as a continuous infusion via a central venous catheter using a controlled infusion device.

**Phenylephrine** (Sovereign) **Injection**, phenylephrine hydrochloride 10 mg/mL (1%), net price 1-mL amp = £5.50

**ADRENALINE/EPINEPHRINE**

**Cautions** diabetes mellitus, hyperthyroidism, hypertension, arrhythmias, cerebrovascular disease, avoid extravasation, monitor urine output, limb perfusion (especially at higher doses), central venous pressures and ECG; **interactions**: Appendix 1 (sympathomimetics)

**Side-effects** nausea, vomiting, sweating, tachycardia, dyspnoea, anxiety, tremor, headache, weakness, dizziness and hyperglycaemia, cold extremities; in overdose hypertension, arrhythmias, cerebral haemorrhage, pulmonary oedema

**Indication and dose**

**Acute hypotension**

- **By continuous intravenous infusion**
  - **Neonate** initially 100 nanograms/kg/minute adjusted according to response; higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension
  - **Child 1 month–18 years** initially 100 nanograms/kg/minute adjusted according to response; higher doses up to 1.5 micrograms/kg/minute have been used in acute hypotension

**Anaphylaxis** section 3.4.3

**Administration** for **continuous intravenous infusion** dilute with Glucose 5% or Sodium Chloride 0.9% and give through a central venous catheter. Incompatible with bicarbonate and alkaline solutions.

**Neonatal intensive care**, dilute 3 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 100 nanograms/kg/minute

**Note** These infusions are usually made up with adrenaline 1 in 1000 (1 mg/mL) solution; this concentration of adrenaline is not licensed for intravenous administration

**Preparations** Section 3.4.3

**2.7.3 Cardiopulmonary resuscitation**

The algorithms for cardiopulmonary resuscitation (see inside back cover) reflect the recommendations of the Resuscitation Council (UK); they cover paediatric basic life support, paediatric advanced life support, and newborn life support. The guidelines are available at www.resus.org.uk.

**Paediatric advanced life support** Cardiopulmonary (cardiac) arrest in children is rare and frequently represents the terminal event of progressive shock or respiratory failure.

During cardiopulmonary arrest in children without intravenous access, the intraosseous route is chosen because it provides rapid and effective response; if circulatory access cannot be gained, the endotracheal tube can be used. When the endotracheal route is used ten times the intravenous dose should be used; the drug should be injected quickly down a narrow bore suction catheter beyond the tracheal end of the tube and then flushed in with 1 or 2 mL of sodium chloride 0.9%. The endotracheal route is useful for lipid-soluble drugs, including lidocaine, adrenaline, atropine, and naloxone. Drugs that are not lipid-soluble (e.g. sodium bicarbonate and calcium chloride) should **not** be administered by this route because they will injure the airways.

For the management of acute anaphylaxis see section 3.4.3.
2.8 Anticoagulants and protamine

2.8.1 Parenteral anticoagulants

Heparin

Heparin initiates anticoagulation rapidly but has a short duration of action. It is now often referred to as being standard or unfractionated heparin to distinguish it from the low molecular weight heparins (see p. 149), which have a longer duration of action. For children at high risk of bleeding, heparin is more suitable than low molecular weight heparin because its effect can be terminated rapidly by stopping the infusion.

Heparin is used in both the treatment and prophylaxis of thromboembolic disease; however, it is mainly used to prevent further clotting rather than to lyse existing clots—surgery or a thrombolytic drug may be necessary if a thrombus obstructs major vessels.

Treatment

For the initial treatment of thrombotic episodes heparin is given as an intravenous loading dose, followed by continuous intravenous infusion (using an infusion pump) or by intermittent subcutaneous injection; the use of intermittent intravenous injection is no longer recommended. Alternatively, a low molecular weight heparin may be given for initial treatment. 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 of coagulation activity, preferably on a daily basis, involves determination of the activated partial thromboplastin time (APTT) or of the anti-Factor Xa concentration. Local guidelines on recommended APTT for neonates and children should be followed.

Prophylaxis

Low-dose heparin by subcutaneous injection is used to prevent thrombotic episodes in 'high-risk' patients; laboratory monitoring of APTT or anti-Factor Xa concentration is also required in prophylactic regimens in children. Aspirin (section 2.9) and warfarin (section 2.8.2) can also be used for prophylaxis.

Pregnancy

Heparins are used for the management of thromboembolic disease 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

Cautions see notes above; concomitant use of drugs that increase risk of bleeding; 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 danaparoid, should be given. Ensure platelet counts return to normal range in those who require warfarin.

Hyperkalaemia Inhibition of aldosterone secretion by heparin (including low molecular weight heparins) can result in hyperkalaemia; patients with diabetes mellitus, chronic renal failure, acidosis, raised plasma potassium, or those taking potassium-sparing drugs seem more susceptible. The risk appears to increase with duration of therapy and the CSM has recommended that plasma-potassium concentration should be measured in children at risk of hyperkalaemia before starting heparin and monitored regularly thereafter, particularly if heparin is to be continued for longer than 7 days.

Hepatic impairment risk of bleeding increased—possibly reduce dose in severe impairment

Renal impairment risk of bleeding increased in severe impairment—dose may need to be reduced

Pregnancy does not cross the placenta; maternal osteoporosis reported after prolonged use; multi-dose vials may contain benzyl alcohol—some manufacturers advise avoid

Breast-feeding not excreted in milk due to high molecular weight

Contra-indications haemophilia and other 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 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)

Licensed use Some preparations licensed for use in children

Indication and dose

Maintenance of neonatal umbilical arterial catheter

- By intravenous administration

Neonate initially 75 units/kg (50 units/kg if under 35 weeks post-menstrual age) by intravenous injection, then by continuous intravenous infusion 25 units/kg/hour, adjusted according to APTT

Child 1 month–1 year initially 75 units/kg by intravenous injection, then by continuous intravenous infusion 25 units/kg/hour, adjusted according to APTT

Child 1–18 years initially 75 units/kg by intravenous injection, then by continuous intravenous infusion 20 units/kg/hour, adjusted according to APTT

- By subcutaneous injection

Child 1 month–18 years 250 units/kg twice daily, adjusted according to APTT

Prophylaxis of thrombotic episodes

- By subcutaneous injection

Child 1 month–18 years 100 units/kg (max. 5000 units) twice daily, adjusted according to APTT

Prevention of clotting in extracorporeal circuits consult product literature

Administration for continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%. Maintenance of neonatal umbilical arterial catheter, dilute 50 units to a final volume of 50 mL with Sodium Chloride 0.45% or use ready-made bag containing 500 units in 500 mL Sodium Chloride 0.9%; infuse at 0.5 mL/hour.

Neonatal intensive care (treatment of thrombosis), dilute 1250 units/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 1 mL/hour provides a dose of 25 units/kg/hour.

Heparin Sodium (Non-proprietary) (Heparin)

Injection, heparin sodium 1000 units/mL, net price 1-mL amp = £7.5, 5-mL amp = £39.5, 5-mL vial = £92, 10-mL amp = £16.5, 20-mL amp = £32.63, 5000 units/mL, 1-mL amp = £7.2, 5-mL amp = £18.87, 5-mL vial = £20.99; 25 000 units/mL, 0.2-mL amp = £2.92, 1-mL amp = £19.00, 5-mL vial = £33.68 Exipients may include benzyl alcohol (avoid in neonates, see Exipients, p. 3)

Heparin Calcium (Non-proprietary) (Heparin)

Injection, heparin calcium 25 000 units/mL, net price 0.2-mL amp = £7.3p

By continuous injection

Child 1 month–1 year initially 75 units/kg by intravenous injection, then by continuous intravenous infusion 25 units/kg/hour, adjusted according to APTT
Low molecular weight heparins

Dalteparin, enoxaparin, and tinzaparin are low molecular weight heparins used for treatment and prophylaxis of thrombotic episodes in children. Their duration of action is longer than that of unfractionated heparin and in adults and older children once-daily subcutaneous dosage is sometimes possible; however, younger children require relatively higher doses (possibly due to larger volume of distribution, altered heparin pharmacokinetics, or lower plasma concentrations of antithrombin) and twice daily dosage is sometimes necessary. Low molecular weight heparins are convenient to use, especially in children with poor venous access. Routine monitoring of anti-Factor Xa activity is not usually required except in neonates; monitoring may also be necessary in severely ill children and those with renal or hepatic impairment.

Haemorrhage See under Heparin.

Hepatic impairment Reduce dose in severe hepatic impairment—risk of bleeding may be increased.

Renal impairment See under individual drug.

Pregnancy Not known to be harmful, low molecular weight heparins do not cross the placenta.

Breast-feeding Due to the relatively high molecular weight of these drugs and inactivation in the gastro-intestinal tract, passage into breast-milk and absorption by the nursing infant are likely to be negligible; however manufacturers advise avoid.

DALTEPARIN SODIUM

Cautions see under Heparin and notes above

Hepatic impairment see notes above

Renal impairment risk of bleeding may be increased—dose reduction and monitoring of anti-factor Xa may be required; use of unfractionated heparin may be preferable

Pregnancy see notes above

Breast-feeding see notes above

Contra-indications see under Heparin

Side-effects see under Heparin

Licensed use not licensed for use in children

Indication and dose

Treatment of thrombotic episodes

• By subcutaneous injection

Neonate 100 units/kg twice daily

Child 1 month–12 years 100 units/kg twice daily

Child 12–18 years 200 units/kg (max. 18 000 units) once daily, if increased risk of bleeding reduced to 100 units/kg twice daily

Prophylaxis of thrombotic episodes

• By subcutaneous injection

Neonate 100 units/kg once daily

Child 1 month–12 years 100 units/kg once daily

Child 12–18 years 2500–5000 units once daily

Fragmin® (Pharmacia) (i.v.)

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

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

Injection (graduated syringe), dalteparin sodium 10 000 units/mL, net price 1-mL (10 000-unit) syringe = £5.65

ENOXAPARIN SODIUM

Cautions see under Heparin and notes above

Hepatic impairment see notes above

Renal impairment risk of bleeding may be increased; reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; mon-
## Enoxaparin Sodium

### Treatment of thrombotic episodes
- **By subcutaneous injection**
  - **Neonate**: 1.5–2 mg/kg twice daily
  - **Child 1–2 months**: 1.5 mg/kg twice daily
  - **Child 2 months–18 years**: 1 mg/kg twice daily

### Treatment of venous thromboembolism in pregnancy
- **By subcutaneous injection**
  - **Child 12–18 years**: 175 units/kg once daily (based on early pregnancy body-weight)

### Prophylaxis of thrombotic episodes
- **By subcutaneous injection**
  - **Neonate**: 750 micrograms/kg twice daily
  - **Child 1–2 months**: 750 micrograms/kg twice daily
  - **Child 2 months–18 years**: 500 micrograms/kg twice daily; max. 40 mg daily

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## Tinzaparin Sodium

### Cautions
- see under Heparin and notes above

### Renal impairment
- risk of bleeding may be increased; dose reduction and monitoring of anti-factor Xa may be required; unfractionated heparin may be preferable

### Pregnancy
- see notes above; also vials contain benzyl alcohol—manufacturer advises avoid

### Contra-indications
- see under Heparin

### Licensed use
- not licensed for use in children

### Indication and dose

#### Treatment of thrombotic episodes
- **By subcutaneous injection**
  - **Neonate**: 50 units/kg once daily
  - **Child 1 month–18 years**: 50 units/kg once daily

#### Treatment of venous thromboembolism in pregnancy
- **By subcutaneous injection**
  - **Child 12–18 years**: 175 units/kg once daily (based on early pregnancy body-weight)

#### Prophylaxis of thrombotic episodes
- **By subcutaneous injection**
  - **Child 1 month–18 years**: 50 units/kg once daily

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## Heparinoids

### Danaparoid

#### Cautions
- recent bleeding or risk of bleeding; concomitant use of drugs that increase risk of bleeding; antibodies to heparins (risk of antibody-induced thrombocytopenia)

#### Hepatic impairment
- use with caution in moderate impairment (increased risk of bleeding); avoid in severe impairment unless no alternative

#### Renal impairment
- use with caution in moderate impairment; increased risk of bleeding (monitoring of anti-factor Xa may be required; use of unfractionated heparin may be preferable)

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## Danaparoid Sodium

### Cautions
- recent bleeding or risk of bleeding; concomitant use of drugs that increase risk of bleeding; antibodies to heparins (risk of antibody-induced thrombocytopenia)

### Hepatic impairment
- use with caution in moderate impairment (increased risk of bleeding); avoid in severe impairment unless no alternative

### Renal impairment
- use with caution in moderate impairment; increased risk of bleeding (monitoring of anti-factor Xa may be required; use of unfractionated heparin may be preferable)
anti-Factor Xa activity); avoid in severe impairment unless child has heparin-induced thrombocytopenia and no alternative available

**Pregnancy** limited information available but not known to be harmful—manufacturer advises avoid

**Breast-feeding** amount probably too small to be harmful but manufacturer advises avoid

**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** haemorrhage; hypersensitivity reactions (including rash)

**Licensed use** not licensed for use in children

### Indication and dose

**Thromboembolic disease in children with history of heparin-induced thrombocytopenia**

- **By intravenous administration**

**Neonate** initially 30 units/kg by intravenous injection then by continuous intravenous infusion 1.2–2 units/kg/hour adjusted according to coagulation activity

**Child 1 month–16 years** initially 30 units/kg (max. 1250 units if bodyweight under 55 kg, 2500 units if over 55 kg) by intravenous injection then by continuous intravenous infusion 1.2–2 units/kg/hour adjusted according to coagulation activity

**Child 16–18 years** initially 2500 units (1250 units if bodyweight under 55 kg, 3750 units if over 90 kg) by intravenous injection then by continuous intravenous infusion 400 units/hour for 2 hours, then 300 units/hour for 2 hours, then 200 units/hour for 5 days adjusted according to coagulation activity

### Administration

**for intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%**

**Orgaran** (Organon) Injection, danaparoid sodium 1250 units/mL, net price 0.6-mL amp (750 units) = £29.80

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### Heparin flushes

The use of heparin flushes should be kept to a minimum. For maintaining patency of peripheral venous catheters, sodium chloride 0.9% injection 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) Solution, heparin sodium 10 units/mL, net price 5-mL amp = 25p; 100 units/mL, 2-mL amp = 28p

**Excipients** may include benzyl alcohol (avoid in neonates, see Excipients, p. 3)

### Epoprostenol

Epoprostenol (prostacyclin) can be given to inhibit platelet aggregation during renal dialysis either alone or with heparin. For its use in pulmonary hypertension, see section 2.5.1.2. It is a potent vasodilator and therefore its side-effects include flushing, headache, and hypotension.

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### 2.8.2 Oral anticoagulants

Oral anticoagulants 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** Warfarin is the drug of choice for the treatment of systemic thromboembolism in children (not neonates) after initial heparinisation. It may also be used occasionally for the treatment of intravascular or intracardiac thrombi. Warfarin is used prophylactically in those with chronic atrial fibrillation, dilated cardiomyopathy, certain forms of reconstructive heart surgery, mechanical prosthetic heart valves, and some forms of hereditary thrombophilia (e.g. homozygous protein C deficiency).

Warfarin or a low molecular weight heparin (section 2.8.1) is usually preferred for the prophylaxis of venous thromboembolism in children undergoing surgery; alternatively warfarin can be continued in selected children currently taking warfarin and who are at a 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.

An induction dose is usually given over 4 days (see under Warfarin Sodium below). The subsequent maintenance dose depends on the prothrombin time, reported as INR (international normalised ratio) and should be taken at the same time each day. The following indications and target INRs for adults take into account recommendations of the British Society for Haematology:

- 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 2);
- 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) 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 are based on the result of the INR and whether there is major or minor bleeding; the recommendations (which take into account the recommendations of the British Society for Haematology) apply to adults taking warfarin:

- Major bleeding—stop warfarin; give phytonadione (vitamin K,) 5–10 mg by slow intravenous injection; give prothrombin complex concentrate (factors II, VII, IX, and X) 30–50 units/kg or (if no concentrate available) fresh frozen plasma 15 mL/kg
- 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
- INR 6.0–8.0, no bleeding or minor bleeding—stop warfarin, restart when INR < 5.0
- INR < 6.0 but more than 0.5 units above target value—reduce dose or stop warfarin, restart when INR < 5.0
- Unexpected bleeding at therapeutic levels—always investigate possibility of underlying cause e.g. unsuspected renal or gastro-intestinal tract pathology

Pregnancy  Oral anticoagulants are teratogenic and should not be given in the first trimester of pregnancy. Adolescents at risk of pregnancy should be warned of this danger since stopping warfarin before the sixth week of gestation largely avoids the risk of fetal abnormality. 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, oral anticoagulants should be avoided in pregnancy, especially in the first and third trimesters. Difficult decisions may have to be made, particularly in those with prosthetic heart valves

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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 child’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.
or with a history of recurrent venous thrombosis, pulmonary embolism, or atrial fibrillation.

Babies of mothers taking warfarin at the time of delivery need to be offered immediate prophylaxis with at least 100 micrograms/kg of intramuscular phytonadione (vitamin K₁), see section 9.6.6.

**Dietary differences** Infant formula is supplemented with vitamin K, which makes formula-fed infants resistant to warfarin; they may therefore need higher doses. In contrast breast milk contains low concentrations of vitamin K making breast-fed infants more sensitive to warfarin.

**Treatment booklets** Anticoagulant treatment booklets should be issued to children or their carers, 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.
Tel: 0845 610 1112
nhsforms@spsl.uk.com

These booklets include advice for children or their carers 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 are also available at www.npsa.nhs.uk/nrls/alerts-and-directives/alerts/anticoagulant.

### WARFARIN SODIUM

**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); **Interactions:** Appendix 1 (warfarin)

**Hepatic impairment** avoid in severe impairment, especially if prothrombin time already prolonged

**Renal impairment** use with caution (avoid in severe impairment)

**Breast-feeding** not excreted in breast milk; no evidence of harm

**Contra-indications** peptic ulcer, severe hypertension

**Pregnancy** see notes above

**Side-effects** haemorrhage—see notes above; other side-effects reported include hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haematocrit, ‘purple toes’, skin necrosis, jaundice, hepatic dysfunction; also nausea, vomiting, and pancreatitis

**Licensed use** not licensed for use in children

#### Indication and dose

**Treatment and prophylaxis of thrombotic episodes**

- **By mouth**

  **Neonate (under specialist advice)** 200 micrograms/kg as a single dose on first day, reduced to 100 micrograms/kg once daily for following 3 days (but if INR still below 1.4 use 200 micrograms/kg once daily, or if INR above 3 use 50 micrograms/kg once daily especially if bottle fed—see notes above)

  **Child 1 month–18 years** 200 micrograms/kg (max. 10 mg) as a single dose on first day, reduced to 100 micrograms/kg (max. 5 mg) once daily for following 3 days (but if INR still below 1.4 use 200 micrograms/kg (max. 10 mg) once daily, or if INR above 3 use 50 micrograms/kg (max. 2.5 mg) once daily, or if INR above 3.5 omit dose); then adjusted according to INR, usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily especially if bottle fed—see notes above)

**Note** Induction dose may need to be altered according to condition (e.g. abnormal liver function tests, cardiac failure), concomitant interacting drugs, and if baseline INR above 1.3

### 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.
2.9 Antiplatelet drugs

Antiplatelet drugs decrease platelet aggregation and may inhibit thrombus formation in the arterial circulation, where anticoagulants have little effect.

Aspirin has limited use in children because it has been associated with Reye’s syndrome. The CSM has advised that aspirin-containing preparations should not be given to children and adolescents under 16 years, unless specifically indicated, such as for Kawasaki syndrome (see below), for prophylaxis of clot formation after cardiac surgery, or for prophylaxis of stroke in children at high risk.

If aspirin causes dyspepsia, or if the child is at a high risk of gastro-intestinal bleeding, a proton pump inhibitor (section 1.3.5) or a H₂-receptor antagonist (section 1.3.1) can be added.

Dipyridamole is also used as an antiplatelet drug to prevent clot formation after cardiac surgery and may be used with specialist advice for treatment of persistent coronary artery aneurysms in Kawasaki syndrome.

Kawasaki syndrome Initial treatment is with high-dose aspirin and a single dose of intravenous normal immunoglobulin (p. 757); this combination has an additive anti-inflammatory effect resulting in faster resolution of fever and a decreased incidence of coronary artery complications. After the acute phase, when the patient is afebrile, aspirin is continued at a lower dose to prevent coronary artery abnormalities.

2.9.1 Antiplatelet drugs—Aspirin

Aspirin (antiplatelet) (Acetylsalicylic Acid)

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); interactions: Appendix 1 (aspirin)

Hepatic impairment avoid in severe impairment—increased risk of gastro-intestinal bleeding

Renal impairment use with caution (avoid in severe impairment); sodium and water retention; deterioration in renal function; increased risk of gastro-intestinal bleeding

Pregnancy use with caution during third trimester; impaired platelet function and risk of
**ASPIRIN (antiplatelet) (continued)**

- 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

**Contra-indications** children under 16 years (risk of Reye’s syndrome) unless for indications below; active peptic ulceration; haemophilia and other bleeding disorders

**Hypersensitivity** Aspirin and other NSAIDs are contra-indicated in 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

**Breast-feeding** avoid—possible risk of Reye's syndrome; regular use of high doses could impair platelet function and produce hypoprothrombinaemia in infant if neonatal vitamin K stores low

**Side-effects** bronchospasm; gastro-intestinal haemorrhage (occasionally major), also other haemorrhage (e.g. subconjunctival)

**Licensed use** Not licensed for use in children under 16 years

### Indication and dose

**Kawasaki syndrome**

- **By mouth**
  - **Neonate** initially 8 mg/kg 4 times daily for 2 weeks or until afebrile, followed by 5 mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice
  - **Child 1 month–12 years** initially 7.5–12.5 mg/kg 4 times daily for 2 weeks or until afebrile, then 2.5–mg/kg once daily for 6–8 weeks; if no evidence of coronary lesions after 8 weeks, discontinue treatment or seek expert advice

**Prevention of thrombus formation after cardiac surgery**

- **By mouth**
  - **Neonate** 1–5 mg/kg once daily
  - **Child 1 month–12 years** 1–5 mg/kg (usual max. 75 mg) once daily
  - **Child 12–18 years** 75 mg once daily

### Aspirin (Non-proprietary)

- **Dispersible tablets**, aspirin 75 mg, net price 28 = £4.93
- **Tablets**, e/c, aspirin 75 mg, net price 28-tab pack = £4.74

**Suppositories**, available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

- **Angettes 75** (Bristol-Myers Squibb)
  - Tablets, aspirin 75 mg, net price 28-tab pack = 94p.
  - **Caprin** (Pinewood)
    - Tablets, e/c, pink, aspirin 75 mg, net price 28-tab pack = £1.55
  - **Nu-Seals** (Alliance)
    - Tablets, e/c, aspirin 75 mg, net price 56-tab pack = £2.60

**DIPYRIDAMOLE**

**Cautions** aortic stenosis, left ventricular outflow obstruction, heart failure; may exacerbate migraine; hypotension; myasthenia gravis (risk of exacerbation); concomitant use of drugs that increase risk of bleeding; coagulation disorders; interactions: Appendix 1 (dipyridamole)

**Pregnancy** not known to be harmful

**Breast-feeding** small amount present in milk—manufacturer advises caution

**Side-effects** gastro-intestinal effects, dizziness, myalgia, throbbing headache, hypotension, hot flushes and tachycardia; hypersensitivity reactions such as rash, urticaria, severe bronchospasm and angioedema; increased bleeding during or after surgery; thrombocytopenia reported

**Licensed use** Not licensed for use in children

### Indication and dose

**Kawasaki syndrome**

- **By mouth**
  - **Child 1 month–12 years** 1 mg/kg 3 times daily
2.10 Myocardial infarction and fibrinolysis

2.10.1 Management of myocardial infarction

Classification not used in BNF for Children.

2.10.2 Fibrinolytic drugs

Fibrinolytic drugs act as thrombolytics by activating plasminogen to form plasmin, which degrades fibrin and so breaks up thrombi.

**Alteplase, streptokinase, and urokinase** are used in children to dissolve intra-vascular thrombi and unblock occluded arteriovenous shunts, catheters, and indwelling central lines blocked with fibrin clots. Treatment should be started as soon as possible after a clot has formed and discontinued once a pulse in the affected limb is detected, or the shunt or catheter unblocked.

The safety and efficacy of treatment remains uncertain, especially in neonates. A fibrinolytic drug is probably only appropriate where arterial occlusion threatens ischaemic damage; an anticoagulant may stop the clot getting bigger. Alteplase is the preferred fibrinolytic in children and neonates; there is less risk of adverse effects including allergic reactions.

**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 (see individual drugs), hypertension, other 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.

**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, embolic or disseminated malignancy, previous allergic reactions to streptokinase, previous anaphylaxis to streptokinase, and oesophageal varices; also in the case of streptokinase, previous allergic reactions to streptokinase.

Prolonged persistence of antibodies to streptokinase can reduce the effectiveness of subsequent treatment; therefore, streptokinase should not be used again beyond 4 days of first administration. Streptokinase should also be avoided in children who have had streptococcal infection in the last 12 months.

**Side-effects**  Side-effects of thrombolytics are mainly bleeding, nausea, and vomiting. Reperfusion can 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). Thrombolytics can cause allergic reactions (including rash, flushing 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.

**ALTEPLASE**  (rt-PA, tissue-type plasminogen activator)

**Cautions**  see notes above; in children who have had an acute stroke, monitor for intracranial haemorrhage and monitor blood pressure

**Hepatic impairment**  avoid in severe impairment—increased risk of bleeding

**Pregnancy**  no evidence of teratogenicity; possibility of premature separation of placenta in first 18 weeks; risk of maternal haemorrhage throughout pregnancy and during post-partum use; theoretical risk of fetal haemorrhage throughout pregnancy
Contra-indications see notes above; in children who have had an acute stroke, convulsion accompanying stroke, severe stroke, history of stroke in children with diabetes, stroke in last 3 months, hypoglycaemia, hyperglycaemia

Side-effects see notes above; also risk of cerebral bleeding increased in acute stroke

Licensed use Not licensed for use in children

Indication and dose

Intravascular thrombosis doses may vary—consult local guidelines

- By intravenous infusion

Neonate 100–500 micrograms/kg/hour for 3–6 hours; use ultrasound assessment to monitor effect before considering a second course of treatment

Child 1 month–18 years 100–500 micrograms/kg/hour for 3–6 hours; max. 100 mg total daily dose; use ultrasound assessment to monitor effect before considering a second course of treatment

Administration dissolve in Water for Injections to a concentration of 1 mg/mL or 2 mg/mL and infuse intravenously; alternatively dilute further in Sodium Chloride 0.9% to a concentration of not less than 200 micrograms/mL; not to be diluted in Glucose

Occluded arteriovenous shunts, catheters, and indwelling central lines

- By injection direct into catheter or central line

Child 1 month–18 years using 1 mg/mL solution, instill up to 2 mL according to dead-space of catheter or central line; aspirate lysate after 4 hours; flush with sodium chloride 0.9% injection

STREPTOKINASE

Cautions see notes above

Hepatic impairment avoid in severe hepatic impairment—increased risk of bleeding

Pregnancy possibility of premature separation of placenta in first 18 weeks; risk of maternal haemorrhage throughout pregnancy and during post-partum use; theoretical risk of fetal haemorrhage throughout pregnancy

Contra-indications see notes above

Side-effects see notes above

Licensed use Licensed for use in children for intravascular dissolution of thrombi and emboli

Indication and dose

Intravascular thrombosis

- By intravenous infusion

Child 1 month–12 years initially 2500–4000 units/kg over 30 minutes, followed by continuous intravenous infusion of 500–1000 units/kg/hour for up to 3 days until reperfusion occurs

Child 12–18 years initially 250 000 units over 30 minutes, followed by continuous intravenous infusion of 100 000 units/hour for up to 3 days until reperfusion occurs

Administration May be diluted with Glucose 5% or Sodium Chloride 0.9% after reconstitution. Monitor fibrinogen concentration closely; if fibrinogen concentration less than 1g/litre, stop streptokinase infusion and start heparin; restart streptokinase once fibrinogen concentration reaches 1g/litre

Streptase® (CSL Behring) Injection, 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)

UROKINASE

Cautions see notes above

Hepatic impairment avoid in severe hepatic impairment—increased risk of bleeding

Pregnancy possibility of premature separation of placenta; risk of maternal haemorrhage throughout pregnancy and during post-partum use; theoretical risk of fetal haemorrhage throughout pregnancy

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children

Indication and dose

Intravascular thrombosis

- By intravenous injection and infusion

Neonate 4400 units/kg as a single dose by intravenous injection in 15 mL diluent, followed by 4400 units/kg/hour by intravenous infusion for 6–12 hours, adjusted according to response

Child 1 month–18 years 4400 units/kg as a single dose by intravenous injection in 15 mL diluent, followed by 4400 units/kg/hour by intravenous infusion for 6–12 hours, adjusted according to response

Administration May be diluted, after reconstitution, with Sodium Chloride 0.9%

Occluded arteriovenous shunts, catheters, and indwelling central lines

- By injection directly into catheter or central line

Neonate 5000–10 000 units in sodium chloride 0.9% to fill catheter dead-space only; leave for 2–4 hours then aspirate the lysate; flush with heparinised saline
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 treat bleeding associated with excessive fibrinolysis (e.g. in prostatectomy, bladder surgery, in dental extraction in children with haemophilia, and in traumatic hyphaema) and in the management of menorrhagia. Tranexamic acid may also be used in hereditary angioedema, epistaxis, and thrombolytic overdose.

Desmopressin (section 6.5.2) is used in the management of mild to moderate haemophilia and von Willebrands’ disease. It is also used for testing fibrinolytic response.

TRANEXAMIC ACID

Cautions
massive haematuria (avoid if risk of ureteric obstruction); not for use in disseminated intravascular coagulation; irregular menstrual bleeding (establish cause before initiating therapy); regular liver function tests in long-term treatment of hereditary angioedema

Renal impairment
manufacturer advises reduce dose in mild to moderate renal impairment; avoid in severe renal impairment

Pregnancy
no evidence of teratogenicity in animal studies; manufacturer advises use only if potential benefit outweighs risk—crosses the placenta

Breast-feeding
small amount present in milk—antifibrinolytic effect in infant unlikely

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

Licensed use
Licensed for inhibition of fibrinolysis

Indication and dose

Inhibition of fibrinolysis, hereditary angioedema (section 3.4.3)

- By mouth
  Child 1 month–18 years 15–25 mg/kg (max. 1.5 g) 2–3 times daily

- By intravenous injection over at least 10 minutes
  Child 1 month–18 years 10 mg/kg (max. 1 g) 2–3 times daily

- By continuous intravenous infusion
  Child 1 month–18 years 45 mg/kg over 24 hours

Prevention of excessive bleeding after dental procedures (e.g. in haemophilia)

- By intravenous injection (pre-operatively) and by mouth (post-operatively)
  Child 6–18 years 10 mg/kg (max. 1.5 g) by intravenous injection pre-operatively, followed by 15–25 mg/kg (max. 1.5 g) 2–3 times daily by mouth for up to 8 days

- Mouthwash 5% solution (specialist use only)
  Child 6–18 years rinse mouth with 5–10 mL 4 times daily for 2 days; not to be swallowed

Menorrhagia

- By mouth
  Child 12–18 years 1 g 3–4 times daily for up to 4 days; max. 4 g daily (initiate when menstruation has started)

Administration

For intravenous administration, dilute with Glucose 5% or Sodium Chloride 0.9%

Tranexamic acid (Non-proprietary)

Tablets, tranexamic acid 500 mg, net price 60-tab pack = £7.80

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

Blood products

Classification not used in BNF for Children.
Atherosclerosis begins in childhood and raised serum-cholesterol in children is associated with cardiovascular disease in adulthood. Lowering the cholesterol, without hindering growth and development in children and adolescents, should reduce the risk of cardiovascular disease in later life.

The risk factors for developing cardiovascular disease include raised serum cholesterol concentration, smoking, hypertension, impaired glucose tolerance, male sex, ethnicity, obesity, triglyceride concentration, chronic kidney disease, and a family history of cardiovascular disease. In children with heterozygous familial hypercholesterolaemia, the family history of cardiovascular disease is most important when considering initiation of a lipid-regulating drug. Homozygous familial hypercholesterolaemia is rare and requires specialist management.

Secondary causes of hypercholesterolaemia should be addressed, these include diet, diabetes mellitus, hypothyroidism (see below), nephrotic syndrome, obstructive biliary disease, glycogen storage disease, and drugs such as corticosteroids.

Treatment Dietary intervention is the mainstay of treatment of hypercholesterolaemia in children. The aim is to reduce the risk of atherosclerosis whilst ensuring adequate growth and development. Advice should also be given on lifestyle measures (e.g. increased exercise, and if appropriate, stopping smoking). Blood pressure should also be reduced if required (section 2.5).

When 6–12 months of dietary intervention alone has failed, drug therapy is indicated in children 10 years and over (rarely necessary in younger children) who are at a high risk of developing cardiovascular disease. Dietary therapy and lifestyle measures should continue even if lipid-regulating drugs have been introduced.

Lipid-regulating drugs are considered if dietary intervention fails to reduce total serum-cholesterol adequately; experience of their use in children is limited and they should be initiated on specialist advice.

Statins (atorvastatin, pravastatin, and simvastatin) are generally well tolerated; atorvastatin and simvastatin are considered to be the drugs of first choice. Bile acid sequestrants are also available but tolerability of and compliance with these drugs is poor, and their use is declining.

Evidence for the use of a fibrate (bezafibrate or fenofibrate) in children is limited; fibrates should be considered only if dietary intervention and treatment with a statin and a bile acid sequestrant is unsuccessful or contra-indicated.

In hypertriglyceridaemia which cannot be controlled by very strict diet, omega-3 fatty acid compounds can be considered.

Hypothyroidism Children with hypothyroidism should receive adequate thyroid replacement therapy before their requirement for lipid-regulating treatment is assessed because correction of hypothyroidism itself may resolve the lipid abnormality. Untreated hypothyroidism increases the risk of myositis with lipid-regulating drugs.

CSM advice (muscle effects)
The CSM has advised that rhabdomyolysis associated with lipid-regulating drugs such as the fibrates and statins appears to be rare (approx. 1 case in every 100,000 treatment years) but may be increased in those with renal impairment and possibly in those with hypothyroidism (see also notes above). Concomitant treatment with drugs that increase plasma-statins concentration increase the risk of muscle toxicity; concomitant treatment with a fibrate and a statin may also be associated with an increased risk of serious muscle toxicity.

Statins The statins (atorvastatin, pravastatin, and simvastatin) competitively inhibit 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, an enzyme involved in cholesterol synthesis, especially in the liver. They are more effective...
than other classes of drugs in lowering LDL-cholesterol but less effective than the fibrates in reducing triglycerides. Statins also increase concentrations of HDL-cholesterol. Statins reduce cardiovascular disease events and total mortality in adults, irrespective of the initial cholesterol concentration.

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. 159). Liver-function tests should be carried out before and within 1–3 months of starting treatment and thereafter at intervals of 6 months for 1 year, unless indicated sooner by signs or symptoms suggestive of hepatotoxicity. Treatment should be discontinued if serum transaminase concentration rises to, and persists at, 3 times the upper limit of the reference range. Statins should be used with caution in those with risk factors for myopathy or rhabdomyolysis; children or their carers should be advised to report unexplained muscle pain (see Muscle Effects below). Statins should be avoided in acute porphyria (section 9.8.2). Interactions: Appendix 1 (statins)

Contra-indications Statins are contra-indicated in active liver disease (or persistently abnormal liver function tests), in pregnancy (adequate contraception required during treatment and for 1 month afterwards), and during breast-feeding.

Side-effects Statins can cause various muscular side-effects, including myositis, which can lead to rhabdomyolysis. Muscular effects are rare but often significant (see below and CSM advice (Muscle effects), p. 159). Statins can cause gastrointestinal disturbances, and very rarely pancreatitis. They can also cause altered liver function tests, and rarely hepatitis and jaundice; hepatic failure has been reported very rarely. Other side-effects include sleep disturbance, headache, dizziness, depression, paraesthesia, hypoesthesia, asthenia, peripheral neuropathy, amnesia, fatigue, sexual dysfunction, thrombocytopenia, arthralgia, visual disturbance, alopecia, and hypersensitivity reactions (including rash, pruritus, urticaria, and very rarely lupus erythematosus-like reactions). In very rare cases statins can cause interstitial lung disease; if patients develop symptoms such as dyspnoea, cough, and weight loss, they should seek medical attention.

Muscle effects Myalgia, myositis, and myopathy have been reported with the statins; if myopathy is suspected and creatine kinase is markedly elevated (more than 5 times upper limit of normal), treatment should be discontinued; in children at high risk of muscle effects, a statin should not be started if creatine kinase is elevated. Children at high risk of myopathy include those with a personal or family history of muscular disorders, previous history of muscular toxicity or liver disease (see also CSM advice, p. 159). There is also an increased incidence of myopathy if the statins are given with a fibrate, with lipid-lowering doses of nicotinic acid, or with immunosuppressants such as ciclosporin; 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.

Counselling Advise children or their carers to report promptly unexplained muscle pain, tenderness, or weakness.

**ATORVASTATIN**

Cautions see notes above; also haemorrhagic stroke

Hepatic impairment avoid in active liver disease or unexplained persistent elevations in serum transaminases

Contra-indications see notes above

Pregnancy avoid—congenital anomalies reported; decreased synthesis of cholesterol possibly affects fetal development

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also chest pain; back pain; pruritus; less commonly anorexia, malaise, weight gain, hypoglycaemia, hyperglycaemia, and tinnitus; rarely cholestatic jaundice and peripheral oedema; very rarely taste disturbances, gynaeacomastia, hearing loss, Stevens-Johnson syndrome, and toxic epidermal necrolysis

**Indication and dose**

Hyperlipidaemia including familial hypercholesterolaemia

- **By mouth**

  **Child 10–17 years** initially 10 mg once daily, increased if necessary, at intervals of at least 4 weeks to usual max. 20 mg once daily

  **Child 17–18 years** initially 10 mg once daily, increased if necessary, at intervals of at least 4 weeks to max. 80 mg once daily

Note Reduced dose required with concomitant ciclosporin, clarithromycin, or itraconazole—seek specialist advice
ATORVASTATIN (continued)

Lipitor® (Pfizer) Tablets, all f/c, 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

PRAVASTATIN SODIUM

Indication and dose

Hyperlipidaemia including familial hypercholesterolaemia

- By mouth

Child 8–14 years 10 mg once daily at night, adjusted at intervals of at least 4 weeks to max. 20 mg once daily at night

Child 14–18 years 10 mg once daily at night, adjusted at intervals of at least 4 weeks to max. 40 mg once daily at night

Pravastatin (Non-proprietary) 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) 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

SIMVASTATIN

Simvastatin (Non-proprietary) Tablets, simvastatin 10 mg, net price 28-tab pack = 85p; 20 mg, 28-tab pack = 95p; 40 mg, 28-tab pack = £1.37; 80 mg, 28-tab pack = £2.94. Counselling, muscle effects, see notes above. Brands include Simvador®

Bile acid sequestrants

Colestyramine (cholestyramine) and colestipol 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. Thus both com-
pounds effectively reduce LDL-cholesterol but can aggravate hypertriglyceridaemia. Bile acid sequestrants are not well tolerated and compliance with treatment is poor, therefore they are rarely used in children.

**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 and the child’s growth and development should be monitored. **Interactions:** Appendix 1 (bile acid sequestrants).

**Side-effects** As bile acid sequestrants are not absorbed, gastro-intestinal side-effects predominate. 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 hypoprothrombinemia 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.

### Colestyramine (Cholestyramine)

**Cautions** see notes above

- **Hepatic impairment** interferes with absorption of fat-soluble vitamins and may aggravate malabsorption in primary biliary cirrhosis; likely to be ineffective in complete biliary obstruction
- **Pregnancy** use with caution—drug not absorbed but may cause fat soluble vitamin deficiency on prolonged use
- **Breast-feeding** use with caution—drug not absorbed but may cause fat soluble vitamin deficiency on prolonged use

**Contra-indications** complete biliary obstruction (not likely to be effective)

**Side-effects** see notes above; intestinal obstruction reported rarely and hyperchlaeremic acidosi reported on prolonged use

**Licensed use** licensed in children over 6 years to reduce cholesterol; see also section 1.9.2

**Indication and dose**

**Familial hypercholesterolaemia**

- **By mouth**
  - **Child 6–12 years** initially 4 g once daily increased to 4 g up to 3 times daily according to response
  - **Child 12–18 years** initially 4 g once daily increased by 4 g at weekly intervals to 12–24 g daily in 1–4 divided doses, then adjusted according to response; max. 36 g daily

### Colestipol Hydrochloride

**Cautions** see notes above

- **Pregnancy** use with caution—drug not absorbed but may cause fat soluble vitamin deficiency on prolonged use
- **Breast-feeding** use with caution—drug not absorbed but may cause fat soluble vitamin deficiency on prolonged use

**Side-effects** see notes above

**Licensed use** not licensed for use in children

**Indication and dose**

**Familial hypercholesterolaemia**

- **By mouth**
  - **Child 12–18 years** initially 5 g 1–2 times daily increased if necessary in 5-g increments at intervals of 1 month to max. of 30 g daily in 1–2 divided doses

**Administration** 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, and pulpy fruits with a high moisture content; total daily dose may be given as a single dose if tolerated
COLESTIPOL HYDROCHLORIDE (continued)

Colestid® (Pharmacia) ▼, 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 given in combination with a statin or alone if a statin is inappropriate. If ezetimibe is used in combination with a statin, there is an increased risk of rhabdomyolysis (see also CSM advice on p. 159).

Ezetimibe

Indication and dose

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

Child 10–18 years 10 mg once daily

Ezetrol® (MSD, Schering-Plough) ▼, Tablets, ezetimibe 10 mg, net price 28-tab pack = £26.31

Fibrates

Bezafibrate and fenofibrate act mainly by decreasing serum triglycerides; they have variable effects on LDL-cholesterol. Fibrates may reduce the risk of coronary heart disease in those with low HDL-cholesterol or with raised triglycerides. Fibrates can cause a myositis-like syndrome, especially in children with impaired renal function. Also, combination of a fibrate with a statin increases the risk of muscle effects (especially rhabdomyolysis) and should be used with caution (see CSM advice, p. 159).

There is limited evidence to support their use in children and they should only be considered if treatment with a statin and a bile acid sequestrant is unsuccessful or contra-indicated.

BEZAFIBRATE

Cautions correct hypothyroidism before initiating treatment (see Lipid-regulating Drugs, p. 159); see under Myotoxicity below; interactions: Appendix 1 (fibrates)

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

Hepatic impairment avoid in severe impairment

Renal impairment reduce dose if estimated glomerular filtration rate 15–60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²; see also Myotoxicity above

Contra-indications hypoalbuminaemia, primary biliary cirrhosis, gall bladder disease, nephrotic syndrome

Pregnancy embryotoxicity in animal studies—manufacturers advise avoid

Breast-feeding manufacturer advises avoid—no information available

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)—particular 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

Licensed use not licensed for use in children

Indication and dose

**BEZAFIBRATE** (Non-proprietary)

Tablets, bezafibrate 200 mg, net price 100-tab pack = £11.23. Label: 21

**Bezalip** (Roche)

Tablets, f/c, bezafibrate 200 mg, net price 100-tab pack = £9.15. Label: 21

**FENOFIBRATE**

Cautions see under Bezafibrate; liver function tests recommended every 3 months for first year (discontinue treatment if significantly raised)

Hepatic impairment avoid in severe impairment

Renal impairment reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²

Contra-indications gall bladder disease; photosensitivity to ketoprofen

Pregnancy embryotoxicity in animal studies—manufacturer advises avoid

Breast-feeding manufacturer advises avoid—no information available

Side-effects see under Bezafibrate; also very rarely hepatitis, pancreatitis, and interstitial pneumopathies

**Lipantil** (Solvay)

Lipantil® Micro 67 capsules, yellow, fenofibrate (micronised) 67 mg, net price 90-cap pack = £23.30. Label: 21

2.13 Local sclerosants

Classification not used in BNF for Children.

2.14 Drugs affecting the ductus arteriosus

**Closure of the ductus arteriosus**

Patent ductus arteriosus is a frequent problem in premature neonates with respiratory distress syndrome. Substantial left-to-right shunting through the ductus arteriosus may increase the risk of intraventricular haemorrhage, necrotising enterocolitis, bronchopulmonary dysplasia, and possibly death.

Indomethacin or ibuprofen can be used to close the ductus arteriosus. **Indomethacin** has been used for many years and is effective but it reduces cerebral blood flow, and causes a transient fall in renal and gastro-intestinal blood flow. **Ibuprofen** may also be used; it has little effect on renal function (there may be a small reduction in sodium excretion) when used in doses for closure of the ductus arteriosus; gastro-intestinal problems are uncommon.

If drug treatment fails to close the ductus arteriosus, surgery may be indicated.

**IBUPROFEN**

Cautions may mask symptoms of infection; monitor for bleeding; monitor gastro-intestinal function; allergic disorders; interactions: Appendix 1 (NSAIDs)

Hepatic impairment avoid in severe liver disease

Renal impairment use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly lead-
**INDOMETACIN**

**Cautions** see notes above; also 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 concomitant use of nephrotoxic drugs; may induce hyponatraemia; 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), delay further doses until renal function returns to normal

**Hepatic impairment** can cause fluid retention; avoid in severe hepatic impairment

**Renal impairment** use lowest effective dose and monitor renal function; sodium and water retention; deterioration in renal function possibly leading to renal failure; avoid if possible in severe impairment

**Contra-indications** untreated infection, bleeding (especially with active intracranial haemorrhage or gastro-intestinal bleeding); thrombocytopenia, coagulation defects, necrotising enterocolitis

**Side-effects** haemorrhagic, renal, gastro-intestinal, metabolic, and coagulation disorders; pulmonary hypertension, intracranial bleeding, fluid retention, and exacerbation of infection

**Indication and dose**

**Closure of ductus arteriosus**

- **By slow intravenous injection**
  - **Neonate** initially 10 mg/kg as a single dose followed at 24-hour intervals by 2 doses of 5 mg/kg; course may be repeated after 48 hours if necessary

**Mild to moderate pain, pain and inflammation of soft tissue injuries and rheumatic disease, pyrexia** section 10.1.1

**Pediaa** (Orphan Europe) [59]

**Intravenous solution**, ibuprofen 5 mg/mL, net price 4 × 2-mL vials = £263.00

**Pain and inflammation in rheumatic disease** section 10.1.1

**Administration** For **intravenous infusion** dilute each vial with 1–2 mL Sodium Chloride 0.9% or Water for Injections

**Indocid PDA® (IDIS)**

**Injection**, powder for reconstitution, indometacin (as sodium trihydrate), net price 3 × 1-mg vials = £43.50 (hosp. only)

**Maintenance of patency**

In the newborn with duct-dependent congenital heart disease it is often necessary to maintain the patency of the ductus arteriosus whilst awaiting surgery.

**Alprostadil** (prostaglandin E1) and **dinoprostone** (prostaglandin E2) are potent vasodilators that are effective for maintaining the patency of the ductus arteriosus. They are usually given by continuous intravenous infusion, but oral dosing of dinoprostone is still used in some centres.
During the infusion of a prostaglandin, the newborn requires careful monitoring of heart rate, blood pressure, respiratory rate, and core body temperature. In the event of complications such as apnoea, profound bradycardia, or severe hypotension, the infusion should be temporarily stopped and the complication dealt with; the infusion should be restarted at a lower dose. Recurrent or prolonged apnoea may require ventilatory support in order for the prostaglandin infusion to continue.

**ALPROSTADIL**

**Cautions** see notes above; also history of haemorrhage; avoid in hyaline membrane disease; monitor arterial pressure, respiratory rate, heart rate, temperature, and venous blood pressure in arm and leg; facilities for intubation and ventilation must be immediately available; **Interactions**: Appendix 1 (alprostadil)

**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; weakening of the wall of the ductus arteriosus and pulmonary artery may follow prolonged use; gastric-outlet obstruction reported

**Indication and dose**

- **Maintaining patency of the ductus arteriosus**
  - **By continuous intravenous infusion**

**Neonate** initially 5–10 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 BNFC may differ from those in product literature

**Administration** dilute 150 micrograms/kg bodyweight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 nanograms/kg/minute. Undiluted solution must not come into contact with the barrel of the plastic syringe; add the required volume of alprostadil to a volume of infusion fluid in the syringe and then make up to final volume

**Prostin VR® (Pharmacia)**

- **Intravenous solution**, alprostadil 500 micrograms/mL in alcohol. For dilution and use as an infusion. Net price 1–mL amp = £75.19 (hosp. only)

**DINOPROSTONE**

**Cautions** see notes above; also history of haemorrhage; avoid in hyaline membrane disease; monitor arterial oxygenation, heart rate, temperature, and blood pressure in arm and leg; facilities for intubation and ventilation must be immediately available; **Interactions**: Appendix 1 (prostaglandins)

**Contra-indications**

- **Hepatic impairment** manufacturer advises avoid in hepatic impairment
- **Renal impairment** manufacturer advises avoid in renal impairment

**Side-effects** nausea, vomiting, diarrhoea; flushing, bradycardia, hypotension, cardiac arrest; respiratory depression and apnoea, particularly with high doses and in low birth-weight neonates, bronchospasm; pyrexia and raised white blood cell count, shivering; local reactions, erythema; if used for longer than 5 days, gastric outlet obstruction; cortical hyperostosis (prolonged use)

**Licensed use** not licensed for use in children

**Indication and dose**

- **Maintaining patency of the ductus arteriosus**
  - **By continuous intravenous infusion**

**Neonate** initially 5–10 nanograms/kg/minute, increased as necessary in 5 nanogram/kg/minute increments to 20 nanograms/kg/minute

**Note** Doses up to 100 nanograms/kg/minute have been used but are associated with increased side-effects

**By mouth**

- **Neonate** 20–25 micrograms/kg every 1–2 hours doubled if necessary; if treatment continues for more than 1 week gradually reduce the dose

**Administration** for **continuous intravenous infusion**, dilute to a concentration of 1 microgram/mL with Glucose 5% or Sodium Chloride 0.9%. For administration by mouth, injection solution can be given orally; dilute with water

**Prostin® E2 (Pharmacia)**

- **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)

▲ Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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3 Respiratory system

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### 3.1 Bronchodilators

**3.1.1 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**

### Asthma

Drugs used in the management of asthma include beta\_2 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 management of acute asthma, see p. 170 and p. 171.

### 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 Inhaler devices, section 3.1.5.

**Solutions for nebulisation** for use in acute severe asthma are administered over 5–10 minutes from a nebuliser, usually driven by oxygen in hospital. See Nebulisers, section 3.1.5.

**Oral** Systemic side-effects occur more frequently when a drug is given orally rather than by inhalation. Oral corticosteroids, theophylline, and leukotriene receptor antagonists are sometimes required for the management of asthma. Oral administration of a beta\_2 agonist is generally not recommended for children, but may be necessary in infants and young children unable to use an inhaler device.

**Parenteral** Drugs such as beta\_2 agonists, corticosteroids, and aminophylline can be given by injection in acute severe asthma when drug administration by nebulisation is inadequate or inappropriate; in these circumstances the child should generally be treated in a high-dependency or intensive care unit.

### Pregnancy and breast-feeding

Women with asthma should be closely monitored during pregnancy. Well-controlled asthma has no important effects on pregnancy, labour, or the fetus. Drugs for asthma should preferably be administered by inhalation to minimise fetal drug exposure. Women planning to become pregnant should be counselled about the importance of taking their asthma medication regularly to maintain good control.

Severe exacerbations of asthma can have an adverse effect on pregnancy and should be treated promptly with conventional therapy, including oral or parenteral administration of a corticosteroid and nebulisation of a beta\_2 agonist; prednisolone is the preferred corticosteroid for oral administration since very little of the drug reaches the fetus. Oxygen should be given immediately to maintain an arterial oxygen saturation of 94–98% and prevent maternal and fetal hypoxia.

Inhaled drugs, theophylline, and prednisolone can be taken as normal during pregnancy and breast-feeding.

### Management of acute asthma\(^1\)

**Important**

Regard each emergency consultation as being for severe acute asthma until shown otherwise.

Failure to respond adequately at any time requires immediate transfer to hospital.

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1. 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)
Severe acute asthma can be fatal and must be treated promptly and energetically. Treatment of severe acute asthma is safer in hospital where resuscitation facilities are immediately available. Treatment should never be delayed for investigations, children should never be sedated, and the possibility of a pneumothorax should be considered. If the child’s condition deteriorates despite pharmacological treatment, urgent transfer to a paediatric intensive care unit should be arranged. For a table outlining the management of severe acute asthma, see Management of acute asthma p. 171.

**Mild to moderate acute asthma**  
Administer a short-acting beta agonist using a pressurised metered-dose inhaler with a spacer device; for a child under 3 years use a close-fitting facemask. Give 1 puff every 15–30 seconds up to a maximum of 10 puffs; repeat dose after 10–20 minutes if necessary.

Give prednisolone by mouth, child under 12 years 1–2 mg/kg (max. 40 mg) once daily for 3–5 days; if the child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily. For children 12–18 years, give prednisolone 40–50 mg daily for at least 5 days.

If response is poor or if a relapse occurs within 3–4 hours, transfer child immediately to hospital for assessment and further treatment.

Children under 18 months often respond poorly to bronchodilators; nebulised beta2 agonists have been associated with mild (but occasionally severe) paradoxical bronchospasm and transient worsening of oxygen saturation; response to prednisolone may also be poor in this age group.

**Severe or life-threatening acute asthma**  
Transfer immediately to hospital. Administer high-flow oxygen (section 3.6) using a close-fitting face mask or nasal prongs.

Treat severe or life-threatening acute exacerbations of asthma with an inhaled short-acting beta2 agonist (as above). Treatment of life-threatening asthma should be initiated with nebulised salbutamol 2.5 mg or terbutaline 5 mg (via an oxygen-driven nebuliser if available); nebulised doses may be doubled for children over 5 years. Repeat the dose every 10–20 minutes or as necessary, then reduce the frequency on improvement.

If response is poor, add nebulised ipratropium bromide 250 micrograms every 20–30 minutes over the first 2 hours, then reduce the frequency on improvement.

Give prednisolone by mouth, child under 12 years 1–2 mg/kg (max. 40 mg) once daily for 3–5 days; if the child has been taking an oral corticosteroid for more than a few days, give prednisolone 2 mg/kg (max. 60 mg) once daily. For children 12–18 years, give prednisolone 40–50 mg daily for at least 5 days. If oral administration is not possible, use intravenous hydrocortisone (preferably as sodium succinate) 4 mg/kg (child under 2 years max. 25 mg, 2–5 years 50 mg, 5–18 years 100 mg) 3–4 times daily.

If the condition does not respond or is life-threatening, transfer the child to an intensive care unit and treat with a parenteral short-acting beta agonist (e.g. salbutamol) (section 3.1.1.1) or parenteral aminophylline (section 3.1.3). Children over 2 years with severe asthma may be helped by intravenous infusion of magnesium sulphate 40 mg/kg (max. 2 g) over 20 minutes (section 9.5.1.3), but evidence of benefit is limited.

**Croup**

Mild croup is largely self-limiting, but treatment with a single dose of a corticosteroid (e.g. dexamethasone 150 micrograms/kg) by mouth is of benefit.

Severe croup (or mild croup that might cause complications) calls for hospital admission—a single dose of either dexamethasone 150 micrograms/kg or prednisolone 1–2 mg/kg, can be administered by mouth 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 be repeated after 12 hours if necessary.

For severe croup not effectively controlled with corticosteroid treatment, nebulised adrenaline (section 3.4.3) solution 1 in 1000 (1 mg/mL) can be given with close clinical monitoring in a dose of 400 micrograms/kg (max. 5 mg) repeated after 30 minutes if necessary (the dose may be diluted with sterile sodium chloride 0.9% solution). The effects of nebulised adrenaline last 2–3 hours; the child needs to be carefully monitored for recurrence of the obstruction.
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.

Child 5–18 years

Step 1: occasional relief bronchodilator
Inhaled short-acting beta₂ 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.

Step 2: regular inhaled preventer therapy
Inhaled short-acting beta₂ agonist as required

plus
Regular standard-dose¹ inhaled corticosteroid (alternatives² are considerably less effective)

Step 3: inhaled corticosteroid + inhaled long-acting beta₂ agonist
Inhaled short-acting beta₂ agonist as required

plus
Regular standard-dose¹ inhaled corticosteroid

plus
Regular inhaled long-acting beta₂ agonist, agonist (salmeterol or formoterol)

If asthma not controlled, increase dose of inhaled corticosteroid to upper end of standard dose range³ and

Either stop long-acting beta₂ agonist, agonist if of no benefit
Or continue long-acting beta₂ agonist, agonist if of some benefit

If asthma still not controlled and long-acting beta₂ agonist, agonist stopped, add one of:
Leukotriene receptor antagonist
Modified-release oral theophylline
Modified-release oral beta₂ agonist

Step 4: high-dose inhaled corticosteroid + regular bronchodilators
Inhaled short-acting beta₂ agonist as required

with
Regular high-dose³ inhaled corticosteroid

plus
Inhaled long-acting beta₂ agonist, agonist (if of benefit)

plus
A 6-week sequential therapeutic trial of one or more of:
Leukotriene receptor antagonist
Modified-release oral theophylline
Modified-release oral beta₂ agonist

Step 5: regular corticosteroid tablets
Refer to respiratory paediatrician
Inhaled short-acting beta₂ agonist as required

with
Regular high-dose³ 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)

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) to the lowest dose which controls asthma

Child under 5 years

Step 1: occasional relief bronchodilator
Inhaled short-acting beta₂ agonist as required (not more than once daily)

Note: Preferably by inhalation (less effective and more side-effects when given as tablets or syrup)

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 last 2 years.

Step 2: regular preventer therapy
Inhaled short-acting beta₂ agonist as required

plus
Regular standard-dose¹ inhaled corticosteroid

Or leukotriene receptor antagonist if inhaled corticosteroid cannot be used

Step 3: add-on therapy
Child under 2 years:
Refer to respiratory paediatrician

Child 2–5 years:
Inhaled short-acting beta₂ agonist, agonist as required

plus
Regular standard-dose¹ inhaled corticosteroid

plus
Leukotriene receptor antagonist

Step 4: persistent poor control
Refer to respiratory paediatrician

Stepping down
Regularly review need for treatment

1. Standard doses of inhaled corticosteroids (metered-dose inhaler used with large-volume spacer)
   Beclometasone dipropionate or budesonide:
   Child under 12 years 100–200 micrograms twice daily;
   Child 12–18 years 100–400 micrograms twice daily.

   Fluticasone propionate:
   Child 4–12 years 50–100 micrograms twice daily;
   Child 12–18 years 50–200 micrograms twice daily.

   Mometasone furoate (given through dry powder inhaler):
   Child 12–18 years 200 micrograms twice daily

2. Alternatives to inhaled corticosteroids are leukotriene receptor antagonists, theophylline, inhaled nedocromil, or inhaled cromoglicate

3. High doses of inhaled corticosteroids (metered-dose inhaler used with large-volume spacer)
   Beclometasone dipropionate or budesonide:
   Child 5–12 years 200–400 micrograms twice daily;
   Child 12–18 years 0.4–1 mg twice daily.

   Fluticasone propionate:
   Child 5–12 years 100–200 micrograms twice daily;
   Child 12–18 years 200–500 micrograms twice daily.

   Mometasone furoate (given through dry powder inhaler):
   Child 12–18 years up to 400 micrograms twice daily

Note: Failure to achieve control with these doses is unusual, see also Side-effects of Inhaled Corticosteroids, section 3.2

4. Lung-function measurements cannot be used to guide management in those under 5 years
Management of acute asthma

**Important** The assessment of acute asthma in early childhood can be difficult. Children 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

- **Respiration**
  - **Child** 2–5 years: ≤ 50 breaths/minute, 5–12 years: ≤ 30 breaths/minute, 12–18 years: < 25 breaths/minute
- **Pulse** **Child** 2–5 years: ≤ 130 beats/minute, 5–12 years: ≤ 120 beats/minute, 12–18 years: < 110 beats/minute
- **Arterial oxygen saturation**: ≥ 92%
- **Peak flow** **Child** 5–12 years: ≥ 50% of predicted or best, 12–18 years: > 50% of predicted or best

Treatment

- **Inhaled short-acting beta<sub>2</sub> agonist** via a large-volume spacer (and a close-fitting face mask if child under 3 years) 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. **Child** under 5 years 2.5 mg, 5–12 years 2.5–5 mg, 12–18 years 5 mg or **terbutaline** **Child** under 5 years 5 mg, 5–12 years 5–10 mg, 12–18 years 10 mg, and repeat at 10–20 minute intervals if necessary
- **Prednisolone** by mouth. **Child** under 12 years 1–2 mg/kg (max. 60 mg); **Child** 12–18 years 40–50 mg daily for at least 5 days

Follow up in all cases

- **Monitor** symptoms and peak flow
- Set up asthma action plan and check inhaler technique with child and carer
- Review by general practitioner within 48 hours; modify treatment according to the Management of Chronic Asthma table, p. 170

### Severe acute asthma

- **Child** under 12 years too breathless to talk or feed, 12–18 years cannot complete sentences in one breath
- **Use** of accessory breathing muscles
- **Respiration** **Child** 2–5 years: > 50 breaths/minute, 5–12 years: > 30 breaths/minute, 12–18 years: > 25 breaths/minute
- **Pulse** **Child** 2–5 years: > 130 beats/minute, 5–12 years: > 120 beats/minute, 12–18 years: > 110 beats/minute
- **Arterial oxygen saturation**: < 92%
- **Peak flow** **Child** 5–12 years: < 50% of predicted or best, 12–18 years: 33–50% of predicted or best

Treat at home or in surgery and assess response to treatment

### Life-threatening acute asthma

- **Arterial oxygen saturation**: < 92%
- **Peak flow** **Child** 5–12 years: < 50% of predicted or best, 12–18 years 33–50% of predicted or best

Send immediately to hospital

Treatment

- **High-flow oxygen** (if available)
- **Inhaled short-acting beta<sub>2</sub> agonist** via a large-volume spacer (and a close-fitting face mask if child under 3 years) 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 or as necessary or give nebulised salbutamol. **Child** under 5 years 2.5 mg, 5–12 years 2.5–5 mg, 12–18 years 5 mg or **terbutaline** **Child** under 5 years 5 mg, 5–12 years 5–10 mg, 12–18 years 10 mg, and repeat at 10–20 minute intervals or as necessary
- **Prednisolone** by mouth as for moderate acute asthma or intravenous hydrocortisone (preferably as sodium succinate) 4 mg/kg. **Child** under 2 years, max. 25 mg, 2–5 years 50 mg, 5–18 years 100 mg 3–4 times daily until conversion to oral prednisolone is possible
- **Inhaled ipratropium bromide** via oxygen-driven nebuliser (if available), **Child** under 12 years 250 micrograms, 12–18 years 500 micrograms and repeat at 20–30 minute intervals if necessary

Monitor response for 15–30 minutes

If response is poor

- **Inhaled ipratropium bromide** via oxygen-driven nebuliser (if available), **Child** under 12 years 250 micrograms, 12–18 years 500 micrograms and repeat at 20–30 minute intervals if necessary
- **Consider intravenous beta<sub>2</sub>, agonists, aminophylline, or magnesium sulphate** (unlicensed indication) only after consultation with senior medical staff
- **If symptoms improve**, follow up as for moderate acute asthma

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)
3.1.1 Adrenoceptor agonists
(Sympathomimetics)

3.1.1.1 Selective beta2 agonists

The selective beta2 agonists (selective beta2-adrenoceptor agonists, selective beta2 stimulants) such as salbutamol or terbutaline are the safest and most effective short-acting beta2 agonists for the treatment of asthma. Less selective beta2 agonists, such as orciprenaline, are no longer recommended for the treatment of asthma.

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); it is also used as a nebuliser solution to treat severe croup.

3.1.1.1 Selective beta2 agonists

Selective beta2 agonists produce bronchodilation. A short-acting beta2 agonist is used for immediate relief of asthma symptoms while a long-acting beta2 agonist is used in addition to an inhaled corticosteroid in children requiring prophylactic treatment.

**Short-acting beta2 agonists** Mild to moderate symptoms of asthma respond rapidly to the inhalation of a selective short-acting beta2 agonist such as salbutamol or terbutaline. If beta2 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, p. 170. Regular treatment with an inhaled short-acting beta2 agonist is less effective than ‘as required’ inhalation and is not appropriate prophylactic treatment.

A short-acting beta2 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 beta2 agonists** Formoterol (eformoterol) and salmeterol are longer-acting beta2 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 Management of Chronic Asthma, p. 170) 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 beta2 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 with rapidly deteriorating asthma;
- be introduced at a low dose and the effect 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.

Children and their carers should be advised to report any deterioration in symptoms following initiation of treatment with a long-acting beta2 agonist, see Management of Chronic Asthma, p. 170.

Management of Chronic Asthma, see p. 170
Management of Acute Asthma, see p. 168
For guidance on the use of inhalers and spacer devices, see section 3.1.5
Inhalation

A pressurised metered-dose inhaler is an effective method of drug administration in mild to moderate chronic asthma; to deliver the drug effectively particularly in children under 12 years, a spacer device should be used (see also NICE guidance, section 3.1.5). When a pressurised metered-dose inhaler with a spacer is unsuitable or inconvenient, a dry-powder inhaler or breath-actuated inhaler may be used instead if the child is able to use the device effectively. At recommended inhaled doses the duration of action of salbutamol and terbutaline is about 3 to 5 hours and for salmeterol and formoterol is about 12 hours. The dose, the frequency, and the maximum number of inhalations in 24 hours of the beta_2 agonist should be stated explicitly to the child and the child’s carer. High doses of beta_2 agonists can be dangerous in some children (see Cautions, below). Excessive use is usually an indication of inadequately controlled asthma and should be managed with a prophylactic drug such as an inhaled corticosteroid. The child and the child’s carer should be advised to seek medical advice when the prescribed dose of beta_2 agonist fails to provide the usual degree of symptomatic relief because this usually indicates a worsening of the asthma and the child may require alternative medication (see Management of Chronic Asthma, p. 170).

Children and their carers should be advised to follow manufacturers’ instructions on the care and cleansing of inhaler devices.

CFC-free inhalers Chlorofluorocarbon (CFC) propellants in pressurised metered-dose inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Children receiving CFC-free inhalers and their carers should be reassured about the efficacy of the new inhalers and counselled that the aerosol may feel and taste different to their previous CFC-based inhaler; any difficulty with the new inhaler should be discussed with the doctor or pharmacist.

Nebuliser (or respirator) solutions of salbutamol and terbutaline are used for the treatment of severe acute asthma both in hospital and in general practice. Children with a severe attack of asthma should have oxygen if possible during nebulisation since beta_2 agonists can increase arterial hypoxaemia, see also section 3.1.5.

Oral Oral preparations of beta_2 agonists may be used for children if an inhaler device cannot be used but inhaled beta_2 agonists are more effective and have fewer side-effects. A modified-release formulation of salbutamol may be of value in nocturnal asthma as an alternative to modified-release theophylline preparations (section 3.1.3), but an inhaled long-acting beta_2 agonist is preferable.

Parenteral Beta_2 agonists can be given intravenously in children with severe or life-threatening acute asthma. Chronic asthma unresponsive to stepwise treatment (see Management of Chronic Asthma, p. 170) may benefit from continuous subcutaneous infusion of a beta_2 agonist but this should be used only under the supervision of a respiratory specialist; the evidence of benefit is uncertain and it may be difficult to withdraw such treatment once started.

Cautions Beta_2 agonists should be used with caution in diabetes—monitor blood glucose (risk of ketoacidosis, especially when a beta_2 agonist is given intravenously). Beta_2 agonists should also be used with caution in hyperthyroidism, cardiovascular disease, arrhythmias, susceptibility to QT-interval prolongation, and hypertension. If high doses of beta_2 agonists are needed during pregnancy they should be given by inhalation because a parenteral beta_2 agonist can affect the myometrium and possibly cause cardiac problems; see also Pregnancy and Breast-feeding, section 3.1. Interactions: Appendix 1 (sympathomimetics, beta_2).

Hypokalaemia The CSM has advised that potentially serious hypokalaemia may result from beta_2 agonist therapy. Particular caution is required in severe asthma, because this effect may be potentiated by concomitant treatment with theophylline and its derivatives, corticosteroids, and diuretics, and by hypoxia. Plasma-potassium concentration should therefore be monitored in severe asthma.

Side-effects Side-effects of the beta_2 agonists include fine tremor (particularly in the hands), nervous tension, headache, peripheral dilatation and palpitation. Other side-effects include tachycardia, arrhythmias, peripheral vasodilation, myocardial ischaemia, and disturbances of sleep and behaviour. Muscle cramps and
hypersensitivity reactions including paradoxical bronchospasm (occasionally severe), urticaria, angioedema, hypotension, and collapse have also been reported. High doses of beta₂ agonists are associated with hypokalaemia (for CSM advice, see Hypokalaemia, p. 173).

**FORMOTEROL FUMARATE**
(Formoterol fumarate)

**Cautions** see notes above

- **Hepatic impairment** metabolism possibly reduced in severe cirrhosis
- **Pregnancy** see section 3.1 (manufacturers advise use only if potential benefit outweighs risk)
- **Breast-feeding** amount in milk probably too small to be harmful but manufacturers advise avoid

**Side-effects** see notes above; nausea, dizziness, rash, taste disturbances, and pruritus also reported

**Indication and dose**

Reversible airways obstruction (including nocturnal asthma and prevention of exercise-induced bronchospasm) in patients requiring long-term regular bronchodilator therapy see also Management of Chronic Asthma, p. 170; for dose see preparations below

- **Counselling** Advise children and carers 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) Dry powder for inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 120-dose unit = £24.80. Counselling, dose

**Brands include Easyhaler® Formoterol**

**Dose**

- **Chronic asthma**
  - By inhalation of powder
    - Child 6–18 years 12 micrograms twice daily, increased to 24 micrograms twice daily in more severe airways obstruction

**Atimos Modulite®** (Chiesi) Aerosol inhalation, formoterol fumarate 12 micrograms/metered inhalation, net price 100-dose unit = £31.28. Counselling, dose

**Dose**

- **Chronic Asthma**
  - By aerosol inhalation
    - Child 12–18 years 12 micrograms twice daily, increased to max. 24 micrograms twice daily in more severe airways obstruction

**Oxis®** (AstraZeneca) Turbohaler® (= dry powder inhaler), formoterol fumarate 6 micrograms/inhalation, net price 60-dose unit = £24.80; 12 micrograms/inhalation, 60-dose unit = £24.80. Counselling, dose

**Dose**

- **Chronic asthma**
  - By inhalation of powder
    - 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); reassess treatment if additional doses required on more than 2 days a week

**Relief of bronchospasm**

- **By inhalation of powder**
  - Child 6–18 years 6–12 micrograms before exercise

**Prevention of exercise-induced bronchospasm**

- **By inhalation of powder**
  - Child 6–18 years 6–12 micrograms before exercise

**Compound preparations**

For compound preparations containing formoterol, see section 3.2

**SALBUTAMOL**
(Albuterol)

**Cautions** see notes above

**Side-effects** see notes above

**Licensed use** not licensed for use in hyperkalaemia; syrup not licensed for use in children under 2 years; modified-release tablets not licensed for use in children under 3 years; injection not licensed for use in children; Pulvinal® Salbutamol not licensed for use in children under 6 years

**Indication and dose**

**Acute asthma**

- **By aerosol or nebulised solution inhalation** See Management of Acute Asthma, p. 168

- **By intravenous injection over 5 minutes (see also Management of Acute Asthma, p. 168)**
  - Child 1 month–2 years 5 micrograms/kg as a single dose
  - Child 2–18 years 15 micrograms/kg (max. 250 micrograms) as a single dose
1 SALBUTAMOL (continued)

- By continuous intravenous infusion
  Child 1 month–18 years 1–2 micrograms/kg/minute, adjusted according to response and heart rate up to 5 micrograms/kg/minute; doses above 2 micrograms/kg/minute should be given in an intensive care setting

- By aerosol inhalation
  Child 1 month–18 years 100–200 micrograms (1–2 puffs); for persistent symptoms up to 4 times daily

- By inhalation of powder
  (for Asmasal Clickhaler®, Salbulin Novolizer®, and Ventolin Accuhaler® doses, see under preparations)
  Child 5–12 years 200 micrograms; for persistent symptoms up to 4 times daily
  Child 12–18 years 200–400 micrograms; for persistent symptoms up to 4 times daily

- By mouth (but use by inhalation preferred)
  Child 1 month–2 years 100 micrograms/kg (max. 2 mg) 3–4 times daily
  Child 2–6 years 1–2 mg 3–4 times daily
  Child 6–12 years 2 mg 3–4 times daily
  Child 12–18 years 4 mg (sensitive patients initially 2 mg) 3–4 times daily; max. single dose 8 mg (but unlikely to provide extra benefit or to be tolerated)

Severe hyperkalaemia (section 9.2.1.1)
- By intravenous injection over 5 minutes
  Neonate 4 micrograms/kg as a single dose; repeat if necessary
  Child 1 month–18 years 4 micrograms/kg as a single dose; repeat if necessary

- By inhalation of nebulised solution (but intravenous injection preferred)
  Neonate 2.5–5 mg as a single dose; repeat if necessary
  Child 1 month–18 years 2.5–5 mg as a single dose; repeat if necessary

Administration for continuous intravenous infusion, dilute to a concentration of 200 micrograms/mL with Glucose 5%, Sodium Chloride 0.9%, or Water for injections; if fluid-restricted, can be given undiluted through central venous catheter. For intravenous injection, dilute to a concentration of 50 micrograms/mL with Glucose 5%, Sodium Chloride 0.9%, or Water for injections. For nebulisation, dilute nebuliser solution with a suitable volume of sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; salbutamol and ipratropium bromide solutions are compatible and can be mixed for nebulisation.

Exacerbations of reversible airways obstruction (including nocturnal asthma) and prevention of allergen- or exercise-induced bronchospasm, see also Management of Chronic Asthma, p. 170

- By continuous intravenous infusion
  Child 1 month–18 years 2 micrograms/kg/minute, adjusted according to response and heart rate up to 5 micrograms/kg/minute; doses above 2 micrograms/kg/minute should be given in an intensive care setting

Oral

Salbutamol (Non-proprietary) 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 (Chiesi) 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

Chronic asthma (but see notes above)
- By mouth
  Child 3–12 years 4 mg twice daily
  Child 12–18 years 8 mg twice daily

Ventolin® (A&H) Syrup, sugar-free, salbutamol (as sulphate) 2 mg/5 mL, net price 150 mL = 60p

Parenteral

Ventolin® (A&H) Injection, salbutamol (as sulphate) 500 micrograms/mL, net price 1-mL amp = 40p

Solution for intravenous infusion, salbutamol (as sulphate) 1 mg/mL. Dilute before use. Net price 5 mL amp = £2.58

Inhalation

Counselling Advise children and carers 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 (see notes above)

Salbutamol (Non-proprietary) Aerosol inhalation, salbutamol 100 micrograms/ metered inhalation, net price 200-dose unit = £2.88. Counselling, dose

Exipients include CFC propellants

Aerosol inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £2.99. Counselling, dose, change to CFC-free inhaler

Exipients include HFA-134a (a non-CFC propellant)

Brands include Salamol®

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

Brands include Easyhaler®, Salbutamol, Pulvinal® Salbutamol

Inhalation powder, hard capsule (for use with Cyclohaler® device), salbutamol 200 micrograms, net price 120-cap pack = £8.99; 400 micrograms, 120-cap pack = £12.99. Counselling, dose

Brands include Salbutamol Cyclocap®
3.1.1 Adrenoceptor agonists

**SALBUTAMOL (continued)**

**Nebuliser solution**, salbutamol (as sulphate) 1 mg/mL, net price 20 × 2.5 mL (2.5 mg) = £1.99; 2 mg/mL, 20 × 2.5 mL (5 mg) = £3.98. May be diluted with sterile sodium chloride 0.9%

Brands include Salamol Steri-Neb®

**Airomir®** (IVAX) (吸入)

Aerosol inhalation, salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £1.97. 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

**Autohaler** (breath-actuated aerosol inhalation), salbutamol (as sulphate) 100 micrograms/metered inhalation, net price 200-dose unit = £6.02. Counselling, dose, change to CFC-free inhaler

**Excipients** include HFA-134a (a non-CFC propellant), Asmasal Clickhaler® (UCB Pharma) (吸入)

Dry powder for inhalation, salbutamol (as sulphate) 95 micrograms/metered inhalation, net price 200-dose unit = £5.88. Counselling, dose

**Dose**

**Acute bronchospasm**

- By inhalation of powder
  - Child 5–18 years: 1–2 puffs; for persistent symptoms up to 4 times daily (but see also Management of Chronic Asthma, p. 170)

**Prophylaxis of allergen- or exercise-induced bronchospasm**

- By inhalation of powder
  - Child 5–18 years: 1–2 puffs

**Salamol Easi-Breathe**® (IVAX) (吸入)

Aerosol inhalation, salbutamol 100 micrograms/metered inhalation, net price 200-dose breath-actuated unit = £6.30. Counselling, dose

**Excipients** include HFA-134a (a non-CFC propellant)

**Salmun Novolizer®** (Meda) (吸入)

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
  - Child 5–12 years: 100-200 micrograms; for persistent symptoms up to 400 micrograms daily but see also Management of Chronic Asthma, p. 170

Child 12–18 years: 100-200 micrograms; for persistent symptoms up to 800 micrograms daily but see also Management of Chronic Asthma, p. 170

**Prophylaxis of allergen- or exercise-induced bronchospasm**

- By inhalation of powder
  - Child 5–12 years: 100–200 micrograms
  - Child 12–18 years: 200 micrograms

**Ventolin®** (A&H) (吸入)

Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salbutamol (as sulphate) 200 micrograms/blister with Accuhaler® device, net price = £5.12. Counselling, dose

**Dose**

**Acute bronchospasm**

- By inhalation of powder
  - Child 5–18 years: 200 micrograms; for persistent symptoms up to 4 times daily but see also Management of Chronic Asthma, p. 170

**Prophylaxis of allergen- or exercise-induced bronchospasm**

- By inhalation of powder
  - Child 5–18 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 × 2.5 mL (2.5 mg) = £1.75; 2 mg/mL, 20 × 2.5 mL (5 mg) = £2.95. May be diluted with sterile sodium chloride 0.9%

**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%

**SALMETEROL**

**Note** Not for immediate relief of acute 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

**Indication and dose**

Reversible airways obstruction (including nocturnal asthma and prevention of exercise-induced bronchospasm) in patients requiring long-term regular bronchodilator therapy see also Management of Chronic Asthma, p. 170

- By inhalation
  - Child 5–12 years: 50 micrograms (2 puffs or 1 blister) twice daily
SALMETEROL (continued)

Child 12–18 years
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.

Counselling
Advise children and carers 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 salmeterol fails to provide adequate relief, a doctor’s advice should be obtained as soon as possible.

Serevent® (A&H) [A]
Accuhaler® (dry powder for inhalation), disk containing 60 blisters of salmeterol (as xinafoate) 50 micrograms/blister 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.

Excipients include HFA-13Ha (a non-CFC propellant).

Diskhaler® (dry powder for inhalation), disks containing 4 blisters of salmeterol (as xinafoate) 50 micrograms/blister, net price 15 disks with Diskhaler® device = £35.79, 15-disk refill = £35.15. Counselling, dose, change to CFC-free inhaler.

Compound preparations
For compound preparations containing salmeterol, see section 3.2.

TERBUTALINE SULPHATE

Cautions
see notes above

Side-effects
see notes above

Licensed use
tablets not licensed for use in children under 7 years; injection not licensed for use in children under 2 years

Indication and dose

Acute asthma

• By inhalation of nebulised solution
  see Management of Acute Asthma, p. 168

• By subcutaneous or slow intravenous injection
  Child 2–15 years 10 micrograms/kg (max. 300 micrograms) up to 4 times daily
  Child 15–18 years 250–500 micrograms up to 4 times daily

• By continuous intravenous infusion
  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 (doses above 10 micrograms/kg/hour with close monitoring)

Exacerbations of reversible airways obstruction (including nocturnal asthma) and prevention of exercise-induced bronchospasm see Management of Chronic Asthma, p. 170

• By inhalation of powder
  Child 5–18 years 500 micrograms (1 inhalation) up to 4 times daily (for occasional use only)

• By mouth (but not recommended)
  Child 1 month–7 years 75 micrograms/kg (max. 2.5 mg) 3 times daily
  Child 7–15 years 2.5 mg 2–3 times daily
  Child 15–18 years initially 2.5 mg 3 times daily, increased if necessary to 5 mg 3 times daily

Administration
For continuous intravenous infusion, dilute to a concentration of 5 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; if fluid-restricted, dilute to a concentration of 100 micrograms/mL.

For nebulisation, dilute nebuliser solution with sterile Sodium Chloride 0.9% solution according to nebuliser type and duration of administration; terbutaline and ipratropium bromide solutions are compatible and may be mixed for nebulisation.

Oral and parenteral

Bricanyl® (AstraZeneca) [A]
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 500 micrograms/mL, net price 1-mL amp = 30p; 5-mL amp = £1.40.

Inhalation

Counselling
Advise children and carers 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) [A]
Turbohaler® (= dry powder inhaler), terbutaline sulphate 500 micrograms/metered inhalation, net price 100-dose unit = £6.92. Counselling, dosage.

Respules® (= single-dose units for nebulisation), terbutaline sulphate 2.5 mg/mL, net price 20 × 2-mL units (5-mg) = £4.04.

3.1.2 Other adrenoceptor agonists

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).
3.1.2 Antimuscarinic bronchodilators

**Ipratropium** by nebulisation can be added to other standard treatment in life-threatening acute asthma or if acute asthma fails to improve with standard therapy (see Management of Acute Asthma, p. 168). Ipratropium can be used to provide short-term relief in chronic asthma, but short-acting beta₂ agonists act more quickly and are preferred.

The aerosol inhalation of ipratropium has a maximum effect 30–60 minutes after use; its duration of action is 3 to 6 hours.

**IPRATROPIUM BROMIDE**

**Cautions** risk of glaucoma (see below), bladder outflow obstruction; **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 the child’s eyes from nebulised drug or from drug powder.

**Side-effects** dry mouth; less commonly nausea and headache; rarely constipation, tachycardia, palpitation, paradoxic bronchospasm, urinary retention, blurred vision, angle-closure glaucoma, and hypersensitivity reactions including rash, urticaria, and angioedema.

**Indication and dose**

**Acute asthma**
- By inhalation of nebulised solution
  - See Management of Acute Asthma, section 3.1

**Reversible airways obstruction** see notes above
- By aerosol inhalation
  - Child 1 month–6 years 20 micrograms 3 times daily
  - Child 6–12 years 20–40 micrograms 3 times daily
  - Child 12–18 years 20–40 micrograms 3–4 times daily
- By inhalation of powder
  - Child 12–18 years 40 micrograms 3–4 times daily (dose may be doubled in less responsive condition)

**Counselling** Advise child and carer not to exceed prescribed dose and to follow manufacturer’s directions

**Rhinitis** section 12.2.2

**Ipratropium Bromide** (Non-proprietary) (BN)

**Nebuliser solution**, ipratropium bromide 250 micrograms/mL, net price 20 x 1-mL (250-microgram) unit-dose vials = £6.75, 60 x 1-mL = £21.78; 20 x 2-mL (500-microgram) = £7.43, 60 x 2-mL = £26.97.

**Atrovent®** (Boehringer Ingelheim) (BN)

**Aerocaps®** (dry powder for inhalation; for use with **Atrovent Aerohaler®**), green, ipratropium bromide 40 micrograms, net price pack of 100 caps with **Aerohaler®** = £14.53; 100 caps = £10.53. Counseling, dose

**Note** One Atrovent Aerocap® is equivalent to 2 puffs of Atrovent® metered aerosol inhalation.

**Aerosol inhalation**, ipratropium bromide 20 micrograms/metered inhalation, net price 200-dose unit = £4.21. Counseling, 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 x 1-mL unit-dose vials = £5.18, 60 x 1-mL vials = £15.55; 20 x 2-mL vials = £6.08, 60 x 2-mL vials = £18.24.

**Ipratropium Steri-Neb®** (IVAX) (BN)

**Nebuliser solution**, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 x 1-mL (250-microgram) unit-dose vials = £5.66; 20 x 2-mL (500-microgram) = £9.94.

**Respontin®** (A&H) (BN)

**Nebuliser solution**, isotonic, ipratropium bromide 250 micrograms/mL, net price 20 x 1-mL (250-microgram) unit-dose vials = £5.07; 20 x 2-mL (500-microgram) = £5.95.

3.1.3 Theophylline

Theophylline is a bronchodilator used for asthma, see Management of Chronic Asthma p. 170. It may have an additive effect when used in conjunction with small doses of beta₂ agonists; the combination may increase the risk of side-effects, including hypokalaemia (see p. 173).

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 rarely needed for severe attacks of asthma (see Management of Acute Asthma, section 3.1). It must be given by very slow intravenous injection (over at least 20 minutes) or by intravenous infusion; it is too irritant for intramuscular use. Intravenous aminophylline may be used as a respiratory stimulant in neonates with apnoea, but **caffeine** (section 3.5.1) is usually preferred. Measurement of plasma-theophylline concentration may be helpful and is essential if a loading dose of aminophylline is to be given to children who are taking theophylline, because serious side-effects such as convulsions and arrhythmias can occasionally precede other symptoms of toxicity.
Theophylline is metabolised in the liver. Plasma-theophylline concentration is increased in heart failure, cirrhosis, viral infections, and by drugs that inhibit its metabolism. The plasma-theophylline concentration is decreased in smokers and by drugs that induce liver metabolism. Particular care is required when introducing or withdrawing drugs that interact with theophylline. For other interactions of theophylline see Appendix 1.

**Plasma-theophylline concentration**  In most individuals a plasma-theophylline concentration of 10–20 mg/litre (55–110 micromol/litre) is required for satisfactory bronchodilation, but a lower concentration of 5–15 mg/litre may be effective. Adverse effects can occur within the range 10–20 mg/litre and both the frequency and severity increase if the concentration exceeds 20 mg/litre. In neonates, toxic symptoms sometimes occur when the plasma-theophylline concentration exceeds 14 mg/litre (78 micromol/litre). If theophylline is used in the treatment of neonatal apnoea, the usual target range is 8–12 mg/litre (44–66 micromol/litre).

Plasma-theophylline concentration is measured 5 days after starting oral treatment and at least 3 days after any dose adjustment. A blood sample should be taken 1–2 hours after an oral dose (after 4–6 hours in the case of a modified-release preparation). If aminophylline is given intravenously, a blood sample should be taken 4–6 hours after starting treatment; in a child already taking theophylline, plasma-theophylline concentration should be determined before giving the intravenous dose.

### THEOPHYLLINE

#### Cautions
- cardiac disease, hypertension, hyperthyroidism; peptic ulcer; epilepsy; fever; CSM advice on hypokalaemia risk, p. 173; avoid in acute porphyria (section 9.8.2); monitor plasma-theophylline concentration (see notes above);
- interactions: Appendix 1 (theophylline) and notes above

#### Hepatic impairment
- reduce dose

#### Pregnancy
- neonatal irritability and apnoea reported

#### Breast-feeding
- present in milk—irritability in infant reported; modified-release preparations preferable

#### 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. 43

#### Licensed use
- **Slo-Phyllin** capsules not licensed for use in children under 2 years

#### Indication and dose

- **Chronic asthma**
  - **SA 250 tablets**, m/r, theophylline 250 mg. Net price 60-tab pack = £4.46. Label: 21, 25
  - Dose
    - **Chronic asthma**
      - **By mouth**
        - Child 6–12 years 175 mg every 12 hours
        - Child 12–18 years 175–350 mg every 12 hours
    - **SA 250 tablets**, m/r, scored, theophylline 250 mg. Net price 60-tab pack = £4.46. Label: 21, 25
    - Dose
      - **Chronic asthma**
        - **By mouth**
          - Child 6–12 years 125–250 mg every 12 hours
          - Child 12–18 years 250–500 mg every 12 hours

- **Nuelin SA** (3M)
  - Dose
    - **Chronic asthma**
      - **By mouth**
        - Child 6–12 years 175 mg every 12 hours
        - Child 12–18 years 175–350 mg every 12 hours

#### Modified release
- **Slo-Phyllin** (Merck)
  - **Capsules**, m/r, theophylline 60 mg (white/clear, enclosing white pellets), net price 56-cap pack = £2.76; 125 mg (brown/clear, enclosing white pellets), 56-cap pack = £3.48; 250 mg (blue/clear, enclosing white pellets), 56-cap pack = £4.34. Label: 25, or counselling, see below
  - Dose
    - **Chronic asthma**
      - **By mouth**
        - Child 6 months–2 years (body-weight under 10 kg) 12 mg/kg every 12 hours
        - Child 2–6 years (body-weight over 10 kg) 60–120 mg every 12 hours
        - Child 6–12 years 125–250 mg every 12 hours
        - Child 12–18 years 250–500 mg every 12 hours
    - **Administration** Contents of the capsule (enteric-coated granules) may be sprinkled on to a spoonful of soft food (e.g. yoghurt) and swallowed without chewing.
**THEOPHYLLINE (continued)**

Uniphyllin Continus® (Napp)

Tablets, m/r, scored, theophylline 200 mg, net price 56-tab pack = £3.13; 300 mg, 56-tab pack = £4.77; 400 mg, 56-tab pack = £5.65. Label: 25

**Dose**

**Chronic asthma**

- **By mouth**
  - **Child 2–12 years** 9 mg/kg (up to 200 mg) every 12 hours; some children with chronic asthma may require 10–16 mg/kg (max. 400 mg) every 12 hours

- **Child 12–18 years** 200 mg every 12 hours, increased according to response to 400 mg every 12 hours

**Note** May be appropriate to give larger evening or morning dose to achieve optimum therapeutic effect when symptoms most severe; in children whose night or daytime symptoms persist despite other therapy, who are not currently receiving theophylline, total daily requirement may be added as a single evening or morning dose.

**AMINOPHYLLINE**

**Note** Aminophylline is a stable mixture or combination of theophylline and ethylenediamine; the ethylenediamine confers greater solubility in water.

**Cautions** see under Theophylline; also rapid intravenous injection can cause arrhythmias.

**Side-effects** see under Theophylline; also allergy to ethylenediamine can cause urticaria, erythema, and exfoliative dermatitis.

**Licensed use** Minijet® Aminophylline not licensed for use in children under 6 months.

**Indication and dose**

- **Note** To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height.

**Chronic asthma** (see also Management of Chronic Asthma, p. 170)

- **By mouth**
  - See under preparations below.

**Severe acute asthma not previously treated with theophylline** (with close monitoring; see also Management of Acute Asthma, section 3.1)

- **By intravenous injection over at least 20 minutes**
  - **Child 1 month–18 years** 5 mg/kg (max. 500 mg) then by intravenous infusion

**Severe acute asthma** (with close monitoring; see also Management of Acute Asthma, section 3.1)

- **By intravenous infusion**
  - **Child 1 month–9 years** 1 mg/kg/hour adjusted according to plasma-theophylline concentration
  - **Child 9–16 years** 800 micrograms/kg/hour adjusted according to plasma-theophylline concentration
  - **Child 16–18 years** 500 micrograms/kg/hour adjusted according to plasma-theophylline concentration

**Note** Plasma-theophylline concentration for optimum response in asthma 10–20 mg/litre (55–110 micromol/litre); narrow margin between therapeutic and toxic dose, see also notes above on plasma-theophylline concentration; children taking oral theophylline or aminophylline should not normally receive intravenous aminophylline unless plasma-theophylline concentration is available to guide dosage.

**Neonatal apnoea** (but see notes above)

- **By intravenous injection over 20 minutes**
  - **Neonate** initially 6 mg/kg, then 2.5 mg/kg every 12 hours (increased if necessary to 3.5 mg/kg every 12 hours)

**Note** Plasma-theophylline concentration for optimum response in neonatal apnoea 8–12 mg/litre (44–66 micromol/litre), see also notes above.

**Administration** For intravenous infusion, dilute to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%.

**Aminophylline** (Non-proprietary) (Nap)

**Injection** aminophylline 25 mg/mL, net price 10-mL amp = 72p

Brands include Minijet® Aminophylline

**Injection** aminophylline 2 mg/mL, 20-mL amp; 5 mg/mL, 20-mL amp

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943.

**Phyllocontin Continus®** (Napp)

Tablets, m/r, yellow, f/c, aminophylline hydrate 225 mg, net price 56-tab pack = £2.54. Label: 25

**Dose**

**Chronic asthma** (see also Management of Chronic Asthma, p. 170)

- **By mouth**

**Note** Brands of modified-release tablets containing aminophylline 225 mg include Norphyllin® SR.

**3.1.4 Compound bronchodilator preparations**

In general, children 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.
Peak flow meters

Peak flow meters may be used to assess lung function in children over 5 years with asthma, but symptom monitoring is the most reliable assessment of asthma control. They are best used for short periods to assess the severity of asthma and to monitor response to treatment; continuous use of peak flow meters may detract from compliance with inhalers.

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)
- 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 (a child’s peak flow meter is 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 30–400 litres/minute, net price = £6.90, 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  A pressurised metered-dose inhaler is an effective method of drug administration in mild to moderate chronic asthma; to deliver the drug effectively, a spacer device should also be used (see also NICE guidance, below). By the age of 3 years, a child can usually be taught to use the spacer device without a mask. As soon as a child is able to use the mouthpiece, then this is the preferred delivery system.

Dry powder inhalers may be useful in children over 5 years, who are unwilling or unable to use a pressurised metered-dose inhaler with a spacer device; breath-actuated inhalers may be useful in older children if they are able to use the device effectively. The child or child’s carer should be instructed carefully on the use of the inhaler. It is important to check that the inhaler is being used correctly; poor inhalation technique may be mistaken for a lack of response to the drug.

On changing from a pressurised metered-dose inhaler to a dry powder inhaler, the child may notice a lack of sensation in the mouth and throat previously associated with each actuation; coughing may occur more frequently following use of a dry-powder inhaler.

CFC-free metered-dose inhalers should be cleaned weekly according to the manufacturer’s instructions.

NICE guidance

Inhaler devices for children with chronic asthma (children under 5 years, August 2000; children 5–15 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 infants, for children with poor inhalation technique, or for nocturnal asthma, because the device reduces 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 and allows more time for evaporation of the propellant so that a larger proportion of the particles can be inhaled and deposited in the lungs. Smaller-volume spacers may be more manageable for pre-school children and infants. The spacer device used must be compatible with the prescribed metered-dose inhaler.

Use and care of spacer devices  The suitability of the spacer device should be carefully assessed; opening the one-way valve is dependent on the child’s inspiratory flow. Some devices can be tipped to 45° to open the valve during inhaler actuation and inspiration to assist the child.

Inhalation from the spacer device should follow the actuation as soon as possible because the drug aerosol is very short-lived. The total dose (which may be more than a single puff) should be administered as single actuations (tidal breathing for 10–20 seconds or 5–6 breaths between each actuation) for children with good inspiratory flow. Larger doses may be necessary for a child with acute bronchospasm; for guidance on the Management of Acute Asthma, see section 3.1.

The device should be cleansed once a month by washing in mild detergent and air-drying. More frequent cleaning should be avoided since any electrostatic charge may affect drug delivery. Spacer devices should be replaced every 6–12 months.

AbleSpacer® (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, paediatric use with Flixotide®, Seretide®, Serevent®, 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. arthritis). For use with Flutotide®, Seretide®, Serevent®, and Ventolin® inhalers. Available as Haleraid®-120 for 120-dose inhalers and Haleraid®-200 for 200-dose inhalers, net price = 80p

Nebuhaler® (AstraZeneca)  
Spacer device, large-volume device. For use with Pulmicort® inhalers, net price 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 Clenil Modulite®, Flixotide®, Seretide®, Serevent®, and Ventolin® inhalers, net price = £2.75; with paediatric mask = £2.75

Nebulisers

In England and Wales nebulisers and compressors are not available on the NHS (but they are free of VAT); some nebulisers (but not compressors) are available on form GP10A in Scotland (for details consult Scottish Drug Tariff). For details of jet nebulisers, home compressors with nebulisers, and compressors, see current BNF.

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 beta₂ agonist or ipratropium to a child with an acute exacerbation of asthma or of airways obstruction;
- to deliver prophylactic medication to a child unable to use other conventional devices;
• to deliver an antibacterial (such as colistin or tobramycin) to a child 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 to a child with AIDS.

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 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 (antibacterial solutions usually being more viscous).

Some jet nebulisers are able to increase drug output during inspiration and hence increase efficiency.

Nebulised bronchodilators are appropriate for children with chronic persistent asthma or those with severe acute asthma. In chronic asthma, nebulised bronchodilators should only be used to relieve persistent daily wheeze (see Management of Chronic Asthma table, p. 170). The use of nebulisers in chronic persistent asthma should be considered only:

• after a review of the diagnosis and use of current inhaler devices;
• if the airflow obstruction is significantly reversible by bronchodilators without unacceptable side-effects;
• if the child does not benefit from use of conventional inhaler device, such as pressurised metered-dose inhaler plus spacer;
• if the child is complying with the prescribed dose and frequency of anti-inflammatory treatment including regular use of high-dose inhaled corticosteroid.

When a nebuliser is prescribed, the child or child’s carer must:

• have clear instructions from doctor, specialist nurse or pharmacist on the use of the nebuliser (and on peak-flow monitoring—see notes above);
• be instructed not to treat acute attacks without also seeking medical help;
• have regular follow up with doctor or specialist nurse.

Jet nebulisers are more widely used than ultrasonic nebulisers. Most jet nebulisers require an optimum flow rate of 6–8 litres/minute and in hospital can be driven by piped air or oxygen; in acute asthma the nebuliser should always be driven by oxygen. Domiciliary oxygen cylinders do not provide an adequate flow rate therefore an electrical compressor is required for domiciliary use.

Safe practice
The Department of Health has reminded users of the need to use the correct grade of tubing when connecting a nebuliser to a medical gas supply or compressor.

For a list of available devices see BNF (section 3.1.5).

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 x 2.5 mL = £5.49
Brands include Saline Steripoule®, Saline Steri-Neb®
Corticosteroids

Corticosteroids are effective in the management of asthma; they reduce airway inflammation.

An inhaled corticosteroid is used regularly for prophylaxis of asthma when a child requires a beta, agonist more than twice a week, or if symptoms disturb sleep more than once a week, or if the child has suffered exacerbations in the last 2 years requiring a systemic corticosteroid or a nebulised bronchodilator (see Management of Chronic Asthma, p.170).

In adults, current or 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 but may take longer. Beclometasone dipropionate (beclomethasone dipropionate), budesonide, fluticasone propionate, and mometasone furoate appear to be equally effective. A spacer device should be used for administering inhaled corticosteroids in children under 15 years (see NICE guidance, section 3.1.5); a spacer device is also useful in children over 15 years, particularly if high doses are required.

High doses of inhaled corticosteroids can be prescribed for children who respond only partially to standard doses of an inhaled corticosteroid and a long-acting beta, agonist or to other long-acting bronchodilators (see Management of Chronic Asthma, p.170). 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 it should be initiated and supervised by a respiratory paediatrician. The use of high doses of an inhaled corticosteroid can minimise the requirement for an oral corticosteroid.

Cautions of inhaled corticosteroids  Systemic therapy may be required during periods of stress, such as during severe infections, or when airways obstruction or mucus prevent drug access to smaller airways. An inhaled corticosteroid may be used during pregnancy and breast-feeding, see p.168; 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 if suitable).

CFC-free inhalers  Chlorofluorocarbon (CFC) propellants in pressurised aerosol inhalers are being replaced by hydrofluoroalkane (HFA) propellants. Carers of children and children receiving CFC-free pressurised 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, asthma nurse specialist, or pharmacist.

Doses for CFC-free corticosteroid inhalers may be different from those that contain CFCs, see also MHRA/CHM advice below.

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 beclometasone dipropionate CFC-containing inhalers, and is approximately twice as potent as Clenil Modulite®.

Side-effects of inhaled corticosteroids  Inhaled corticosteroids have considerably fewer systemic effects than oral corticosteroids, but adverse effects have been reported.

High doses of inhaled corticosteroids (see Management of Chronic Asthma, p.170) used for prolonged periods can induce adrenal suppression. Inhaled corticosteroids have occasionally been associated with adrenal crisis and coma in children; excessive doses should be avoided. Children using high doses of inhaled corticosteroids should be under the supervision of a paediatrician for the duration of the treatment; they 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 a severe intercurrent illness or an operation.

In adults, bone mineral density is sometimes 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 child’s asthma under good control.

Growth restriction associated with systemic corticosteroid therapy does not seem to occur with recommended doses of inhaled corticosteroids; 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 with inhaled corticosteroid is monitored; if growth is slowed, referral to a paediatrician should be considered.

Hoarseness and candidiasis of the mouth or throat have been reported, usually only with high doses (see also below). Hypersensitivity reactions (including rash and angioedema) have been reported rarely. Other side-effects that have very rarely been reported 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 the 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 while continuing corticosteroid therapy.

Oral An acute attack of asthma should be treated with a short course (3–5 days) of oral corticosteroid, see Management of Acute Asthma, p. 168. 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 children with poorer asthma control, to reduce the possibility of serious relapse.

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.

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.

Parenteral For the use of hydrocortisone injection in the emergency treatment of acute severe asthma, see Management of Acute Asthma, p. 168.

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**BECLOMETASONE DIPROPIONATE**
(Beclometasone Dipropionate)

**Cautions** see notes above

**Side-effects** see notes above

**Licensed use** Becodisk®-400, Clenil Modulate®-200 and -250, and Qvar® are not licensed for use in children under 12 years

**Indication and dose**

**Prophylaxis of asthma** see Management of Chronic Asthma, p. 170 Important for Asmabec Clickhaler®, Becodisks®, and Qvar® doses see under preparations below

Beclometasone (Non-proprietary) (BN)
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

Brands include Beclazone®, Beclometasone Dipropionate, Easyhaler®, Pulsinal®

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

Brands include Pulvina® 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

Brands include Beclometasone Cyclocaps®
Respiratory system

Asmabec Clickhaler® (UCB Pharma) [Note]
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

- Prophylaxis of asthma
  - By inhalation of powder
    - Child 6–12 years 50–200 micrograms twice daily, adjusted as necessary
    - Child 12–18 years 100–400 micrograms twice daily, adjusted as necessary; max. 1 mg twice daily

Beclazone Easi-Breathe® (IVAX) [Note]
Aerosol inhalation (breath-actuated), beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £3.26; 100 micrograms/metered inhalation, 200-dose unit = £10.30; 50 micrograms/metered inhalation, 200-dose unit = £20.25. Label: 8, counselling, dose; also 10 and steroid card with high doses

Excipients include CFC propellants

Becodisks® (A&H) [Note]
Dry powder for inhalation, disks containing 8 blisters of beclometasone dipropionate 100 micrograms/b blister, net price 15 disks with Diskhaler® device = £12.00, 15-disk refill = £11.42; 200 micrograms/b blister, 15 disks with Diskhaler® device = £22.87, 15-disk refill = £22.28; 400 micrograms/b blister, 15 disks with Diskhaler® device = £45.14, 15-disk refill = £44.57. Label: 8, counselling, dose; also 10 and steroid card with high doses

Excipients include CFC propellants

Clenil Modulite® (Chiesi) ▼ [Note]
Aerosol inhalation, beclometasone dipropionate 50 micrograms/metered inhalation, net price 200-dose unit = £3.85; 100 micrograms/metered inhalation, 200-dose unit = £7.72; 200 micrograms/metered inhalation = £16.83. 50 micrograms/metered inhalation = £16.95. Label: 8, counselling, dose; also 10 and steroid card with high doses

Excipients include HFA-134a (a non-CFC propellant)

Dose

- Prophylaxis of asthma
  - By aerosol inhalation
    - Child 12–18 years 50–200 micrograms twice daily, increased if necessary to max. 400 micrograms twice daily

Important: When switching a child with well-controlled asthma from another corticosteroid inhaler, initially a 100-microgram metered dose of Qvar® should be prescribed for:

- 200–250 micrograms of beclometasone dipropionate or budesonide
- 100 micrograms of fluticasone propionate

When switching a child 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.

Note: The MHRA has advised (August 2006 and July 2008) that beclometasone dipropionate CFC-free inhalers should be prescribed by brand name.

Qvar® (IVAX) [Note]
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

Excipients include HFA-134a (a non-CFC propellant)

Autohaler® (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

Excipients include HFA-134a (a non-CFC propellant)

Dose

- Prophylaxis of asthma
  - By aerosol inhalation
    - Child 12–18 years 50–200 micrograms twice daily

BUDESONIDE

Cautions see notes above
Side-effects see notes above
Licensed use Pulmicort® nebuliser solution not licensed for use in children under 3 months; not licensed for use in bronchopulmonary dysplasia

Indication and dose

Prophylaxis of asthma see Management of Chronic Asthma, p. 170, and preparations below

Croup

- By inhalation of nebuliser suspension
  - Child over 1 month 2 mg as single dose or in 2 divided doses separated by 30 minutes; dose may be repeated after 12 hours if necessary
Budesonide (continued)

**Bronchopulmonary dysplasia with assisted ventilation**
- By aerosol inhalation

**Neonate** 400 micrograms twice daily

**Child 1–4 months** 400 micrograms twice daily

**Bronchopulmonary dysplasia with spontaneous respiration**
- By inhalation of nebuliser suspension

**Neonate** 500 micrograms twice daily

**Child 1–4 months** 500 micrograms twice daily; for severe symptoms in child body-weight 2.5 kg or over, 1 mg twice daily

**Administration** For aerosol inhalation in ventilated babies with bronchopulmonary dysplasia, use medium-volume spacer (section 3.1.5) attached directly to endotracheal tube; hand-ventilate through spacer, using a bag system; inflate chest 10 times between activations of inhaler

**Budesonide** (Non-proprietary) (AstraZeneca)

Dry powder for inhalation, budesonide 100 micrograms/metered inhalation, net price 200-dose unit = £9.25; 400 micrograms/metered inhalation, 100-dose unit = £18.50. Label: 8, counselling, dose; also 10 and steroid card with high doses

Brands include Easyhaler®, Budesonide

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

Brands include Budesonide Cyclohaler®

**Dose**

**Prophylaxis of asthma**
- By inhalation of powder
  - Child 6–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses
  - Child 12–18 years 100–400 micrograms twice daily, adjusted as necessary; max. 800 micrograms twice daily

**Novolizer®** (Viatris)(AstraZeneca) (AstraZeneca)

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

**Dose**

**Prophylaxis of asthma**
- By inhalation of powder
  - Child 6–12 years 200–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses
  - Child 12–18 years 200–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses (max. 800 micrograms)

**Compound preparations**

**Symbicort®** (AstraZeneca) (AstraZeneca)

Symbicort 100/6 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**

**Prophylaxis of asthma**
- By inhalation of powder
  - Child 6–12 years 100–400 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses
  - Child 12–18 years 100–800 micrograms twice daily, adjusted as necessary; alternatively, in mild to moderate asthma, 200–400 micrograms as a single dose each evening if stabilised on daily dose given in 2 divided doses (max. 800 micrograms)

**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

**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 nebuliser suspension
  - Child 3 months–12 years initially 0.5–1 mg twice daily, reduced to 250–500 micrograms twice daily
  - Child 12–18 years initially 1–2 mg twice daily, reduced to 0.5–1 mg twice daily

**Pulmicort®** (AstraZeneca) (AstraZeneca)

Aerosol inhalation, budesonide 100 micrograms/ metered inhalation, net price 120-dose unit = £9.60; 200 micrograms/metered inhalation, net price 120-dose unit = £13.20. Label: 8, counselling, dose, change to CFC-free inhaler; also 10 and steroid card with high doses

Excipients include HFA–134a (a non-CFC propellant)
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

Prophylaxis of asthma
• By inhalation of powder
Child 12–18 years 1–2 puffs twice daily reduced in well-controlled asthma to 1 puff once daily

Ciclesonide

Cautions see notes above
Side-effects see notes above
Indication and dose

Prophylaxis of asthma see Management of Chronic Asthma, p. 170, and preparations below

FLUTICASONE PROPIONATE

Cautions see notes above
Side-effects see notes above; also very rarely dyspepsia, hyperglycaemia, and arthralgia
Indication and dose

Prophylaxis of asthma see Management of Chronic Asthma, p. 170, and preparations below

Flixotide® (A&H) (Nycomed)

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 = £21.26; 500 micrograms/blister with Accuhaler® device = £36.14. Label: 8, counselling, dose; also 10 and steroid card with high doses

Dose

Prophylaxis of asthma
• By inhalation of powder
Child 5–16 years 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily
Child 16–18 years 100–500 micrograms twice daily, adjusted as necessary; max. 1 mg twice daily

Diskhaler® (dry powder for inhalation), fluticasone propionate 100 micrograms/blister, net price 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 10 and steroid card with high doses

Dose

Prophylaxis of asthma
• By inhalation of powder
Child 5–16 years 100–200 micrograms twice daily
Child 16–18 years 100–500 micrograms twice daily adjusted as necessary; max. 1 mg 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

Prophylaxis of asthma
• By inhalation of powder
Child 12–18 years 1 puff twice daily; may be reduced in well-controlled asthma to 1 puff once daily

Alvesco® (Nycomed) (A&H)

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)

Dose

Prophylaxis of asthma
• By aerosol inhalation
Child 4–16 years 50–100 micrograms twice daily adjusted as necessary; max. 200 micrograms twice daily
Child 16–18 years 100–500 micrograms twice daily adjusted as necessary; max. 1 mg twice daily

Nebules® (= 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

Prophylaxis of asthma
• By inhalation of nebuliser suspension
Child 4–16 years 1 mg twice daily
Child 16–18 years 0.5–2 mg twice daily

Compound preparations

Seretide® (A&H) (Nycomed)

Seretide 100 Accuhaler® (dry powder for inhalation), disk containing 60 blisters of fluticasone propionate 100 micrograms, salmeterol (as xinafoate) 50 micrograms/blister with Accuhaler® device, net price = £31.19. Label: 8, counselling, dose

Dose

Prophylaxis of asthma
• By inhalation of powder
Child 5–18 years 1 blister twice daily, reduced to 1 blister once daily if control maintained
Asmanex® (Schering-Plough) ▼ [3M]
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.

**3.3.1 Cromoglicate and related therapy**

The mode of action of sodium cromoglicate and nedocromil is not completely understood; they may be of value as prophylaxis in asthma with an allergic basis, but the evidence for benefit of sodium cromoglicate in children is contentious. Prophylaxis with cromoglicate or nedocromil is less effective than with inhaled corticosteroids (see Management of Chronic Asthma, p. 170).

Nedocromil may be of some benefit in the prophylaxis of exercise-induced asthma.
For the use of sodium cromoglicate and nedocromil in allergic conjunctivitis see section 11.4.2; sodium cromoglicate is used also in allergic rhinitis (section 12.2.1) and allergy-related diarrhoea (section 1.5.4).

### SODIUM CROMOGLICATE
(Sodium Cromoglycate)

**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

**Indication and dose**
Prophylaxis of asthma (see also Management of Chronic Asthma, p. 170)
- By aerosol inhalation
  - Child 5–18 years 10 mg (2 puffs) 4 times daily, increased if necessary to 6–8 times daily; an additional dose may also be taken before exercise; maintenance, 5 mg (1 puff) 4 times daily

**Food allergy** section 1.5.4

**Allergic conjunctivitis** section 11.4.2

**Allergic rhinitis** section 12.2.1

**Intal® CFC-free inhaler** (Sanofi-Aventis) • 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

**Side-effects** see under Sodium Cromoglicate; also headache, nausea, vomiting, dyspepsia and abdominal pain; bitter taste (masked by mint flavour)

**Licensed use** not licensed for use in children under 6 years

**Indication and dose**
Prophylaxis of asthma (but see notes above)
- Counselling Regular use is necessary
- By aerosol inhalation
  - Child 5–18 years 4 mg (2 puffs) 4 times daily, when control achieved may be possible to reduce to twice daily

**Allergic conjunctivitis** section 11.4.2

**Tilade CFC-free inhaler®** (Sanofi-Aventis) ▼ • 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)

### Leukotriene receptor antagonists

**MONTELUKAST**

**Cautions** interactions: Appendix 1 (leukotriene receptor antagonists)
- Pregnancy manufacturer advises avoid unless essential
- Breast-feeding manufacturer advises avoid unless essential

**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, palpitation, oedema, increased bleeding, hypersensitivity reactions (including anaphylaxis and skin reactions), depression, tre-
mor, asthenia, dizziness, hallucinations, suicidal thoughts and behaviour, paraesthesia, hypoaesthesia, sleep disturbances, abnormal dreams, agitation, aggression, seizures, arthr-algia, and myalgia also reported

Indication and dose

Prophylaxis of asthma see notes above and Management of Chronic Asthma, p. 170
- By mouth
  - Child 6 months–6 years 4 mg once daily in the evening
  - Child 6–15 years 5 mg once daily in the evening
  - Child 15–18 years 10 mg once daily in the evening

Symptomatic relief of seasonal allergic rhinitis in children with asthma
- By mouth
  - Child 15–18 years 10 mg once daily in the evening

Singular® (MSD)
Chewable tablets, pink, cherry-flavoured, monte-lukast (as sodium salt) 4 mg, net price 28-tab pack = £25.69; 5 mg, 28-tab pack = £26.69. Label: 24
Excipients include aspartame equivalent to phenylalanine 67.6 micrograms/4-mg tablet and 84.2 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 whole or mixed with cold food (but not fluid) and taken immediately
Tablets, beige, f/c, 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

Cautions interactions: Appendix 1 (leukotriene receptor antagonists)
Hepatic disorders Children 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
Renal impairment manufacturer advises caution in moderate to severe impairment
Pregnancy manufacturer advises use only if potential benefit outweighs risk
Contra-indications hepatic impairment
Breast-feeding present in milk—manufacturer advises avoid
Side-effects gastro-intestinal disturbances; headache; rarely bleeding disorders, hypersensitivity reactions including angioedema and skin reactions, arthr-algia, myalgia, hepatitis, hyperbiliru-binaemia, thrombocytopenia; very rarely Churg-Strauss syndrome (see notes above), agranulo-cytosis

Indication and dose

Prophylaxis of asthma see notes above and Management of Chronic Asthma, p. 170
- By mouth
  - Child 12–18 years 20 mg twice daily

Accolate® (AstraZeneca)
Tablets, f/c, zafirlukast 20 mg, net price 56-tab pack = £28.26. Label: 23

3.4 Antihistamines, immunotherapy, and allergic emergencies

3.4.1 Antihistamines

Antihistamines (histamine H1-receptor antagonists) are classified as sedating or non-sedating, according to their relative potential for CNS depression. Antihistamines differ in their duration of action, incidence of drowsiness, and antimuscarinic effects; the response to an antihistamine may vary from child to child (see Side-effects, p. 192). Either a sedating or a non-sedating antihistamine may be used to treat an acute allergic reaction; for conditions with more persistent symptoms, a non-sedating antihistamine should be used regularly.

Oral antihistamines are used in the treatment of nasal allergies, particularly seasonal allergic rhinitis (hay fever), and may be of some value in vasomotor rhinitis; rhinorrhoea and sneezing is reduced, but antihistamines are usually less effective for nasal congestion. Antihistamines are used topically to treat allergic
reactions in the eye (section 11.4.2) and in the nose (section 12.2.1). Topical application of antihistamines to the skin is not recommended (section 13.3).

An oral antihistamine may be used to prevent urticaria, and for the treatment of acute urticarial rashes, pruritus, insect bites, and stings. Antihistamines are also used in the management of nausea and vomiting (section 4.6), of migraine (section 4.7.4.1), and the adjunctive management of anaphylaxis and angioedema (section 3.4.3).

Sedating antihistamines are occasionally useful when insomnia is associated with urticaria and pruritus (section 4.1.1). Most of the sedating antihistamines are relatively short acting, but promethazine may be effective for up to 12 hours. **Alimemazine** (trimeprazine) and **promethazine** have a more sedative effect than **chlorphenamine** (chlorpheniramine) and **cyclizine** (section 4.6). Chlorphenamine is used as an adjunct to adrenaline (epinephrine) in the emergency treatment of anaphylaxis and angioedema (section 3.4.3).

The non-sedating antihistamine **ceﬁrizine** is safe and effective in children; it causes less sedation and psychomotor impairment than the sedating antihistamines. Other non-sedating antihistamines that are used in children include **desloratadine** (an active metabolite of loratadine), **fexofenadine** (an active metabolite of terfenadine), **levocetirizine** (an isomer of cetirizine), **loratadine**, and **mizolastine**. Most non-sedating antihistamines are long-acting (usually 12–24 hours). There is little evidence that desloratadine or levocetirizine confer any additional benefit—they should be reserved for children who cannot tolerate other therapies.

**Cautions and contra-indications** Antihistamines should be used with caution in hepatic impairment (see below) and in children with epilepsy. Most antihistamines should be avoided in acute porphyria, but some are thought to be safe (see section 9.8.2). Sedating antihistamines should not be given to children under 2 years, except on specialist advice, because the safety of such use has not been established. Sedating antihistamines have signiﬁcant antimuscarinic activity—they should not be used in neonates and should be used with caution in children with urinary retention, glaucoma, or pyloroduodenal obstruction. **Interactions**: see Appendix 1 (antihistamines).

**Hepatic impairment** Sedating antihistamines should be avoided in children with severe liver disease—increased risk of coma.

**Pregnancy and breast-feeding** There is no evidence of teratogenicity associated with the use of antihistamines, except for hydroxyzine and loratadine where embryotoxicity has been reported with high doses in animal studies. However, manufacturers of some antihistamines advise avoiding use during pregnancy. The use of sedating antihistamines in the latter part of the third trimester may cause adverse effects in neonates such as irritability, paradoxical excitability, and tremor. Significant amounts of some antihistamines are present in breast milk; although not known to be harmful, manufacturers advise avoiding use in mothers who are breast-feeding.

**Side-effects** Drowsiness is a significant side-effect with most of the older antihistamines although paradoxical stimulation may occur rarely in children, especially with high doses. Drowsiness may diminish after a few days of treatment and is considerably less of a problem with the newer antihistamines (see also notes above). Side-effects that are more common with the older antihistamines include headache, psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances. Other rare side-effects of antihistamines include hypotension, palpitation, arrhythmias, extrapyramidal effects, dizziness, confusion, depression, sleep disturbances, tremor, convulsions, hypersensitivity reactions (including bronchospasm, angioedema, anaphylaxis, rashes, and photosensitivity reactions), blood disorders, and liver dysfunction.

**Non-sedating antihistamines**

**Skilled tasks** Although drowsiness is rare, children and their carers should be advised that it can occur and may affect performance of skilled tasks (e.g. cycling or driving); alcohol should be avoided.
CETIRIZINE HYDROCHLORIDE

Cautions see notes above

Renal impairment use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 6 years except for use in children 2–6 years for treatment of seasonal allergic rhinitis

Indication and dose

Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria, atopic dermatitis

Child 1–2 years 250 micrograms/kg twice daily

Cetirizine (Non-proprietary)

Tablets, cetirizine hydrochloride 10 mg, net price 30-tab pack = £9.76. Counselling, skilled tasks

Dental prescribing on NHS Cetirizine 10 mg tablets may be prescribed

Oral solution, cetirizine hydrochloride 5 mg/5 mL, net price 200 mL = £2.43. Counselling, skilled tasks

DESLORATADINE

Note Desloratadine is a metabolite of loratadine

Cautions see notes above; also hypersensitivity to loratadine

Contra-indications see notes above

Side-effects see notes above; rarely myalgia; very rarely hallucinations

Indication and dose

Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria

Child 1–6 years 1.25 mg once daily

Child 6–12 years 2.5 mg once daily

Neoclarityn® (Schering-Plough) [P] Tablets, blue, f/c, desloratadine 5 mg, net price 30-tab pack = £7.04. Counselling, skilled tasks

Syrup, desloratadine 2.5 mg/5 mL, net price 100 mL (bubblegum-flavour) = £7.04. Counselling, skilled tasks

FEXOFENADINE HYDROCHLORIDE

Note Fexofenadine is a metabolite of terfenadine

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Indication and dose

Symptomatic relief of seasonal allergic rhinitis

Child 6–12 years 30 mg twice daily

Child 12–18 years 120 mg once daily

Symptomatic relief of chronic idiopathic urticaria

Child 12–18 years 180 mg once daily

Fexofenadine (Non-proprietary) [P] Tablets, f/c, fexofenadine hydrochloride 120 mg, net price 30-tab pack = £5.92; 180 mg, 30-tab pack = £7.49. Label: 5, counselling, skilled tasks

Telfast® (Aventis Pharma) [P] 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, skilled tasks

LEVOCETIRIZINE HYDROCHLORIDE

Note Levocetirizine is an isomer of cetirizine

Cautions see notes above

Renal impairment estimated glomerular filtration rate 30–50 mL/minute/1.73 m², reduce dose frequency to alternate days; estimated glomerular filtration rate 10–30 mL/minute/1.73 m², reduce dose frequency to every 3 days; estimated glomerular filtration rate less than 10 mL/minute/1.73 m², avoid

Contra-indications see notes above

Side-effects see notes above; very rarely weight gain

Licensed use tablets not licensed for use in children under 6 years

Indication and dose

Symptomatic relief of allergy such as hay fever, urticaria

Child 2–6 years 1.25 mg twice daily

Child 6–18 years 5 mg once daily
LEVOCETIRIZINE HYDROCHLORIDE (continued)

Xyzal® (UCB Pharma) (58)
Tablets, f/c, levocetirizine hydrochloride 5 mg, net price 30-tab pack = £5.20. Counselling, skilled tasks

LORATADINE

Cautions  see notes above
Contra-indications  see notes above
Side-effects  see notes above

Indication and dose
Symptomatic relief of allergy such as hay fever, chronic idiopathic urticaria
• By mouth
  Child 2–6 years 5 mg once daily
  Child 6–18 years 10 mg once daily

Loratadine (Non-proprietary)
Tablets, loratadine 10 mg, net price 30-tab pack = £1.24. Counselling, skilled tasks
Dental prescribing on NHS Loratadine 10 mg tablets may be prescribed
Syrup, loratadine 5 mg/5 mL, net price 100 mL = £5.16. Counselling, skilled tasks

MIZOLASTINE

Cautions  see notes above
Contra-indications  see notes above; also susceptibility to QT-interval prolongation (including cardiac disease and hypokalaemia)
Hepatic impairment  manufacturer recommends avoid in significant hepatic impairment
Side-effects  see notes above; weight gain; anxiety, asthenia; less commonly arthralgia and myalgia

Indication and dose
Symptomatic relief of allergy such as hay fever, urticaria
• By mouth
  Child 12–18 years 10 mg once daily

Mizollen® (Sanofi-Aventis) (76)
Tablets, m/r, f/c, scored, mizolastine 10 mg, net price 30-tab pack = £5.77. Label: 25, counselling, skilled tasks

Sedating antihistamines

Skilled tasks  Drowsiness may affect performance of skilled tasks (e.g. cycling or driving); sedating effects enhanced by alcohol.

ALIMEMAZINE TARTRATE
(Trimeprazine tartrate)

Cautions  see notes above
Contra-indications  see notes above
Renal impairment  avoid
Side-effects  see notes above
Licensed use  not licensed for use in children under 2 years

Indication and dose
Urticaria, pruritus
• By mouth
  Child 6 months–2 years 250 micrograms/kg (max. 2.5 mg) 3–4 times daily—specialist use only
  Child 2–5 years 2.5 mg 3–4 times daily
  Child 5–12 years 5 mg 3–4 times daily
  Child 12–18 years 10 mg 2–3 times daily, in severe cases up to max. 100 mg daily

Premedication  section 15.1.4
• By mouth
  Child 2–7 years up to max. 2 mg/kg 1–2 hours before operation

Vallergan® (Sanofi-Aventis) (76)
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

CHLORPHENAMINE MALEATE
(Chlorpheniramine maleate)

Cautions  see notes above
Contra-indications  see notes above

Side-effects  see notes above; also exfoliative dermatitis and tinnitus reported; injections may cause transient hypotension or CNS stimulation and may be irritant
CHLORPHENAMINE MALEATE (continued)

Licensed use  syrup not licensed for use in children under 1 year; tablets not licensed for use in children under 6 years; injection not licensed for use in neonates

Indication and dose
Symptomatic relief of allergy such as hay fever, urticaria
- By mouth
  - Child 1 month–2 years 1 mg twice daily
  - Child 2–6 years 1 mg every 4–6 hours, max. 6 mg daily
  - Child 6–12 years 2 mg every 4–6 hours, max. 12 mg daily
  - Child 12–18 years 4 mg every 4–6 hours, max. 24 mg daily

Emergency treatment of anaphylactic reactions, symptomatic relief of allergy
- By intramuscular or intravenous injection
  - Child under 6 months 250 micrograms/kg (max. 2.5 mg), repeated if required up to 4 times in 24 hours
  - Child 6 months–6 years 2.5 mg, repeated if required up to 4 times in 24 hours
  - Child 6–12 years 5 mg, repeated if required up to 4 times in 24 hours
  - Child 12–18 years initially 25 mg at night, increased if necessary to 100 mg in 3–4 divided doses

Administration for intravenous injection, give over 1 minute; if small dose required, dilute with Sodium Chloride 0.9%

Chlorphenamine (Non-proprietary)
- Tablets, chlorphenamine maleate 4 mg, net price 28 = £1.12. Label: 2
- Oral solution, chlorphenamine maleate 2 mg/5 mL, net price 150 mL = £2.25. Label: 2

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

HYDROXYZINE HYDROCHLORIDE

Cautions see notes above
- Renal impairment use half normal dose
Contra-indications see notes above

Licensed use Ucerax® syrup not licensed for use in children under 1 year

Indication and dose
Pruritus
- By mouth
  - Child 6 months–6 years initially 5–15 mg at night, increased if necessary to 50 mg daily in 3–4 divided doses
  - Child 6–12 years initially 15–25 mg at night, increased if necessary to 50–100 mg daily in 3–4 divided doses

Atarax® (Alliance)
- 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)
  - 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

Cautions see notes above
Contra-indications see notes above

Licensed use Zaditen® tablets, scored, ketotifen (as hydrogen fumarate) 1 mg, net price 60-tab pack = £10.75. Label: 2, 21

Indication and dose
Symptomatic relief of allergy such as allergic rhinitis
- By mouth
  - Child 3–18 years 1 mg twice daily

Zaditen® (Novartis)
- Tablets, scored, ketotifen (as hydrogen fumarate) 1 mg, net price 60-tab pack = £10.75. Label: 2, 21
- Elixir, ketotifen (as hydrogen fumarate), 1 mg/5 mL, net price 300 mL (strawberry-flavoured) = £12.73. Label: 2, 21
**PROMETHAZINE HYDROCHLORIDE**

**Cautions**  
see notes above

**Contra-indications**  
see notes above; severe coronary artery disease

**Side-effects**  
see notes above; also restlessness

**Indication and dose**

Symptomatic relief of allergy such as hay fever, insomnia associated with urticaria and pruritus

- **By mouth**
  - **Child 2–5 years**  5 mg twice daily or 5–15 mg at night
  - **Child 5–10 years**  5–10 mg twice daily or 10–25 mg at night
  - **Child 10–18 years**  10–20 mg 2–3 times daily or 25 mg at night increased to 25 mg twice daily if necessary

**Sedation**  
section 4.1.1

**Nausea and vomiting**  
section 4.6

**Phenergan®**  (Sanofi-Aventis)

*Tablets*, both blue, f/c, promethazine hydrochloride 10 mg, net price 56-tab pack = £2.05; 25 mg, 56-tab pack = £3.06. Label: 2

*Dental prescribing on NHS*  
May be prescribed as Promethazine Hydrochloride Tablets 10 mg or 25 mg

*Elixir*, golden, promethazine hydrochloride 5 mg/5 mL. Net price 100 mL = £1.93. Label: 2

*Dental prescribing on NHS*  
May be prescribed as Promethazine Hydrochloride Oral Solution 5 mg/5 mL

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**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 improve symptoms of asthma and allergic rhino-conjunctivitis in children. A vaccine containing extracts of wasp and bee venom is used to reduce the risk of severe anaphylaxis and systemic reactions in children with hypersensitivity to wasp and bee stings. Children requiring immunotherapy must be referred to a hospital specialist for accurate allergy diagnosis, assessment, and treatment.

In view of concerns about the safety of desensitising vaccines, it is recommended that they are used by specialists and only for the following indications:

- seasonal allergic hay fever (caused by pollen) that has not responded to anti-allergic drugs;
- hypersensitivity to wasp and bee venom.

Desensitising vaccines should generally be avoided or used with particular care in children with asthma.

Desensitising vaccines should be avoided in pregnant women, in children under 5 years, and in those taking beta-blockers (adrenaline will be ineffective if a hypersensitivity reaction occurs), 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 the child needs to be monitored for at least 1 hour after injection. If symptoms or signs of hypersensitivity develop (e.g. rash, urticaria, bronchospasm, faintness), **even when mild**, the child 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. Maintenance sets containing vials at the highest strength are also available. Product literature must be consulted for details of allergens, vial strengths, and administration.

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**BEE AND WASP ALLERGEN EXTRACTS**

**Cautions**  
see notes above and consult product literature

**CSM advice**  
The CSM has advised that facilities for cardiopulmonary resuscitation must be immediately available and children monitored closely for 1 hour after each injection

**Contra-indications**  
see notes above and consult product literature

**Side-effects**  
consult product literature

**Indication and dose**

**Hypersensitivity to wasp or bee venom**  
(see notes above)

- **By subcutaneous injection**
  Consult product literature
Pharmalgen® (ALK-Abelô) ▼

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

#### Cautions

See notes above and consult product literature

**CSM advice** The CSM has advised that facilities for cardiopulmonary resuscitation must be immediately available and children must be monitored closely for 1 hour after each injection

#### Contra-indications

See notes above and consult product literature

#### Side-effects

Consult product literature

#### Indication and dose

**Treatment of seasonal allergic hay fever due to grass or tree pollen** (see notes above)

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 mouth*

Child 5–18 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 children over 12 years with proven IgE-mediated sensitivity to inhaled allergens, whose severe persistent allergic asthma cannot be controlled adequately with high-dose inhaled corticosteroid together with a long-acting beta2 agonist. 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 or withdrawal 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.
OMALIZUMAB

Cautions
- autoimmune disease; susceptibility to helminth infections—discontinue if infection does not respond to anthelmintic
- Hepatic impairment: manufacturer advises caution—no information available
- Renal impairment: manufacturer advises caution—no information available
- Pregnancy: manufacturer advises avoid unless essential; no evidence of teratogenicity in animal studies

Contra-indications
- Breast-feeding: manufacturer advises avoid—present in milk in animal studies

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, laryngoedema, rash, pruritus, serum sickness, and anaphylaxis); Churg-Strauss syndrome (see notes above), thrombocytopenia, arthralgia, myalgia, and alopecia also reported

Indication and dose
- Prophylaxis of severe persistent allergic asthma (see notes above)
  - By subcutaneous injection
    - Child 12–18 years according to immunoglobulin E concentration and body-weight, consult product literature

Xolair® (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, allergen immunotherapy 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 when giving injections associated with special risk. 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.

Treatment of anaphylaxis

First-line treatment includes:
- securing the airway, restoration of blood pressure (laying the child flat and raising the legs, or in the recovery position if unconscious or nauseous and at risk of vomiting);
- administering adrenaline (epinephrine) by intramuscular injection (for doses see Intramuscular Adrenaline, p. 199); the dose should be repeated if necessary at 5-minute intervals according to blood pressure, pulse, and respiratory function [important: possible need for intravenous route using dilute solution (Adrenaline 1 in 10 000), see Intravenous Adrenaline p. 199];
- administering high-flow oxygen (section 3.6) and intravenous fluids (section 9.2.2);
- administering an antihistamine, such as chlorphenamine (chlorpheniramine), by slow intravenous injection or intramuscular injection (section 3.4.1) as adjunctive treatment given after adrenaline injection and the antihistamine continued orally for 24 to 48 hours according to clinical response to prevent relapse.

Continuing respiratory deterioration requires further treatment with bronchodilators including inhaled or intravenous salbutamol (see p. 174), inhaled ipratropium (see p. 178), intravenous aminophylline (see p. 180), or intravenous magnesium sulphate [unlicensed indication] (see Management of Acute Asthma,
In addition to oxygen, assisted respiration and possibly emergency tracheotomy may be necessary. An intravenous corticosteroid (section 6.3.2) such as hydrocortisone (as sodium succinate) 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 children and continued for 24–48 hours according to clinical response. When a child is so ill that there is doubt as to the adequacy of the circulation, the initial injection of adrenaline may need to be given as a dilute solution by the intravenous route, or by the intraosseous route if venous access is difficult—for details of cautions, dose and strength, see under Intravenous Adrenaline (Epinephrine), below. Some children with severe allergy to insect stings or foods are encouraged to carry prefilled adrenaline syringes for self-administration during periods of risk. Children 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 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 Intravenous Adrenaline (Epinephrine), below.

Carers of children or the child with severe allergy should ideally be instructed in the self-administration of adrenaline by intramuscular injection (for details see Self-administration of Adrenaline (Epinephrine), p. 200).

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 range</th>
<th>Dose</th>
<th>Volume of adrenaline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 in 1000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(1 mg/mL)</td>
</tr>
<tr>
<td>Under 6 years</td>
<td>150 micrograms</td>
<td>0.15 mL&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>6–12 years</td>
<td>300 micrograms</td>
<td>0.3 mL&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>12–18 years</td>
<td>500 micrograms</td>
<td>0.5 mL&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

These doses may be repeated several times if necessary at 5-minute intervals according to blood pressure, pulse and respiratory function.

1. Use suitable syringe for measuring small volume  
2. 300 micrograms (0.3 mL) if child is small or prepubertal

### Intravenous adrenaline (epinephrine)

Intravenous adrenaline should be given only by those experienced in its use, in a setting where patients can be carefully monitored; it should be given to children only when intravenous access is already available.

Where the child is severely ill and there is real doubt about adequacy of the circulation and absorption from the intramuscular injection site, adrenaline may be given by slow intravenous injection. 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, repeated according to response. A single dose of adrenaline by intravenous injection should not exceed 50 micrograms; if multiple doses are required consider giving adrenaline by slow intravenous infusion. 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 acute hypotension, see section 2.7.2.

Self-administration of adrenaline (epinephrine)

Children at considerable risk of anaphylaxis need to carry (or have available) adrenaline at all times and the child, or child’s carers, need to be instructed in advance how to inject it. Packs for self-administration need to be clearly labelled with instructions on how to administer adrenaline (intramuscularly, preferably at the midpoint of the outer thigh, through light clothing if necessary). 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 (e.g. Anapen® or EpiPen®) 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). A syringe delivering 300 micrograms of adrenaline is recommended for a child over 30 kg. A syringe delivering 150 micrograms of adrenaline is recommended for a child 15–30 kg, but on the basis of a dose of 10 micrograms/kg, 300 micrograms may be more appropriate for some children.
ADRENALINE/EPINEPHRINE (continued)

Intravenous

Extreme caution, see notes above

Adrenaline/Epinephrine 1 in 10 000, Dilute (Non-proprietary) [PH]

Injection, adrenaline (as acid tartrate) 100 micrograms/mL, 10-mL amp, 1-mL and 10-mL prefilled syringe
Excipients include sulphites

Minijet® Adrenaline 1 in 10 000 (UCB Pharma) [PH]

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

Intramuscular injection for self-administration

Anapen® (Lincoln Medical) [PH]

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

Acute anaphylaxis
• By intramuscular injection
  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

Acute anaphylaxis
• 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 10–15 minutes as necessary

EpiPen® (ALK-Abelô) [PH]

1 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

Acute anaphylaxis
• By intramuscular injection
  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

Acute anaphylaxis
• 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. In some children with laryngeal oedema, adrenaline 1 in 1000 (1 mg/mL) solution may be given by nebuliser. However, nebulised adrenaline cannot be relied upon for a systemic effect—intramuscular adrenaline should be used.

Hereditary angioedema

The administration of C_1_ esterase inhibitor (in fresh frozen plasma or in partially purified form) may terminate acute attacks of hereditary angioedema, but is not practical for long-term prophylaxis. Tranexamic acid (section 2.11) is used for short-term or long-term prophylaxis of hereditary angioedema; short-term prophylaxis is started several days before planned procedures which may trigger an acute attack of hereditary angioedema (e.g. dental work) and continued for 2–5 days afterwards. Danazol [unlicensed indication, see BNF section 6.7.2] is best avoided in children because of its androgenic effects but it can be used for short-term prophylaxis of hereditary angioedema.

1. [PH] restriction does not apply to adrenaline injection 1 mg/mL where administration is for saving life in emergency
Respiratory stimulants and pulmonary surfactants

3.5 Respiratory stimulants

3.5.1 Respiratory stimulants

Respiratory stimulants (anaesthetic drugs), such as caffeine and doxapram, should only be given under expert supervision in hospital; it is important to rule out any underlying disorder, such as seizures, hypoglycaemia, or infection, causing respiratory exhaustion before starting treatment with a respiratory stimulant.

Caffeine (as caffeine base) is licensed for the treatment of idiopathic apnoea in preterm neonates; it is used in preference to theophylline. Caffeine has fewer adverse effects and a longer half-life than theophylline in neonates. It is well absorbed when given orally; intravenous treatment is rarely necessary. Plasma-caffeine concentration should be measured if the child has previously been treated with theophylline. The therapeutic range for plasma-caffeine concentration is usually 10–20 mg/litre (50–100 micromol/litre), but a concentration of 25–35 mg/litre (130–180 micromol/litre) may be required.

Doxapram may be given by continuous intravenous infusion or by mouth for preterm neonates and infants who continue to have troublesome apnoea despite treatment with caffeine. When given by continuous intravenous infusion, blood pressure monitoring and frequent measurement of arterial blood gas and pH are necessary to ensure correct dosage.

Caffeine

Cautions gastro-oesophageal reflux; cardiovascular disease; monitor plasma-caffeine concentration (see notes above); monitor closely for 1 week after stopping treatment

Side-effects hypertension, tachycardia; irritability, restlessness; hypoglycaemia, hyperglycaemia; fluid and electrolyte imbalance

Licensed use not licensed for use as an adjunct to extubation in pre-term neonates

Indication and dose

Neonatal apnoea, adjunct to extubation in pre-term neonates

By mouth

Neonate initially 10 mg/kg, then 2.5–5 mg/kg once daily starting 24 hours after initial dose (some neonates may require 10 mg/kg/day)

By intravenous infusion

Neonate initially 10 mg/kg over 30 minutes, then 2.5–5 mg/kg over 10 minutes once daily starting 24 hours after initial dose (some neonates may require 10 mg/kg/day)

Note Dose expressed as caffeine base

Safe practice When prescribing, always state dose in terms of caffeine base

Caffeine base 1 mg = caffeine citrate 2 mg

Caffeine (Non-proprietary) [H3] Injection, caffeine 5 mg/mL, net price 1-mL amp = £4.44

Electrolytes Na⁺ < 0.5 mmol/amp

Caffeine citrate preparations

Caffeine citrate oral liquid available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Doxapram hydrochloride

Cautions impaired cardiac reserve; risk of QT interval prolongation; interactions: Appendix 1 (doxapram)

Contra-indications severe hypertension, thyro-toxicosis, epilepsy, physical obstruction of respiratory tract

Side-effects perineal warmth, dizziness, sweating, moderate increase in blood pressure and heart rate; hyperexcitability; high doses may cause convulsions; oral dose may cause slowed gastric emptying

Licensed use not licensed for use in children

Indication and dose

Neonatal apnoea (see notes above)

By intravenous infusion

Neonate initially 2.5 mg/kg over 5–10 minutes, then by continuous intravenous infusion 300 microgram/kg/hour adjusted according to response, up to max. 1.5 mg/kg/hour

By mouth (after initial intravenous dose)

Neonate 6 mg/kg 4 times daily
DOXAPRAM HYDROCHLORIDE (continued)

Administration for intravenous infusion, dilute injection solution (20 mg/mL) to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%
For administration by mouth, dilute doxapram injection solution with Glucose 5% if necessary

Dopram® (Anpharm) 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 = £21.33

3.5.2 Pulmonary surfactants

Pulmonary surfactants derived from animal lungs, beractant and poractant alfa are used to prevent and treat respiratory distress syndrome (hyaline membrane disease) in preterm neonates. Prophylactic use of a pulmonary surfactant may reduce the need for mechanical ventilation and is more effective than ‘rescue treatment’ in preterm neonates of 29 weeks or less post-menstrual age.

Pulmonary surfactants may also be of benefit in neonates with meconium aspiration syndrome or intrapartum streptococcal infection.

Pulmonary immaturity with surfactant deficit is the commonest reason for respiratory failure in the neonate, especially in those of less than 30 weeks post-menstrual age. Betamethasone (section 6.3.2) given to the mother (at least 12 hours but preferably 48 hours) before delivery substantially enhances pulmonary maturity in the neonate.

Cautions Continuous monitoring is required to avoid hyperoxaemia caused by rapid improvement in arterial oxygen concentration.

Side-effects Pulmonary haemorrhage has been rarely associated with pulmonary surfactants, especially in more preterm neonates. Obstruction of the endotracheal tube by mucous secretions has also been reported.

BERACTANT

Cautions see notes above
Side-effects see notes above
Licensed use licensed for use in respiratory distress syndrome in newborn premature infants, birth-weight over 700 g, and as prophylaxis in neonates less than 32 weeks post-menstrual age

Indication and dose

Treatment of respiratory distress syndrome in preterm neonate; prophylaxis of respiratory distress syndrome in preterm neonate
- By endotracheal tube

Neonate 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) Suspension, beractant (bovine lung extract) providing phospholipid 25 mg/mL, with lipids and proteins, net price 8-mL vial = £306.43

PORACTANT ALFA

Cautions see notes above
Side-effects see notes above
Licensed use licensed for use in respiratory distress syndrome in newborn premature infants, birth-weight over 700 g, and as prophylaxis in neonates 24–32 weeks post-menstrual age

Indication and dose

Treatment of respiratory distress syndrome or hyaline membrane disease in preterm neonate; prophylaxis of respiratory distress syndrome in preterm neonate
- By endotracheal tube

Neonate treatment, 100–200 mg/kg; further doses of 100 mg/kg may be repeated 12 hours later and after further 12 hours if still intubated; max. total dose 300–400 mg/kg; prophylaxis, 100–200 mg/kg soon after birth (preferably within 15 minutes); further doses of 100 mg/kg may be repeated 6–12 hours later and after further 12 hours if still intubated; max. total dose 300–400 mg/kg

Curosurf® (Chiesi) Suspension, poractant alfa (porcine lung phospholipid fraction) 80 mg/mL, net price 1.5-mL vial = £298.74; 3-mL vial = £580.64
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; administration of an inappropriate concentration of oxygen may have serious or even fatal consequences. High concentrations of oxygen can cause pulmonary epithelial damage (bronchopulmonary dysplasia), convulsions, and retinal damage, especially in preterm neonates.

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 children with an expected or known normal or low arterial carbon dioxide ($P_{aCO2}$), oxygen saturation should be maintained above 92%; some clinicians may aim for a target of 94–98%. In some clinical situations, such as carbon monoxide poisoning, (see also Emergency Treatment of Poisoning, p. 46), it is more appropriate to aim for the highest possible oxygen saturation until the child is stable. Hypercapnic respiratory failure is rare in children; in those children at risk, a lower oxygen saturation target of 88-92% is indicated, see below.

High concentration oxygen therapy, with concentrations of up to 60%, is safe in uncomplicated cases of conditions such as pneumonia, pulmonary embolism, pulmonary fibrosis, shock, severe trauma, sepsis, or anaphylaxis. In such conditions, low arterial oxygen ($P_{aO2}$) is usually associated with low or normal arterial carbon dioxide ($P_{aCO2}$) and there is little risk of hypoventilation and carbon dioxide retention.

In severe acute asthma, the arterial carbon dioxide ($P_{aCO2}$) is usually subnormal but as asthma deteriorates it may rise steeply. These patients usually require a high concentration (40–60%) of oxygen and if the arterial carbon dioxide ($P_{aCO2}$) remains high despite treatment, intermittent positive pressure ventilation needs to be considered urgently. Where facilities for blood gas measurements are not immediately available, for example while transferring the patient to hospital, 35% to 50% oxygen delivered through a conventional mask is recommended.

For neonates and infants with breathing difficulties, high concentration oxygen therapy is usually given in an incubator or by nasal cannula if the concentration of oxygen required is less than 50%; a humidified headbox must be used for concentration of oxygen greater than 60%.

Low concentration oxygen therapy (controlled oxygen therapy) is reserved for children at risk of hypercapnic respiratory failure, which is more likely in children with:

- advanced cystic fibrosis;
- advanced 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.

Until blood gases can be measured, initial oxygen should be given using a controlled concentration of 28% or less, titrated towards a target concentration of 88-92%. The aim is to provide the child with enough oxygen to achieve an acceptable arterial oxygen tension without worsening carbon dioxide retention and respiratory acidosis.

Domiciliary oxygen Oxygen should only be prescribed for use in the home after careful evaluation in hospital by a respiratory care specialist. Children and their carers should be advised of the risks of continuing to smoke when receiving oxygen, including the risk of fire. Smoking cessation therapy (section 4.10) should be tried before home oxygen prescription.

Long-term oxygen therapy

The aim of long-term oxygen therapy is to maintain oxygen saturation of at least 92%. Children (especially those with chronic neonatal lung disease) often require
supplemental oxygen, either for 24-hours a day or during periods of sleep; many children are eventually weaned off long-term oxygen therapy as their condition improves.

Long-term oxygen therapy should be considered for children with conditions such as:

- bronchopulmonary dysplasia (chronic neonatal lung disease);
- congenital heart disease with pulmonary hypertension;
- pulmonary hypertension secondary to pulmonary disease;
- interstitial lung disease and obliterative bronchiolitis;
- cystic fibrosis;
- obstructive sleep apnoea syndrome;
- neuromuscular or skeletal disease requiring non-invasive ventilation;
- pulmonary malignancy or other terminal disease with disabling dyspnoea.

Increased respiratory depression is seldom a problem in children with stable respiratory failure treated with low concentrations of oxygen although it may occur during exacerbations; children and their carers should be warned to call for medical help if drowsiness or confusion occurs.

Short-burst oxygen therapy

Oxygen is occasionally prescribed for short-burst (intermittent) use for episodes of breathlessness.

Ambulatory oxygen therapy

Ambulatory oxygen is prescribed for children on long-term oxygen therapy who need to be away from home on a regular basis.

Oxygen therapy equipment

Under the NHS oxygen may be supplied as oxygen cylinders. Oxygen flow can be adjusted by means of an oxygen flow meter. Oxygen delivered from a cylinder should be passed through a humidifier if used for long periods.

Oxygen concentrators are more economical for children 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 child 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 to a face mask for long-term oxygen therapy from an oxygen concentrator. Nasal cannulas can, however, cause dermatitis and mucosal drying in sensitive individuals.

Giving oxygen by nasal cannula allows the child to talk, eat, and drink, but the concentration is not controlled and the method 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 child is underventilating.

Arrangements for supplying oxygen

The following 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.

HOOF and further instructions are available at www.bprs.co.uk/oxygen.html.

Eastern England
South West

BOC Medical
to order:
Tel: 0800 136 603
Fax: 0800 169 9989

North East
South East London
Kent, Surrey, and Sussex
South West London
Thames Valley, Hampshire, and Isle of Wight

Air Liquide
to order:
Tel: 0500 823 773
Fax: 0800 781 4610

North West
Yorkshire and Humberside
East Midlands
West Midlands
North London
Wales

Air Products
to order:
Tel: 0800 373 580
Fax: 0800 214 709

In Scotland, refer the child for assessment by a paediatric 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 oxygen cylinders and accessories can be dispensed by pharmacies contracted to provide domiciliary oxygen services.

### 3.7 Mucolytics

Mucolytics, such as **carbocisteine** and **mecysteine**, are used to facilitate mucociliary clearance and expectoration by reducing sputum viscosity but evidence of efficacy is limited.

**Dornase alfa** is a genetically engineered version of a naturally occurring human enzyme which cleaves extracellular deoxyribonucleic acid (DNA); it is used to reduce sputum viscosity in children with cystic fibrosis. Dornase alfa is administered by inhalation using a jet nebuliser (section 3.1.5), usually once daily at least 1 hour before physiotherapy; however, alternate-day therapy may be as effective as daily treatment. Not all children benefit from treatment with dornase alfa; improvement occurs within 2 weeks, but in more severely affected children a trial of 6–12 weeks may be required.

Nebulised **hypertonic sodium chloride** solution may improve mucociliary clearance in children with cystic fibrosis.

**Mesna** (**Mistabron®**, available from ‘special-order’ manufacturers or specialist importing companies, see p.943) is used in some children with cystic fibrosis when other mucolytics have failed to reduce sputum viscosity; 3–6 mL of a 20% solution is nebulised twice daily.

**Acetylcysteine** has been used to treat meconium ileus in neonates and distal intestinal obstruction syndrome in children with cystic fibrosis, but evidence of efficacy is lacking. **Gastrografin®** (section 1.6.5), or a bowel cleansing preparation containing macrogols (section 1.6.5), is usually more effective. Acetylcysteine may be used as a mucolytic to prevent further obstruction.
**ACETYLCYSTEINE**

**Cautions**  history of peptic ulceration; asthma

**Side-effects**  hypersensitivity-like reactions including rashes and anaphylaxis

**Licensed use**  not licensed for use in meconium ileus or for distal intestinal obstructive syndrome in children with cystic fibrosis

**Indication and dose**

- **Meconium ileus** (but see notes above)
  - **By mouth**
    - **NEONATE**  200–400 mg up to 3 times daily if necessary

- **Treatment of distal intestinal obstructive syndrome** (but see notes above)
  - **By mouth**
    - Child 1 month–2 years  0.4–3 g as a single dose
    - Child 2–7 years  2–3 g as a single dose
    - Child 7–18 years  4–6 g as a single dose

**Administration**  For oral administration, use oral granules, or dilute injection solution (200 mg/mL) to a concentration of 50 mg/mL; orange or blackcurrant juice or cola drink may be used as a diluent to mask the bitter taste

**Acetylcysteine** (Non-proprietary)  
- **Oral granules**, acetylcysteine 100 mg/sachet; 200 mg/sachet. Label: 13
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Prevention of distal intestinal obstruction syndrome**

- **By mouth**
  - Child 1 month–2 years  100–200 mg 3 times daily
  - Child 2–12 years  200 mg 3 times daily
  - Child 12–18 years  200–400 mg 3 times daily

**CARBOCISTEINE**

**Cautions**  history of peptic ulceration

**Pregnancy**  manufacturer advises avoid in first trimester

**Contra-indications**  active peptic ulceration

**Side-effects**  rarely gastro-intestinal bleeding; hypersensitivity reactions (including rash and anaphylaxis) also reported

**Indication and dose**

- **Reduction of sputum viscosity**
  - **By mouth**
    - Child 2–5 years  62.5–125 mg 4 times daily
    - Child 5–12 years  250 mg 3 times daily
    - Child 12–18 years  initially 2.25 g daily in divided doses, then 1.5 g daily in divided doses as condition improves

**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® Paediatric 125 mg/5 mL (cherry- and raspberry-flavoured) and Mucodyne® 250 mg/5 mL (cinnamon- and rum-flavoured)

**DORNASE ALFA**  
Phosphorylated glycosylated recombinant human deoxyribonuclease 1 (rhDNase)

**Cautions**  no evidence of teratogenicity; manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding**  amount probably too small to be harmful—manufacturer advises caution

**Side-effects**  pharyngitis, voice changes, chest pain; occasionally laryngitis, rashes, urticaria, conjunctivitis

**Indication and dose**

Management of cystic fibrosis patients with a forced vital capacity (FVC) of greater than 40% of predicted to improve pulmonary function

- **By inhalation of nebulised solution (by jet nebuliser)**
  - Child 5–18 years  2500 units (2.5 mg) once daily

**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

**MECYSTEINE HYDROCHLORIDE**  
(Methyl Cysteine Hydrochloride)

**Cautions**  history of peptic ulceration

**Contra-indications**  manufacturer advises avoid

**Indication and dose**

- **Reduction of sputum viscosity**
  - **By mouth**
    - Child 5–12 years  100 mg 3 times daily
3.8 Aromatic inhalations

Inhalations containing volatile substances such as eucalyptus oil are traditionally used to relieve congestion and ease breathing. Although the vapour may contain little of the additive it encourages deliberate inspiration of warm moist air which is often comforting. Boiling water should not be used for inhalations owing to the risk of scalding.

Strong aromatic decongestants (applied as rubs or to pillows) are not recommended for infants under the age of 3 months. Sodium chloride 0.9% solution given as nasal drops can be used to liquefy mucous secretions and relieve nasal congestion in infants and young children.

Benzoin Tincture, Compound, BP
(Friars’ Balsam)

Tincture, balsamic acids approx. 4.5%. Label: 15

Dose

Nasal congestion

• By inhalation
Add one teaspoonful to a pint of hot, not boiling, water and inhale the vapour.

Menthol and Eucalyptus Inhalation, BP 1980

Inhalation, racementh or levomenth 2 g, eucalyptus oil 10 mL, light magnesium carbonate 7 g, water to 100 mL.

Dose

Nasal congestion

• By inhalation
Add one teaspoonful to a pint of hot, not boiling, water and inhale the vapour.

Dental prescribing on the NHS May be prescribed as Menthol and Eucalyptus Inhalation BP, 1980

Visclair® (Ranbaxy)
Tablets, yellow, s/c, e/c, mecysteine hydrochloride 100 mg, net price 100= £17.65. Label: 5, 22, 25

3.9 Cough preparations

3.9.1 Cough suppressants

3.9.2 Expectorant and demulcent cough preparations

3.9.1 Cough suppressants

Cough may be a symptom of an underlying disorder such as asthma (section 3.1), gastro-oesophageal reflux disease (section 1.1), or rhinitis (section 12.2.1), which should be addressed before prescribing cough suppressants. Cough may be associated with smoking or environmental pollutants. Cough can also result from bronchiectasis including that associated with cystic fibrosis; cough can also have a significant habit component. There is little evidence of any significant
benefit from the use of cough suppressants in children with acute cough in ambulatory settings. Cough suppressants may cause sputum retention and this can be harmful in children with bronchiectasis.

The use of cough suppressants containing pholcodine or similar opioid analgesics is not generally recommended in children and should be avoided altogether in children under 6 years, see MHRA/CHM advice below.

Sedating antihistamines (section 3.4.1) 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.

MHRA/CHM advice (March 2008 and February 2009)
Children under 6 years should not be given over-the-counter cough and cold medicines containing the following ingredients:

- brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine, or triprolidine (antihistamines);
- dextromethorphan or pholcodine (cough suppressants);
- guaifenesin or ipecacuanha (expectorants);
- phenylephrine, pseudoephedrine, ephedrine, oxymetazoline, or xylometazoline (decongestants).

Over-the-counter cough and cold medicines can be considered for children aged 6–12 years after basic principles of best care have been tried. Children should not be given more than one 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.

### PHOLCODINE

**Cautions**  may cause sputum retention  
**Contra-indications**  Hepatic impairment — avoid or reduce dose—may precipitate coma  
**Pregnancy**  avoid in third trimester, respiratory depression and withdrawal effects in neonate  
**Side-effects**  nausea, sputum retention, constipation  
**Indication and dose**  
**Dry or painful cough**  (but not generally recommended for children, see notes above)  
- By mouth  
  - Child 6–12 years  2–5 mg 3–4 times daily  
  - Child 12–18 years  5–10 mg 3–4 times daily

**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), Galenphol® (sugar-free)

**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  
Brands include Galenphol®

**Galenphol®** (Thorton & Ross)  
Paediatric linctus (= oral solution), orange, sugar-free, pholcodine 2 mg/5 mL. Net price 90-mL pack = £1.11

**3.9.2 Expectorant and demulcent cough preparations**

**Simple linctus** and other demulcent cough preparations containing soothing substances, such as syrup or glycerol, may temporarily relieve a dry irritating cough. These preparations have the advantage of being harmless and inexpensive and sugar-free versions are available.

**Expectorants** are claimed to promote expulsion of bronchial secretions but there is no evidence that any drug can specifically facilitate expectoration.

**Compound cough preparations** for children are on sale to the public but should not be used in children under 6 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 above.

**Simple Linctus, Paediatric, BP**  
Linctus (= oral solution), citric acid monohydrate 0.625% in a suitable vehicle with an anise flavour.  
Net price 100 mL = 72p  
A sugar-free version is also available  

**Dose**

**Cough**  
- By mouth  
  - Child 1 month–12 years  5–10 mL 3–4 times daily
Simple Linctus, BP
Linctus (= oral solution), citric acid monohydrate 2.5% in a suitable vehicle with an anise flavour. Net price 100 mL = 42p
A sugar-free version is also available

Systemic nasal decongestants
Nasal congestion in children due to allergic or vasomotor rhinitis should be treated with oral antihistamines (section 3.4.1), topical nasal preparations containing corticosteroids (section 12.2.1), or topical decongestants (section 12.2.2).

There is little evidence to support the use of systemic decongestants in children. Pseudoephedrine has few sympathomimetic effects, and is commonly combined with other ingredients (including antihistamines) in preparations intended for the relief of cough and cold symptoms but it should not be used in children under 6 years, see MHRA/CHM advice, p. 209.

PSEUDOEPHEDRINE HYDROCHLORIDE

Cautions hypertension, heart disease, diabetes, hyperthyroidism, raised intra-ocular pressure; interactions: Appendix 1 (sympathomimetics)

Hepatic impairment caution in severe hepatic impairment

Renal impairment manufacturer advises caution in moderate to severe renal impairment

Pregnancy defective closure of the abdominal wall (gastrochisis) reported very rarely in newborns after first trimester exposure

Breast-feeding amount too small to be harmful

Contra-indications treatment with MAOI within 2 weeks

Side-effects tachycardia, anxiety, restlessness, insomnia; rarely hallucinations, rash; urinary retention also reported

Indication and dose
Congestion of mucous membranes of upper respiratory tract

By mouth
Child 6–12 years 30 mg 3–4 times daily
Child 12–18 years 60 mg 3–4 times daily

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

1 Sudafed® (McNeil)
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

Most anxiolytics (‘sedatives’) will induce sleep when given at night and most hypnotics will sedate when given during the day. Hypnotics and anxiolytics should be reserved for short courses to alleviate acute conditions after causal factors have been established.

The role of drug therapy in the management of anxiety disorders in children and adolescents is uncertain; drug therapy should be initiated only by specialists after psychosocial interventions have failed. Benzodiazepines and tricyclic antidepressants have been used but adverse effects may be problematic.
Skilled tasks  Hypnotics and anxiolytics may impair judgement and increase reaction time, and so affect ability to drive or perform skilled tasks; they increase the effects of alcohol. Moreover the hangover effects of a night dose may impair performance on the following day.

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.

Hypnotics
The prescribing of hypnotics to children, except for occasional use such as for sedation for procedures (section 15.1.4), is not justified. There is a risk of habituation with prolonged use. Problems settling children at night should be managed with behavioural therapy.

Dental procedures  Some anxious children 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.

Chloral and derivatives
Chloral hydrate and derivatives were formerly popular hypnotics for children. Triclofos causes fewer gastro-intestinal disturbances than chloral hydrate. Chloral hydrate and triclofos are now mainly used for sedation during diagnostic procedures (section 15.1.4) and in intensive care units. These drugs accumulate on prolonged use.

CHLORAL HYDRATE

Cautions  reduce dose in debilitated; avoid prolonged use (and abrupt withdrawal thereafter); avoid contact with skin and mucous membranes; interactions: Appendix 1 (anxiolytics and hypnotics)
Hepatic impairment  can precipitate coma; reduce dose in mild to moderate hepatic impairment; avoid in severe impairment
Skilled tasks  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, acute porphyria (section 9.8.2)
Renal impairment  manufacturer advises avoid in severe impairment
Pregnancy  avoid
Breast-feeding  sedation in infant—manufacturer advises avoid

Side-effects  gastric irritation (nausea and vomiting reported), abdominal distention, flatulence, headache, tolerance, dependence, excitement, delirium (especially on abrupt withdrawal), ketonuria, and rash

Licensed use  not licensed for sedation for painless procedures

Indication and dose

<table>
<thead>
<tr>
<th>Insomnia (but not recommended)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth or by rectum</strong> (if oral route not available)</td>
</tr>
<tr>
<td><strong>Neonate</strong> 30–50 mg/kg at bedtime</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong> 30–50 mg/kg (max. 1 g) at night</td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> 0.5–1 g (max. 2 g) at night</td>
</tr>
</tbody>
</table>

Sedation for painless procedures

<table>
<thead>
<tr>
<th>By mouth or by rectum (if oral route not available)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate</strong> 30–50 mg/kg 45–60 minutes before procedure; doses up to 100 mg/kg may be used with respiratory monitoring</td>
</tr>
<tr>
<td><strong>Child 1 month–12 years</strong> 30–50 mg/kg (max. 1 g) 45–60 minutes before procedure; higher doses up to 100 mg/kg (max. 2 g) may be used</td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> 1–2 g 45–60 minutes before procedure</td>
</tr>
</tbody>
</table>

Administration  for administration by mouth dilute liquid with plenty of water or juice to mask unpleasant taste.
CHLORAL HYDRATE (continued)

Chloral Mixture, BP 2000 (Chloral Oral Solution) Mixture, chloral hydrate 500 mg/5 mL in a suitable vehicle. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Chloral Elixir, Paediatric, BP 2000 (Chloral Oral Solution, Paediatric) Elixir, chloral hydrate 200 mg/5mL (4%) in a suitable vehicle with a black currant flavour. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Chloral Hydrate (Non-proprietary) Suppositories, chloral hydrate 25 mg, 50 mg, 60 mg, 100 mg, 200 mg, 500 mg. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Cloral betaine Welldorm® (Alphashow) Tablets, blue-purple, f/c, cloral betaine 707 mg (≈ chloral hydrate 414 mg). Net price 30-tab pack = £7.90. Label: 19, 27

Dose Short-term treatment of insomnia • By mouth Child 12–18 years 1–2 tablets with water or milk at bedtime, max. 5 tablets (chloral hydrate 2 g) daily

Elixir, red, chloral hydrate 143.3 mg/5 mL. Net price 150-mL pack = £6.67. Label: 19, 27

Dose Short-term treatment of insomnia • By mouth Neonate 1–1.75 mL/kg (chloral hydrate 30–50 mg/kg) with water or milk at bedtime

Child 1 month–12 years 1–1.75 mL/kg (chloral hydrate 30–50 mg/kg) with water or milk at bedtime; max. 35 mL (chloral hydrate 1 g) daily

Child 12–18 years 15–45 mL (chloral hydrate 0.4–1.3 g) with water or milk at bedtime; max. 70 mL (chloral hydrate 2 g) daily

TRICLOFOS SODIUM

Cautions • avoid prolonged use (and abrupt withdrawal thereafter); • interactions: Appendix 1 (anxiolytics and hypnotics)

Hepatic impairment can precipitate coma

Renal impairment start with small doses in severe impairment, increased cerebral sensitivity

Skilled tasks 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

Side-effects abdominal distension, flatulence, gastric irritation including nausea and vomiting, dependence, malaise, ataxia, drowsiness, headache, lightheadedness, vertigo, confusion, paranoia, excitement, nightmares, delirium (especially on abrupt withdrawal), ketonuria, blood disorders, skin reactions, and urticaria

Licensed use not licensed for sedation for painless procedures

Indication and dose Insomnia (but not recommended) • By mouth Neonate 25–30 mg/kg at night

Sedation for painless procedures • By mouth Neonate 25–30 mg/kg 45–60 minutes before procedure

Child 1 month–1 year 25–30 mg/kg at night

Child 1–5 years 25–50 mg/kg at night

Child 6–12 years 50–150 mg/kg at night

Child 12–18 years 150–500 mg/kg at night

Triclofos Oral Solution, BP (Triclofos Elixir) Oral solution, triclofos sodium 500 mg/5 mL. Net price 300 mL = £28.23. Label: 19

Antihistamines Some antihistamines (section 3.4.1) such as promethazine are used for occasional insomnia in adults; 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.

The use of antihistamines as hypnotics in children is not usually justified.
Melatonin

Melatonin is a pineal hormone which may affect sleep pattern. Clinical experience suggests that it may be of value for treating sleep onset insomnia and delayed sleep phase syndrome in children with conditions such as visual impairment, cerebral palsy, attention deficit hyperactivity disorder, autism, and learning difficulties. It is also sometimes used before magnetic resonance imaging (MRI), computed tomography (CT), or EEG investigations. Little is known about its long-term effects in children, but there is a theoretical basis for an effect on sexual development. Treatment with melatonin should be initiated and supervised by a specialist, but may be continued by general practitioners under a shared-care arrangement. The need for continuing melatonin therapy should be reviewed every 6 months.

MELATONIN

Cautions interactions: Appendix 1 (melatonin)
Renal impairment no information available—manufacturer advises caution
Contra-indications autoimmune disease
Hepatic impairment manufacturer advises avoid
Pregnancy no information available—manufacturer advises avoid
Breast-feeding present in milk—manufacturer advises avoid
Side-effects abdominal pain, constipation, dry mouth, weight gain, drowsiness, dizziness, migraine, asthenia, sleep disorders, restlessness, nervousness, irritability, and sweating; rarely flatulence, halitosis, hypersalivation, vomiting, hypertriglyceridaemia, aggression, agitation, fatigue, impaired memory, mood changes, hot flushes, priapism, increased libido, leucopenia, thrombocytopenia, muscle cramp, lacrimation, visual disturbances, and skin reactions
Licensed use not licensed for use in children
Indication and dose
Sleep onset insomnia and delayed sleep phase syndrome (see notes above)
• By mouth
Child 1 month–18 years initially 2–3 mg increased if necessary after 1–2 weeks to 4–6 mg; max. 10 mg
Circadin® (Lundbeck) ▼Tablets, m/r, melatonin 2 mg, net price 21-tab pack = £10.77. Label: 2, 21, 25
Note Other formulations of melatonin are available from 'special-order' manufacturers or specialist importing companies, see p. 943

4.1.2 Anxiolytics

Anxiolytic treatment should be used in children only to relieve acute anxiety (and related insomnia) caused by fear (e.g. before surgery, section 15.1.4.1).

Anxiolytic treatment should be limited to the lowest possible dose for the shortest possible time (see CSM advice, section 4.1).
Buspirone

Buspirone is thought to act at specific serotonin (5HT₁₉) receptors; safety and efficacy in children have yet to be determined.

4.1.3 Barbiturates

Classification not used in *BNF for Children*.

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 on doses above *BNF for Children* upper limit

1. Consider alternative approaches including adjuvant therapy.
2. Bear in mind risk factors, including obesity.
3. Consider potential for drug interactions—see interactions: Appendix 1 (antipsychotics).
4. Carry out ECG to exclude untoward abnormalities such as prolonged QT interval; repeat ECG periodically and reduce dose if prolonged QT interval or other adverse abnormality develops.
5. Increase dose slowly and not more often than once weekly.
6. Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake.
7. Consider high-dose therapy to be for limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage).

Important When prescribing an antipsychotic for administration on an emergency basis, the intramuscular dose should be lower than the corresponding oral dose (owing to absence of first-pass effect), particularly if the child is very active (increased blood flow to muscle considerably increases the rate of absorption). The prescription should specify the dose for each route and should not imply that the same dose can be given by mouth or by intramuscular injection. The dose of antipsychotic for emergency use should be reviewed at least daily.

4.2.1 Antipsychotic drugs

There is little information on the efficacy and safety of antipsychotic drugs in children and adolescents and much of the information available has been extrapolated from adult data; in particular, little is known about the long-term effects of antipsychotic drugs on the developing nervous system. Antipsychotic drugs should be initiated and managed under the close supervision of an appropriate specialist.

Antipsychotic drugs are also known as ‘neuroleptics’ and (misleadingly) as ‘major tranquillisers’. Antipsychotic drugs generally tranquilise without impairing consciousness and without causing paradoxical excitement but they should not be regarded merely as tranquillisers. For conditions such as schizophrenia the tranquilising effect is of secondary importance.

In the short term they are used to calm disturbed children 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 children, they sometimes appear to have an activating influence. Children with acute schizophrenia generally respond better than those with chronic symptoms.

Long-term treatment of a child with a definite diagnosis of schizophrenia may be necessary even after the first episode of illness in order to prevent the manifest illness from becoming chronic. Withdrawal of drug treatment requires careful surveillance because children who appear 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 D₂ receptors, which may give rise to the extrapyramidal effects described below, and also to hyperprolactinemia. Antipsychotic drugs may also affect cholinergic, alpha-adrenergic, histaminergic, and serotoninergic receptors.

Choice of drug is influenced by the potential for side-effects and is often guided by individual circumstances e.g. the psychological effects of potential weight gain. The drugs most commonly used in children are haloperidol, risperidone, and olanzapine.

**Cautions and contra-indications** Antipsychotic drugs should be used with caution in children with hepatic impairment (can precipitate coma), renal impairment (start with small dose; increased cerebral sensitivity), cardiovascular disease, epilepsy (and conditions predisposing to epilepsy), depression, myasthenia gravis, or a personal or family history of angle-closure glaucoma (avoid chlorpromazine, pericyazine and prochlorperazine in these conditions). Caution is also required in severe respiratory disease and in children 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, children should avoid direct sunlight.

Antipsychotic drugs may be contra-indicated in comatose states, CNS depression, and phaeochromocytoma. Most antipsychotic drugs are best avoided during pregnancy unless essential; extrapyramidal effects may occur in neonates. Although the amount present in breast milk is probably too small to be harmful, animal studies indicate possible adverse effects of these drugs on developing nervous system and therefore it is advisable to discontinue breast-feeding during treatment; **interactions**: Appendix 1 (antipsychotics).

**Skilled tasks** 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 (such as perphenazine, prochlorperazine, and trifluoperazine), the butyrophenones (such as 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.

Extrapiramidal symptoms consist of:

- **parkinsonian symptoms** (including tremor), which may appear gradually (but less commonly than in adults);
- **dystonia** (abnormal face and body movements) and **dyskinesia**, which 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 children 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 vermicular movements of the tongue) may halt its full development. Tardive dyskinesia may occur and treatment must be carefully and regularly reviewed.
Hypotension and interference with temperature regulation are dose-related side-effects.

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 antipsychotic 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); cardiovascular symptoms (such as hypotension, 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. 43.

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: 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 (e.g. haloperidol); diphenylbutylpiperidines (e.g. pimozide); thioxanthenes (flupentixol and zuclopenthixol); and the substituted benzamides (e.g. sulpiride).

For details of the newer antipsychotic drugs amisulpride, clozapine, olanzapine, quetiapine, and risperidone, see under Atypical Antipsychotics, p. 221.

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 child’s susceptibility to extrapyramidal side-effects. However, the differences between antipsychotic drugs are less important than the great variability in response; moreover, tolerance to secondary effects such as sedation usually develops. The atypical antipsychotic drugs may be appropriate if extrapyramidal side-effects are a particular concern (see under Atypical Antipsychotics, p. 221). Clozapine is used for schizophrenia when other antipsychotic drugs are ineffective or not tolerated.

Prescribing of more than one antipsychotic drug 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 children without causing stupor.

Pimozide (see CSM warning, p. 220) is less sedating than chlorpromazine.

Sulpiride in high doses controls florid positive symptoms, but in lower doses it has an alerting effect on children with apathetic withdrawn schizophrenia.
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.

Other uses  Nausea and vomiting (section 4.6), choreas, motor tics, and intractable hiccup.

### Equivalent doses of oral antipsychotic drugs

<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 max. 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, the total daily oral dose can be given as a single dose in most children. For the advice of The Royal College of Psychiatrists on doses above the BNF for Children upper limit, see p. 215.

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### 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.

**Cautions**  see notes above; also children 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.

**Indication and dose**

**Childhood schizophrenia and other psychoses**

(under specialist supervision)

- **By mouth**
  - Child 1–6 years 500 micrograms/kg every 4–6 hours adjusted according to response (max. 40 mg daily)
  - Child 6–12 years 10 mg 3 times daily, adjusted according to response (max. 75 mg daily)
  - Child 12–18 years 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)

**Relief of acute symptoms of psychoses**

(under specialist supervision) but see also Cautions and Side-effects

- **By deep intramuscular injection**
  - Child 1–6 years 500 micrograms/kg every 4–6 hours (max. 75 mg daily)
  - Child 12–18 years 25–50 mg every 6–8 hours

**Induction of hypothermia (to prevent shivering)**

(under specialist supervision)

- **By deep intramuscular injection**
  - Child 1–12 years initially 0.5–1 mg/kg, followed by maintenance 500 micrograms/kg every 4–6 hours
  - Child 12–18 years 25–50 mg every 6–8 hours

**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

**Largactil**® (Sanofi-Aventis)  

**Injection**, chlorpromazine hydrochloride 25 mg/mL. Net price 2-mL amp = 63p
HALOPERIDOL

Cautions see notes above; also subarachnoid haemorrhage and metabolic disturbances such as hypokalaemia, hypocalcaemia, or hypomagnesaemia

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 and akathisia especially in thyrotoxic patients; rarely weight loss; hypoglycaemia; inappropriate antidiuretic hormone secretion

Licensed use not licensed for use in children for nausea and vomiting in palliative care

Indication and dose

Schizophrenia and other psychoses, mania, short-term adjunctive management of psychomotor agitation, excitement and violent or dangerously impulsive behaviour (under specialist supervision)

• By mouth
  Child 12–18 years initially 0.5–3 mg 2–3 times daily or 3–5 mg 2–3 times daily in severely affected or resistant disease; 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)

Motor tics (including Tourette syndrome) (under specialist supervision)

• By mouth
  Child 5–12 years 12.5–25 micrograms/kg twice daily, adjusted according to response up to 10 mg daily
  Child 12–18 years 1.5 mg 3 times daily, adjusted according to response up to 10 mg daily

Nausea and vomiting in palliative care

• By mouth
  Child 12–18 years 1.5 mg once daily at night, increased to 1.5 mg twice daily if necessary; max. 5 mg twice daily

• By continuous intravenous or subcutaneous infusion
  Child 1 month–12 years 25–85 micrograms/kg over 24 hours
  Child 12–18 years 1.5–5 mg over 24 hours

Haloperidol (Non-proprietary) Tablets, haloperidol 500 micrograms, net price 28-tab pack = 91p; 1.5 mg, 28-tab pack = £1.62; 5 mg, 28-tab pack = £3.93; 10 mg, 28-tab pack = £4.27; 20 mg, 28-tab pack = £11.17. Label: 2

Dozić® (Rosemont) Oral liquid, sugar-free, haloperidol 1 mg/mL, net price 100-mL pack = £6.86. Label: 2

Haldol® (Janssen-Cilag) Tablets, both scored, haloperidol 5 mg (blue), net price 100-tab pack = £7.35; 10 mg (yellow), 100-tab pack = £14.37. 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

Serenate® (IVAX) Capsules, green, haloperidol 500 micrograms, net price 30-cap pack = 98p. 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

LEVOMEPROMAZINE (Methotrimeprazine)

Cautions see notes above; children receiving large initial doses should remain supine

Contra-indications see notes above

Side-effects see notes above; occasionally raised erythrocyte sedimentation rate occurs

Indication and dose

Restlessness and confusion in palliative care

• By continuous subcutaneous infusion
  Child 1–12 years 0.35–3 mg/kg over 24 hours
  Child 12–18 years 12.5–200 mg over 24 hours

Nausea and vomiting in palliative care

• By continuous intravenous or subcutaneous infusion
  Child 1 month–12 years 100–400 micrograms/kg over 24 hours
  Child 12–18 years 5–25 mg over 24 hours

Administration for administration by subcutaneous infusion dilute with a suitable volume of Sodium Chloride 0.9%

Nozinan® (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

PERICYZANE (Periciazine)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; more sedating; hypotension common when treatment initiated; respiratory depression
PERICYAZINE (continued)

Licensed use tablets not licensed for use in children

Indication and dose

Schizophrenia, psychoses (severe mental or behavioural disorders only) (under specialist supervision)

• By mouth
  Child 1–12 years initially 500 micrograms daily for 10-kg child, increased by 1 mg for each additional 5 kg to max. total daily dose of 10 mg; dose may be gradually increased according to response but maintenance should not exceed twice initial dose
  
Child 12–18 years initially 25 mg 3 times daily increased at weekly intervals by steps of 25 mg according to response; usual max. 100 mg 3 times daily; total daily dose may alternatively be given in 2 divided doses

Neulactil® (Sanofi-Aventis) Tablets, 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. Net price 100-mL pack = £12.08. Label: 2

PERPHENAZINE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above; less sedating; extrapyramidal symptoms, especially dystonia, more frequent, particularly at high dosage; rarely systemic lupus erythematosus

Indication and dose

Schizophrenia and other psychoses, mania, short-term adjunctive management of anxiety, severe psychomotor agitation, excitement, violent or dangerously impulsive behaviour (under specialist supervision)

• By mouth
  Child 14–18 years initially 4 mg 3 times daily adjusted according to the response; max. 24 mg daily

Fentazin® (Goldshield) Tablets, both s/c, perphenazine 2 mg, net price 100-tab pack = £22.38; 4 mg, 100-tab pack = £26.34. Label: 2

PIMOZIDE

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, anti-arrhythmic drugs 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, hyponatraemia reported

Licensed use not licensed for use in Tourette syndrome

Indication and dose

Schizophrenia (under specialist supervision)

• By mouth
  Child 12–18 years initially 1 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

Tourette syndrome (under specialist supervision)

• By mouth
  Child 2–12 years 1–4 mg daily
  Child 12–18 years 2–10 mg daily

Orap® (Janssen-Cilag) Tablets, scored, green, pimozide 4 mg, net price 100-tab pack = £27.41. Label: 2

SULPIRIDE

Cautions see notes above; also excited, agitated, or aggressive children (even low doses may aggravate symptoms)

Pregnancy limited experience in humans but no evidence of harm in animal studies

Contra-indications see notes above; also acute porphyria (section 9.8.2)

Side-effects see notes above; also hepatitis

Licensed use not licensed for use in Tourette syndrome

Indication and dose

Schizophrenia (under specialist supervision)

• By mouth
  Child 14–18 years 200–400 mg twice daily; max. 800 mg daily in predominantly negative
SULPIRIDE (continued)

symptoms, dose increased to max. 2.4 g daily in mainly positive symptoms

Tourette syndrome (under specialist supervision)
- By mouth
  - Child 2–12 years 50–400 mg twice daily
  - Child 12–18 years 100–400 mg twice daily

Sulpiride (Non-proprietary)
Tablets, sulpiride 200 mg, net price 30-tab pack = £6.92; 56-tab pack = £6.46; 400 mg, 30-tab pack = £12.87. Label: 2

TRIFLUOPERAZINE

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; hyperthermia; anorexia

Indication and dose
Schizophrenia and other psychoses, short-term adjunctive management of psychomotor agitation, excitement and violent or dangerously impulsive behaviour (under specialist supervision)
- By mouth
  - Child 12–18 years initially 5 mg twice daily, increased by 5 mg daily after 1 week, then at intervals of 3 days, according to response

Short-term adjunctive management of severe anxiety (under specialist supervision)
- By mouth
  - Child 3–6 years up to 500 micrograms twice daily

Child 6–12 years up to 2 mg twice daily
Child 12–18 years 1–2 mg twice daily, increased if necessary to 3 mg twice daily

Antiemetic section 4.6

Atypical antipsychotics

The ‘atypical antipsychotic’ drugs amisulpride, clozapine, olanzapine, quetiapine, and risperidone may be better tolerated than other antipsychotic drugs; extrapyramidal symptoms may be less frequent than with older antipsychotic drugs.

Clozapine, olanzapine, and quetiapine cause little or no elevation of prolactin concentration; when changing from other antipsychotic drugs, a reduction in prolactin may increase fertility.

Clozapine is used for the treatment of schizophrenia only in children 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 Clozapine).

Cautions and contra-indications While atypical antipsychotic drugs 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 antipsychotic drugs should be used with caution in children with cardiovascular disease, or a history of epilepsy; interactions: Appendix 1 (antipsychotics).

Skilled tasks Atypical antipsychotic drugs 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 antipsychotic drugs include weight gain, dizziness, postural hypotension (especially during initial dose titration) which may be associated with syncope or reflex tachycardia in some children, 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, olanzapine and risperidone; 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 (p. 245) provided that patients are not at particular risk from the additive antimuscarinic side-effects of hyoscine and clozapine.

AMISULPRA

Cautions  see notes above

Renal impairment  halve dose if estimated glomerular filtration rate 30–60 mL/minute/1.73 m²; use one-third dose if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; no information available if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Contra-indications  see notes above; phaeochromocytoma, prolactin-dependent tumours

Pregnancy  avoid

Breast-feeding  avoid

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

Indication and dose

Acute psychotic episode (under specialist supervision)

• By mouth

Child 15–18 years  200–400 mg twice daily adjusted according to response; max. 1.2 g daily

CLOZAPINE

Cautions  see notes above; monitor leucocyte and differential blood counts (see Agranulocytosis, below); susceptibility to angle-closure glaucoma; taper off other antipsychotics before starting; close medical supervision during initiation (risk of collapse because of hypotension)

Hepatic impairment  monitor hepatic function regularly; avoid in symptomatic, or progressive liver disease or hepatic failure

Pregnancy  manufacturers advise caution

Withdrawal  On planned withdrawal reduce dose over 1–2 weeks to avoid risk of rebound psychosis. If abrupt withdrawal necessary observe child carefully

Agranulocytosis  Neutropenia and potentially fatal agranulocytosis reported. Leucocyte and differential blood counts must be normal before starting; monitor counts every week for 18 weeks then at least every 2 weeks and if clozapine continued and blood count stable after 1 year at least every 4 weeks (and 4 weeks after discontinuation); if leucocyte count below 3000/mm³ or if absolute neutrophil count below 1500/mm² discontinue permanently and refer to haematologist. Avoid drugs which depress leucopoiesis; children (or carers) should report immediately symptoms of infection, especially influenza-like illness

Myocarditis and cardiomyopathy  Fatal myocarditis (most commonly in first 2 months) and cardiomyopathy reported. The CSM has advised:

• physical examination and medical history before starting clozapine;

• specialist examination if cardiac abnormalities or history of heart disease found—clozapine initiated only in absence of severe heart disease and if benefit outweighs risk;

• persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy;

• if myocarditis or cardiomyopathy suspected clozapine should be stopped and child evaluated urgently by cardiologist;

• discontinue permanently in clozapine-induced myocarditis or cardiomyopathy

Gastro-intestinal obstruction  Reactions resembling gastro-intestinal obstruction reported. Clozapine should be used cautiously with drugs which cause constipation (e.g. antimuscarinic drugs) or in children with history of colo-
CLOZAPINE (continued)

Indication and dose

**Schizophrenia in children unresponsive to, or intolerant of, conventional antipsychotic drugs** (under specialist supervision)
- **By mouth**
  - **Child 12–18 years** 12.5 mg once or twice on first day then 25–50 mg on second day then increased gradually (if well tolerated) in steps of 25–50 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** Restoring 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

Contraindications severe cardiac disorders (e.g. myocarditis; see Cautions); history of neutropenia or agranulocytosis (see Cautions); bone-marrow disorders; paralytic ileus (see Cautions); alcoholic and toxic psychoses; history of circulatory collapse; drug intoxication; severe CNS depression; uncontrolled epilepsy

Renal impairment 

Breast-feeding 

Side-effects

see notes above; also mild, transient antimuscarinic effects; drowsiness, speech difficulty, abnormal gait, hallucinations, akathisia, asthenia, increased appetite, increased body temperature, raised triglyceride concentration, oedema, hyperprolactinaemia (but clinical manifestations rare); urinary incontinence; eosinophilia; less commonly hypotension, bradycardia, QT interval prolongation, photosensitivity; rarely seizures, leucopenia, rash; very rarely thromboboemolism, hypercholesterolaemia, hypoventilation, urinary retention, priapism, thrombocytopenia, thrombocythaemia, hyperlipidaemia, fulminant hepatic necrosis, and skin reactions

Licensed use not licensed for use in children under 16 years

Cautions see notes above; also susceptibility to angle-closure glaucoma, paralytic ileus, diabetes mellitus (risk of exacerbation or ketoacidosis), low leucocyte or neutrophil count, bone-marrow depression, hyper-eosinophilic disorders, myeloproliferative disease

Hepatic impairment initial dose 5 mg daily, increased slowly

Renal impairment initial dose 5 mg daily, increased slowly

Pregnancy 

Breast-feeding 

Side-effects

see notes above; also mild, transient antimuscarinic effects; drowsiness, speech difficulty, abnormal gait, hallucinations, akathisia, asthenia, increased appetite, increased body

OLANZAPINE

Cautions see notes above; also susceptibility to angle-closure glaucoma, paralytic ileus, diabetes mellitus (risk of exacerbation or ketoacidosis), low leucocyte or neutrophil count, bone-marrow depression, hyper-eosinophilic disorders, myeloproliferative disease

Hepatic impairment initial dose 5 mg daily, increased slowly

Renal impairment initial dose 5 mg daily, increased slowly

Pregnancy manufacturer advises use only if potential benefit outweighs risk; neonatal lethargy, tremor and hypertonia reported when used in third trimester

Contra-indications

Breast-feeding manufacturer advises avoid—present in milk

Side-effects

see notes above; also mild, transient antimuscarinic effects; drowsiness, speech difficulty, abnormal gait, hallucinations, akathisia, asthenia, increased appetite, increased body

temperature, raised triglyceride concentration, oedema, hyperprolactinaemia (but clinical manifestations rare); urinary incontinence; eosinophilia; less commonly hypotension, bradycardia, QT interval prolongation, photosensitivity; rarely seizures, leucopenia, rash; very rarely thromboboemolism, hypercholesterolaemia, hypoventilation, urinary retention, priapism, thrombocytopenia, neutropenia, rhabdomyolysis, hepatitis, pancreatitis; with injection, injection-site reactions, sinus pause, hyperventilation

Licensed use not licensed for use in children

Indication and dose

Schizophrenia, combination therapy for mania (under specialist supervision)
- **By mouth**
  - **Child 12–18 years** initially 5–10 mg daily adjusted to usual range of 5–20 mg daily; doses greater than 10 mg daily only after reassessment; max. 20 mg daily

4.2.1 Antipsychotic drugs 223

Central nervous system

Clozaril® (Novartis)

Tablets, 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 Child, prescriber, and supplying pharmacist must be registered with the Clozaril Patient Monitoring Service—takes several days to do this

Denzapine® (Merz)

Tablets, 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 Child, prescriber, and supplying pharmacist must be registered with the Denzapine Patient Monitoring Service—takes several days to do this

Zaponex® (IVAX)

Tablets, 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 Child, prescriber, and supplying pharmacist must be registered with the Zaponex Treatment Access System—takes several days to do this
OLANZAPINE (continued)

Monotherapy for mania (under specialist supervision)

- **By mouth**
  - **Child 12–18 years** 15 mg daily adjusted to usual range of 5–20 mg daily; doses greater than 15 mg only after reassessment; max. 20 mg daily

**Note** When one or more factors present that might result in slower metabolism (e.g. female gender, non-smoker) consider lower initial dose and more gradual dose increase

Zyprexa® (Lilly) [\(\text{\textregistered}\)]

Tablets, f/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

Orodispersible tablet (Velotab®, 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

QUETIAPINE

Cautions see notes above; cerebrovascular disease

- **Hepatic impairment** manufacturer advises initial dose of 25 mg daily
- **Renal impairment** manufacturer advises initial dose of 25 mg daily
- **Pregnancy** manufacturer advises use only if potential benefit outweighs risk

Contra-indications

- **Breast-feeding** avoid

Side-effects see notes above; also drowsiness, dyspepsia, constipation, dry mouth, mild asthenia, rhinitis, tachycardia; leucopenia, neutropenia and occasionally eosinophilia reported; elevated plasma-triglyceride and cholesterol concentrations, reduced plasma-thyroid hormone concentrations; possible QT interval prolongation; restless leg syndrome; rarely oedema; very rarely priapism

Licensed use not licensed for use in children

Indication and dose

- **Schizophrenia** (under specialist supervision)
  - **By mouth**
  - **Child 12–18 years** initially 25 mg twice daily adjusted in steps of 25–50 mg according to response; max. 750 mg daily

Seroquel® (AstraZeneca) [\(\text{\textregistered}\)]

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

RISPERIDONE

Cautions see notes above; monitor height, body-weight, bowel habit, pulse, blood pressure, and developmental status including sexual maturation; assess for movement disorders before starting and monitor neurological parameters during treatment; family history of sudden cardiac death (perform ECG)

- **Hepatic impairment** initially 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily
- **Renal impairment** initially 500 micrograms twice daily increased in steps of 500 micrograms twice daily to 1–2 mg twice daily
- **Pregnancy** manufacturer advises use only if potential benefit outweighs risk; extrapyramidal effects reported in neonate when taken in third trimester

Contra-indications breast-feeding

Side-effects see notes above; also sleep disturbances, agitation, anxiety, and headache; less commonly constipation, nausea and vomiting, dyspepsia, abdominal pain, hypertension, impaired concentration, dizziness, fatigue, hyperprolactinaemia, sexual dysfunction, urinary incontinence, abnormal vision, and rash; rarely seizures, hyponatraemia, abnormal temperature regulation, and epistaxis; oedema and blood disorders also reported

Licensed use not licensed for use in children under 15 years for psychoses; not licensed for use in autism

Indication and dose

- **Acute and chronic psychoses** (under specialist supervision)
  - **By mouth**
  - **Child 12–18 years** 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 children); usual dose range 4–6 mg daily; doses above 10 mg daily only if benefit considered to outweigh risk (max. 16 mg daily)

Short-term treatment (up to 6 weeks) of persistent aggression in conduct disorder (under specialist supervision)

- **By mouth**
  - **Child 5–18 years and body-weight under 50 kg** initially 250 micrograms once daily increased according to response in steps of 250 micrograms on alternate days; usual dose 500 micrograms daily (up to 750 micrograms once daily has been required)
### Risperidone (continued)

**Child 5–18 years and body-weight over 50 kg**

Initially 500 micrograms once daily increased according to response in steps of 500 micrograms on alternate days; usual dose 1 mg daily (up to 1.5 mg once daily has been required).

**Short-term treatment of severe aggression in autism (under specialist supervision)**

- **By mouth**
  - **Child over 5 years and 15–20 kg**
    - 250 micrograms daily increased if necessary after 3 days to 500 micrograms daily; thereafter increased by 250 micrograms daily at 2-week intervals to max. 1.5 mg daily.
  - **Child over 20 kg up to 12 years**
    - 250 micrograms daily increased if necessary after 3 days to 750 micrograms daily; thereafter increased by 500 micrograms daily at 2-week intervals; max. daily dose 2.5 mg if under 45 kg; max. daily dose 3.5 mg if over 45 kg.

**Risperidone**

**Tablets**, risperidone 500 micrograms, net price 20-tab pack = £4.34; 1 mg, 20-tab pack = £7.06; 2 mg, 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

**Orodispersible tablets**

- **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

**Counselling**

Tablets should be placed on the tongue, allowed to dissolve and swallowed.

**Liquid**

- **Risperidone 1 mg/mL**, net price 100-mL pack = £55.25. Label: 2, counselling, use of dose syringe.

**Note**

Liquid may be diluted with mineral water, orange juice or black coffee (should be taken immediately).

**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

**Orodispersible 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 pack = £56.12. Label: 2, counselling, use of dose syringe.

**Note**

Liquid may be diluted with mineral water, orange juice or black coffee (should be taken immediately).

### 4.2.2 Antipsychotic depot injections

There is limited information on the use of antipsychotic depot injections in children and use should be restricted to specialist centres.

### 4.2.3 Antimanic drugs

**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 child’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 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 children unresponsive to lithium; it seems to be...
particularly effective in those with rapid-cycling manic-depressive illness (4 or more affective episodes per year).

**Valproic acid**

Valproic acid (as the semisodium salt) is licensed in adults for the treatment of manic episodes associated with bipolar disorder. It may be useful in children unresponsive to lithium. Sodium valproate (section 4.8.1) has also been used.

**Lithium**

Lithium salts are used in the prophylaxis and treatment of mania, in the prophylaxis of bipolar disorder (manic-depressive disorder) and in the prophylaxis of recurrent depression (unipolar illness or unipolar depression). Lithium should be used in children only on the advice of a specialist.

The decision to give prophylactic lithium must be based on careful consideration of the likelihood of recurrence in the individual child, and the benefit weighed against the risks. In long-term use lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with regular monitoring of thyroid function. The need for continued therapy should be assessed regularly and children should be maintained on lithium after 3–5 years only if benefit persists.

**Serum concentrations**

Lithium salts have a narrow therapeutic/toxic ratio and should not be prescribed unless facilities for monitoring serum-lithium concentrations are available. There seem few if any reasons for preferring one or other of the salts of lithium available. Doses are adjusted to achieve serum-lithium concentration of 0.4–1 mmol/litre on samples taken 12 hours after the preceding dose. It is important to determine the optimum range for each individual child.

Overdosage, usually with serum-lithium concentration of over 1.5 mmol/litre, may be fatal and toxic effects include tremor, ataxia, dysarthria, nystagmus, renal impairment, and convulsions. If these potentially hazardous signs occur, treatment should be stopped, serum-lithium concentrations redetermined, and steps taken to reverse lithium toxicity. In mild cases withdrawal of lithium and administration of generous amounts of sodium and fluid will reverse the toxicity. Serum-lithium concentration in excess of 2 mmol/litre require urgent treatment as indicated under Emergency Treatment of Poisoning, p. 42.

**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 children and carers should be warned of possible relapse if it is discontinued abruptly.

**Lithium cards**

A lithium treatment card available from pharmacies tells children and carers how to take lithium preparations, what to do if a dose is missed, and what side-effects to expect. It also explains why regular blood tests are important and warns that some medicines and illnesses can change serum-lithium concentration.

Cards may be purchased from the National Pharmacy Association.

Tel: (01727) 858 687 sales@npa.co.uk

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**LITHIUM CARBONATE**

**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 children and carers to seek attention if symptoms of hypothyroidism develop (females are 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 cardiac disease, and conditions with sodium imbalance such as Addison’s disease; reduce dose or discontinue in diarrhoea,
LITHIUM CARBONATE (continued)

vomiting and intercurrent infection (especially if sweating profusely); psoriasis (risk of exacerbation); diuretic treatment, myasthenia gravis; surgery (section 15.1); if possible avoid abrupt withdrawal (see notes above); interactions: Appendix I (lithium)

Counselling Children should maintain adequate fluid intake and avoid dietary changes which reduce or increase sodium intake; lithium treatment cards are available from pharmacies (see above)

Renal impairment avoid if possible or reduce dose and monitor serum-lithium concentration carefully

Pregnancy avoid if possible in first trimester (risk of teratogenicity, including cardiac abnormalities); dose requirements increased in second and third trimesters (but return to normal abruptly on delivery); close monitoring of serum-lithium concentration advised (risk of toxicity in neonate)

Breast-feeding present in milk and risk of toxicity in infant—manufacturer advises avoid

Side-effects gastro-intestinal 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 gastro-intestinal 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 antidiuretic hormone concentration, hypothyroidism, hypocalcaemia, ECG changes, and kidney changes may also occur; see also Emergency Treatment of Poisoning, p. 42

Indication and dose

Treatment and prophylaxis of mania, bipolar disorder, recurrent depression (see also notes above), aggressive or self-mutilating behaviour

• By mouth
  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) PM
Camcolit 250® tablets, f/c, scored, lithium carbonate 250 mg (Li+ 6.8 mmol), net price 100-tab pack = £3.09 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 100-tab pack = £4.13 Label: 10, lithium card, 25, counselling, see above

Dose

Treatment • By mouth (see above for advice on bioavailability and serum-lithium monitoring)
Child 12–18 years initially 1–1.5 g daily

Prophylaxis • By mouth (see above for advice on bioavailability and serum-lithium monitoring)
Child 12–18 years initially 300–400 mg daily

Liskonum® (GSK) PM
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, counselling, see above

Dose

Treatment • By mouth (see above for advice on bioavailability and serum-lithium monitoring)
Child 12–18 years initially 225–675 mg twice daily

Prophylaxis • By mouth (see above for advice on bioavailability and serum-lithium monitoring)
Child 12–18 years initially 225–450 mg twice daily

LITHIUM CITRATE

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

Licensed use not licensed for use in children
4.3 Antidepressant drugs

4.3.1 Tricyclic antidepressant drugs

Depression in children should be managed by an appropriate specialist and treatment should involve psychological therapy.

The major classes of antidepressant drugs include the tricyclics and related antidepressant drugs, the selective serotonin re-uptake inhibitors (SSRIs), and the monoamine oxidase inhibitors (MAOIs).

Choice of antidepressant drug should be based on the individual child’s requirements, including the presence of concomitant disease, existing therapy, suicide risk, and previous response to antidepressant therapy.

When drug treatment of depression is considered necessary in children, the SSRIs should be considered first-line treatment; following a safety and efficacy review, fluoxetine is licensed to treat depression in children.

Tricyclic antidepressant drugs should generally be avoided for the treatment of depression in children.

St John’s wort (Hypericum perforatum) is a popular unlicensed herbal remedy for treating mild depression in adults. In the absence of adequate evidence of safety or efficacy in children, St John’s wort should not be used for the treatment of depression in children. It interacts with a number of conventional drugs, see Appendix 1 (St John’s wort).

Hyponatraemia and antidepressant therapy

Hyponatraemia (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 antidepressant drugs. The CSM has advised that hyponatraemia should be considered in all children who develop drowsiness, confusion, or convulsions while taking an antidepressant drug.

Suicidal behaviour and antidepressant therapy

The use of antidepressant drugs has been linked with suicidal thoughts and behaviour. Where necessary, children should be monitored for suicidal behaviour, self-harm, and hostility, particularly at the beginning of treatment or if the dose is changed.

Withdrawal

Gastro-intestinal symptoms of nausea, vomiting, and anorexia, accompanied by headache, giddiness, ‘chills’, and insomnia, and sometimes by hypomania, panic-anxiety, and extreme motor restlessness may occur if an antidepressant 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 children who have been on long-term maintenance treatment). SSRIs have been associated with a specific withdrawal syndrome (section 4.3.3).

Anxiety

Management of acute anxiety in children with drug treatment is contentious (section 4.1.2). For chronic anxiety (of longer than 4 weeks’ duration), it may be appropriate to use an antidepressant drug before a benzodiazepine.
4.3.1 Tricyclic antidepressant drugs

The safety and efficacy of tricyclic antidepressant drugs in the treatment of depression in children has not been established. Treatment should be managed by an appropriate specialist and should involve psychological therapy.

For reference to the role of some tricyclic antidepressant drugs in some forms of neuralgia, see section 4.7.3, and in nocturnal enuresis in children, see section 7.4.2.

Dosage It is important to use doses that are sufficiently high for effective treatment but not so high as to cause toxic effects. Low doses should be used for initial treatment.

In most children the long half-life of tricyclic antidepressant drugs allows once-daily administration, usually at night; the use of modified-release preparations is therefore unnecessary.

Choice Tricyclic antidepressant drugs should generally be avoided for the treatment of depression in children (see above). Tricyclic and related antidepressant drugs 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 antidepressant drugs can be roughly divided into those with additional sedative properties and those without. Those with sedative properties include amitriptyline and doxepin. Those with less sedative properties include imipramine and nortriptyline.

Amitriptyline and imipramine have more marked antimuscarinic and cardiac side-effects than some other tricyclic or related antidepressant drugs, such as doxepin; this may be important in some children.

Side-effects Arrhythmias and heart block occasionally follow the use of tricyclic antidepressant drugs, particularly amitriptyline, and may be a factor in the sudden death of children 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).

Other side-effects of tricyclic antidepressant drugs include drowsiness, dry mouth, blurred vision, constipation, and urinary retention (all attributed to antimuscarinic activity), and sweating. The child 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.

Neuroleptic malignant syndrome (section 4.2.1) may, very rarely, arise in the course of antidepressant drug treatment.

Suicidal behaviour has been linked with antidepressant drugs (see p. 228).

Overdosage Limited quantities of tricyclic antidepressant drugs should be prescribed at any one time because their cardiovascular effects are dangerous in overdosage. In particular, overdosage with amitriptyline is associated with a relatively high rate of fatality. For advice on overdosage see Emergency Treatment of Poisoning, p. 40.

Withdrawal If possible tricyclic antidepressant drugs should be withdrawn slowly (see also section 4.3.1).

**AMITRIPTYLINE HYDROCHLORIDE**

Cautions cardiac disease (particularly with arrhythmias, see Contra-indications below), history of epilepsy, 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)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

Hepatic impairment sedative effects increased; avoid in severe hepatic impairment

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding amount too small to be harmful but manufacturer advises avoid
AMITRIPTYLINE HYDROCHLORIDE (continued)

Contra-indications  arrhythmias (particularly heart block), not indicated in manic phase, severe liver disease

Side-effects  dry mouth, sedation, blurred vision (disturbance of accommodation, increased intraocular 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, hypomania or mania, confusion or delirium, headache, interference with sexual function, blood—glucose 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. 228), abnormal liver function tests (jaundice); for a general outline of side-effects see also notes above; overdose: see Emergency Treatment of Poisoning, p. 40 (high rate of fatality—see Overdosage, p. 229)

Licensed use  not licensed for use in neuropathic pain

Indication and dose

Depression (but see notes above)

- By mouth
  - Child 16–18 years 10–25 mg 3 times daily (total daily dose may alternatively be given as a single dose at bedtime) increased gradually as necessary to 150–200 mg daily

Doxepin

Cautions  see under Amitriptyline Hydrochloride

Contra-indications  see under Amitriptyline Hydrochloride

Breast-feeding  manufacturer advises avoid—accumulation of doxepin metabolite may cause sedation and respiratory depression

Side-effects  see under Amitriptyline Hydrochloride

Indication and dose

Depressive illness, particularly where sedation is required (but see notes above)

- By mouth
  - Child 12–18 years initially 75 mg daily in divided doses or as a single dose at bedtime, adjusted according to response; usual maintenance 30–300 mg daily (doses above 100 mg given in 3 divided doses)

Sinepin® (Marlborough)®

Capsules, doxepin (as hydrochloride) 25 mg, net price 28-cap pack = £3.77; 50 mg, 28-cap pack = £5.71. Label: 2

IMIPRAMINE HYDROCHLORIDE

Cautions  see under Amitriptyline Hydrochloride

Pregnancy  tachycardia, irritability, and muscle spasms reported in neonates when used in third trimester

Contra-indications  see under Amitriptyline Hydrochloride

Side-effects  see under Amitriptyline Hydrochloride, but less sedating

Licensed use  not licensed for use for attention deficit hyperactivity disorder
Indication and dose

Nocturnal enuresis
- **By mouth**
  - **Child 6–8 years** 25 mg at bedtime
  - **Child 8–11 years** 25–50 mg at bedtime
  - **Child 11–18 years** 50–75 mg at bedtime
  
  **Note**: Period of treatment (including gradual withdrawal) 3 months—full physical examination before further course, see also section 7.4.2

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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 Amitripsyline Hydrochloride

Side-effects see under Amitriptyline Hydrochloride, but less sedating

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2

**Nortriptyline**

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

Indication and dose

Depression (but see notes above)
- **By mouth**
  - **Child 12–18 years** low dose initially increased as necessary to 30–50 mg daily in divided doses or as a single dose (max. 150 mg daily)

Attention deficit hyperactivity disorder (under specialist supervision)
- **By mouth**
  - **Child 6–18 years** 10–30 mg twice daily

**Imipramine** (Non-proprietary) ➤ Tablets, coated, imipramine hydrochloride 10 mg, net price 28-tab pack = £1.20; 25 mg, 28-tab pack = £1.17. Label: 2
reported with fluoxetine). SSRIs may also impair performance of skilled tasks (e.g. driving). **Interactions**: 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.

**Contra-indications** SSRIs should not be used if the child enters a manic phase.

**Side-effects** SSRIs are less sedating and have fewer antimuscarinic and cardiotoxic effects than tricyclic antidepressant drugs (section 4.3.1). 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, hypomania or mania (see Cautions above), movement disorders and dyskinesias, visual disturbances, hyponatraemia (see Hyponatraemia and Antidepressant Therapy, p. 228), and bleeding disorders including ecchymoses and purpura. Suicidal behaviour has been linked with antidepressants, see p. 228.

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**CITALOPRAM**

**Cautions** see notes above

**Hepatic impairment** use doses at lower end of range

**Renal impairment** no information available for estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

**Pregnancy** manufacturers advise use only if potential benefit outweighs risk; risk of neonatal withdrawal

**Breast-feeding** present in milk—manufacturer advises avoid

**Contra-indications** see notes above

**Side-effects** see notes above; also palpitation, tachycardia, postural hypotension, coughing, yawning, confusion, impaired concentration, malaise, amnesia, migraine, paraesthesia, abnormal dreams, taste disturbance, increased salivation, rhinitis, tinnitus, polyuria, micturition disorders, euphoria

**Licensed use** not licensed for use in children

**Indication and dose**

**Major depression** (but see CSM advice, above)

- **By mouth as oral drops**
  - Child 12–18 years initially 8 mg once daily increased if necessary to 16 mg once daily over 2–4 weeks; max. 48 mg once daily

**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

- **Oral drops**, citalopram (as hydrochloride) 40 mg/mL, net price 15-mL pack = £19.66. Counselling, driving, administration

**Note** 4 drops (8 mg) can be considered equivalent in therapeutic effect to 10-mg tablet Mix with water, orange juice, or apple juice before taking

**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 pack = £20.16. Counselling, driving, administration

**Note** 4 drops (8 mg) can be considered equivalent in therapeutic effect to 10-mg tablet Mix with water, orange juice, or apple juice before taking

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**FLUOXETINE**

**Cautions** see notes above

**Hepatic impairment** reduce dose; avoid in severe hepatic impairment

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk (no evidence of teratogenicity)

**Breast-feeding** present in breast milk, manufacturer advises avoid

**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

**Indication and dose**

**Major depression**

- **By mouth**
  - **Child 8–18 years** 10 mg once daily increased after 1–2 weeks if necessary, max. 20 mg once daily
  - **Long duration of action** Consider the long half-life of fluoxetine when adjusting dosage (or in overdosage)

**FLUOXETINE (continued)**

Fluoxetine (Non-proprietary) (PMI)

- **Capsules**, fluoxetine (as hydrochloride) 20 mg, net price 30-cap pack = £1.02; 60 mg, 30-cap pack = £55.76. Counselling, driving

- **Liquid**, fluoxetine (as hydrochloride) 20 mg/5 mL, net price 70 mL = £7.41. Counselling, driving

Brands include Oxactin®, Prozac® (Lilly)

**FLUVOXAMINE MALEATE**

**Cautions** see notes above

- **Hepatic impairment** reduce dose
- **Renal impairment** start with smaller dose

- **Pregnancy** manufacturers advise use only if potential benefit outweighs risk; risk of neonatal withdrawal

- **Breast-feeding** present in milk—manufacturer advises avoid

**Contra-indications** see notes above

**Side-effects** see notes above; palpitation, tachycardia (may also cause bradycardia); rarely postural hypotension, confusion, ataxia, paraesthesia, malaise, taste disturbance, neuroleptic malignant syndrome-like event, abnormal liver function tests, usually symptomatic (discontinue treatment)

**Indication and dose**

- **Obsessive-compulsive disorder**
  - **By mouth**
    - **Child 8–18 years** initially 25 mg daily increased if necessary in steps of 25 mg every 4–7 days according to response (total daily doses above 50 mg in 2 divided doses); max. 100 mg twice daily
  - **Note** If no improvement in obsessive-compulsive disorder within 10 weeks, treatment should be reconsidered

Fluvoxamine (Non-proprietary) (PMI)

- **Tablets**, fluvoxamine maleate 50 mg, net price 60-tab pack = £6.80; 100 mg, 30-tab pack = £8.34. Counselling, driving

- **Tablets**, f/c, scored, fluvoxamine maleate 50 mg, net price 60-tab pack = £17.10; 100 mg, 30-tab pack = £17.10. Counselling, driving

Faverin® (Solvay)

**SERTRALINE**

**Cautions** see notes above; renal impairment

- **Hepatic impairment** reduce dose in mild or moderate hepatic impairment; avoid in severe impairment

- **Pregnancy** manufacturers advise use only if potential benefit outweighs risk; risk of neonatal withdrawal

- **Breast-feeding** present in milk but not known to be harmful in short-term use

**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

**Licensed use** not licensed for use in children for depression

**Indication and dose**

**Obsessive-compulsive disorder**

- **By mouth**
  - **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
  - **Child 12–18 years** initially 50 mg daily increased if necessary in steps of 50 mg over several weeks; usual range 50–200 mg daily

Sertraline (Non-proprietary) (PMI)

- **Tablets**, sertraline (as hydrochloride) 50 mg, net price 28-tab pack = £1.37; 100 mg, 28-tab pack = £1.80. Counselling, driving

- **Tablets**, both f/c, sertraline (as hydrochloride) 50 mg (scored), net price 28-tab pack = £17.82; 100 mg, 28-tab pack = £29.16. Counselling, driving

**Major depression** (but see CSM advice, above)

- **By mouth**
  - **Child 12–18 years** initially 50 mg once daily increased if necessary in steps of 50 mg daily at intervals of at least a week; max. 200 mg once daily

Lustral® (Pfizer) (PMI)
4.3.4 Other antidepressant drugs

Classification not used in BNF for Children.

4.4 CNS stimulants and other drugs for attention deficit hyperactivity disorder

CNS stimulants should only be prescribed for children with severe and persistent symptoms of attention deficit hyperactivity disorder (ADHD), when the diagnosis has been confirmed by a specialist; treatment may be continued by general practitioners under a shared-care arrangement. Treatment often needs to be continued into adolescence, and may need to be continued into adulthood.

Drug treatment of ADHD should be part of a comprehensive treatment programme. The 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, and preferences of the child and carers. Methylphenidate and atomoxetine are used for the management of ADHD; dexamfetamine (dexamphetamine) is an alternative in children who do not respond to these drugs. Growth is not generally affected by treatment with CNS stimulants but it is advisable to monitor growth during treatment.

A tricyclic antidepressant such as imipramine (section 4.3.1) is sometimes used in the treatment of ADHD; it should not be prescribed concomitantly with a CNS stimulant.

Modafinil is used for the treatment of daytime sleepiness associated with narcolepsy; dependence with long-term use cannot be excluded and it should therefore be used with caution.

Dexamfetamine and methylphenidate [both unlicensed] are also used to treat narcolepsy.

ATOMOXETINE

Cautions cardiovascular disease including hypertension and tachycardia; monitor growth; QT-interval prolongation (avoid concomitant administration of drugs that prolong QT-interval); history of seizures; susceptibility to angle-closure glaucoma; interactions: Appendix 1 (atomoxetine)

Hepatic disorders Following rare reports of hepatic disorders, the CSM has advised that children 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, CSM has advised that children and carers should be informed about the risk and told to report clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression

Hepatic impairment see hepatic disorders above; also halve dose in moderate liver disease; quarter dose in severe liver disease

Pregnancy no information available; manufacturer advises avoid unless potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—present in milk in animal studies

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; less commonly suicidal ideation

(see Suicidal Ideation, above), cold extremities; very rarely hepatic disorders (see Hepatic Disorders, above), seizures, Raynaud’s phenomenon, and angle-closure glaucoma

Indication and dose

Attention deficit hyperactivity disorder initiated by specialist

• By mouth

Child over 6 years (body-weight under 70 kg) initially 500 micrograms/kg daily for 7 days then increased according to response to usual maintenance dose 1.2 mg/kg daily; usual max. 100 mg daily, but may be increased to 1.8 mg/kg (max. 120 mg) daily under the direction of a specialist

Child (body-weight over 70 kg) initially 40 mg daily for 7 days then increased according to response to usual maintenance dose 80 mg daily; usual max. 100 mg daily, but may be increased to max. 120 mg daily under the direction of a specialist

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

Strattera® (Lilly) ▼ (HR)

Capsules, atomoxetine (as hydrochloride) 10 mg (white), net price 7-cap pack = £15.02, 28-cap pack = £60.06; 18 mg (gold/white), 7-cap pack = £15.02, 28-cap pack = £80.06; 25 mg (blue/white), 7-cap pack = £15.02, 28-cap pack = £60.06; 40 mg (blue), 7-cap pack = £15.02, 28-cap pack = £60.06; 60 mg (blue/gold), 28-cap pack = £60.06. Label: 3
DEXAMFETAMINE SULPHATE
(Dexamphetamine sulphate)

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 (see also below); avoid abrupt withdrawal; data on safety and efficacy of long-term use not complete; acne porphyria (see section 9.8.2); interactions: Appendix 1 (sympathomimetics) Growth restriction Monitor height and weight as growth restriction may occur during prolonged therapy (drug-free periods may allow catch-up in growth but withdrawal slowly to avoid inducing depression or renewed hyperactivity).

Contra-indications cardiovascular disease including moderate to severe hypertension, hyperexcitability or agitated states, hyperthyroidism, history of drug or alcohol abuse, glaucoma

Skilled tasks May affect performance of skilled tasks (e.g. driving); effects of alcohol unpredictable

Pregnancy manufacturer advises avoid (retrospective evidence of uncertain significance suggesting possible embryotoxicity)

Breast-feeding significant amount in milk—avoid

Side-effects insomnia, restlessness, irritability and excitability, nervousness, night terrors, euphoria, tremor, dizziness, headache; convulsions (see also Cautions); dependence and tolerance, sometimes psychosis, anorexia, gas-
tro-intestinal symptoms, growth restriction (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); overdose: see Emergency Treatment of Poisoning. p. 43

Indication and dose
Refractory attention deficit hyperactivity disorder initiated by specialist

• By mouth
Child 4–6 years initially 2.5 mg once daily, increased if necessary by 2.5 mg at intervals of 1 week; usual max. 20 mg daily, maintenance dose given in 2–3 divided doses
Child 6–18 years initially 5–10 mg once daily, increased if necessary by 5 mg at intervals of 1 week; usual max. 20 mg daily (older children have received max. 40 mg); maintenance dose given in 2–3 divided doses

Administration tablets can be halved

Dexedrine® (UCB Pharma) [ ] Tablets, scored, dexamfetamine sulphate 5 mg. Net price 28-tab pack = £3.00. Counselling, driving

METHYLPHENIDATE HYDROCHLORIDE

Cautions monitor growth (if prolonged treatment), blood pressure and full blood count; anxiety or agitation; tics or a family history of Tourette syndrome; epilepsy (discontinue if increased seizure frequency); avoid abrupt withdrawal; interactions: Appendix 1 (sympathomimetics)

Pregnancy limited experience—manufacturer advises avoid unless potential benefit outweighs risk; toxicity in animals

Contra-indications severe depression, suicidal ideation; drug or alcohol dependence, psychosis; hyperthyroidism; cardiovascular disease

Breast-feeding no information available—manufacturer advises avoid

Side-effects abdominal pain, nausea, vomiting, dyspepsia, dry mouth, anorexia, reduced weight gain; tachycardia, palpitation, arrhythmias, changes in blood pressure; tics (very rarely Tourette syndrome), insomnia, nervousness, asthenia, depression, irritability, aggression, headache, drowsiness, dizziness, movement disorders; fever, arthralgia; rash, pruritus, alopecia; less commonly diarrhoea, abnormal dreams, confusion, suicidal ideation, urinary frequency, haematuria, muscle cramps, epistaxis; rarely growth restriction, visual disturbances; very rarely hepatic dysfunction, cerebral arteritis, psychosis, seizures, neuroleptic malignant syndrome, tolerance and dependence, blood disorders including leucopenia and thrombocytopenia, exfoliative dermatitis, and erythema multiforme

Licensed use not licensed for use in children under 6 years

Indication and dose
Attention deficit hyperactivity disorder initiated by specialist

• By mouth
Child 4–6 years 2.5 mg twice daily increased if necessary at weekly intervals by 2.5 mg daily to max. 1.4 mg/kg daily in divided doses; discontinue if no response after 1 month, suspend treatment every 1–2 years to assess condition
Child 6–18 years initially 5 mg 1–2 times daily, increased if necessary at weekly intervals by 5–10 mg daily; usual max. 60 mg daily in divided doses but may be increased to 2.1 mg/kg daily (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month, suspend treatment every 1–2 years to assess 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) Note Treatment may be started using a modified-release preparation

Administration Equasym® and Ritalin® tablets may be halved; contents of Equasym XL® capsules can be sprinkled on a tablespoon of apple sauce, then swallowed immediately without chewing
METHYLPHENIDATE HYDROCHLORIDE (continued)

Methylphenidate Hydrochloride (Non-proprietary)  
Tablets, methylphenidate hydrochloride 5 mg, net price 30-tab pack = £5.80; 10 mg, 30-tab pack = £5.57; 20 mg, 30-tab pack = £9.98. Brands include Equasym®, Medikinet®

Ritalin® (Novartis)  
Tablets, scored, methylphenidate hydrochloride 10 mg, net price 30-tab pack = £5.57

Modified release  
Concerta® XL (Janssen-Cilag)  
Tablets, m/r, methylphenidate hydrochloride 18 mg (yellow), net price 30-tab pack = £29.70; 27 mg (grey), 30-tab pack = £35.06; 36 mg (white), 30-tab pack = £40.43. Label: 25

Cautions  
Tablet membrane may pass through gastrointestinal tract unchanged

Dose  
• By mouth  
Child 6–18 years initially 18 mg once daily (in the morning), increased if necessary in weekly steps of 18 mg according to response; usual max. 54 mg once daily, but may be increased to 2.1 mg/kg daily (max. 108 mg daily) under the direction of a specialist; discontinue if no response after 1 month; suspend treatment every 1–2 years to assess condition

Note  
Total daily dose of 15 mg of standard-release formulation is considered equivalent to Concerta® XL 18 mg once daily

Equasym XL® (UCB Pharma)  
Capsules, m/r, methylphenidate hydrochloride 10 mg (white/green), net price 30-cap pack = £25.00; 20 mg (white/blue), 30-cap pack = £30.00; 30 mg (white/brown), 30-cap pack = £35.00. Label: 25

Dose  
• By mouth  
Child 6–18 years initially 10 mg once daily in the morning before breakfast, increased gradually if necessary; usual max. 60 mg daily; but may be increased to 2.1 mg/kg daily (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month; suspend treatment every 1–2 years to assess condition

Medikinet XL® (Flynn)  
Capsules, m/r, methylphenidate hydrochloride 10 mg (lilac/white), net price 28-cap pack = £21.00; 20 mg (lilac), 28-cap pack = £28.00; 30 mg (purple/light grey), 28-cap pack = £33.72; 40 mg (purple/grey), 28-cap pack = £44.95. Label: 25

Dose  
• By mouth  
Child 6–18 years 10 mg once daily in the morning with breakfast, adjusted according to response; usual max. 60 mg daily, but may be increased to 2.1 mg/kg daily (max. 90 mg daily) under the direction of a specialist; discontinue if no response after 1 month; suspend treatment every 1–2 years to assess condition

Note  
Contents of capsule can be sprinkled on a tablespoon of apple sauce (then swallowed immediately without chewing)

MODAFINIL

Cautions  
monitor blood pressure and heart rate in hypertension (see Contra-indications); possibility of dependence; interactions: Appendix 1 (modafinil)

Hepatic impairment  
halve dose in severe liver disease

Renal impairment  
manufacturer advises use half normal dose in severe impairment

Contra-indications  
mild-to-severe uncontrolled hypertension, arrhythmia; history of left ventricular hypertrophy, of cor pulmonale, or of clinically significant stimulant-induced mitral-valve prolapse (including ischaemic ECG changes, chest pain and arrhythmias)

Pregnancy  
manufacturer advises avoid

Breast-feeding  
manufacturer advises avoid—no information available

Side-effects  
dry mouth, appetite changes, gastrointestinal disturbances (including nausea, diarrhoea, constipation, and dyspepsia), abdominal pain; tachycardia, vasodilation, chest pain, palpitation; headache (uncommonly migraine), anxiety, sleep disturbances, dizziness, depression, confusion, paraesthesia, asthenia; visual disturbances; less commonly mouth ulcers, glossitis, pharyngitis, dysphagia, taste disturbance, increased thirst, hypertension, hypotension, bradycardia, arrhythmia, peripheral oedema, hypercholesterolaemia, rhinitis, dyspnoea, agitation, dyskinesia, amnesia, emotional lability, abnormal dreams, tremor, decreased libido, weight changes, hyperglycaemia, urinary frequency, menstrual disturbances, eosinophilia, leucopenia, myasthenia, muscle cramps, dry eye, sinusitis, epistaxis, myalgia, arthralgia, acne, sweating, rash, and pruritus; very rarely psychosis, mania, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Licensed use  
not licensed for use in children under 12 years

Indication and dose

Narcolepsy  
• By mouth  
Child 5–12 years initially 100 mg daily in the morning, dose adjusted according to response to 100–400 mg daily either in 2 divided doses morning and at noon or as a single dose in the morning

Child 12–18 years 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

Provigil® (Cephalon)  
Tablets, modafinil 100 mg, net price 30-tab pack = £55.80; 200 mg, 30-tab pack = £111.60
4.5 Drugs used in the treatment of obesity

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 or carer, with appropriate support and encouragement; increased physical activity should also be encouraged. If appropriate, smoking cessation (while maintaining body weight) may be worthwhile before attempting supervised weight loss, since cigarette smoking may be more harmful than obesity.

Obesity should be managed in an appropriate setting by staff who have been trained in the management of obesity in children; the individual or carer should receive advice on diet and lifestyle modification and should be monitored for changes in weight as well as in blood pressure, blood lipids, and other associated conditions.

NICE has recommended (December 2006) that drug treatment should only be considered for obese children after dietary, exercise, and behavioural approaches have been started, and who have associated conditions such as orthopaedic problems or sleep apnoea; treatment is intended both to facilitate weight loss and to maintain reduced weight. Initial treatment should involve a 6–12 month trial of orlistat or sibutramine, with regular reviews of effectiveness, tolerance, and adherence.

Choice

Orlistat, a lipase inhibitor, reduces the absorption of dietary fat. Some weight loss in those taking orlistat probably results from a reduction in 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.

Sibutramine is a centrally acting appetite suppressant that inhibits the re-uptake of noradrenaline and serotonin.

There is little evidence to guide selection between orlistat and sibutramine, but it may be appropriate to choose orlistat for those who have a high intake of fat whereas sibutramine may be chosen for those who cannot control their eating; the cautions, contra-indications and side-effects of the two drugs should also be considered. On stopping treatment with orlistat or sibutramine there may be a gradual reversal of weight loss.

Combination therapy involving more than one anti-obesity drug should not be used 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 children. The use of diuretics, chorionic gonadotrophin, or amphetamines is not appropriate for weight reduction.

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. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis, or in digoxin or antiepileptic 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 may be considered 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 (see below). Other antipsychotic drugs including
haloperidol and levomepromazine (methotrimeprazine) (section 4.2.1) are also used for the relief of nausea in palliative care (see p. 27 and p. 28). Some phenothiazines are available as rectal suppositories, which can be useful in children with persistent vomiting or with severe nausea; for children over 12 years 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 has limited efficacy. For the role of metoclopramide in cytotoxic-induced nausea and vomiting see section 8.1.

**Acute dystonic reactions**
Phenothiazines and metoclopramide can all induce acute dystonic reactions such as facial and skeletal muscle spasms and oculogyric crises; children (especially girls, young women, and those under 10 kg) are particularly susceptible. With metoclopramide, dystonic effects usually occur shortly after starting treatment and subside within 24 hours of stopping it. An antimuscarinic drug such as procyclidine (section 4.9.2) is used to abort dystonic attacks.

Domperidone acts at the chemoreceptor trigger zone; 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. For the role of domperidone in cytotoxic-induced nausea and vomiting see section 8.1. Domperidone is also used to treat vomiting due to emergency hormonal contraception (section 7.3.5).

Granisetron and ondansetron are specific 5HT3 antagonists which block 5HT3 receptors in the gastro-intestinal tract and in the CNS. They are of value in the management of nausea and vomiting in children receiving cytotoxics and in postoperative nausea and vomiting.

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.

Dexamethasone (section 6.3.2) has antiemetic effects. For the role of dexamethasone in cytotoxic-induced nausea and vomiting see section 8.1.

**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, and the type and duration of surgery. The aim is to prevent postoperative nausea and vomiting from occurring. Drugs used include some phenothiazines (e.g. prochlorperazine), metoclopramide, 5HT3 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.

**Opioid-induced nausea and vomiting**
Cyclizine, ondansetron, and prochlorperazine are used to relieve opioid-induced nausea and vomiting; ondansetron has the advantage of not producing sedation.
### 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 hydrobromide**. For children over 10 years old, 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 5HT₃ antagonists, domperidone, metoclopramide, and the phenothiazines (except the antihistamine phenothiazine promethazine) are ineffective in motion 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.

**Antihistamines** (such as cinnarizine), and **phenothiazines** (such as prochlorperazine) are effective for prophylaxis and treatment of nausea and vertigo resulting from vestibular disorders; however, when nausea and vertigo are associated with middle ear surgery, treatment can be difficult.

### 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. 27 and p. 28.

### Migraine

For the management of nausea and vomiting associated with migraine, see p. 263.

### Antihistamines

**CINNARIZINE**

**Cautions** see section 3.4.1

- **Hepatic impairment** sedation inappropriate in severe liver disease—avoid
- **Pregnancy** manufacturer advises avoid
- **Breast-feeding** although not known to be harmful, manufacturer advises avoid

**Contra-indications** see section 3.4.1

**Side-effects** see section 3.4.1; also rarely weight gain, sweating, lichen planus, and lupus-like skin reactions

**Indication and dose**

- **Relief of symptoms of vestibular disorders**
  - **By mouth**
    - **Child 5–12 years** 15 mg 3 times daily
    - **Child 12–18 years** 30 mg 3 times daily

**Cinnarizine** (Non-proprietary)

- **Tablets**, cinnarizine 15 mg, net price 84-tab pack = £15.91. Label: 2

**Stugeron** (Janssen-Cilag)

- **Tablets**, scored, cinnarizine 15 mg, net price 15-tab pack = £1.48, 100-tab pack = £3.49. Label: 2

**CYCLIZINE**

**Cautions** see section 3.4.1; severe heart failure; may counteract haemodynamic benefits of opioids; **interactions**: Appendix 1 (antihistamines)

- **Hepatic impairment** sedation inappropriate in severe liver disease—avoid
- **Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Contra-indications** see section 3.4.1

**Side-effects** see section 3.4.1

**Licensed use** tablets not licensed for use in children under 6 years; injection not licensed for use in children

**Indication and dose**

- **Motion sickness**
  - **By mouth**
    - **Child 5–12 years** 15 mg 2 hours before travel then 7.5 mg every 8 hours during journey if necessary
    - **Child 12–18 years** 30 mg 2 hours before travel then 15 mg every 8 hours during journey if necessary

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4 Central nervous system
Indication and dose

Nausea and vomiting of known cause; nausea and vomiting associated with vestibular disorders and palliative care

- By mouth or by intravenous injection over 3–5 minutes

  Child 1 month–6 years 0.5–1 mg/kg up to 3 times daily; max. single dose 25 mg

  Child 6–12 years 25 mg up to 3 times daily

  Child 12–18 years 50 mg up to 3 times daily

- By rectum

  Child 2–6 years 12.5 mg up to 3 times daily

  Child 6–12 years 25 mg up to 3 times daily

  Child 12–18 years 50 mg up to 3 times daily

- By continuous intravenous or subcutaneous infusion

  Child 1 month–2 years 3 mg/kg over 24 hours

  Child 2–5 years 5 mg at bedtime on night before travel, repeat following morning if necessary

  Child 5–10 years 10 mg at bedtime on night before travel, repeat following morning if necessary

  Child 10–18 years 20–25 mg at bedtime on night before travel, repeat following morning if necessary

Administration for administration by mouth, tablets may be crushed

Valoid® (Amdipharm)

Tablets, scored, cyclizine hydrochloride 50 mg. Net price 100 = £7.41. Label: 2

Injection®, cyclizine lactate 50 mg/mL. Net price 1-mL amp = 49p

Cyclizine (Non-proprietary)

Suppositories, 12.5 mg, 25 mg, 50 mg, 100 mg. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

PROMETHAZINE HYDROCHLORIDE

Cautions see section 3.4.1

Contra-indications see section 3.4.1

Side-effects see section 3.4.1 but more sedating

Indication and dose

Nausea and vomiting

- By mouth

  Child 2–5 years 5 mg at bedtime on night before travel, repeat following morning if necessary

  Child 5–10 years 10 mg at bedtime on night before travel, repeat following morning if necessary

  Child 10–18 years 25 mg at bedtime on night before travel, repeat following morning if necessary

  Severe vomiting during pregnancy

    - By mouth

      25 mg at bedtime increased if necessary to max. 100 mg daily (but see also Vomiting During Pregnancy, p. 238)

Preparations

Section 3.4.1

PROMETHAZINE TEOCLATE

Cautions see section 3.4.1

Contra-indications see section 3.4.1

Side-effects see section 3.4.1

Licensed use not licensed to treat vomiting of pregnancy

Indication and dose

Nausea, vomiting, labyrinthine disorders

- By mouth

  Child 5–10 years 12.5–37.5 mg daily

  Child 10–18 years 25–75 mg daily (max. 100 mg)

Motion sickness prevention

- By mouth

  Child 5–10 years 12.5 mg at bedtime on night before travel or 12.5 mg 1–2 hours before travel

Severe vomiting during pregnancy

- By mouth

  25 mg at bedtime increased if necessary to max. 100 mg daily (but see also Vomiting During Pregnancy, p. 238)

Preparations

Avomine® (Manx)

Phenothiazines and related drugs

**CHLORPROMAZINE HYDROCHLORIDE**

**Cautions** see Chlorpromazine Hydrochloride, section 4.2.1

**Contra-indications** see Chlorpromazine Hydrochloride, section 4.2.1

**Side-effects** see Chlorpromazine Hydrochloride, section 4.2.1

**Indication and dose**

- Nausea and vomiting of terminal illness (where other drugs are unsuitable)
  - **By mouth**
    - **Child 1–6 years** 500 micrograms/kg every 4–6 hours; max. 40 mg daily
    - **Child 6–12 years** 500 micrograms/kg every 4–6 hours; max. 75 mg daily
  - **Child 12–18 years** initially 25 mg then 25–50 mg every 3–4 hours until vomiting stops

**Preparations**

Section 4.2.1

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**PERPHENAZINE**

**Cautions** see Perphenazine, section 4.2.1

**Contra-indications** see Perphenazine, section 4.2.1

**Side-effects** see Perphenazine, section 4.2.1; extrapyramidal symptoms

**Indication and dose**

- Severe nausea and vomiting unresponsive to other antiemetics
  - **By mouth**
    - **Child 14–18 years** 4 mg 3 times daily, adjusted according to response, max. 24 mg daily

**Preparations**

Section 4.2.1

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**PROCLORPERAZINE**

**Cautions** see Prochlorperazine, section 4.2.1; hypotension more likely after intramuscular injection

**Contra-indications** see Prochlorperazine, section 4.2.1

**Side-effects** see Prochlorperazine, section 4.2.1; extrapyramidal symptoms, particularly dystonias, more frequent; respiratory depression may occur in susceptible children

**Licensed use** injection not licensed for use in children

**Indication and dose**

- Prevention and treatment of nausea and vomiting
  - **By mouth**
    - **Child 1–12 years and over 10 kg** 250 micrograms/kg 2–3 times daily
    - **Child 12–18 years** 5–10 mg, repeated if necessary up to 3 times daily
  - **By intramuscular injection**
    - **Child 2–5 years**, 1.25–2.5 mg, repeated if necessary up to 3 times daily
    - **Child 5–12 years** 5–6.25 mg, repeated if necessary up to 3 times daily
    - **Child 12–18 years** 12.5 mg, repeated if necessary up to 3 times daily

**Note** Doses are expressed as prochlorperazine maleate or mesilate; 1 mg prochlorperazine maleate = 1 mg prochlorperazine mesilate

**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**

**Buccastem® (R&C)**

- **Tablets (buccal)**, pale yellow, prochlorperazine maleate 3 mg. Net price 5 × 10-tab pack = £5.75. Label: 2, counselling, administration, see under Dose below

**Dose**

- **By mouth**
  - **Child 12–18 years** 1–2 tablets twice daily; tablets are placed high between upper lip and gum and left to dissolve

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4 Central nervous system
## TRIFLUOPERAZINE

**Cautions** see Trifluoperazine section 4.2.1

**Contra-indications** see Trifluoperazine section 4.2.1

**Side-effects** see Trifluoperazine section 4.2.1; extrapyramidal symptoms

### Indication and dose

**Severe nausea and vomiting unresponsive to other antiemetics**

- **By mouth**
  - **Child 3–5 years** up to 500 micrograms twice daily

### Preparations

Section 4.2.1

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## DOMPERIDONE

**Cautions** children; **interactions**: Appendix 1 (domperidone)

**Renal impairment** manufacturer advises reduce dose in renal impairment

**Breast-feeding** amount probably too small to be harmful

**Contra-indications** prolactinaemia; where increased gastro-intestinal motility harmful

**Hepatic impairment** avoid

**Pregnancy** manufacturer advises avoid

### Side-effects

rarely gastro-intestinal disturbances (including cramps), and hyperprolactinemia; very rarely extrapyramidal effects and rashes

### Indication and dose

**Nausea and vomiting**

- **By mouth**
  - **Child over 1 month and body-weight up to 35 kg** 250–500 micrograms/kg 3–4 times daily; max. 2.4 mg/kg in 24 hours
  - **Body-weight 35 kg and over** 10–20 mg 3–4 times daily, max. 80 mg daily

### Preparations

- **By rectum**
  - **Body-weight 15–35 kg** 30 mg twice daily
  - **Body-weight over 35 kg** 60 mg twice daily

### Gastro-intestinal stasis section 1.2

**Domperidone** (Non-proprietary) **(H1)**

- **Tablets**, 10 mg (as maleate), net price 30-tab pack = £1.37; 100-tab pack = £2.55
- **Suspension**, domperidone 5 mg/mL, net price 200-mL pack = £7.00

**Motilium**® (Winthrop) **(H1)**

- **Tablets**, f/c, domperidone 10 mg (as maleate), net price 30-tab pack = £2.82; 100-tab pack = £9.41
- **Suspension**, sugar-free, domperidone 5 mg/5 mL, net price 200-mL pack = £2.16
- **Suppositories**, domperidone 30 mg, net price 10 = £3.18

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## METOCLOPRAMIDE HYDROCHLORIDE

**Cautions** atopic allergy (including asthma); may mask underlying disorders such as cerebral irritation; epilepsy; acute porphyria (section 9.8.2); **interactions**: Appendix 1 (metoclopramide)

**Hepatic impairment** reduce dose

**Renal impairment** avoid or use small dose; increased risk of extrapyramidal reactions in severe impairment

**Pregnancy** not known to be harmful but manufacturer advises use only when compelling reasons

**Contra-indications** gastro-intestinal obstruction, perforation or haemorrhage; 3–4 days after gastro-intestinal surgery; phaeochromocytoma

**Breast-feeding** small amount present in milk; manufacturer advises avoid large single doses

**Side-effects** extrapyramidal effects (see p. 238), 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 methaemoglobinaemia (more severe in G6PD deficiency)

**Licensed use** not licensed for use in neonates as a prokinetic

### Indication and dose

**Severe intractable vomiting of known cause**, vomiting associated with radiotherapy and cytotoxics, aid to gastro-intestinal intubation, as a prokinetic in neonates

- **By mouth, or by intramuscular injection or by intravenous injection over 1–2 minutes**
  - **Neonate** 100 micrograms/kg every 6–8 hours (by mouth or by intravenous injection only)
  - **Child 1 month–1 year and body-weight up to 10 kg** 100 micrograms/kg (max. 1 mg) twice daily
### METOCLOPRAMIDE HYDROCHLORIDE (continued)

**Child 1–3 years and body-weight 10–14 kg** 1 mg 2–3 times daily  
**Child 3–5 years and body-weight 15–19 kg** 2 mg 2–3 times daily  
**Child 5–9 years and body-weight 20–29 kg** 2.5 mg 3 times daily  
**Child 9–18 years and body-weight 30–60 kg** 5 mg 3 times daily  
**Child 15–18 years and body-weight over 60 kg** 10 mg 3 times daily  

Note: Daily dose of metoclopramide should not normally exceed 500 micrograms/kg

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**Premedication in diagnostic procedures**  
- By mouth as a single dose 5–10 minutes before examination  
  **Child 1 month–3 years and body-weight up to 14 kg** 100 micrograms/kg, max. 1 mg  
  **Child 3–5 years and body-weight 15–19 kg** 2 mg  
  **Child 5–9 years and body-weight 20–29 kg** 2.5 mg  
  **Child 9–15 years and body-weight 30–60 kg** 5 mg  
  **Child 15–18 years and body-weight over 60 kg** 10 mg

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**GRANISETRON**

**Cautions**  
- **Pregnancy** manufacturer advises use only when compelling reasons—no information available  
- **Breast-feeding** manufacturer advises avoid—no information available  

**Side-effects** constipation, headache, rash; hypersensitivity reactions reported; rarely movement disorders  

**Licensed use** sterile solution not licensed for use in children under 2 years  

**Indication and dose**  
Treatment and prevention of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy  
- **By mouth**  
  **Child 12–18 years** 1–2 mg within 1 hour before start of treatment, then 1 mg twice daily during treatment (total daily dose may alternatively be given as a single dose); when intravenous infusion also used, max. combined total 9 mg in 24 hours  
- **By intravenous infusion**  
  **Child 1 month–12 years** prevention, 40 micrograms/kg (max. 3 mg) repeated within 24 hours if necessary (not less than 10 minutes after initial dose)  

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**Compound preparations (for migraine)**  
Section 4.7.4.1

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**5HT3 antagonists**

**GRANISETRON**

**Cautions**  
- **Pregnancy** manufacturer advises use only when compelling reasons—no information available  
- **Breast-feeding** manufacturer advises avoid—no information available  

**Side-effects** constipation, headache, rash; hypersensitivity reactions reported; rarely movement disorders  

**Licensed use** sterile solution not licensed for use in children under 2 years  

**Indication and dose**  
Treatment and prevention of nausea and vomiting induced by cytotoxic chemotherapy or radiotherapy  
- **By mouth**  
  **Child 12–18 years** 1–2 mg within 1 hour before start of treatment, then 1 mg twice daily during treatment (total daily dose may alternatively be given as a single dose); when intravenous infusion also used, max. combined total 9 mg in 24 hours  
- **By intravenous infusion**  
  **Child 1 month–12 years** prevention, 40 micrograms/kg (max. 3 mg) repeated within 24 hours if necessary (not less than 10 minutes after initial dose)  

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**By intravenous injection or by intravenous infusion**  
**Child 12–18 years** prevention, 3 mg before start of cytotoxic therapy (up to 2 additional 3-mg doses may be given within 24 hours); treatment, 3 mg repeated if necessary (doses must not be given less than 10 minutes apart), max. 9 mg in 24 hours

**Administration** for *intravenous infusion*, dilute 3 mL in 10–30 mL Glucose 5% or Sodium Chloride 0.9%, or Compound Sodium Lactate; give over 5 minutes

**Kytril®** (Roche)  
**Tablets**, f/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

Cautions  QT interval prolongation (avoid concommitant administration of drugs that prolong QT interval)
Hepatic impairment  reduce dose in moderate or severe hepatic impairment
Pregnancy  no information available; manufacturer advises avoid unless potential benefit outweighs risk
Breast-feeding  manufacturer advises avoid—no information available
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)

Licensed use  oral and parenteral preparations not licensed for use in children under 2 years

Indication and dose
Prevention and treatment of chemotherapy- and radiotherapy-induced nausea and vomiting

• By slow intravenous injection or by intravenous infusion
Child 1–12 years  5 mg/m² immediately before chemotherapy (max. single dose 8 mg), then either repeat every 8–12 hours during chemotherapy and for at least 24 hours afterwards or give by mouth
Child 12–18 years  8 mg immediately before chemotherapy, then either repeated every 8–12 hours during chemotherapy and for at least 24 hours afterwards or give by mouth

• By mouth following intravenous administration
Child 1–12 years  4 mg every 8–12 hours for up to 5 days
Child 12–18 years  8 mg every 8–12 hours for up to 5 days

Treatment and prevention of postoperative nausea and vomiting
• By slow intravenous injection
Child 2–12 years  100 micrograms/kg (max. 4 mg), as a single dose before, during, or after induction of anaesthesia
Child 12–18 years  4 mg, as a single dose at induction of anaesthesia

Administration for slow intravenous injection, give over 2–5 minutes
For intravenous infusion, dilute to a concentration of 320–640 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% or Ringer’s Solution; give over at least 15 minutes

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, t/c, ondansetron (as hydrochloride) 4 mg, net price 30-tab pack = £107.91; 8 mg, 10-tab pack = £71.94
Oral lyophilisates (Zofran Melt®), ondansetron 4 mg, net price 10-tab pack = £53.97, 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

Cannabinoid

NABILONE

Cautions  history of psychiatric disorder; hyper-tension; heart disease; adverse effects on mental state can persist for 48–72 hours after stopping; interactions: Appendix 1 (nabilone)
Skilled tasks  Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced
Contra-indications  Hepatic impairment  avoid in severe hepatic impairment
Pregnancy  manufacturer advises avoid unless essential
Breast-feeding  no information available—manufacturer advises avoid
Side-effects  drowsiness, vertigo, euphoria, dry mouth, ataxia, visual disturbance, concentration difficulties, sleep disturbance, dysphoria, hypotension, headache and nausea; also confusion, disorientation, hallucinations, psychosis, depres-

sion, decreased coordination, tremors, tachy-cardia, decreased appetite, and abdominal pain

Behavioural effects  Children and carers should be made aware of possible changes of mood and other adverse behavioural effects

Licensed use  not licensed for use in children

Indication and dose
Nausea and vomiting caused by cytotoxic chemotherapy, unresponsive to conventional antiemetics (under close observation, preferably in hospital setting)
• By mouth
Consult local treatment protocol for details

Nabilone (Valent)  Capsules, blue/white, nabilone 1 mg. Net price 20-cap pack = £125.84. Label: 2, counselling, behavioural effects
HYOSCINE HYDROBROMIDE
(Scopolamine Hydrobromide)

Cautions urinary retention, cardiovascular disease, gastro-intestinal obstruction; interactions: Appendix I (antimuscarinics)

Skilled tasks Drowsiness may affect performance of skilled tasks (e.g. driving) and may persist for up to 24 hours or longer after removal of patch; effects of alcohol enhanced

Hepatic impairment manufacturer advises caution

Renal impairment manufacturer advises caution

Pregnancy manufacturer advises use only if potential benefit outweighs risk; injection may depress neonatal respiration

Breast-feeding amount too small to be harmful

Contra-indications closed-angle glaucoma

Side-effects drowsiness, dry mouth, dizziness, blurred vision, difficulty with micturition

Licensed use not licensed for use in excessive respiratory secretions or hypersalivation associated with clozapine therapy

Indication and dose

Motion sickness
- By mouth
  Child 4–10 years 75–150 micrograms 30 minutes before start of journey, repeated every 6 hours if required; max. 3 doses in 24 hours
  Child 10–18 years 150–300 micrograms 30 minutes before start of journey, repeated every 6 hours if required; max. 3 doses in 24 hours
- By topical application
  Child 10–18 years apply 1 patch (1 mg) to hairless area of skin behind ear 5–6 hours before journey; replace if necessary after 72 hours, siting replacement patch behind the other ear

Excessive respiratory secretions
- By mouth or by sublingual administration
  Child 2–12 years 10 micrograms/kg, max. 300 micrograms 4 times daily
  Child 12–18 years 300 micrograms 4 times daily
- By transdermal route
  Child 1 month–3 years 250 micrograms every 72 hours (quarter of a patch)

Child 3–10 years 500 micrograms every 72 hours (half a patch)

Child 10–18 years 1 mg every 72 hours (one patch)

By subcutaneous injection, intravenous injection, intravenous infusion, or subcutaneous infusion

See Prescribing in Palliative Care, p. 26 and p. 28

Hypersalivation associated with clozapine therapy
- By mouth
  Child 12–18 years 300 micrograms up to 3 times daily; max. 900 micrograms daily

Premedication section 15.1.3

Administration patch applied to hairless area of skin behind ear; if less than whole patch required either cut with scissors along full thickness ensuring membrane is not peeled away or cover portion to prevent contact with skin For administration by mouth, injection solution may be given orally

Joy-Rides® (GSK Consumer Healthcare)
Chewable tablets, hyoscine hydrobromide 150 micrograms, net price 12-tab pack = £1.49. Label: 2, 24

Kwells® (Bayer Consumer Care)
Chewable tablets, hyoscine hydrobromide 150 micrograms (Kwells® Kids), net price 12-tab pack = £1.52; 300 micrograms, 12-tab pack = £1.52. Label: 2

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

Counselling Explain accompanying instructions to child and carer, in particular emphasise advice to wash hands after handling and to wash application site after removing, and to use one patch at a time

4.7 Analgesics

4.7.1 Non-opioid analgesics
4.7.2 Opioid analgesics
4.7.3 Neuropathic pain
4.7.4 Antimigraine drugs

The non-opioid drugs (section 4.7.1), paracetamol and ibuprofen (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. 24.

Pain in sickle-cell disease The pain of mild sickle-cell crises is managed with paracetamol, an NSAID, codeine, or dihydrocodeine. Severe crises may require the use of morphine or diamorphine; concomitant use of an NSAID (section 10.1.1) may potentiate analgesia and allow lower doses of the opioid to be used. A mixture of nitrous oxide and oxygen (Entonox®, Equanox®) may also be used.

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 pulpitis, apical infection, localised 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 pulpitis, intra-osseous infection or abscess, reliance on analgesics alone is usually inappropriate.

Similarly the pain and discomfort associated with acute problems of the oral mucosa (e.g. acute herpetic gingivostomatitis, erythema multiforme) may be relieved by benzydamine (p. 655) or topical anaesthetics until the cause of the mucosal disorder has been dealt with. However, where a child is febrile, the antipyretic action of paracetamol (p. 247) or ibuprofen (p. 604) is often helpful.

The choice of an analgesic for dental purposes should be based on its suitability for the child. Most dental pain is relieved effectively by non-steroidal anti-inflammatory drugs (NSAIDs) e.g. ibuprofen (section 10.1.1). Paracetamol has analgesic and antipyretic effects but no anti-inflammatory effect.

Opioid analgesics (section 4.7.2) such as dihydrocodeine act on the central nervous system and are traditionally used for moderate to severe pain. However, opioid analgesics are relatively ineffective in dental pain and their side-effects can be unpleasant.

Combining a non-opioid with an opioid analgesic can provide greater relief of pain than either analgesic given alone. However, this applies only when an adequate dose of each analgesic is used. Most combination analgesic preparations have not been shown to provide greater relief of pain than an adequate dose of the non-opioid component given alone. Moreover, combination preparations have the disadvantage of an increased number of side-effects.

Any analgesic given before a dental procedure should have a low risk of increasing postoperative bleeding. In the case of pain after the dental procedure, taking an analgesic before the effect of the local anaesthetic has worn off can improve control. Postoperative analgesia with ibuprofen is usually continued for about 24 to 72 hours.

Dysmenorrhoea Paracetamol or a NSAID (section 10.1.1) will generally provide adequate relief of pain from dysmenorrhoea. Alternatively use of a combined hormonal contraceptive in adolescent girls may prevent the pain.

4.7.1 Non-opioid analgesics

Paracetamol has analgesic and antipyretic properties but no demonstrable anti-inflammatory activity; unlike opioid analgesics, it does not cause respiratory depression and is less irritant to the stomach than the NSAIDs. Overdosage 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. 37).

Non-steroidal anti-inflammatory analgesics (NSAIDs, section 10.1.1) are particularly useful for the treatment of children 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 paracetamol is now often preferred. 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. 24). Due to an association with Reye’s syndrome (section 2.9), aspirin should be avoided in children under 16 years except in Kawasaki syndrome or for its antiplatelet action (section 2.9). NSAIDs are also used for peri-operative analgesia (section 15.1.4.2).
Dental and orofacial pain

Most dental pain is relieved effectively by NSAIDs (section 10.1.1).

Paracetamol is less irritant to the stomach than NSAIDs. 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 notes above, p. 246.

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 titration of the individual components in the management of pain of varying intensity.

Compound analgesic preparations containing paracetamol or aspirin with a low dose of an opioid analgesic (e.g. 8 mg of codeine phosphate per compound tablet) may be used in older children but the advantages have not been substantiated. The low dose of the opioid may be enough to cause opioid side-effects (in particular, constipation) and can complicate the treatment of overdosage (see p. 39) 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 effectively augments the analgesic activity but is associated with the full range of opioid side-effects (including nausea, vomiting, severe constipation, drowsiness, respiratory depression, and risk of dependence on long-term administration). For details of the side-effects of opioid analgesics, see p. 249.

PARACETAMOL

(Acetaminophen)

Cautions alcohol dependence; interactions: Appendix 1 (paracetamol)

Hepatic impairment dose-related toxicity— avoid large doses

Renal impairment increase infusion dose interval to every 6 hours if estimated glomerular filtration rate less than 30 mL/min/1.73m²

Pregnancy not known to be harmful

Breast-feeding amount too small to be harmful

Side-effects side-effects rare, but rashes, blood disorders (including thrombocytopenia, leucopenia, neutropenia) reported; hypotension also reported on infusion; important: liver damage (and less frequently renal damage) following overdosage, see Emergency Treatment of Poisoning, p. 37

Licensed use not licensed for use in children under 2 months by mouth; doses for severe symptoms not licensed

Indication and dose

Pain; pyrexia with discomfort

- By mouth

Neonate 28–32 weeks postmenstrual age 20 mg/kg as a single dose then 10–15 mg/kg every 8–12 hours as necessary; max. 30 mg/kg daily in divided doses

Neonate over 32 weeks postmenstrual age 20 mg/kg as a single dose then 10–15 mg/kg every 6–8 hours as necessary; max. 60 mg/kg daily in divided doses

Child 1–3 months 30–60 mg every 8 hours as necessary; for severe symptoms 20 mg/kg as a single dose then 15–20 mg/kg every 6–8 hours; max. 60 mg/kg daily in divided doses

- By rectum

Neonate 28–32 weeks postmenstrual age 20 mg/kg as a single dose then 15 mg/kg every 12 hours as necessary; max. 30 mg/kg daily in divided doses

Neonate over 32 weeks postmenstrual age 30 mg/kg as a single dose then 20 mg/kg every 8 hours as necessary; max. 60 mg/kg daily in divided doses

Child 1–3 months 30–60 mg every 8 hours as necessary; for severe symptoms 30 mg/kg as a single dose then 20 mg/kg every 8 hours; max. 60 mg/kg daily in divided doses

Child 3–12 months 60–120 mg every 4–6 hours (max. 4 doses in 24 hours); for severe symptoms 20 mg/kg every 6 hours (max. 90 mg/kg daily in divided doses) for 48 hours (or longer if necessary and if adverse effects ruled out) then 15 mg/kg every 6 hours

Child 1–5 years 120–250 mg every 4–6 hours (max. 4 doses in 24 hours); for severe symptoms 20 mg/kg every 6 hours (max. 90 mg/kg daily in divided doses) for 48 hours (or longer if necessary and if adverse effects ruled out) then 15 mg/kg every 6 hours

Child 6–12 years 250–500 mg every 4–6 hours (max. 4 doses in 24 hours); for severe symptoms 20 mg/kg (max. 1 g) every 6 hours (max. 90 mg/kg daily in divided doses, not to exceed 4 g) for 48 hours (or longer if necessary and if adverse effects ruled out) then 15 mg/kg every 6 hours; max. 4 g daily

Child 12–18 years 500 mg every 4–6 hours; for severe symptoms 1 g every 4–6 hours (max. 4 doses in 24 hours)

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**PARACETAMOL (continued)**

**Paediatric soluble tablets** (= Paediatric dispersible tablets), paracetamol 120 mg. Net price 16-tab pack = 89p. Label: 13, 30

Brands include Disprin® Soluble Paracetamol.

**Oral suspension 120 mg/5 mL** (= Paediatric Mixture), paracetamol 120 mg/5 mL. Net price 100 mL = 42p. Label: 30

**Note** BP directs that when Paediatric Paracetamol Oral Suspension or Paediatric Paracetamol Mixture is prescribed Paracetamol Oral Suspension 120 mg/5 mL should be dispensed; sugar-free versions can be ordered by specifying 'sugar-free' on the prescription.

Brands include Calpol® Paediatric, Calpol® Paediatric sugar-free, Disprin® Paediatric, Medinol® Paediatric sugar-free, Paldeks®, Panado® sugar-free.

**Oral suspension 250 mg/5 mL** (= Mixture), paracetamol 250 mg/5 mL. Net price 100 mL = 66p. Label: 30

Brands include Calpol® 6 Plus®, Medinol® Over 6®, Paldeks®.

**Suppositories**, paracetamol 60 mg, net price 10 = £9.96; 125 mg, 10 = £11.50; 250 mg, 10 = £23.00; 500 mg, 10 = £10.36. Label: 30

Brands include Alvedon®.

**Note** other strengths available from 'special-order' manufacturers or specialist importing companies, see p. 943.

**Dental prescribing on NHS** Paracetamol Tablets, Paracetamol Soluble Tablets 500 mg, and Paracetamol Oral Suspension may be prescribed.

perfalgan® (Bristol-Myers Squibb) ▼ Paracetamol Intravenous infusion, paracetamol 10 mg/mL. Net price 50-mL vial = £1.80, 100-mL vial = £1.98

**Administration** give undiluted or dilute to a concentration of 1 mg/mL in Glucose 5% or Sodium Chloride 0.9%; use within 1 hour of dilution

**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)**

**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**

**Pain, pyrexia**

**By mouth**

**Child 6–12 years** ½–1 tablet every 4–6 hours; max. 4 tablets daily

**Child 12–18 years** 1–2 tablets every 4–6 hours; max. 8 tablets daily

**Effervescent or dispersible tablets**, co-codamol 8/500 (codeine phosphate 8 mg, paracetamol

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1. Can be sold to the public provided packs contain no more than 32 capsules or tablets; pharmacists can sell multiple packs up to a total quantity of 100 capsules or tablets in justifiable circumstances; for details see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available).
2. Can be sold to the public under certain circumstances; for exemptions see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available).
4.7.2 Opioid analgesics

Opioid analgesics are usually used to relieve moderate to severe pain particularly of visceral origin. Repeated administration may cause tolerance, but this is no deterrent in the control of pain in terminal illness, for guidelines see Prescribing in Palliative Care, p. 24. 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 child should be assessed at regular intervals.

Cautions Opioids should be used with caution in children with impaired respiratory function and asthma (avoid during an acute attack), hypotension, shock, obstructive or inflammatory bowel disorders, diseases of the biliary tract, and convulsive disorders. A reduced dose is recommended in hypothyroidism or 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 children whose analgesic requirements are changing rapidly, because the long time to steady state prevents rapid titration of the dose.

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 children 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 children 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); neonates, particularly if preterm, may be more susceptible. 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, urination retention, ureteric spasm, miosis, visual disturbances, sweating, flushing, rash, urticaria, and pruritus. Overdose: see Emergency Treatment of Poisoning, p. 39.

Interactions See Appendix 1 (opioid analgesics) (important: special hazard with pethidine and possibly other opioids and MAOIs).

Skilled tasks 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. 24.

Buprenorphine has both opioid agonist and antagonist properties and may precipitate withdrawal symptoms, including pain, in children 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. It is used rarely in children.

Codeine is used for the relief of mild to moderate pain but is too constipating for long-term use.

Diamorphine (heroin) is a powerful opioid analgesic. It may cause less nausea and hypotension than morphine. In palliative care the greater solubility of diamorphine allows effective doses to be injected in smaller volumes and this is important in the emaciated child.

Diamorphine is sometimes given by the intranasal route to treat acute pain in children, for example, in accident and emergency units; however, as yet, there is limited safety and efficacy data to support this practice.

Dihydrocodeine has an analgesic efficacy similar to that of codeine; doses may be given every 4 hours.

Alfentanil, fentanyl and remifentanil are used by injection for intra-operative analgesia (section 15.1.4.3). Fentanyl is available in a transdermal drug delivery system as a self-adhesive patch which is changed every 72 hours.

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 when excitation (or exacerbation of pain) occurs with morphine. Methadone may also be used to treat children with neonatal abstinence syndrome (section 4.10).

Papaveretum should not be used in children; morphine is easier to prescribe and less prone to error with regard to the strength and dose.

Pethidine produces prompt but short-lasting analgesia; it is less constipating than morphine, but even in high doses is a less potent analgesic. Its use in children is not recommended. Pethidine is used for analgesia in labour; however, other opioids, such as morphine or diamorphine, are often preferred for obstetric pain.

Tramadol is used in older children and 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**  
Doses of opioids may need to be adjusted individually according to the degree of analgesia and side-effects; response to opioids varies widely, particularly in the neonatal period. Opioid overdosage can have serious consequences and the dose should be calculated and checked with care.

**Postoperative analgesia**  
A combination of opioid and non-opioid analgesics is used to treat post-operative pain (section 15.1.4.2). The use of intra-operative opioids affects the prescribing of postoperative analgesics and in many cases delays the need for a postoperative 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).

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
unsuitable for post-operative pain because it is metabolised to norpethidine which may accumulate, particularly in neonates and 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) and nurse-controlled analgesia (NCA) 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 post-operative dental pain.

For the management of dental and orofacial pain, see p. 246.

**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.

**Dependence and withdrawal**  
Psychological dependence rarely occurs when opioids are used for pain relief but tolerance can develop during long-term treatment; they should be withdrawn gradually to avoid abstinence symptoms. For information on the treatment of neonatal abstinence syndrome, see section 4.10.

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**BUPRENORPHINE**

**Cautions** see notes above; also impaired consciousness; effects only partially reversed by naloxone

**Hepatic impairment** avoid or reduce dose—may precipitate coma

**Renal impairment** reduce dose or avoid, increased and prolonged effect; increased cerebral sensitivity

**Pregnancy** depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

**Breast-feeding** amount too small to be harmful; manufacturer advises contra-indicated in the treatment of opioid dependence

**Contra-indications** see notes above; also myasthenia gravis

**Side-effects** see notes above; can induce mild withdrawal symptoms in children dependent on opioids; also diarrhoea, abdominal pain, anorexia, dyspepsia; vasodilatation; dysphoria; paraesthesia, asthenia, fatigue, agitation, anxiety; less commonly flattulence, taste disturbance, hypertension, syncope, hypoxia, wheezing, cough, restlessness, depersonalisation, dysthria, impaired memory, hypoaesthesia, tremor, influenza-like symptoms, pyrexia, rhinitis, rigors, muscle cramp, myalgia, tinnitus, dry eye, and dry skin; rarely paralytic ileus, dysphagia, diverticulitis, impaired concentration, and psychosis; very rarely retching, hyperventilation, hiccup, and muscle fasciculation

**Licensed use**  
sublingual tablets not licensed for use in children under 6 years; injection not licensed for use in children under 6 months

**Indication and dose**

**Moderate to severe pain**

- **By sublingual administration**
  - **Child body-weight 16–25 kg** 100 micrograms every 6–8 hours
  - **Child body-weight 25–37.5 kg** 100–200 micrograms every 6–8 hours
  - **Child body-weight 37.5–50 kg** 200–300 micrograms every 6–8 hours
  - **Child body-weight over 50 kg** 200–400 micrograms every 6–8 hours

- **By intramuscular or by slow intravenous injection**
  - **Child 6 months–12 years** 3–6 micrograms/kg every 6–8 hours, max. 9 micrograms/kg
  - **Child 12–18 years** 300–600 micrograms every 6–8 hours

**Administration** for administration by mouth, tablets may be halved

**Temgesic** (Schering-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
CODEINE PHOSPHATE

Cautions  see notes above; also cardiac arrhythmias; myasthenia gravis; acute abdomen; gallstones

Variation in metabolism  The capacity to metabolise codeine can vary considerably between individuals and lead to either reduced therapeutic effect or marked increase in side-effects

Hepatic impairment  avoid or reduce dose—may precipitate coma

Renal impairment  reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Pregnancy  depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

Breast-feeding  amount usually too small to be harmful; however, mothers vary considerably in their capacity to metabolise codeine—risk of morphine overdose in infant

Contra-indications  see notes above

Side-effects  see notes above; also abdominal pain, anorexia, seizures, malaise, hypothermia, and muscle fasciculation; pancreatitis also reported

Licensed use  tablets not licensed for use in children; injection not licensed for use in children under 1 year

Indication and dose

Mild to moderate pain

- By mouth or by rectum or by subcutaneous injection or by intramuscular injection

<table>
<thead>
<tr>
<th>Neonate</th>
<th>0.5–1 mg/kg, every 4–6 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–12 years</td>
<td>0.5–1 mg/kg, every 4–6 hours, max. 240 mg daily</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>30–60 mg every 4–6 hours, max. 240 mg daily</td>
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</tbody>
</table>

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

Syrup  codeine phosphate 25 mg/5 mL. Net price 100 mL = 90p. Label: 2

Injection  codeine phosphate 60 mg/mL. Net price 1-mL amp = £2.44

DIAMORPHINE HYDROCHLORIDE  (Heroin Hydrochloride)

Cautions  see notes above; also severe diarrhoea; toxic psychosis, CNS depression; severe cor pulmonale

Hepatic impairment  avoid or reduce dose—may precipitate coma

Renal impairment  reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Pregnancy  depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

Breast-feeding  therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring

Contra-indications  see notes above; also delayed gastric emptying; phaeochromocytoma

Side-effects  see notes above; also anorexia, taste disturbance; syncope; asthenia, raised intracranial pressure; myocardial infarction also reported

Licensed use  intranasal route not licensed

Indication and dose

Acute or chronic pain

- By mouth

| Child 1 month–12 years | 100–200 micrograms/kg (max. 10 mg) every 4 hours as necessary |
| Child 12–18 years | 5–10 mg every 4 hours as necessary |

- By intravenous injection

| Child 1–3 months | 20 micrograms/kg every 6 hours as necessary |
| Child 3–6 months | 25–50 micrograms/kg every 6 hours as necessary |
| Child 6–12 months | 75 micrograms/kg every 4 hours as necessary |
| Child 1–12 years | 75–100 micrograms/kg every 4 hours as necessary |
| Child 12–18 years | 2.5–5 mg every 4 hours as necessary |

- By continuous subcutaneous infusion

See Prescribing in Palliative Care, p. 24

- By subcutaneous or by intramuscular injection

| Child 12–18 years | 5 mg every 4 hours as necessary |

Administration  for intravenous infusion, dilute in Glucose 5% or Sodium Chloride 0.9%; Glucose 5% is preferable. For intranasal administration, diamorphine powder should be dissolved in sufficient volume of Water for Injections to provide the requisite dose
in 0.2mL of solution; use solution immediately after preparation

Diamorphine (Non-proprietary)  
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

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

DIHYDROCODEINE TARTRATE

Cautions  see notes above; also pancreatitis; severe cor pulmonale

Hepatic impairment  avoid or reduce dose—may precipitate coma

Renal impairment  reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Pregnancy  depresses neonatal respiration—withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

Breast-feeding  manufacturer advises use only if potential benefit outweighs risk

Contra-indications  see notes above

Side-effects  see notes above; also paralytic ileus, abdominal pain, and parasthesia

Licensed use  most preparations not licensed for use in children under 4 years

Indication and dose

Moderate to severe pain

• By mouth or by intramuscular injection or by subcutaneous injection

Child 1–4 years  500 micrograms/kg every 4–6 hours

Child 4–12 years  0.5–1 mg/kg (max. 30 mg) every 4–6 hours

Child 12–18 years  30 mg (max. 50 mg by intramuscular or deep subcutaneous injection) every 4–6 hours

Severe pain

• By mouth

Child 12–18 years  40–80 mg 3 times daily; max. 240 mg daily

Modified release

DHC Continus® (Napp)  
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

Chronic severe pain

• By mouth

Child 12–18 years  60–120 mg every 12 hours

FENTANYL

Cautions  see notes above; also diabetes mellitus, impaired consciousness, cerebral tumour, myasthenia gravis

Transdermal fentanyl

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)

Respiratory depression  Risk of fatal respiratory depression, particularly in patients not previously treated with a strong opioid analgesic; manufacturer recommends use only in opioid tolerant patients

Hepatic impairment  avoid or reduce dose—may precipitate coma

Renal impairment  reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Pregnancy  depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

Breast-feeding  amount too small to be harmful

Contra-indications  see notes above

Side-effects  see notes above; also abdominal pain, anorexia, dyspepsia, mouth ulcer, taste disturbance, dry mouth; vasodilatation; apnoea; anxiety; myoclonus; less commonly flatulence, diarrhoea, laryngospasm, dyspnoea, hypoventilation, depersonalisation, dysarthria, amnesia, incoordination, paraesthesia, malaise, agitation, tremor, and muscle weakness; rarely hiccups and arrhythmia; very rarely paralytic ileus, haemoptysis, psychosis, and seizures; shock, asystole, pyrexia, ataxia, and muscle fasciculation also reported; with patches, local reactions such as rash, erythema, and itching reported

Licensed use  lozenges not licensed for use in children
Indication and dose

Severe chronic pain

- By transdermal route
  
  **Child 2–16 years currently treated** with strong opioid analgesic, initial dose based on previous 24-hour opioid requirement (consult product literature)

  **Child 16–18 years child not currently treated** with strong opioid analgesic (but see Cautions, p. 249), one ‘12’ or ‘25 micrograms/hour’ patch replaced after 72 hours; child currently treated with strong opioid analgesic, initial dose based on previous 24-hour opioid requirement (consult product literature)

  **Dose adjustment** When starting, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours (to allow for the gradual increase in plasma-fentanyl concentration)—previous analgesic therapy should be phased out gradually from time of first patch application; if necessary dose should be adjusted at 72-hour intervals in steps of 12–25 micrograms/hour. More than one patch may be used at a time for doses greater than 100 micrograms/hour (but applied at same time to avoid confusion)—consider additional or alternative analgesic therapy if dose required exceeds 300 micrograms/hour (important: it 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, children who have had severe side-effects should be monitored for up to 24 hours after patch removal

Breakthrough pain and premedication analgesia, see under preparation below

Peri-operative analgesia section 15.1.4.3

**Conversion** (from oral morphine to transdermal fentanyl), see Prescribing in Palliative Care, p. 25

**Administration** For patches, apply to dry, non-irritated, non-hairy skin on torso or upper arm, removing after 72 hours and siting replacement patch on a different area (avoid using the same area for several days).

Lozenges

**Actiq** (Cephalon)

**Lozenge,** with oromucosal applicator, fentanyl (as citrate) 200 micrograms, net price 3 = £18.58, 30 = £185.80; 400 micrograms, 3 = £18.58, 30 = £185.80; 600 micrograms, 3 = £18.58, 30 = £185.80; 800 micrograms, 3 = £18.58, 30 = £185.80; 1.2 mg, 3 = £18.58, 30 = £185.80; 1.6 mg, 3 = £18.58, 30 = £185.80. Label: 2

Dose

**Breakthrough pain**

- By transmucosal application (lozenge with oromucosal applicator)
  
  **Child 2–18 years (over 10 kg body-weight)** 15–20 micrograms/kg as a single dose; max. dose 400 micrograms

  **Note** If more than 4 episodes of breakthrough pain each day, adjust dose of background analgesic

Patches

Prescriptions Prescriptions for fentanyl patches can be written to show the strength in terms of the release rate and it is acceptable to write ‘Fentanyl 25 patches’ to prescribe patches that release fentanyl 25 micrograms per hour. The dosage should be expressed in terms of the interval between applying a patch and replacing it with a new one, e.g. ‘one patch to be applied every 72 hours’. The total quantity of patches should be written in words and figures.

**Fentanyl** (Non-proprietary)

**Patches,** self-adhesive, 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 = £86.46. Label: 2, counselling, administration.

Brands include Matrifen®, Osmanil®, Tilofy®, Victanyl®

**Durogesic DTrans** (Janssen-Cilag)

**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, counselling, administration

HYDROMORPHONE HYDROCHLORIDE

Cautions see notes above; also paralytic ileus, seizures, asthenia, agitation, and myoclonus

Hepatic impairment avoid or reduce dose—may precipitate coma

Renal impairment reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Pregnancy depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gestational stasis and risk of inhalation pneumonia in mother during labour

Breast-feeding manufacturer advises avoid—no information available

Contra-indications see notes above; also acute abdomen

Side-effects see notes above; also paralytic ileus, seizures, asthenia, agitation, and myoclonus
Indication and dose

**Severe pain in cancer**

- **By mouth**
  
  **Child 12–18 years** 1.3 mg every 4 hours, increased if necessary according to severity of pain

**Administration** Swallow whole capsule or sprinkle contents on soft food

**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

**Modified release**

Palladone® SR (Napp)

Capsules, m/r, 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**

- **Severe pain in cancer**
  
  - **By mouth**
  
  **Child 12–18 years** 4 mg every 12 hours, increased if necessary according to severity of pain

**Counselling** Swallow whole or open capsule and sprinkle contents on soft food

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**METHADONE HYDROCHLORIDE**

**Cautions** see notes above; also myasthenia gravis; history of cardiac conduction abnormalities, family history of sudden death (ECG monitoring recommended; see also QT Interval Prolongation, below)

**QT interval prolongation** The CHM has recommended that children with the following risk factors for QT interval prolongation are carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; children requiring more than 100 mg daily should also be monitored

**Hepatic impairment** avoid or reduce dose in liver disease—may precipitate coma

**Renal impairment** reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

**Pregnancy** depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

**Breast-feeding** withdrawal symptoms in infant; breast-feeding permissible during maintenance but dose should be as low as possible and infant monitored to avoid sedation

**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

**Licensed use** not licensed for use in children

**Indication and dose**

**Neonatal opioid withdrawal** dose may vary, consult local guidelines

- **By mouth**
  
  **Neonate** initially 100 micrograms/kg increased by 50 micrograms/kg every 6 hours until symptoms are controlled; for maintenance, total daily dose that controls symptoms given in 2 divided doses; to withdraw, reduce dose over 7–10 days

**Methadone (Non-proprietary)**

Oral solution 1 mg/mL, methadone hydrochloride 1 mg/mL, net price 30 mL = 60p, 50 mL = £1.03, 100 mL = £1.35, 500 mL = £9.52. Label: 2

**Brands** include Eptadone®, Metharose® (sugar-free), Physeptone (also as sugar-free)

**Safe Practice** This preparation is 2½ times the strength of Methadone Linctus; many preparations of this strength are licensed for opioid dependence only but some are also licensed for analgesia in severe pain

**MORPHINE SALTS**

**Cautions** see notes above; also pancreatitis, myasthenia gravis, cardiac arrhythmias, severe cor pulmonale

**Hepatic impairment** may precipitate coma in hepatic impairment—avoid or reduce dose (although many such children tolerate morphine well)

**Renal impairment** reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

**Pregnancy** depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

**Breast-feeding** therapeutic doses unlikely to affect infant; withdrawal symptoms in infants of dependent mothers; breast-feeding not best method of treating dependence in offspring

**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
Licensed use  
**Oramorph®** solution not licensed for use in children under 1 year; **Oramorph®** unit dose vials not licensed for use in children under 6 years; **Sevedol®** tablets not licensed for use in children under 3 years; **MST Continus®** preparations licensed to treat children with cancer pain (age-range not specified by manufacturer); **MXL®** capsules not licensed for use in children under 1 year

### Indication and dose

**Pain**  
- **By subcutaneous injection**  
  - **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 intravenous injection over at least 5 minutes**  
  - **Neonate**  
    - initially 50 micrograms/kg every 6 hours, adjusted according to response  
  - **Child 1–6 months**  
    - initially 100 micrograms/kg every 6 hours, adjusted according to response  
  - **Child 6 months–12 years**  
    - initially 100 micrograms/kg every 4 hours, adjusted according to response  
  - **Child 12–18 years**  
    - initially 2.5 mg every 4 hours, adjusted according to response  
- **By intravenous injection and infusion**  
  - **Neonate**  
    - initially by intravenous injection (over at least 5 minutes) 25–100 micrograms/kg then by continuous intravenous infusion 5–40 micrograms/kg/hour adjusted according to response  
  - **Child 1–6 months**  
    - initially by intravenous injection (over at least 5 minutes) 100–200 micrograms/kg then by continuous intravenous infusion 10–30 micrograms/kg/hour adjusted according to response  
  - **Child 6 months–12 years**  
    - initially by intravenous injection (over at least 5 minutes) 100–200 micrograms/kg then by continuous intravenous infusion 20–30 micrograms/kg/hour adjusted according to response  
  - **Child 12–18 years**  
    - initially by intravenous injection (over at least 5 minutes) 2.5–10 mg then by continuous intravenous infusion 20–30 micrograms/kg/hour adjusted according to response

**Neonatal opioid withdrawal** under specialist supervision  
- **By mouth**  
  - **Neonate**  
    - initially 40 micrograms/kg every 4 hours until symptoms controlled, increase dose if necessary; reduce frequency gradually over 6–10 days, and stop when 40 micrograms/kg once daily achieved; dose may vary, consult local guidelines

### Administration

For **continuous intravenous infusion**, dilute with **Glucose 5% or 10%** or **Sodium Chloride 0.9%**

**Neonatal intensive care**, dilute 2.5 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 micrograms/kg/hour

#### Oral solutions

**Note**  
For advice on transfer from oral solutions of morphine to modified-release preparations of morphine, see Prescribing in Palliative Care, p. 24

### Morphine Oral Solutions

**Oramorph®** (Boehringer Ingelheim)  
- **Oramorph® oral solution**  
  - 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  
  - morphine concentrated oral solution**  
    - 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

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**BNFC 2009**
\( \text{\textbf{1 MORPHINE SALTS (continued)}} \)

\section*{Tablets}

\textbf{Sevredol\textsuperscript{c} (Napp)}\textsuperscript{[8]}

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

\section*{Modified-release 12-hourly oral preparations}

\textbf{MST Continus\textsuperscript{c} (Napp)}\textsuperscript{[8]}

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 = £40.69; 200 mg (green), 60-tab pack = £81.34. Label: 2, 25

\textbf{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, 30-sachet pack = £170.30. Label: 2, 13

\textbf{Dose. By mouth}

Every 12 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 24; dosage requirements should be reviewed if the brand is altered

\textbf{Note} Prescriptions must also specify ‘tablets’ or ‘suspension’ (i.e. ‘MST Continus tablets’ or ‘MST Continus suspension’)

\section*{Modified-release 24-hourly oral preparations}

\textbf{MXL\textsuperscript{c} (Napp)}\textsuperscript{[8]}

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

\textbf{Dose. By mouth}

Every 24 hours, dose adjusted according to daily morphine requirements; for further advice on determining dose, see Prescribing in Palliative Care, p. 24; dosage requirements should be reviewed if the brand is altered

\textbf{Counselling} Swallow whole or open capsule and sprinkle contents on soft food

\textbf{Note} Prescriptions must also specify ‘capsules’ (i.e. ‘MXL capsules’)

\section*{Suppositories}

\textbf{Morphine (Non-proprietary)}\textsuperscript{[8]}

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

\textbf{Note} Available from Aurum, Martinindale

Morphine sulphate 5 mg suppositories available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

\section*{Injections}

\textbf{Morphine Sulphate (Non-proprietary)}\textsuperscript{[8]}

\textbf{Injection, morphine sulphate} 10, 15, 20, and 30 mg/mL, net price 1- and 2-mL amp (all) = 72p–£1.40

\textbf{Intravenous infusion, morphine sulphate} 1 mg/mL, net price 50-mL vial = £5.00; 2 mg/mL, 50-mL vial = £5.89

\textbf{Minijet\textsuperscript{c} Morphine Sulphate (UCB Pharma)}\textsuperscript{[8]}

\textbf{Injection, morphine sulphate} 1 mg/mL, net price 10-mL disposable syringe = £7.58

\textbf{Injection with antiemetic}

\textbf{Caution} Not recommended in palliative care, see Nausea and Vomiting, p. 27

\textbf{Cyclimorph\textsuperscript{c} (Amdipharm)}\textsuperscript{[8]}

\textbf{Cyclimorph-10\textsuperscript{c} Injection, morphine tartrate 10 mg, cyclizine tartrate} 50 mg/mL. Net price 1-mL amp = £1.34

\textbf{Dose. Moderate to severe pain} (short-term use only)

\textbf{By subcutaneous, intramuscular, or intravenous injection}

\textbf{Child} 12–18 years 1 mL, repeated not more often than every 4 hours, max. 3 doses in any 24-hour period

\textbf{Cyclimorph-15\textsuperscript{c} Injection, morphine tartrate} 15 mg, cyclizine tartrate 50 mg/mL. Net price 1-mL amp = £1.39

\textbf{Dose. Moderate to severe pain} (short-term use only)

\textbf{By subcutaneous, intramuscular, or intravenous injection}

\textbf{Child} 12–18 years 1 mL, repeated not more often than every 4 hours, max. 3 doses in any 24-hour period

\section*{OXYCODONE HYDROCHLORIDE}

\textbf{Cautions} see notes above; also toxic psychosis; pancreatitis

\textbf{Contra-indications} see notes above; also acute abdomen; delayed gastric emptying; chronic constipation; cor pulmonale; acute porphyria (section 9.8.2)

\textbf{Hepatic impairment} avoid in moderate to severe impairment

\textbf{Renal impairment} reduce dose or avoid, increased and prolonged effect; increased cerebral sensitivity

\textbf{Pregnancy} depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

\textbf{Breast-feeding} present in milk—manufacturer advises avoid
Side-effects  see notes above; also diarrhoea, abdominal pain, anorexia, dyspepsia; bronchospasm, dyspnoea, impaired cough reflex; asthma, anxiety; chills; muscle fasciculation; less commonly paralytic ileus, gastritis, flatulence, dysphagia, taste disturbance, malaise, agitation, speech disorder, tremor, and dry skin

Licensed use  not licensed for use in children

**Indication and dose**  Moderate to severe pain in palliative care  (see also Prescribing in Palliative Care, p. 25)

- **By mouth**
  - Child 1 month–12 years initially 200 micrograms/kg (up to 5 mg) every 4–6 hours, dose increased if necessary according to severity of pain
  - Child 12–18 years initially 5 mg every 4–6 hours, dose increased if necessary according to severity of pain

**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

**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, 25

**Dose**

- **By mouth**
  - Child 8–12 years initially, 5 mg every 12 hours, increased if necessary according to severity of pain
  - Child 12–18 years initially, 10 mg every 12 hours, increased if necessary according to severity of pain

**PAPAVERETUM**

Safe Practice  Do not confuse with papaverine

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

Cautions  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

**Indication and dose**

- **Premedication, postoperative analgesia, severe chronic pain**
  - **By subcutaneous or intramuscular injection**
    - Neonate 115 micrograms/kg repeated every 4 hours if necessary

**Pethidine hydrochloride**

Cautions  see notes above; not suitable for severe continuing pain; accumulation of metabolites may result in neurotoxicity; myasthenia gravis; cardiac arrhythmias, severe cor pulmonale

Hepatic impairment  avoid or reduce dose—may precipitate coma

Renal impairment  reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity

Pregnancy  depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour

Breast-feeding  present in milk but not known to be harmful

Contra-indications  see notes above; phaeochromocytoma

Side-effects  see notes above; also restlessness and hypothermia; convulsions reported in overdose

**Papaveretum (Non-proprietary)**

Injection, papaveretum 15.4 mg/mL (providing the equivalent of 10 mg of anhydrous morphine/mL), net price 1-mL amp = £1.64
PETHIDINE HYDROCHLORIDE (continued)

Indication and dose

Obstetric analgesia
- By subcutaneous or by intramuscular injection
  
  Child 12–18 years 50–100 mg, repeated 1–3 hours later if necessary; max. 400 mg in 24 hours

Pethidine (Non-proprietary)

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

TRAMADOL HYDROCHLORIDE

Cautions
- see notes above; impaired consciousness; excessive bronchial secretions; not suitable as substitute in opioid-dependent patients
- General anaesthesia Not recommended for analgesia during potentially light planes of general anaesthesia (possibly increased intra-operative recall reported)
- Hepatic impairment avoid or reduce dose—may precipitate coma
- Renal impairment reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity
- Pregnancy embryotoxic in animal studies—manufacturers advise avoid; depresses neonatal respiration; withdrawal effects in neonates of dependent mothers; gastric stasis and risk of inhalation pneumonia in mother during labour
- Breast-feeding amount probably too small to be harmful, but manufacturer advises avoid
- 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, dyspnoea, wheezing, seizures, paraesthesia, and muscle weakness; blood disorders also reported
- Licensed use not licensed for use in children under 12 years

Indication and dose

Moderate to severe pain
- By mouth
  
  Child 12–18 years 50–100 mg not more often than every 4 hours; total of more than 400 mg daily not usually required

- By intramuscular injection or by intravenous injection (over 2–3 minutes) or by intravenous infusion
  
  Child 12–18 years 50–100 mg every 4–6 hours

Postoperative pain
- By mouth
  
  Child 12–18 years 100 mg initially then 50 mg every 10–20 minutes if necessary during first hour to total max. 250 mg (including initial dose) in first hour, then 50–100 mg every 4–6 hours; max. 600 mg daily

Administration for intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9% or Compound Sodium Lactate or Ringer’s Solution

Modular-release 12-hourly preparations

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

Moderate to severe pain
- By mouth
  
  Child 12–18 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

Moderate to severe pain
- By mouth
  
  Child 12–18 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

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<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
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<td>Child 12–18 years</td>
<td>100 mg twice daily increased if necessary, usual max. 200 mg twice daily</td>
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</table>

**Maxitram SR®** (Chiesi) 
Capsules, m/r, tramadol hydrochloride 50 mg (white), net price 60-cap pack = £4.55; 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

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>initially 100 mg twice daily increased if necessary, usual max. 200 mg twice daily</td>
</tr>
</tbody>
</table>

**Tramquil SR®** (Meda) 
Capsules, m/r, tramadol hydrochloride 50 mg (dark green), net price 60-cap pack = £7.64; 100 mg (white), 60-cap pack = £15.28; 150 mg (dark green), 60-cap pack = £22.92; 200 mg (yellow), 60-cap pack = £30.55. Label: 2, counselling, administration

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>50–100 mg twice daily increased if necessary, usual max. 200 mg twice daily</td>
</tr>
</tbody>
</table>

**Zamadol® SR (Meda)**
Capsules, m/r, tramadol hydrochloride 50 mg (green), net price 60-cap pack = £7.64; 100 mg, 60-cap pack = £15.28; 150 mg (dark green), 60-cap pack = £22.92; 200 mg (yellow), 60-cap pack = £30.55. Label: 2, counselling, administration

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>50–100 mg twice daily increased if necessary, usual max. 200 mg twice daily</td>
</tr>
</tbody>
</table>

**Zydol SR®** (Grüenthal)
Tablets, m/r, f/c, tramadol hydrochloride 100 mg, net price 60-tab pack = £18.26; 150 mg (beige), 60-tab pack = £27.39; 200 mg (orange), 60-tab pack = £36.52. Label: 2, 25

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>100 mg twice daily increased if necessary, up to 200 mg twice daily</td>
</tr>
</tbody>
</table>

**Modified-release 24-hourly preparations**

**Tradorec XL®** (Labopharm) 
Tablets, m/r, tramadol hydrochloride 100 mg, net price 30-tab pack = £14.10; 200 mg, 30-tab pack = £14.98; 300 mg, 30-tab pack = £22.47. Label: 2, 25

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>initially 100 mg once daily increased if necessary, up to max. 400 mg once daily</td>
</tr>
</tbody>
</table>

**Zamadol® 24hr (Meda)**
Tablets, f/c, m/r, tramadol hydrochloride 150 mg, net price 28-tab pack = £10.70; 200 mg, 28-tab pack = £14.26; 300 mg, 28-tab pack = £21.39; 400 mg, 28-tab pack = £28.51. Label: 2, 25

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>initially 150 mg once daily increased if necessary, up to max. 400 mg once daily</td>
</tr>
</tbody>
</table>

**Zydol XL®** (Grüenthal)
Tablets, m/r, f/c, tramadol hydrochloride 150 mg, net price 30-tab pack = £15.22; 200 mg, 30-tab pack = £20.29; 300 mg, 30-tab pack = £30.44; 400 mg, 30-tab pack = £40.59. Label: 2, 25

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>150 mg once daily increased if necessary, up to max. 400 mg once daily</td>
</tr>
</tbody>
</table>

**With paracetamol**

**Tramacet (Janssen-Cilag)**
Tablets, f/c, yellow, tramadol hydrochloride 37.5 mg, paracetamol 325 mg, net price 60-tab pack = £10.07. Label: 2, 25, 29, 30

<table>
<thead>
<tr>
<th>Dose</th>
<th>Moderate to severe pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>By mouth</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>2 tablets not more than every 6 hours; max. 8 tablets daily</td>
</tr>
</tbody>
</table>
### 4.7.3 Neuropathic pain

Neuropathic pain, which occurs as a result of damage to neural tissue, includes postherpetic neuralgia, 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 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).

Neuropathic pain is generally managed with a tricyclic antidepressant such as amitriptyline (p. 229) or antiepileptic drugs such as carbamazepine (p. 267). Neuropathic pain may respond only partially to opioid analgesics. Nerve blocks, transcutaneous electrical nerve stimulation (TENS) and, in selected cases, central electrical stimulation may help. Many children with chronic neuropathic pain require multidisciplinary management, including physiotherapy and psychological support. A corticosteroid may help to relieve pressure in compression neuropathy and thereby reduce pain.

For the management of neuropathic pain in palliative care, see p. 25.

### 4.7.4 Antimigraine drugs

#### 4.7.4.1 Treatment of acute migraine

Treatment of a migraine attack should be guided by response to previous treatment and the severity of the attacks. A simple analgesic such as paracetamol (preferably in a soluble or dispersible form) or an NSAID, usually ibuprofen, is often effective; concomitant antiemetic treatment may be required. If treatment with an analgesic is inadequate, an attack may be treated with a specific antimigraine compound such as the 5HT1 agonist sumatriptan. Ergot alkaloids are associated with many side-effects and should be avoided.

Excessive use of acute treatments for migraine (opioid and non-opioid analgesics, 5HT1 agonists, and ergotamine) is associated with medication-overuse headache (analgesic-induced headache); therefore, increasing consumption of these medicines needs careful management.

#### 4.7.4.2 Prophylaxis of migraine

#### 4.7.4.3 Cluster headache

### ANALGESICS

- **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. Net price 48-tab Migraleve® (32 pink + 16 yellow) = £5.10; 48 pink (Migraleve Pink) = £5.56. Label: 2, (Migraleve Pink), 17, 30

**Dose**

- **Treatment of acute migraine**
  - By mouth
  - Child under 10 years only under close medical supervision
Paramax® (Sanofi-Synthelabo) Tablets, scored, paracetamol 500 mg, metoclopramide hydrochloride 5 mg. Net price 42-tab pack = £8.03. Label: 17, 30

5HT, agonists

5HT, agonists are used in the treatment of acute migraine attacks; treatment of children should be initiated by a specialist. The 5HT (serotonin) 1B/1D receptors and they are therefore sometimes referred to as 5HT1B/1D-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.

Sumatriptan is used for migraine in children and it may also be of value in cluster headache (section 4.7.4.3).

SUMATRIPTAN

Cautions  pre-existing cardiac disease; history of seizures; 5HT, agonists are recommended as monotherapy and should not be taken concurrently with other therapies for acute migraine; sensitivity to sulphonamides; interactions: Appendix 1 (5HT, agonists)

Skilled tasks  Drowsiness may affect performance of skilled tasks (e.g. driving)

Hepatic impairment  reduce dose of oral therapy; avoid in severe impairment

Renal impairment  manufacturer advises caution

Pregnancy  limited experience—avoid unless potential benefit outweighs risk

Breast-feeding  present in milk but not known to be harmful; withhold breast-feeding for 12 hours

Contra-indications  vasospasm; previous cerebrovascular accident or transient ischaemic attack; peripheral vascular disease; moderate and severe hypertension

Side-effects  nausea, vomiting; 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), transient increase in blood pressure, flushing; drowsiness, dizziness, weakness; very rarely ischaemic colitis, hypotension, bradycardia or tachycardia, palpitation, arrhythmias, myocardial infarction, Raynaud’s syndrome, seizures, tremor, dystonia, nystagmus, and visual disturbances; nasal irritation and epistaxis with nasal spray

Licensed use  tablets not licensed for use in children

Indication and dose

Treatment of acute migraine

• By mouth
  
  Child 6–10 years  25 mg as a single dose, repeated once after at least 2 hours if migraine recurs
  
  Child 10–12 years  50 mg as a single dose, repeated once after at least 2 hours if migraine recurs
  
  Child 12–18 years  50–100 mg as a single dose, repeated once after at least 2 hours if migraine recurs

• Intranasally
  
  Child 12–18 years  10–20 mg as a single dose, repeated once after at least 2 hours if migraine recurs; max. 40 mg in 24 hours

Note  Child not responding to initial dose should not take second dose for same attack

1 Sumatriptan (Non-proprietary) 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) 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

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
Antiemetics

Antiemetics (section 4.6), including metoclopramide, domperidone, phenothiazines, and antihistamines, 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 the added advantage of promoting gastric emptying and normal peristalsis; a single dose should be given at the onset of symptoms (important: for warnings relating to extrapyramidal effects of metoclopramide see p. 238 and p. 242).

4.7.4.2 Prophylaxis of migraine

Where migraine attacks are frequent, possible provoking factors such as stress should be sought; combined oral contraceptives may also provoke migraine. Preventive treatment should be considered if migraine attacks interfere with school and social life, particularly for children 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.

In children it is often possible to stop prophylaxis after a period of treatment.

Propranolol (section 2.4) may be effective in preventing migraine in children but it is contra-indicated in those with asthma. Side-effects such as depression and postural hypotension can further limit its use.

Pizotifen, an antihistamine and serotonin antagonist, taken at night or twice daily, may also be used but its efficacy in children has not been clearly established. Common side-effects include drowsiness and weight gain.

Topiramate (section 4.8.1) is licensed for migraine prophylaxis. Treatment should be supervised by a specialist.

PIZOTIFEN

Cautions

urinary retention; susceptibility to angle-closure glaucoma, renal impairment; interactions: Appendix 1 (pizotifen)
Skilled tasks

Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced
Pregnancy

manufacturer advises avoid unless potential benefit outweighs risk
Breast-feeding

amount probably too small to be harmful but manufacturer advises avoid
Side-effects

antimuscarinic effects, drowsiness, increased appetite and weight gain; occasionally nausea, dizziness; rarely anxiety, aggression and depression; CNS stimulation may occur
Licensed use

Sanomigran® elixir and 500-microgram tablets not licensed for use in children under 2 years; 1.5-mg tablets not licensed for use in children

Indication and dose

Prophylaxis of migraine

- By mouth

Child 5–10 years initially 500 micrograms at night increased according to response up to 500 micrograms 3 times daily; max. single dose at night 1 mg; max. 1.5 mg in 24 hours

Child 10–12 years initially 1 mg at night increased according to response up to 500 micrograms 3 times daily; max. single dose at night 1 mg; max. 1.5 mg in 24 hours

Child 12–18 years initially 1.5 mg at night increased according to response to 1.5 mg 3 times daily; max. single dose 3 mg; max. 4.5 mg in 24 hours

Pizotifen (Non-proprietary)

Tablets, pizotifen (as hydrogen malate), 500 micrograms, net price 28-tab pack = £1.37; 1.5 mg, 28-tab pack = £2.75. Label: 2

Sanomigran® (Novartis)

Tablets, both ivory-yellow, s/c, pizotifen (as hydrogen malate), 500 micrograms, net price 60-tab pack = £2.57; 1.5 mg, 28-tab pack = £4.28. Label: 2

Elixir, pizotifen (as hydrogen malate) 250 micrograms/5 mL, net price 300 mL = £4.51. Label: 2
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; treatment should be initiated by a specialist. Alternatively, 100% oxygen at a rate of 7–12 litres/minute is useful in aborting an attack.

4.8 Antiepileptics

4.8.1 Control of epilepsy

4.8.2 Drugs used in status epilepticus

4.8.3 Febrile convulsions

4.8.1 Control of epilepsy

The decision about when to start treatment with an antiepileptic drug and the choice of medication depend on frequency of seizures, neurological findings, the identification of an epilepsy syndrome, and the wishes of the child and carers. For the majority of children, epilepsy is controlled with a single antiepileptic drug.

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 to use, 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. 266.

The frequency of administration is often determined by the plasma half-life, and should be kept as low as possible to encourage better adherence. Most antiepileptics, when used in usual dosage, may be given twice daily. Lamotrigine, phenobarbital and phenytoin, which have long half-lives, can be given as a daily dose at bedtime. However, with large doses, some antiepileptics may need to be given 3 times daily to avoid adverse effects associated with high peak plasma-drug concentrations. Young children metabolise antiepileptics more rapidly than adults and therefore require more frequent doses and a higher amount per kilogram body-weight.

Management  When monotherapy with a first-line antiepileptic drug has failed, monotherapy with a second drug should be tried. The changeover from one antiepileptic drug to another should be cautious, slowly withdrawing the first drug only when the new regimen has been established. Combination therapy with 2 or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs may increase adverse effects and the risk of drug interactions (see below). If combination therapy does not bring about worthwhile benefits, revert to the regimen (monotherapy or combination therapy) that provided the best balance between tolerability and efficacy.

Interactions  Interactions between antiepileptics are complex and may increase toxicity without a corresponding increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or hepatic enzyme inhibition; displacement from protein binding sites is not usually a problem. These interactions are highly variable and unpredictable.

Significant interactions that occur between antiepileptics themselves are as follows:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Often lowers plasma concentration of clobazam, clonazepam, lamotrigine, an</td>
</tr>
<tr>
<td></td>
<td>active metabolite of oxcarbazepine, and of phenytoin (but may also raise</td>
</tr>
<tr>
<td></td>
<td>phenytoin concentration), tiagabine, topiramate, and valproate</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Sometimes lowers plasma concentration of ethosuximide, and primidone (but</td>
</tr>
<tr>
<td></td>
<td>tendency for corresponding increase in plasma-phenobarbital concentration)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Sometimes lowers plasma concentration of ethosuximide, and primidone (but</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Tendency for corresponding increase in plasma-phenobarbital concentration)</td>
</tr>
</tbody>
</table>

Note  Check under each drug for possible interactions when two or more antiepileptic drugs are used.
Gabapentin  
no interactions with gabapentin reported

Lamotrigine  
sometimes raises plasma concentration of an active metabolite of carbamazepine  
(but evidence is conflicting)

Levetiracetam  
no interactions with levetiracetam reported

Oxcarbazepine  
sometimes lowers plasma concentration of carbamazepine (but may raise concentration of an active metabolite of carbamazepine)  
sometimes raises plasma concentration of phenytoin  
often raises plasma concentration of phenobarbital

Phenobarbital or Primidone  
often lowers plasma concentration of carbamazepine, clonazepam, lamotrigine, an active metabolite of oxcarbazepine, and of phenytoin (but may also raise phenytoin concentration), tiagabine, and valproate  
sometimes lowers plasma concentration of ethosuximide

Phenytoin  
often lowers plasma concentration of clonazepam, carbamazepine, lamotrigine, an active metabolite of oxcarbazepine, and of tiagabine, topiramate, and valproate  
often raises plasma concentration of phenobarbital  
sometimes lowers plasma concentration of ethosuximide, and primidone (by increasing conversion to phenobarbital)

Stiripentol  
often raises plasma concentration of carbamazepine, clobazam, phenobarbital, and phenytoin

Topiramate  
sometimes raises plasma concentration of phenytoin

Valproate  
sometimes lowers plasma concentration of an active metabolite of oxcarbazepine  
often raises plasma concentration of an active metabolite of carbamazepine, and of lamotrigine, primidone, phenobarbital, and phenytoin (but may also lower)  
sometimes raises plasma concentration of ethosuximide, and primidone (and tendency for significant increase in plasma-phenobarbital concentration)

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  
Antiepileptics 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, the withdrawal process may take months.

The decision to withdraw antiepileptics from a seizure-free child, and its timing, depends on individual circumstances such as the type of epilepsy and its cause. Even in children who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal.

Drugs should be gradually withdrawn over at least 2–3 months by reducing the daily dose by 10–25% at intervals of 1–2 weeks. Benzodiazepines may need to be withdrawn over 6 months or longer.

In children receiving several antiepileptic drugs, only one drug should be withdrawn at a time.
Monitoring  Routine measurement of plasma concentrations of antiepileptic drugs is not usually justified, because the target concentration ranges are arbitrary and often vary between individuals. However, plasma-drug concentrations may be measured in children with worsening seizures, status epilepticus, suspected non-compliance, or suspected toxicity. Similarly, haematological and biochemical monitoring should only be undertaken if clinically indicated.

Driving  Older children suffering from epilepsy may drive a motor vehicle provided that they have been seizure-free for one year or, if subject to attacks only while asleep, have established a 3-year period of asleep attacks without awake attacks. Those 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.

Pregnancy and breast-feeding  There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if the child takes two or more antiepileptic drugs). However, the benefit of antiepileptic treatment usually outweighs the potential teratogenic risk, and treatment should not be stopped during pregnancy without discussing with a specialist (see also under individual drugs). 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. Young women who become pregnant should be counselled and offered antenatal screening (including 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; to prevent recurrence of neural tube defects, women should receive folic acid 5 mg daily (section 9.1.2)—this dose may also be appropriate for women receiving antiepileptic drugs.

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 under individual drugs.

### 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, tiagabine, and topiramate.

### Generalised seizures

**Tonic-clonic seizures**  The drugs of choice for tonic-clonic seizures are carbamazepine, lamotrigine, levetiracetam, and sodium valproate. For children who have tonic-clonic seizures as part of the syndrome of primary generalised epilepsy, sodium valproate is the drug of choice. Second-line drugs include clobazam, oxcarbazepine, and topiramate.

**Absence seizures**  Ethosuximide and sodium valproate are the drugs of choice in typical absence seizures; lamotrigine can be used if these are unsuitable. Sodium valproate is also highly effective in treating the generalised tonic-clonic seizures which may 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 and clobazam, clonazepam, ethosuximide, lamotrigine, levetiracetam, or topiramate are second-line drugs for treating myoclonic seizures.

Atypical absence, atonic, and tonic seizures  Atypical absence and atonic seizures may be managed with sodium valproate, lamotrigine, or ethosuximide. Tonic seizures may be treated with sodium valproate. Second-line drugs for atypical absence, atonic, and tonic seizures include clobazam, clonazepam, levetiracetam, and topiramate; tonic seizures may rarely be aggravated by benzodiazepines.

Epilepsy syndromes

Infantile spasms  Vigabatrin is the drug of choice for infantile spasms associated with tuberous sclerosis. In spams of other causes, high doses of corticosteroids such as prednisolone (section 6.3.2) or tetracosactide (section 6.5.1) may be more effective. Second-line alternatives include clobazam, clonazepam, sodium valproate, and topiramate; nitrazepam is used but it is sedating.

Lennox-Gastaut syndrome  Lamotrigine, sodium valproate, and topiramate are first-line drugs for treating Lennox-Gastaut syndrome. Clobazam, clonazepam, ethosuximide, levetiracetam, and rufinamide are also used.

Landau-Kleffner syndrome  Prednisolone, lamotrigine, and sodium valproate are commonly used to treat Landau-Kleffner syndrome. Alternatives include clobazam, levetiracetam and topiramate.

Neonatal seizures  Seizures can occur before delivery, but they are most common up to 24 hours after birth. Seizures in neonates occur as a result of biochemical disturbances, inborn errors of metabolism, hypoxic ischaemic encephalopathy, drug withdrawal, severe jaundice (kernicterus), meningitis, stroke, or cerebral haemorrhage or malformation.

Seizures caused by biochemical imbalance and those in neonates with inherited abnormal pyridoxine or biotin metabolism should be corrected by treating the underlying cause (section 9.6.2). Seizures caused by drug withdrawal following intra-uterine exposure are treated with a drug withdrawal regimen.

Phenobarbital may be preferred when there is a risk of seizure recurrence in neonates; phenytoin is an alternative. The benzodiazepines (clonazepam, diazepam, lorazepam, and midazolam) and rectal paraldehyde may be useful in the management of seizures which are likely to be brief with little risk of recurrence.

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 can exacerbate myoclonic and absence seizures. It is essential to initiate carbamazepine therapy at a low dose and build this up slowly in small increments every 3–7 days. 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 may be used 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

Cautions 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 the 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; avoid abrupt with-
CARBAMAZEPINE (continued)

drawal; interactions: see p. 264 and Appendix 1 (carbamazepine)

Hepatic impairment metabolism impaired in advanced liver disease

Renal impairment manufacturer advises caution

Pregnancy see Pregnancy and Breast-feeding, p. 266

Breast-feeding see notes above; amount probably too small to be harmful

Blood, hepatic or skin disorders Children or their carers should be told how to recognise signs of blood, liver, 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).

Contra-indications AV conduction abnormalities (unless paced); history of bone marrow depression, acute porphyria (section 9.8.2)

Side-effects nausea and vomiting, dizziness, glossoptosis, headache, ataxia, confusion and agitation, visual disturbances (especially diplopia and often associated with peak plasma concentrations); constipation or diarrhoea, anorexia; mild transient generalised erythematous rash may occur in a large number of children (withdraw if worsens or is accompanied by other symptoms); leucopenia and other blood disorders including thrombocytopenia, agranulocytosis and aplastic anaemia; other side-effects include cholestatic jaundice, hepatic and renal failure, Stevens-Johnson syndrome, toxic epidermal necrolysis, alopecia, thromboembolism, arthralgia, fever, proteinuria, lymph node enlargement, cardiac conduction disturbances (sometimes arrhythmias), dyskinesias, paraesthesia, depression, impotence (and impaired fertility), gynaecomastia, galactorrhoea, aggression, activation of psychosis; photosensitivity, pulmonary hypersensitivity (with dyspnoea and pneumonitis), pyrexia, oedema, and disturbances of bone metabolism (with osteomalacia) also reported; suicidal ideation; suppositories may cause occasional rectal irritation

Pharmacokinetics plasma concentration for optimum response 4–12 mg/litre (20–50 micromol/litre) measured after 1–2 weeks

Licensed use licensed for use in children with generalised tonic-clonic and partial seizures only

Indication and dose

Partial and generalised tonic-clonic seizures, neuropathic pain, some movement disorders (e.g. paroxysmal kinesigenic choreathetosis), mood stabilisation

By mouth

Child 1 month–18 years initially 5 mg/kg at night or 2.5 mg/kg twice daily, increased as necessary by 2.5–5 mg/kg every 3–7 days; usual maintenance dose 5 mg/kg 2–3 times daily; doses up to 20 mg/kg daily have been used

Child 12–18 years initially 100–200 mg 1–2 times daily, increased slowly to usual maintenance dose 200–400 mg 2–3 times daily; in some cases doses up to 1.8 g daily may be needed

Note Different preparations may vary in bioavailability; to avoid reduced effect or excessive side-effects, it may be prudent to avoid changing the formulation (see also notes above on how side-effects may be reduced)

Administration Oral liquid has been used rectally—should be retained for at least 2 hours (but may have laxative effect)

Carbamazepine (Non-proprietary) Tablets, carbamazepine 100 mg, net price 28 = £5.40; 200 mg, 28 = £4.71; 400 mg, 28 = £6.59. Label: 3, 8, counselling, blood, hepatic or skin disorder symptoms (see above), driving (see notes above)

Brands include Epimaz®

Dental prescribing on NHS Carbamazepine Tablets may be prescribed

Tegretol® (Novartis) Tablets, all scored, carbamazepine 100 mg, net price 84-tab pack = £2.43; 200 mg, 84-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)

Liquid, sugar-free, carbamazepine 100 mg/5 mL. Net price 300-mL pack = £7.20. Label: 3, 8, 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

Note Suppositories of 125 mg may be considered to be approximately equivalent in therapeutic effect to tablets of 100 mg but final adjustment should always depend on clinical response (plasma concentration monitoring recommended); max. dose by rectum 250 mg 4 times daily

Modified release

Carbagen® 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

Child 5–18 years as above; total daily dose given in 1–2 divided doses
CARBAMAZEPINE (continued)

Tegretol® Retard (Novartis)  
Tablets, m/r, 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)

OXCARBAZEPINE

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); interactions: see p. 264 and Appendix 1 (oxcarbazepine)

Hepatic impairment  manufacturer advises caution in severe impairment—no information available

Renal impairment  use half initial dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m², increased according to response at intervals of at least 1 week

Pregnancy  see Pregnancy and Breast-feeding, p. 266

Breast-feeding  present in milk; amount probably too small to be harmful but manufacturer advises avoid

Blood, hepatic or skin disorders  Children or their carers should be told how 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, hyponatraemia, acne, alopecia, rash, nystagnus, visual disorders including diplopia; less commonly urticaria, leucopenia; very rarely hepatitis, pancreatitis, arrhythmias, hypersensitivity reactions, thrombocytopenia, systemic lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis; suicidal ideation

Dose  
For Child 5–18 years as above; total daily dose given in 2 divided doses

Administration  Tegretol® Retard tablets can be halved but should not be chewed

Indication and dose  
Monotherapy and adjunctive therapy of partial seizures with or without secondarily generalised tonic-clonic seizures

By mouth  
For Child 6–18 years initially 4–5 mg/kg (max. 300 mg) twice daily, increased according to response in steps of up to 5 mg/kg twice daily at weekly intervals (usual maintenance dose for adjunctive therapy 15 mg/kg twice daily); max. 23 mg/kg twice daily

Note  In adjunctive therapy the dose of concomitant antiepileptics 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)

Trileptal® (Novartis)  
Tablets, f/c, scored, oxcarbazepine 150 mg (green), net price 50-tab pack = £10.00; 300 mg (yellow), 50-tab pack = £20.00; 600 mg (pink), 50-tab pack = £40.00. 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 disorders (see above), driving (see notes above)

Excipients  include propylene glycol (see Excipients, p. 3)

Ethosuximide is used in typical absence seizures; it may also be used in myoclonic seizures and in atypical absence, tonic, and tonic seizures.

ETHOSUXIMIDE

Cautions  avoid abrupt withdrawal; hepatic impairment; renal impairment; avoid in acute porphyria (section 9.8.2); interactions: see p. 264 and Appendix 1 (ethosuximide)

Pregnancy  may be teratogenic but see Pregnancy and Breast-feeding, p. 266

Breast-feeding  present in milk but unlikely to be harmful; manufacturer advises avoid

Blood disorders  Children 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  gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, abdominal pain, and anorexia), weight loss; less frequently headache, fatigue, drowsiness, dizziness, hiccup, ataxia, mild euphoria, irritability, aggression, and 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 Stevens-Johnson syndrome; suicidal ideation.

**Indication and dose**

**Absence seizures, atypical absence, myoclonic seizures**

- **By mouth**
  - **Child 1 month–6 years** initially 5 mg/kg (max. 125 mg) twice daily, increased gradually over 2–3 weeks up to maintenance dose of 10–20 mg/kg (max. 500 mg) twice daily; total daily dose may rarely be given in 3 divided doses.
  - **Child 6–18 years** initially 250 mg twice daily, increased by 250 mg at intervals of 4–7 days to usual dose of 500–750 mg twice daily; occasionally up to 1 g twice daily may be needed.

**Gabapentin**

**Gabapentin** is used as adjunctive therapy for the treatment of partial seizures with or without secondary generalisation; it can be used as monotherapy in children over 12 years.

**Indication and dose**

**Adjunctive treatment of partial seizures with or without secondary generalisation**

- **By mouth**
  - **Child 2–6 years** 10 mg/kg once daily on day 1, then 10 mg/kg twice daily on day 2, then 10 mg/kg 3 times daily on day 3, increased according to response to usual dose of 30–70 mg/kg daily in 3 divided doses.
  - **Child 6–12 years** 10 mg/kg once daily (max. 300 mg) on day 1, then 10 mg/kg (max. 300 mg) twice daily on day 2, then 10 mg/kg (max. 300 mg) 3 times daily on day 3; usual dose 25–35 mg/kg daily in 3 divided doses; max. 70 mg/kg daily in 3 divided doses.
  - **Child 12–18 years** 300 mg once daily 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.

**Monotherapy for partial seizures with or without secondary generalisation**

- **By mouth**
  - **Child 12–18 years** 300 mg once daily 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.

**Note** Some children may not tolerate daily increments; longer intervals (up to weekly) may be more appropriate.

**Administration** capsules can be opened but the bitter taste is difficult to mask.
Lacosamide

Lacosamide is licensed for adjunctive treatment of partial seizures with or without secondary generalisation.

The Scottish Medicines Consortium (p. 4) has advised (January 2009) that lacosamide (Vimpat®) is accepted for restricted use within NHS Scotland as adjunctive treatment for partial seizures with or without secondary generalisation in patients from 16 years. It is restricted for specialist use in refractory epilepsy.

**Cautions**
- conduction problems or severe cardiac disease (increased risk of PR-interval prolongation);
- interactions: Appendix 1 (lacosamide)
- Hepatic impairment: manufacturer advises caution in severe hepatic impairment—no information available
- Renal impairment: manufacturer advises caution; max. 250 mg daily if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m²
- Pregnancy: see Pregnancy and Breast-feeding, p. 266; manufacturer advises avoid unless potential benefit outweighs risk
- Breast-feeding: manufacturer advises avoid—present in milk in animal studies
- Contra-indications: second- or third-degree AV block

**Side-effects**
- nausea, vomiting, flatulence, constipation; dizziness, headache, depression, diplopia, nystagmus, impaired coordination, impaired memory, cognitive disorder, drowsiness, tremor, asthenia, fatigue; pruritus; less commonly PR-interval prolongation; suicidal ideation

**Indication and dose**

**Adjunctive treatment of partial seizures with or without secondary generalisation**
- By intravenous infusion over 15–60 minutes (for up to 5 days) or by mouth
  - Child 16–18 years initially 50 mg twice daily, increased in steps of 50 mg twice daily every week to max. 200 mg twice daily

**Administration**
- for intravenous infusion, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9% or Compound Sodium Lactate solution

**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 (salmon), 14-tab pack = £27.03, 56-tab pack £108.12; 200 mg (blue), 56-tab pack = £144.16. 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)

**Intravenous infusion**
- lacosamide 10 mg/mL, net price 200-mg vial = £29.70
- Electrolytes Na⁺ 2.6 mmol/200-mg vial

Lamotrigine

Lamotrigine is an antiepileptic for partial seizures and primary and secondarily generalised tonic-clonic seizures. It may be tried for atypical absence, atonic, and tonic seizures particularly in children with Lennox-Gastaut syndrome. Lamotrigine may cause serious skin rash; 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

Cautions closely monitor and consider withdrawal if rash, fever, or signs of hypersensitivity syndrome develop; avoid abrupt withdrawal (taper off over 2 weeks or longer) unless serious skin reaction occurs; interactions: see p. 264 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

Hepatic impairment halve dose in moderate impairment; quarter dose in severe impairment

Renal impairment manufacturer advises caution in renal failure; metabolite may accumulate

Pregnancy see Pregnancy and Breast-feeding, p. 266; risk of teratogenesis

Breast-feeding present in milk, but limited data suggest no harmful effect on neonate

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; nystagmus, diplopia, blurred vision, conjunctivitis; suicidal ideation

Skin reactions Serious skin reactions including 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 children and their carers to see their doctor immediately if rash or signs or symptoms of hypersensitivity syndrome develop

Indication and dose

Monotherapy and adjunctive treatment of partial seizures and primary and secondarily generalised tonic-clonic seizures; seizures associated with Lennox-Gastaut syndrome

By mouth

Adjuvent therapy with valproate

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. of 300 micrograms/kg daily every 7–14 days; usual maintenance 1–5 mg/kg daily in 1–2 divided doses (max. single dose 10 mg)

Child 12–18 years initially 25 mg on alternate days for 14 days then 25 mg 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

Adjuvent therapy (with enzyme inducing drugs) without valproate

Child 2–12 years initially 300 micrograms/kg twice daily for 14 days then 600 micrograms/kg twice daily for further 14 days, thereafter increased by max. 1.2 mg/kg daily every 7–14 days; usual maintenance 2.5–7.5 mg/kg (max. single dose 200 mg) twice daily

Child 12–18 years initially 50 mg 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 100–200 mg twice daily (up to 700 mg daily has been required)

Adjuvent therapy with oxcarbazepine

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

Child 12–18 years initially 25 mg daily for 14 days, increased to 50 mg 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

Monotherapy

Child 12–18 years initially 25 mg daily for 14 days, increased to 50 mg daily for further 14 days, then increased by max. 50–100 mg daily every 7–14 days; usual maintenance as monotherapy, 100–200 mg daily in 1–2 divided doses (up to 500 mg daily has been required)

Note Dose titration should be repeated if restarting after interval of more than 5 days

Safe Practice Do not confuse the different combinations; see also notes above

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 (see 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 (see above)

Levetiracetam

Levetiracetam is used for monotherapy and adjunctive treatment of partial seizures with or without secondary generalisation, and for adjunctive treatment of myoclonic seizures and generalised tonic-clonic seizures.

Cautions
- Avoid abrupt withdrawal
- Hepatic impairment: halve dose in severe hepatic impairment if creatinine clearance less than 70 mL/minute/1.73 m²
- Renal impairment: reduce dose if estimated glomerular filtration is less than 80 mL/minute/1.73 m²
- Pregnancy: see Pregnancy and Breast-feeding, p. 266; manufacturer advises use only if potential benefit outweighs risk—toughness in animal studies
- Breast-feeding: present in milk—manufacturer advises avoid; see also notes above

Side-effects: nausea, vomiting, dyspepsia, diarrhoea, abdominal pain, anorexia, weight changes; cough; drowsiness, asthenia, amnesia, ataxia, seizures, dizziness, headache, tremor, hyperkinesia, depression, emotional lability, insomnia, anxiety, impaired balance and attention, aggression, irritability; thrombocytopenia; myalgia; visual disturbances; pruritus, rash; also reported pancreatitis, hepatic dysfunction, confusion, psychosis, hallucinations, suicidal ideation, paraesthesia, leucopenia, pancytopenia, and alopecia

Indication and dose

Monotherapy of partial seizures with or without secondary generalisation
- By mouth or by intravenous infusion
Child 16–18 years initially 250 mg once daily increased according to response in steps of 250 mg twice daily every 2 weeks; max. 1.5 g twice daily

Adjunctive treatment of partial seizures with or without secondary generalisation; adjunctive treatment of myoclonic seizures; adjunctive treatment of tonic-clonic seizures
- By mouth or by intravenous infusion
Child 4–18 years under 50 kg initially 10 mg/kg once daily, adjusted in steps not exceeding 10 mg/kg twice daily every 2 weeks; max. 30 mg/kg twice daily
Child 12–18 years, body-weight over 50 kg initially 250 mg twice daily, adjusted in steps of 500 mg twice daily every 2–4 weeks; max. 1.5 g twice daily

Administration for intravenous infusion, dilute requisite dose with at least 100 mL Glucose 5% or Sodium Chloride 0.9% or Compound Sodium Lactate solution; give over 15 minutes
For administration of oral solution, requisite dose may be diluted in a glass of water

Keppra® (UCB Pharma) (FR)
Tablets, 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, partial seizures and neonatal seizures but may cause behavioural disturbances and hyperkinesia. 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. It is used rarely in children.

PHENOBARBITAL

(Phenobarbitone)

Cautions: see also notes above; debilitated; respiratory depression (avoid if severe); avoid abrupt withdrawal (dependence with prolonged use); history of drug and alcohol abuse; avoid in acute
porphyria (see section 9.8.2); 

**Interactions:**
see p. 264 and Appendix 1 (barbiturates)

**Hepatic impairment** may precipitate coma; avoid in severe impairment

**Renal impairment** use with caution

**Pregnancy** see Pregnancy and Breast-feeding, p. 266

**Breast-feeding** avoid if possible; drowsiness may occur

**Side-effects** hepatitis, cholestasis; hypotension; respiratory depression; drowsiness, lethargy, depression, ataxia, behavioural disturbances, nystagmus, irritability, hallucinations, impaired memory and cognition, hyperactivity; osteomalacia; megaloblastic anaemia (may be treated with folic acid); agranulocytosis, thrombocytopenia, allergic skin reactions; very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis; suicidal ideation; overdosage: see Emergency Treatment of Poisoning, p. 35

**Pharmacokinetics** trough plasma concentration for optimum response 15–40 mg/litre (60–180 micromol/litre)

**Indication and dose**

- **All forms of epilepsy except absence seizures**

  **By mouth or by intravenous injection**

  **Neonate** initially 20 mg/kg by slow intravenous injection then 2.5–5 mg/kg once daily either by slow intravenous injection or by mouth; dose and frequency adjusted according to response

**PRIMIDONE**

**Cautions** see under Phenobarbital; interactions: see p. 264 and Appendix 1 (primidone)

**Hepatic impairment** reduce dose, may precipitate coma

**Renal impairment** see Phenobarbital

**Pregnancy** see Phenobarbital

**Breast-feeding** see Phenobarbital

**Side-effects** see under Phenobarbital; also nausea and visual disturbances; less commonly vomiting, headache, and dizziness; rarely arthralgia

**Pharmacokinetics** monitor plasma concentrations of derived phenobarbital. Optimum range as for phenobarbital

**Indication and dose**

- **All forms of epilepsy except absence seizures**

  **By mouth**

  **Child under 2 years** initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, 125–250 mg twice daily

**Phenytoin**

Phenytoin is effective for tonic-clonic, partial, and neonatal seizures but it may worsen myoclonus. It has a narrow therapeutic index and the relationship between dose and plasma concentration is non-linear; small dosage increases in some children may produce large rises in plasma concentrations with acute overdosage: see Emergency Treatment of Poisoning, p. 35

**Pharmacokinetics**

- **trough plasma concentration for optimum response 15–40 mg/litre (60–180 micromol/litre)**

**Indication and dose**

- **All forms of epilepsy except absence seizures**

  **By mouth**

  **Child 1 month–12 years** initially 1–1.5 mg/kg twice daily, increased by 2 mg/kg daily as required; usual maintenance dose 2.5–4 mg/kg once or twice daily

  **Child 12–18 years** 60–180 mg once daily

**Status epilepticus** section 4.8.2

**Note** For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect

**Administration** for administration by mouth, tablets may be crushed

For intravenous injection, dilute to a concentration of 20 mg/mL with Water for Injections; give over 20 minutes (no faster than 1 mg/kg/minute)

**Phenobarbital** (Non-proprietary)

**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**, phenobarbital sodium 200 mg/mL in propylene glycol 90% and water for injections 10%, net price 1-mL amp = £2.00

**Note** Must be diluted before intravenous administration (see Administration)

**Mysoline** (Acorus)

**Tablets**, scored, primidone 250 mg, net price 100-tab pack = £12.60. Label: 2, 8, counselling, driving (see notes above)

**Child 2–5 years** initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, 250–375 mg twice daily

**Child 5–9 years** initially 125 mg daily at bedtime, increased by 125 mg every 3 days according to response; usual maintenance, 375–500 mg twice a day

**Child 9–18 years** initially 125 mg daily at bedtime, increased by 125 mg every 3 days to 250 mg twice daily, then increased according to response by 250 mg every 3 days to max. 750 mg twice daily

**Phenytoin** is effective for tonic-clonic, partial, and neonatal seizures but it may worsen myoclonus. It has a narrow therapeutic index and the relationship between dose and plasma concentration is non-linear; small dosage increases in some children may produce large rises in plasma concentrations with acute...
toxic side-effects. Monitoring of plasma concentration can assist 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**

**Cautions** see notes above; avoid abrupt withdrawal; manufacturer recommends blood counts (but evidence of practical value unsatisfactory); avoid in acute porphyria (section 9.8.2); interactions: see p. 264 and Appendix 1 (phenytoin)

**Hepatic impairment** reduce dose

**Pregnancy** see Pregnancy and Breast-feeding, p. 266; changes in plasma protein binding may make interpretation of plasma-phenytoin concentrations difficult; increased doses may be required in the third trimester

**Breast-feeding** small amounts present in milk, but not known to be harmful

Blood or skin disorders Children and 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, dizziness, 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; suicidal ideation; with excessive dosage nystagmus, diplopia, slurred speech, ataxia, confusion, and hyperglycaemia

**Pharmacokinetics** therapeutic plasma-phenytoin concentrations reduced in first 3 months of life because of reduced protein binding

Trough plasma concentration for optimum response:

**Neonate–3 months**, 6–15 mg/litre (25–60 micromol/litre)

**Child 3 months–18 years**, 10–20 mg/litre (40–80 micromol/litre)

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

**All forms of epilepsy except absence seizures**

- By intravenous injection (over 20–30 minutes) and by mouth

**Neonate** initial loading dose by slow intravenous injection (section 4.8.2) 18 mg/kg then by mouth 2.5–5 mg/kg twice daily adjusted according to response and plasma-phenytoin concentration (usual max. 7.5 mg/kg twice daily)

- By mouth

  **Child 1 month–12 years** initially 1.5–2.5 mg/kg twice daily, then adjusted according to response and plasma-phenytoin concentration to 2.5–5 mg/kg twice daily (usual max. 7.5 mg/kg twice daily or 300 mg daily)

  **Child 12–18 years** initially 75–150 mg twice daily then adjusted according to response and plasma-phenytoin concentration to 150–200 mg twice daily (usual max. 300 mg twice daily)

**Status epilepticus, acute symptomatic seizures associated with head trauma or neurosurgery** section 4.8.2

**Administration** for administration by mouth, interrupt enteral feeds for at least 1–2 hours before and after giving phenytoin; give with water to enhance absorption

For administration by intravenous injection and intravenous infusion, see p. 287

**Phenytoin (Non-proprietary)** (ΦΗ)

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)** (ΦΗ)

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

Parenteral preparations
Section 4.8.2

Rufinamide

Rufinamide is licensed for the adjunctive treatment of seizures in Lennox-Gastaut syndrome.

The Scottish Medicines Consortium (p. 4) 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 4 years and above. It is restricted for use when alternative traditional antiepileptic drugs are unsatisfactory.

Cautions closely monitor and consider withdrawal if rash, fever, or other signs of hypersensitivity syndrome (see Side-effects) develop; avoid abrupt withdrawal; interactions: see p. 264 and Appendix 1 (rufinamide)

Hepatic impairment manufacturer advises caution and careful dose titration in mild to moderate hepatic impairment and to avoid in severe impairment

Pregnancy see Pregnancy and Breast-feeding, p. 266; manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies; effective contraception must be used during treatment

Contra-indications
Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting, constipation, diarrhoea, dyspepsia, abdominal pain; rhinitis, epistaxis; weight loss, anorexia, dizziness, headache, drowsiness, insomnia, anxiety, fatigue, increase in seizure frequency, impaired coordination, hyperactivity, tremor, gait disturbances; influenza-like symptoms; oligomenorrhoea; back pain; nystagmus, diplopia, blurred vision; rash, and acne; hypersensitivity syndrome (possibly including rash, fever, lymphadenopathy, hepatic dysfunction, haematuria, and multi-organ dysfunction) also reported

Hypersensitivity syndrome Serious hypersensitivity syndrome (see above) has developed especially in children and upon initiation of therapy; consider withdrawal if rash or signs or symptoms of hypersensitivity syndrome develop

Counselling Warn children and their carers to seek immediate medical attention if signs or symptoms of hypersensitivity syndrome develop

Indication and dose
Adjunctive treatment of seizures in Lennox-Gastaut syndrome

By mouth
Child 4–18 years body-weight less than 30 kg, initially 100 mg twice daily increased according to response in steps of 100 mg twice daily up to every 2 days; max. 500 mg twice daily (max. 300 mg twice daily if adjunctive therapy with valproate)

Child 4–18 years body-weight over 30 kg, initially 200 mg twice daily increased according to response in steps of 200 mg twice daily up to every 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

Administration Tablets may be crushed and given in half a glass of water

Inovelon® (Eisai) ▼ 36

Tablets, pink, f/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)

Stiripentol

Stiripentol is licensed for use in combination with clobazam and valproate as adjunctive therapy of refractory generalised tonic-clonic seizures in children with severe myoclonic epilepsy in infancy (Dravet Syndrome). It should be used under specialist supervision.
**STIRIPENTOL**

**Cautions** perform full blood count and liver function tests prior to initiating treatment and every 6 months thereafter; monitor growth; **interactions:** Appendix 1 (stiripentol)

**Pregnancy** see Pregnancy and Breast-feeding, p.266; manufacturer advises use only if the potential benefit outweighs risk

**Breast-feeding** present in milk in animal studies

**Contra-indications** history of psychosis

**Hepatic impairment** manufacturer advises avoid—no information available

**Renal impairment** manufacturer advises avoid—no information available

**Side-effects** nausea, vomiting; aggression, anorexia, ataxia, drowsiness, dystonia, hyperexcitability, hypokinesia, hypotonia, irritability, sleep disorders, weight loss; neutropenia; less commonly fatigue, photosensitivity, rash, and urticaria

**Indication and dose**

**Severe myoclonic epilepsy in infancy**

- **By mouth**
  - **Child 3–18 years** initially 10 mg/kg in 2–3 divided doses; titrate dose over minimum of 3 days to max. 50 mg/kg/day in 2–3 divided doses

**Diacomit® (Alan Pharmaceuticals)**

- **Capsules**, stiripentol 250 mg (pink), net price 60-cap pack = £248.00; 500 mg (white), 60-cap pack = £493.00. Label: 1, 8, 21, counselling, administration
- **Powder**, stiripentol 250 mg, net price 60-sachet pack = £284.00; 500 mg, 60-sachet pack = £493.00. Label: 1, 8, 13, 21, counselling, administration

**Excipients** include aspartame (section 9.4.1)

**Counselling** Do not take with milk, diary products, carbonated drinks, fruit juice, or with food or drink that contains caffeine

**TIAGABINE**

**Tiagabine** is used as adjunctive treatment for partial seizures, with or without secondary generalisation.

**Cautions** avoid in acute porphyria (section 9.8.2); avoid abrupt withdrawal; **interactions:** Appendix 1 (tiagabine)

**Hepatic impairment** in mild to moderate impairment, initial maintenance dose is 5–10 mg 1–2 times daily; avoid in severe impairment

**Pregnancy** see Pregnancy and Breast-feeding, p.266; no evidence of teratogenicity in animal studies, but manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** manufacturer advises avoid unless potential benefit outweighs risk

**Driving** May impair performance of skilled tasks (e.g. driving)

**Side-effects** diarrhoea; dizziness, tiredness, nervousness, tremor, impaired concentration, emotional lability, speech impairment; rarely confusion, depression, drowsiness, psychosis, non-convulsive status epilepticus, bruising, and visual disturbances; suicidal ideation; leucopenia also reported

**Indication and dose**

**Adjunctive treatment with enzyme-inducing drugs for partial seizures with or without secondary generalisation not satisfactorily controlled by other antiepileptics**

- **By mouth**
  - **Child 12–18 years** initially 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 in 2–3 divided doses (doses above 30 mg daily given in 3 divided doses)

**Gabitril® (Cephalon)**

- **Tablets**, 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**

**Topiramate** can be given alone or as adjunctive treatment in generalised tonic-clonic seizures or partial seizures with or without secondary generalisation. It can also 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).
**TOPIRAMATE**

**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); *interactions*: see p. 264 and Appendix 1 (topiramate)

**Hepatic impairment** use with caution—clearance may be decreased

**Renal impairment** longer time to steady-state plasma concentration

**Pregnancy** see Pregnancy and Breast-feeding, p. 266; manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies

**Breast-feeding** manufacturer advises avoid—present in milk

**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

**Side-effects** nausea, abdominal pain, dyspepsia, diarrhoea, dry mouth, taste disturbances, weight loss, anorexia; paraesthesia, hypoaesthesia, headache, fatigue, dizziness, speech disorder, drowsiness, insomnia, impaired memory and concentration, anxiety, depression; visual disturbances; *less commonly* suicidal ideation; *rarely* reduced sweating, metabolic acidosis, and alopecia; *very rarely* leucopenia, thrombocytopenia, and serious skin reactions

**Indication and dose**

- **Monotherapy of generalised tonic-clonic seizures or partial seizures with or without secondary generalisation**
  - **By mouth**
    - **Child 6–16 years** initially 0.5–1 mg/kg at night for 1 week then increased in steps of 250–500 micrograms/kg twice daily at intervals of 1–2 weeks; usual dose 1.5–3 mg/kg twice daily; max. 7.5 mg/kg twice daily

- **Adjunctive treatment of generalised tonic-clonic seizures or partial seizures with or without secondary generalisation, adjunctive treatment of seizures in Lennox-Gastaut syndrome**
  - **By mouth**
    - **Child 2–16 years** initially 25 mg at night for 1 week then increased in steps of 0.5–1.5 mg/kg twice daily at intervals of 1–2 weeks; usual dose 2.5–4.5 mg/kg twice daily; max. 7.5 mg/kg twice daily
    - **Child 16–18 years** initially 25 mg at night for 1 week then increased in steps of 12.5–25 mg twice daily at intervals of 1–2 weeks; usual dose 100–200 mg twice daily; max. 400 mg twice daily

- **Migraine prophylaxis**
  - **By mouth**
    - **Child 16–18 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 child cannot tolerate titration regimens recommended above then smaller steps or longer interval between steps may be used

**Topamax® (Janssen-Cilag)**

- **Tablets**, 25, 50, 100 mg, net price 60-tab pack = £20.48; 200 mg (light yellow), 60-tab pack = £33.64; 500 mg (yellow), 60-tab pack = £60.26; 1000 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**

Valproate (as either sodium valproate or valproic acid) 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. Valproate should generally be avoided in children under 2 years especially if they are on other antiepileptics, but may be required in infants with continuing epileptic tendency. Sodium valproate has widespread metabolic effects, and may have dose-related side-effects.

Valproic acid (as semisodium valproate) (section 4.2.3) is licensed for acute mania associated with bipolar disorder.

**SODIUM VALPROATE**

**Cautions** see notes above; monitor liver function before therapy and during first 6 months especially in children most at risk (see also below); measure full blood count and ensure no undue
Indication and dose

- By mouth or by rectum

### Neonate
initially 20 mg/kg once daily; usual maintenance dose 10 mg/kg twice daily

### Child 1 month–12 years
initially 5–7.5 mg/kg twice daily; usual maintenance dose 12.5–15 mg/kg twice daily (up to 30 mg/kg twice daily in infantile spams; monitor clinical chemistry and haemoglobin parameters if dose exceeds 20 mg/kg twice daily)

- By intravenous injection over 3–5 minutes

### Neonate
10 mg/kg twice daily

### Child 1 month–18 years
10 mg/kg twice daily

- By continuous intravenous infusion

### Child 1 month–12 years
initially 10 mg/kg by intravenous injection then by continuous intravenous infusion 20–40 mg/kg daily

### Child 12–18 years
initially 10 mg/kg by intravenous injection then up to max. 2.5 g daily by continuous intravenous infusion

Administration for rectal administration, sodium valproate oral solution may be given rectally and retained for 15 minutes (may require dilution with water to prevent rapid expulsion).

For intravenous injection, may be diluted in Glucose 5% or Sodium Chloride 0.9%.

For continuous intravenous infusion, dilute injection solution with Glucose 5% or Sodium Chloride 0.9%.

#### Oral

**Sodium Valproate** (Non-proprietary)

- **Tablets** (crushable), scored, sodium valproate 100 mg, net price 100 = £4.67. Label: 8, counselling, pancreatitis, 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, pancreatitis, 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 = £6.20. Label: 8, counselling, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

Brands include **Orlept** sugar-free

**Epilem** (Sanofi-Synthelabo)

- **Tablets** (crushable), scored, sodium valproate 100 mg, net price 100 = £4.67. Label: 8, counselling, pancreatitis, 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, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

Brands include **Epilem** sugar-free

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**SODIUM VALPROATE** (continued)

potential for bleeding before starting and before surgery; systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal; interactions: see p. 264 and Appendix 1 (valproate)

**Hepatic impairment** avoid if possible; see also Contra-indications and Liver Toxicity below

**Renal impairment** reduce dose; adjust dosage according to free serum valproic acid concentration

**Pregnancy** see Pregnancy and Breast-feeding, p. 266; neonatal bleeding (related to hypofibrinemia) and neonatal hepatotoxicity also reported

**Breast-feeding** amount too small to be harmful

**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 children should be reassessed clinically and liver function (including prothrombin time) monitored until return to normal—discontinue if abnormally prolonged prothrombin time (particularly in association with other relevant abnormalities)

**Blood or hepatic disorders** Children and their carers should be told how to recognise signs of blood or liver disorders and advised to seek immediate medical attention if symptoms develop

**Pancreatitis** Children and 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 curly); rarely hepatic dysfunction (see under Cautions; withdraw treatment immediately if persistent vomiting and abdominal pain; discontinue if pancreatitis is diagnosed)

**Chemistry** and haematological parameters if dose exceeds 20 mg/kg twice daily

**Child 12–18 years** initially 300 mg twice daily increased in steps of 200 mg daily at 3-day intervals; usual maintenance dose 0.5–1 g twice daily; max. 1.25 g twice daily

**Note** If switching from oral therapy to intravenous therapy, the intravenous dose should be the same as the established oral dose

- By intravenous injection over 3–5 minutes

### Neonate
10 mg/kg twice daily

### Child 1 month–18 years
10 mg/kg twice daily

- By continuous intravenous infusion

### Child 1 month–12 years
initially 10 mg/kg by intravenous injection then by continuous intravenous infusion 20–40 mg/kg daily

### Child 12–18 years
initially 10 mg/kg by intravenous injection then up to max. 2.5 g daily by continuous intravenous infusion

**Administration** for rectal administration, sodium valproate oral solution may be given rectally and retained for 15 minutes (may require dilution with water to prevent rapid expulsion).

For intravenous injection, may be diluted in Glucose 5% or Sodium Chloride 0.9%.

For continuous intravenous infusion, dilute injection solution with Glucose 5% or Sodium Chloride 0.9%.

**Oral Sodium Valproate** (Non-proprietary)

- **Tablets** (crushable), scored, sodium valproate 100 mg, net price 100 = £4.67. Label: 8, counselling, pancreatitis, 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, pancreatitis, 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 = £6.20. Label: 8, counselling, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

Brands include **Orlept** sugar-free

**Epilem** (Sanofi-Synthelabo)

- **Tablets** (crushable), scored, sodium valproate 100 mg, net price 100 = £4.67. Label: 8, counselling, pancreatitis, 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, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

Brands include **Epilem** sugar-free
SODIUM VALPROATE (continued)

Syrup, red, sodium valproate 200 mg/5 mL, net price 300-mL pack = £7.78. Label: 8, counselling, pancreatitis, 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, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Dose**

*Child* body-weight over 20 kg 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

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. Label: 8, 25, counselling, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Dose**

*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, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Dose**

*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

Episenta® (Beacon) Injection, powder for reconstitution, sodium valproate, net price 400-mg vial (with 4-mL amp water for injections) = £11.58

**Parenteral**

Epilim® Intravenous (Sanofi-Synthelabo) 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, counselling, pancreatitis, blood or hepatic disorder symptoms (see above), driving (see notes above)

**Dose**

*Child* as for sodium valproate, total daily dose given in 2–4 divided doses

**Equivalence to sodium valproate** Manufacturer advises that Convulex® has a 1:1 dose relationship with products containing sodium valproate, but nevertheless care is needed in making changes

**Vigabatrin**

For partial epilepsy with or without secondary generalisation, vigabatrin is given in combination with other antiepileptic treatment; its use is restricted to children in whom all other combinations are inadequate or are not tolerated. It can be used as sole therapy in the management of infantile spasms.

About one-third of those treated with vigabatrin 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 children.

**Cautions**

closely monitor neurological function; avoid sudden withdrawal (taper off over 2–4 weeks); history of psychosis, depression or behavioural problems; absence seizures (may be exacerbated); interactions: see p. 264 and Appendix 1 (vigabatrin)

Renal impairment consider reduced dose or increased dose interval if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²

Pregnancy see Pregnancy and Breast-feeding, p. 266

Breast-feeding see notes above; present in milk—manufacturer advises avoid

**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 discontinuation. Product literature advises visual field testing before treatment and at 6-month intervals; a pro-
VIGABATRIN (continued)

- Procedure for testing visual fields in those with a developmental age of less than 9 years is available from the manufacturers. Children and their carers 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

- Drowsiness (rarely encephalopathic symptoms consisting of marked sedation, stupor, and confusion with non-specific slow wave EEG—reduce dose or withdraw), fatigue, visual field defects (see also under Cautions), dizziness, nervousness, irritability, behavioural effects such as excitement and agitation; depression, abnormal thinking, headache, nystagmus, ataxia, tremor, paraesthesia, impaired concentration; less commonly confusion, aggression, psychosis, mania, memory disturbance, visual disturbance (e.g. diplopia); also weight gain, oedema, gastrointestinal disturbances, alopecia, rash; less commonly urticaria, occasional increase in seizure frequency (especially if myoclonic), decrease in liver enzymes, slight decrease in haemoglobin; photophobia and retinal disorders (e.g. peripheral retinal atrophy); optic neuritis, optic atrophy, hallucinations also reported

Indication and dose

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>initially 15–20 mg/kg twice daily increased over 2–3 weeks to usual maintenance dose 30–40 mg/kg twice daily; max. 75 mg/kg twice daily</td>
</tr>
<tr>
<td>Child 1 month–2 years</td>
<td>initially 15–20 mg/kg twice daily increased over 2–3 weeks to usual maintenance dose 30–40 mg/kg twice daily; max. 75 mg/kg twice daily</td>
</tr>
<tr>
<td>Child 2–12 years</td>
<td>initially 15–20 mg/kg (max. 250 mg) twice daily increased over 2–3 weeks to usual maintenance dose 30–40 mg/kg (max. 1.5 g) twice daily</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>initially 250 mg twice daily increased over 2–3 weeks to usual maintenance dose 1–1.5 g twice daily</td>
</tr>
</tbody>
</table>

Administration

- Tablets may be crushed and dispersed in liquid
- Tablets, f/c, 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, 13, counselling, driving (see notes above)

Note

- The contents of a sachet should be dissolved in water or a soft drink immediately before taking

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, but the effectiveness of these and other benzodiazepines may wane considerably after weeks or months of continuous therapy.

CLOBAZAM

Cautions

- Hepatic impairment may precipitate coma
- Renal impairment start with small doses in severe impairment; increased cerebral sensitivity
- Pregnancy 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)
- Breast-feeding present in milk—avoid if possible

Contra-indications

- See under Diazepam (section 4.8.2)

Side-effects

- See under Diazepam (section 4.8.2)

Licensed use

- Not licensed for use in children under 3 years

Indication and dose

- Adjunctive therapy for epilepsy, monotherapy under specialist supervision for catamenial (menstruation) seizures (usually for 7–10 days each month, just before and during menstruation), cluster seizures
- By mouth

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–12 years</td>
<td>initially 125 micrograms/kg twice daily increased every 5 days to usual maintenance dose of 250 micrograms/kg twice daily; max. 500 micrograms/kg twice daily, not exceeding 15 mg twice daily</td>
</tr>
</tbody>
</table>

Sabril® (Aventis Pharma) (NW)

- Tablets, f/c, 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, 13, counselling, driving (see notes above)

- The contents of a sachet should be dissolved in water or a soft drink immediately before taking
CLONAZEPAM

Cautions  
- see notes above; respiratory disease; spinal or cerebellar ataxia; myasthenia gravis (avoid if unstable); history of alcohol or drug abuse, depression or suicidal ideation; debilitating; avoid sudden withdrawal, acute porphyria (section 9.8.2); 
- interactions: see p. 264 and Appendix 1 (anxiolytics and hypnotics)

Hepatic impairment  
- can precipitate coma; reduce dose in mild to moderate impairment; avoid in severe impairment

Renal impairment  
- start with small doses; increased cerebral sensitivity

Pregnancy  
- 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)

Breast-feeding  
- present in milk—avoid if possible

Contra-indications  
- respiratory depression; acute pulmonary insufficiency; sleep apnoea syndrome

Side-effects  
- drowsiness, fatigue, dizziness, muscle hypotonia, coordination 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 and anxiety, sexual dysfunction, urinary incontinence, urticaria, pruritus, reversible hair loss, skin pigmentation changes; dysarthria, and visual disturbances on long-term treatment; blood disorders reported; overdose: see Emergency Treatment of Poisoning, p. 41

Nitrazepam

Cautions  
- avoid abrupt withdrawal; respiratory disease; acute porphyria (section 9.8.2); muscle weakness and myasthenia gravis; 
- interactions: Appendix 1 (anxiolytics and hypnotics)

Hepatic impairment  
- can precipitate coma; avoid in severe hepatic impairment

Renal impairment  
- start with small doses; increased cerebral sensitivity

Contra-indications  
- respiratory depression, acute pulmonary insufficiency, sleep apnoea syndrome; marked neuromuscular respiratory weakness including myasthenia gravis

Side-effects  
- drowsiness, confusion, ataxia; see also under Diazepam (section 4.8.2); overdose: see Emergency Treatment of Poisoning, p. 41

LICENSED USE  
- not licensed for use in children

INDICATION AND DOSE  
- Infantile spasms

- By mouth

Child 1 month–1 year  
- initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 0.5–1 mg at night (may be given in 3 divided doses if necessary)

Child 1–5 years  
- initially 250 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance of 1–3 mg at night (may be given in 3 divided doses if necessary)

Child 5–12 years  
- initially 500 micrograms at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 3–6 mg at night (may be given in 3 divided doses if necessary)

Child 12–18 years  
- initially 1 mg at night for 4 nights, increased over 2–4 weeks to usual maintenance dose of 4–8 mg at night (may be given in 3–4 divided doses if necessary)

Note  
- Clonazepam doses in BNFC may differ from those in product literature

Administration  
- for administration by mouth, injection solution may be given orally

Rivotril® (Roche)  
- 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

Liquid, clonazepam 2.5 mg/mL
- Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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®
- Tablets, clobazam 5 mg available on a named patient basis

1. Except for epilepsy and endorsed ‘SLS’

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
NITRAZEPAM (continued)

Nitrazepam (Non-proprietary) PM
Oral suspension, nitrazepam 2.5 mg/5 mL, net
price 150 mL = £5.30. Label: 1, 8
Brands include Somnite®

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 in conjunction with other antiepileptics for tonic-clonic or partial seizures.

Piracetam 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 child to avoid injury, supporting respiration including the provision of oxygen, maintaining blood pressure, and the correction of any hypoglycaemia. Pyridoxine (section 9.6.2) should be administered if the status epilepticus is caused by pyridoxine deficiency.

Convulsive status epilepticus should be treated urgently with intravenous lorazepam. Intravenous diazepam is effective but it is associated with a high risk of venous thrombophlebitis (reduced by using an emulsion formulation of diazepam injection). Clonazepam can also be used as an alternative.

Where facilities for resuscitation are not immediately available, midazolam can be given into the buccal cavity, or diazepam can be administered as a rectal solution; the buccal route may be more acceptable in children.

Important

If seizures recur or fail to respond within 30 minutes, phenytoin sodium, fosphenytoin, or phenobarbital sodium should be used.

If these measures fail to control seizures within 60 minutes, anaesthesia with thiopental (section 15.1.1) or midazolam (section 15.1.4) should be instituted with full intensive care support. Lidocaine infusion has also been used but requires specialist management.

Phenytoin sodium may be given by slow intravenous injection, with ECG monitoring, followed by the maintenance dosage if appropriate. 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 given rectally causes little respiratory depression and is therefore useful where facilities for resuscitation are poor.

For neonatal seizures, see p. 267.

Non-convulsive status epilepticus The urgency to treat non-convulsive status epilepticus depends upon the severity of the child’s condition. If there is incomplete loss of awareness, oral antiepileptic therapy should be restarted or continued. Children who fail to respond to oral antiepileptic therapy or have complete lack of awareness can be treated in the same way as convulsive status epilepticus although anaesthesia is rarely needed.

CLONAZEPAM

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)
DIAZEPAM

Cautions  respiratory disease, muscle weakness and myasthenia gravis, history of drug or alcohol abuse, marked personality disorder; avoid prolonged use (and abrupt withdrawal thereafter); when given parenterally, close observation required until full recovery from sedation; when given intravenously, facilities for reversing respiratory depression with mechanical ventilation must be at hand (but see also notes above); porphyria (section 9.8.2); interactions: Appendix 1 (anxiolytics and hypnotics)
Hepatic impairment  reduce dose as may precipitate coma; avoid in severe impairment
Renal impairment  start with small doses; increased cerebral sensitivity
Pregnancy  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 hyperthermia, hypotonia, and respiratory depression)
Breast-feeding  avoid if possible—present in milk
Skilled tasks 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; 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 light-headedness the next day; confusion and ataxia; amnesia; depersonalisation; 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; overdosage: see Emergency Treatment of Poisoning, p. 41
Licensed use  Diazepam Rectubes® and Stesolid Rectal Tubes® not licensed for use in children under 1 year

Indication and dose

Status epilepticus, febrile convulsions (section 4.8.3), convulsions caused by poisoning
• By intravenous injection over 3–5 minutes
Neonate  300–400 micrograms/kg repeated once after 10 minutes if necessary
Child 1 month–12 years  300–400 micrograms/kg repeated once after 10 minutes if necessary
Child 12–18 years  10–20 mg repeated once after 10 minutes if necessary
• By rectum (as rectal solution)
Neonate  1.25–2.5 mg repeated once after 10 minutes if necessary
Child 1 month–2 years  5 mg repeated once after 10 minutes if necessary
Child 12–18 years  10 mg repeated once after 10 minutes if necessary

Muscle spasm  section 10.2.2

Peri-operative use  section 15.1.4.1

Other forms of epilepsy section 4.8.1

Administration  for intravenous injection, dilute to a concentration of 500 micrograms/mL with Water for Injections
For intravenous infusion, dilute to a concentration of 12 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; incompatible with bicarbonate; adsorbed on PVC—glass infusion apparatus preferred (if PVC apparatus used, complete infusion within 2 hours)

Rivotril® (Roche) 
Injection, clonazepam 1 mg/mL in solvent, net price 1-ml amp (with 1 mL water for injections) = 63p
Excipients include benzyl alcohol (avoid in neonates unless there is no safer alternative available, see Excipients, p. 3), ethanol, propylene glycol

Oral preparations  Section 4.8.1
FOSPHENYTOIN SODIUM

Note Fosphenytoin is a pro-drug of phenytoin

Cautions see Phenytoin Sodium; resuscitation facilities must be available; interactions: see p. 264 and Appendix 1 (phenytoin)

Hepatic impairment consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

Renal impairment consider 10–25% reduction in dose or infusion rate (except initial dose for status epilepticus)

Pregnancy see Phenytoin (section 4.8.1)

Breast-feeding see Phenytoin (section 4.8.1)

Contra-indications see Phenytoin Sodium

Side-effects see Phenytoin Sodium

CSM advice Intravenous infusion of fosphenytoin has been associated with severe cardiovascular reactions including asystole, ventricular fibrillation, and cardiac arrest. Hypotension, bradycardia, and heart block have also been reported. The CSM advises:

- monitor heart rate, blood pressure, and respiratory function for duration of infusion
- observe patient for at least 30 minutes after infusion
- if hypotension occurs, reduce infusion rate or discontinue
- reduce dose or infusion rate in renal or hepatic impairment

Indication and dose

Expressed as phenytoin sodium equivalent (PE); fosphenytoin sodium 1.5 mg = phenytoin sodium 1 mg

Status epilepticus

• By intravenous infusion (at a rate of 2–3 mg(PE)/kg/minute)
• Child 5–18 years initially 20 mg(PE)/kg, then

Temporary substitution for oral phenytoin

• By intravenous infusion (at a rate of 1–2 mg(PE)/kg/minute)
• Child 5–18 years same dose and dosing frequency as oral phenytoin therapy

Note Fosphenytoin sodium doses in BNFC may differ from those in product literature

Administration for intermittent intravenous infusion, dilute to a concentration of 1.5–25 mg (PE)/mL with Glucose 5% or Sodium Chloride 0.9%

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

Cautions see under Diazepam; facilities for reversing respiratory depression with mechanical ventilation must be at hand

Contra-indications see under Diazepam

Side-effects see under Diazepam; hypotension and apnoea

Indication and dose

Status epilepticus

• By slow intravenous injection
• Neonate 100 micrograms/kg as a single dose, repeated once after 10 minutes if necessary
• Child 1 month–12 years 100 micrograms/kg (max. 4 mg) as a single dose, repeated once after 10 minutes if necessary

Child 12–18 years 4 mg as a single dose, repeated once after 10 minutes if necessary

Administration for intravenous injection, dilute with an equal volume of Sodium Chloride 0.9% or Water for Injections (for neonates, dilute injection solution to a concentration of 100 micrograms/mL); give slowly into a large vein at a rate not exceeding 50 micrograms/kg over 3–5 minutes.

Preparations

Section 15.1.4.1
### MIDAZOLAM

**Cautions** section 15.1.4  
**Contra-indications** section 15.1.4  
**Side-effects** section 15.1.4  
**Licensed use** buccal liquid and injection not licensed for use in status epilepticus

#### Indication and dose

**Status epilepticus**

- **By buccal administration**
  - **Neonate** 300 micrograms/kg repeated once after 10 minutes if necessary  
  - **Child 1–6 months** 300 micrograms/kg (max. 2.5 mg), repeated once after 10 minutes if necessary  
  - **Child 6 months–1 year** 2.5 mg, repeated once after 10 minutes if necessary  
  - **Child 1–5 years** 5 mg, repeated once after 10 minutes if necessary  
  - **Child 5–10 years** 7.5 mg, repeated once after 10 minutes if necessary  
  - **Child 10–18 years** 10 mg, repeated once after 10 minutes if necessary

- **By intravenous administration**
  - **Neonate** initially by intravenous injection 150–200 micrograms/kg followed by continuous infusion of 1 microgram/kg/minute (increased by 1 microgram/kg/minute every 15 minutes until seizure controlled; max. 5 micrograms/kg/minute)  
  - **Child 1 month–18 years** initially by intravenous injection 150–200 micrograms/kg followed by continuous intravenous infusion of 1 microgram/kg/minute (increased by 1 microgram/kg/minute every 15 minutes) until seizure controlled; max. 5 micrograms/kg/minute

#### Administration

- **for intravenous injection**, dilute with Glucose 5% or Sodium Chloride 0.9%; rapid intravenous injection (less than 2 minutes) may cause seizure-like myoclonus in preterm neonate  
- For **buccal administration**, injection solution may be given bucally or by mouth

#### Preparations

Section 15.1.4

### PARALDEHYDE

**Cautions** bronchopulmonary disease, hepatic impairment; **interactions**: Appendix 1 (paraldehyde)  
**Pregnancy** manufacturer advises avoid—crosses placenta  
**Breast-feeding** present in milk—manufacturer advises avoid unless essential

**Contra-indications** gastric disorders; rectal administration in colitis

**Side-effects** rashes; rectal irritation after enema

**Licensed use** not licensed for use in children as an enema

#### Indication and dose

**Status epilepticus**

- **By rectum** (doses expressed as undiluted paraldehyde)
  - **Neonate** 0.4 mL/kg (max. 0.5 mL) as a single dose  
  - **Child 1–3 months** 0.5 mL as a single dose  
  - **Child 3–6 months** 1 mL as a single dose  
  - **Child 6 months–1 year** 1.5 mL as a single dose  
  - **Child 1–2 years** 2 mL as a single dose  
  - **Child 2–5 years** 3–4 mL as a single dose  
  - **Child 5–18 years** 5–10 mL as a single dose

#### Administration

- **for rectal administration**, do not administer paraldehyde undiluted

**Paraldehyde** (Non-proprietary)  
**Enema**, 8–50%, available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

### PHENOBARBITAL SODIUM

**Phenobarbitone sodium**

**Cautions** see under Phenobarbital (section 4.8.1)  
**Side-effects** see under Phenobarbital (section 4.8.1)

#### Indication and dose

**Status epilepticus**

- **By slow intravenous injection**
  - **Neonate** initially 20 mg/kg then 2.5–5 mg/kg once or twice daily  
  - **Child 1 month–12 years** initially 20 mg/kg (max. 1 g) then 300 mg twice daily  
  - **Child 12–18 years** initially 20 mg/kg (max. 1 g) then 300 mg twice daily

#### Other forms of epilepsy

**Note** For therapeutic purposes phenobarbital and phenobarbital sodium may be considered equivalent in effect

**Administration** for **intravenous injection**, dilute to a concentration of 20 mg/mL with Water for Injections; give over 20 minutes (no faster than 1 mg/kg/minute)
### PHENOBARBITAL SODIUM (continued)

**Phenobarbital** (Non-proprietary)

**Injection**, phenobarbital sodium 200 mg/mL, net price 1-mL amp = £2.00

**Excipients** include propylene glycol 90% (see Excipients, p. 3)

**Note** Must be diluted before intravenous administration (see Administration)

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### PHENYTOIN SODIUM

**Cautions** hypotension and heart failure; resuscitation facilities must be available; injection solutions alkaline (irritant to tissues); see also p. 274; interactions: see p. 264 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. 274

### Indication and dose

**Status epilepticus**, acute symptomatic seizures associated with trauma or neurosurgery

- **By slow intravenous injection or infusion (with blood-pressure and ECG monitoring)**
  - **Neonate** initially 18 mg/kg as a loading dose then 2.5–5 mg/kg twice daily
  - **Child 1 month–12 years** initially 18 mg/kg as a loading dose then 2.5–5 mg/kg twice daily
  - **Child 12–18 years** initially 18 mg/kg as a loading dose then up to 100 mg 3–4 times daily

- **By intramuscular injection** Not recommended (see notes above)

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### Other forms of epilepsy section 4.8.1

**Note** Phenytin sodium doses in BNFC may differ from those in product literature

**Administration** before and after administration flush intravenous line with Sodium Chloride 0.9%.

For **intravenous injection**, give at rate not exceeding 1 mg/kg/minute (max. 50 mg/minute).

For **intravenous infusion**, dilute to a concentration not exceeding 10 mg/mL with Sodium Chloride 0.9% and give through an in-line filter (0.22–0.50 micron) at a rate not exceeding 1 mg/kg/minute (max. 50 mg/minute); complete administration within 1 hour of preparation

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### 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** (section 4.8.2) is the drug of choice given either by slow intravenous injection or preferably rectally in solution, repeated if necessary. The rectal solution is generally preferred as 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; rectal administration of **diazepam** is the treatment of choice.

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 Drugs used in dystonias and related disorders

4.9.1 Dopaminergic drugs used in dystonias

Levodopa, 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 inhibitor most commonly used in children is carbidopa (in co-careldopa).

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 child.

In severe dystonias related to cerebral palsy, improvement can be expected within 2 weeks. Children with Segawa syndrome are particularly sensitive to levodopa; they may even become symptom free on small doses. Levodopa also has a role in treating metabolic disorders such as defects in tetrahydrobiopterin synthesis and dihydrobiopterin reductase deficiency. For the use of tetrahydrobiopterin in metabolic disorders see section 9.4.1.

Children may experience nausea within 2 hours of taking a dose; nausea and vomiting with co-careldopa is rarely dose-limiting but domperidone (section 4.6) may be useful in controlling these effects.

In dystonic cerebral palsy treatment with larger doses of levodopa is associated with the development of potentially troublesome motor complications including response fluctuations and dyskinesias. 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.

Sudden onset of sleep

Excessive daytime sleepiness and sudden onset of sleep can occur with co-careldopa.

Children starting treatment with these drugs, and their carers, should be warned of the possibility of these effects and of the need to exercise caution when performing skilled tasks e.g. driving or operating machinery.

Children who have suffered excessive sedation or sudden onset of sleep should refrain from performing skilled tasks 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

Cautions see also notes above; pulmonary disease, peptic ulceration, cardiovascular disease, diabetes mellitus, osteomalacia, open-angle glaucoma, history of skin melanoma (risk of activation), psychiatric illness (avoid if severe); warn children and carers about excessive drowsiness (see notes above); in prolonged therapy, psychiatric, hepatic, haematological, renal, and cardiovascular surveillance is advisable; warn patients to resume normal activities gradually; avoid abrupt withdrawal; interactions: Appendix 1 (levodopa)

Contra-indications closed-angle glaucoma

Pregnancy manufacturers advise toxicity in animal studies

Breast-feeding may suppress lactation; present in milk—manufacturers advise avoid

Side-effects see also notes above; anorexia, nausea and vomiting, insomnia, agitation, postural hypotension (rarely labile hypertension), dizziness, tachycardia, arrhythmias, reddish discoloration of urine and other body fluids, rarely hypersensitivity; abnormal involuntary movements and psychiatric symptoms which include hypomania and psychosis may be dose-limiting; depression, drowsiness, headache, flushing.
sweating, gastro-intestinal bleeding, peripheral neuropathy, taste disturbance, pruritus, rash, and liver enzyme changes also reported; syndrome resembling neuroleptic malignant syndrome reported on withdrawal

**Licensed use** not licensed for use in children

**Indication and dose**

Dopamine-sensitive dystonias including Segawa syndrome and dystonias related to cerebral palsy

- **By mouth, expressed as levodopa**
  - **Child 3 months–18 years** initially 250 micrograms/kg 2–3 times daily of a preparation containing 1:4 carbidopa:levodopa, increased according to response every 2–3 days to max. 1 mg/kg three times daily

Treatment of defects in tetrahydrobiopterin synthesis and dihydrobiopterin reductase deficiency

- **By mouth, expressed as levodopa**
  - **Neonate** initially 250–500 micrograms/kg 4 times daily of a preparation containing 1:4 carbidopa:levodopa, increased according to response every 4–5 days to maintenance dose of 2.5–3 mg/kg 4 times daily; at higher doses consider preparation containing 1:10 carbidopa:levodopa; review regularly (every 3–6 months in early childhood)

**Sinemet®** (Bristol-Myers Squibb)

- **Sinemet-62.5® tablets**, yellow, scored, co-careldopa 12.5/50 (carbidopa 12.5 mg (as monohydrate), levodopa 50 mg), net price 90-tab pack = £6.54. Label: 14, counselling, driving, see notes above
  - **Note** 2 tablets Sinemet-62.5® = 1 tablet Sinemet Plus®, Sinemet-62.5® previously known as Sinemet LS®

- **Sinemet-110® tablets**, blue, scored, co-careldopa 10/100 (carbidopa 10 mg (as monohydrate), 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 (as monohydrate), 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 (as monohydrate), levodopa 250 mg), net price 90-tab pack = £14.28. Label: 14, counselling, driving, see notes above

**4.9.2 Antimuscarinic drugs used in dystonias**

Antimuscarinic drugs help to control dystonias.

The antimuscarinic drugs procyclidine and trihexyphenidyl (benzhexol) reduce the symptoms of dystonias, including those induced by antipsychotic drugs; there is no justification for giving them routinely in the absence of dystonic symptoms. Tardive dyskinesia is not improved by antimuscarinic drugs and may be made worse.

No important differences exist between the antimuscarinic drugs, but some children tolerate one better than another.

**Cautions** Antimuscarinics should be used with caution in cardiovascular disease, hypertension, psychotic disorders, pyrexia, and in those susceptible to angle-closure glaucoma. Antimuscarinics should not be withdrawn abruptly in children receiving long-term treatment. Antimuscarinics are liable to abuse. They should also be used with caution in hepatic impairment, renal impairment, pregnancy, and breast-feeding. **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.

**PROCYCLIDINE HYDROCHLORIDE**

**Cautions** see notes above

**Pregnancy** manufacturers advise use only if potential benefit outweighs risk

**Breast-feeding** no information available

**Contra-indications** see notes above

**Side-effects** see notes above
4.9.3 Drugs used in essential tremor, chorea, tics, and related disorders

Haloperidol may be useful in improving motor tics and symptoms of Tourette syndrome and related choras (see section 4.2.1). Pimozide (section 4.2.1) and sulpiride (section 4.2.1) are also used in Tourette syndrome.

Propranolol or another beta-adrenoceptor blocking drug (section 2.4) may be useful in treating essential tremor or tremor associated with anxiety or thyrotoxicosis.

BOTULINUM TOXIN TYPE A

Cautions neurological disorders; history of dysphagia or aspiration

Pregnancy manufacturers advise avoid unless essential—toxicity in animal studies

Breast-feeding manufacturers advise avoid (or avoid unless essential)—no information available

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

Specific side-effects in paediatric cerebral palsy Drowsiness, paraesthesia, urinary incontinence, myalgia

Indication and dose

In children over 2 years for dynamic equinus foot deformity caused by spasticity in ambulant paediatric cerebral palsy for dose consult product literature (important: information specific to each individual preparation and not interchangeable)
4.10 Drugs used in substance dependence

This section includes drugs used in the treatment of neonatal abstinence syndrome and cigarette smoking.

Treatment of alcohol or opioid dependence in children requires specialist management. 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 booksellers.

Neonatal abstinence syndrome Neonatal abstinence syndrome occurs at birth as a result of intra-uterine exposure to opioids or high-dose benzodiazepines. Treatment is usually initiated if:

- feeding becomes a problem and tube feeding is required;
- there is profuse vomiting or watery diarrhoea;
- the baby remains very unsettled after two consecutive feeds despite gentle swaddling and the use of a pacifier.

Treatment involves weaning the baby from the drug on which it is dependent. Morphine or methadone (section 4.7.2) can be used in babies of mothers who have been taking opioids. Morphine is widely used because the dose can be easily adjusted, but methadone may provide smoother control of symptoms. Weaning babies from opioids usually takes 7–10 days.

Weaning babies from benzodiazepines that have a long half-life is difficult to manage; chlorpromazine (section 4.2.1) may be used in these situations but excessive sedation may occur. For babies who are dependent on barbiturates, phenobarbital (section 4.8.1) may be tried, although it does not control gastrointestinal symptoms.

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 where appropriate.

Where possible, smokers should have access to a smoking cessation clinic for behavioural support. Nicotine replacement therapy is an effective aid to smoking cessation for those smoking more than 10 cigarettes a day. It is regarded as the pharmacological treatment of choice in the management of smoking cessation.

Cigarette smoking should stop completely before starting a smoking cessation regimen including 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.
Nicotine replacement therapy for smoking cessation (March 2002)

Nicotine replacement therapy should be prescribed only for a smoker who commits to a target stop date. The smoker should be offered advice and encouragement to aid smoking cessation.

Therapy to aid smoking cessation is chosen according to the smoker’s likely compliance, availability of counselling and support, previous experience of smoking-cessation aids, contra-indications and adverse effects of the products, and the smoker’s preferences.

Initial supply of the prescribed smoking-cessation therapy should be sufficient to last only 2 weeks after the target stop date. A second prescription should be issued only if the smoker demonstrates a continuing attempt to stop smoking.

If an attempt to stop smoking is unsuccessful, the NHS should not normally fund a further attempt within 6 months.

**Cautions**

Severe or unstable cardiovascular disease (including hospitalisation for severe arrhythmias, recent myocardial infarction, or recent cerebrovascular 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, exercise may increase absorption and side-effects, skin disorders (patches should not be placed on broken skin).

**Hepatic impairment**

Manufacturers advise caution in moderate to severe hepatic impairment.

**Renal impairment**

Manufacturers advise caution in severe renal impairment.

**Pregnancy**

Use only if smoking cessation without nicotine replacement therapy fails; intermittent therapy preferred but avoid liquorice-flavoured nicotine products.

**Breast-feeding**

Present in milk; intermittent therapy preferred.

**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 changes; with patches or lozenges, sleep disturbances, nightmares, chest pain; with gum or lozenges, mouth ulceration, increased salivation; with gum, lozenge, sublingual tablets, or inhalator, hiccups, throat irritation.

**Indication and dose**

See under preparations, below.

Nicorette® (McNeil)

**Nicorette Microtab** (sublingual), nicotine (as a cyclodextrin complex) 2 mg, net price starter pack of 2 × 15-tablet discs with dispenser = £3.99; refill pack of 7 × 15-tablet discs = £11.12. Label: 26

**Dose**

- **By sublingual administration**

  **Child 12–18 years** individuals smoking 20 cigarettes or less daily, 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, 4 mg each hour. Max. 80 mg daily; treatment continued for up to 8 weeks followed by gradual reduction over 4 weeks; review treatment if abstinence not achieved within 3 months.

**Nicorette 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, freshmint, and icy white flavours.

**Dose**

- **Smoking cessation**

  **Child 12–18 years** 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 gum; max. 15 pieces of 4-mg gum daily; treatment continued for up to 8 weeks followed by gradual reduction over 4 weeks; review treatment if abstinence not achieved within 3 months.

**Child 12–18 years** chew one piece when urge to smoke occurs between smoking episodes (chew gum until taste becomes strong, then rest gum between cheek and gum, when taste fades start chewing again); 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.
BNFC 2009

4.10 Drugs used in substance dependence

**NICOTINE (continued)**

**Nicorette patches**, self-adhesive, all 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**

- **By transdermal route**

  **Child 12–18 years** apply on waking to dry, 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 2 weeks; review treatment if abstinence not achieved within 3 months—further courses may be given if considered beneficial

**Nicorette Invisi patches**, self-adhesive, beige, nicotine, '10 mg' patch (releasing approx. 10 mg/16 hours), net price £7 = £14.83; '15 mg' patch (releasing approx. 15 mg/16 hours), 7 = £14.83, '25 mg' patch (releasing approx. 25 mg/16 hours), 7 = £14.83

**Dose**

**Smoking cessation**

- **By transdermal route**

  **Child 12–18 years** apply on waking to dry, 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); individuals smoking 10 or more cigarettes daily, initially '25-mg' patch for 16 hours daily for 8 weeks then if abstinence achieved '15-mg' patch for 16 hours daily for 2 weeks then '10-mg' patch for 16 hours daily for 2 weeks; review treatment if abstinence not achieved within 3 months—further courses may be given if considered beneficial

**Note** Patients using the '25-mg' patch who experience excessive side-effects that do not resolve within a few days should change to '15-mg' patch for the remainder of the initial 8-week course before switching to the '10-mg' patch for the final 4 weeks

**Nicorette nasal spray**, nicotine 500 micrograms/ metered spray, net price 200-spray unit = £12.26

**Dose**

**Smoking cessation**

- **By intranasal route**

  **Child 12–18 years** apply 1 spray into each nostril as required to max. twice an hour for 16 hours daily (max. 64 sprays daily) for 8 weeks, then reduce gradually over next 4 weeks (reduce by half at end of first 2 weeks, stop altogether at end of next 2 weeks); review treatment if abstinence not achieved within 3 months

**Nicorette inhalator** (nicotine-impregnated plug for use in inhalator mouthpiece), nicotine 10 mg/cartridge, net price 6-cartridge (starter) pack = £3.99, 42-cartridge (refill) pack = £12.82

**Dose**

**Smoking cessation**

- **By inhalation**

  **Child 12–18 years** inhale when urge to smoke occurs; initially use between 6 and 12 cartridges daily for up to 8 weeks, then reduce gradually over 4 weeks (reduce by half over first 2 weeks, stop altogether at end of next 2 weeks); review treatment if abstinence not achieved within 3 months

**Nicoretine®** (Novartis Consumer Health)

**Chewing gum**, sugar-free, nicotine 2 mg, net price pack of 12 = £1.71, pack of 24 = £3.01, pack of 96 = £8.26; 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**

- **By mouth**

  **Child 12–18 years** 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; review treatment if abstinence not achieved within 3 months

**Nicoretine 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 = £1.99, pack of 36 = £4.95, pack of 96 = £10.60. Label: 24

**Excipients** include aspartame (section 9.4.1)

**Dose**

**Smoking cessation**

- **By mouth**

  **Child 12–18 years** 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 2-mg strength; max. 30 mg daily; withdraw gradually; review treatment if abstinence not achieved within 3 months

**TTS Patches**, self-adhesive, all yellowish-ochre, nicotine, '10 mg' patch (releasing approx. 7 mg/24 hours), net price 7 = £9.12; '20 mg' patch (releasing approx. 14 mg/24 hours), net price 2 = £2.57, 7 = £9.40; '30 mg' patch (releasing approx. 21 mg/24 hours), net price 2 = £2.85, 7 = £9.97, 21 = £24.51

**Dose**

**Smoking cessation**

- **By transdermal route**

  **Child 12–18 years** apply to dry, non-hairy skin on trunk or upper arm, removing after 24 hours and sitting replacement patch on a different area (avoid using the same area for several days); individuals smoking less than 20 cigarettes daily, initially '20 mg' patch daily; individuals smoking more than 20 cigarettes daily should use the 4-mg strength; max. 30 mg daily; withdraw gradually; review treatment if abstinence not achieved within 3 months
NiQuitin® (GSK Consumer Healthcare)

Chewing gum, sugar-free, mint-flavour, nicotine
2 mg (white), net price pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55; 4 mg (yellow), pack of 12 = £1.71, pack of 24 = £2.85, pack of 96 = £8.55

Dose

Smoking cessation

• By mouth

Child 12–18 years initially chew 1 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; max. 15 pieces daily; withdraw gradually; review treatment if abstinence not achieved within 3 months

Smoking reduction

• By mouth

Child 12–18 years suck 1 lozenge when urge to smoke occurs between smoking episodes (max. 15 lozenges 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 a smoking-reduction regimen

Temporary abstinence

• By mouth

Child 12–18 years suck 1 lozenge every 1–2 hours when urge to smoke occurs between smoking episodes; max. 15 pieces daily; review treatment if unable to undertake permanent quit attempt within 6 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

• By mouth

Child 12–18 years initially suck 1 lozenge every 1–2 hours when urge to smoke occurs (max. 15 lozenges daily) for 6 weeks, then 1 lozenge every 2–4 hours for 3 weeks, then 1 lozenge every 4–8 hours for 3 weeks; withdraw gradually; review treatment if abstinence not achieved within 3 months

Smoking reduction

• By mouth

Child 12–18 years suck 1 lozenge when urge to smoke occurs between smoking episodes (max. 15 lozenges 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 a smoking-reduction regimen

Temporary abstinence

• By mouth

Child 12–18 years suck 1 lozenge every 1–2 hours when urge to smoke occurs between smoking episodes (max. 15 lozenges daily); review treatment if unable to undertake permanent quit attempt within 6 months

Note Also available as a clear patch

Patches, self-adhesive, pink/beige, nicotine ‘7 mg’ patch (releasing approx. 7 mg/24 hours), net price 7 = £9.97; ‘14 mg’ patch (releasing approx. 14 mg/24 hours), 7 = £9.97; ‘21 mg’ patch (releasing approx. 21 mg/24 hours), 7 = £9.97, 14 = £18.79

Note Patients using the ‘21-mg’ patch who experience excessive side-effects, which do not resolve within a few days, should change to ‘14-mg’ patch for the remainder of the initial 6 weeks before switching to the ‘7-mg’ patch for the final 2 weeks

Dose

Smoking cessation

• By transdermal route

Child 12–18 years apply on waking to dry, non-hairy skin, removing after 24 hours and siting replacement patch on different area (avoid using same area for 7 days); individuals smoking 10 or more cigarettes daily, initially ‘21-mg’ patch daily for 6 weeks then ‘14-mg’ patch daily for 2 weeks then ‘7-mg’ patch daily for 2 weeks. Individuals smoking less than 10 cigarettes daily, initially ‘14-mg’ patch daily for 6 weeks then ‘7-mg’ patch daily for 2 weeks; review treatment if abstinence not achieved within 3 months

Note Patients using the ‘21-mg’ patch who experience excessive side-effects, which do not resolve within a few days, should change to ‘14-mg’ patch for the remainder of the initial 6 weeks before switching to the ‘7-mg’ patch for the final 2 weeks

4.11 Drugs for dementia

Classification not used in BNF for Children.
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  anthrax, p. 357
  bacterial infections (summary of treatment and prophylaxis), p. 298–308
  Lyme disease, p. 312
  MRSA infections, p. 310
  oral infections, p. 297 and p. 302
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.

<table>
<thead>
<tr>
<th>Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthrax</td>
</tr>
<tr>
<td>Cholera</td>
</tr>
<tr>
<td>Diphtheria</td>
</tr>
<tr>
<td>Dysentery (amoebic or bacillary)</td>
</tr>
<tr>
<td>Encephalitis, acute</td>
</tr>
<tr>
<td>Food poisoning</td>
</tr>
<tr>
<td>Haemorrhagic fever (viral)</td>
</tr>
<tr>
<td>Hepatitis, viral</td>
</tr>
<tr>
<td>Leprosy</td>
</tr>
<tr>
<td>Leptospirosis</td>
</tr>
<tr>
<td>Malaria</td>
</tr>
<tr>
<td>Measles</td>
</tr>
<tr>
<td>Meningitis</td>
</tr>
<tr>
<td>Meningococcal septicaemia (without meningitis)</td>
</tr>
<tr>
<td>Mumps</td>
</tr>
<tr>
<td>Ophthalmia neonatorum</td>
</tr>
<tr>
<td>Paratyphoid fever</td>
</tr>
<tr>
<td>Plague</td>
</tr>
<tr>
<td>Poliomyelitis, acute</td>
</tr>
<tr>
<td>Rabies</td>
</tr>
<tr>
<td>Relapsing fever</td>
</tr>
<tr>
<td>Rubella</td>
</tr>
<tr>
<td>Scarlet fever</td>
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<tr>
<td>Smallpox</td>
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<tr>
<td>Tetanus</td>
</tr>
<tr>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Typhoid fever</td>
</tr>
<tr>
<td>Typhus</td>
</tr>
<tr>
<td>Whooping cough</td>
</tr>
<tr>
<td>Yellow fever</td>
</tr>
</tbody>
</table>

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

5.1.1 Penicillins
5.1.2 Cephalosporins, carbapenems, and other beta-lactams
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
5.1.12 Quinolones
5.1.13 Urinary-tract infections

Choice of a suitable drug

Before selecting an antibacterial the clinician must first consider two factors—the child and the known or likely causative organism. Factors related to the child 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, and, if an adolescent 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. The principles involved in selection of an antibacterial must allow for a number of variables including age, changing renal and hepatic function, increasing bacterial resistance, and new information on side-effects. Duration of therapy, dosage, and route of administration depend on site, type and severity of infection and response.

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 paediatric infectious diseases specialist.
Before starting therapy

The following principles 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 infections);
- Samples should be taken for culture and sensitivity testing whenever possible; ‘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 often 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 (e.g. in neonates and young children). 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.

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. A sample should always be taken for bacteriology in the case of severe oral infection.

Oral infections which may require antibacterial treatment include acute periapical or periodontal abscess, cellulitis, acutely created oral-antral communication (and acute sinusitis), severe pericoronitis, localised osteitis, acute necrotising ulcerative gingivitis, and destructive 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. Certain rarer infections including bacterial sialadenitis, osteomyelitis, actinomycosis, and infections involving fascial 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 or resistant oral infections.

See also Penicillins (section 5.1.1), Cephalosporins (section 5.1.2.1), 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.

Switching from parenteral to oral treatment The ongoing parenteral administration of an antibacterial should be reviewed regularly. In older children it may be possible to switch to an oral antibacterial; in neonates and infants this should be done more cautiously because of the relatively high incidence of bacteraemia and the possibility of variable oral absorption.

Prophylaxis Infections for which antibacterial prophylaxis is useful are listed in Table 2. In most situations, only a short course of prophylactic antibacterial is needed. Longer-term antibacterial prophylaxis is appropriate in specific indications such as vesico-ureteric reflux

### Table 1. Summary of antibacterial therapy

<table>
<thead>
<tr>
<th>Infection</th>
<th>Antibacterial Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastro-intestinal system</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Gastro-enteritis</strong></td>
<td>Antibacterial not usually indicated. Frequently self-limiting and may not be bacterial</td>
</tr>
<tr>
<td><strong>Campylobacter enteritis</strong></td>
<td>Erythromycin(^1) or ciprofloxacin. Frequently self-limiting; treat severe infection.</td>
</tr>
<tr>
<td><strong>Salmonella</strong></td>
<td>Ciprofloxacin or cefotaxime. Treat invasive or severe infection; treat less severe infection in those at risk of developing invasive infection (e.g. immunocompromised, haemoglobinopathy, or child under 3 months).</td>
</tr>
<tr>
<td><strong>Shigellosis</strong></td>
<td>Azithromycin [unlicensed indication] or ciprofloxacin. Antibacterial not indicated for mild cases. Amoxicillin or trimethoprim may be used if organism sensitive.</td>
</tr>
<tr>
<td><strong>Typhoid fever</strong></td>
<td>Ciprofloxacin or cefotaxime or ceftriaxone. Chloramphenicol may be an alternative; 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 disease caused by multiple-antibacterial-resistant organisms.</td>
</tr>
<tr>
<td><strong>Clostridium difficile infection</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Necrotising enterocolitis in neonates</strong></td>
<td>Benzylpenicillin + gentamicin + metronidazole or amoxicillin(^2) + gentamicin + metronidazole or amoxicillin(^2) + cefotaxime + metronidazole.</td>
</tr>
</tbody>
</table>

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1. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.

2. Where amoxicillin is suggested ampicillin may be used.
Peritonitis
A cephalosporin (or amoxicillin + gentamicin) + metronidazole

Peritoneal dialysis-associated peritonitis
Either vancomycin + ceftazidime 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
Flucloxacillin (or benzylpenicillin if symptoms less severe) + gentamicin
Substitute flucloxacillin (or benzylpenicillin) with vancomycin + rifampicin if cardiac prostheses present, or if penicillin-allergic, or if meticillin-resistant Staphylococcus aureus suspected

Endocarditis caused by staphylococci
Flucloxacillin (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 flucloxacillin add rifampicin for at least 2 weeks

Endocarditis caused by streptococci (e.g. viridans streptococci)
Benzylpenicillin (or vancomycin1 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 intra-cardiac 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)
Amoxicillin2 (or vancomycin1 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)
Amoxicillin2 (or ceftriaxone if amoxicillin-resistant) + gentamicin
Treat for 4 weeks (6 weeks for prosthetic valve endocarditis); stop gentamicin after 2 weeks

Respiratory system

Haemophilus influenzae epiglottitis
Cefotaxime or ceftriaxone or chloramphenicol

Uncomplicated community-acquired pneumonia
Neonate and child under 6 months, treat as for severe community acquired pneumonia of unknown aetiology
Child 6 months–5 years, oral amoxicillin2 or oral erythromycin3
Child 5–18 years, oral erythromycin3 (or oral amoxicillin2 if Streptococcus pneumoniae suspected)
Add flucloxacillin if staphylococci suspected, e.g. in influenza or measles; 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; use erythromycin3 if atypical pathogens suspected (more common in children over 5 years) or if penicillin-allergic

Severe community-acquired pneumonia of unknown aetiology
Neonate, benzylpenicillin + gentamicin
Child 1 month–18 years, cefuroxime or co-amoxiclav (or benzylpenicillin if lobar or Streptococcus pneumoniae suspected)
Use erythromycin3 if atypical pathogens such as mycoplasma (more common in children under 5 years) or chlamydia suspected or if penicillin allergic; in pneumococcal infection add vancomycin to beta-lactam antibacterial if organism highly penicillin- and cephalosporin-resistant; add flucloxacillin if staphylococci suspected; treat for 10 days (14–21 days if staphylococci, legionella, or Gram-negative enteric bacilli suspected)

Pneumonia possibly caused by atypical pathogens
Erythromycin3
Severe Legionella infections may require addition of rifampicin; tetracycline is an alternative for chlamydial and mycoplasma infections in children over 12 years; treat for at least 14 days (14–21 days for legionella)

1. Where vancomycin is suggested teicoplanin may be used.
2. Where amoxicillin is suggested ampicillin may be used.
3. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.
Hospital-acquired pneumonia

Early-onset infection (less than 5 days after admission to hospital), treat as for severe community-acquired pneumonia of unknown aetiology; if life-threatening infection or if resistant organisms suspected, treat as for late-onset hospital-acquired pneumonia

Late-onset infection (more than 5 days after admission to hospital), an antipseudomonal penicillin (e.g. piperacillin with tazobactam) or a broad-spectrum cephalosporin (e.g. ceftazidime) or another antipseudomonal beta-lactam

Treatment for 7 days (longer if pseudomonas confirmed); add vancomycin if MRSA suspected; add an aminoglycoside for severe illness caused by *Pseudomonas aeruginosa*.

Cystic fibrosis

Staphylococcal lung infection in cystic fibrosis

Fluclaxacillin (or erythromycin1 or clindamycin if penicillin-allergic)
In severe exacerbation use fluclaxacillin or a broad-spectrum cephalosporin (e.g. cefuroxime); substitute with vancomycin if meticillin-resistant *Staphylococcus aureus* suspected, and if necessary, add either rifampicin or sodium fusidate

*Haemophilus influenzae* lung infection in cystic fibrosis

Amoxicillin or a broad-spectrum cephalosporin
In severe exacerbation use a third-generation cephalosporin (e.g. cefotaxime)

Pseudomonal lung infection in cystic fibrosis

Ciprofloxacin + nebulised colistin
In severe exacerbation treat with a parenteral aminoglycoside + an antipseudomonal beta-lactam antibacterial, and continue nebulised antibacterial

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. 309 for dose) before urgent transfer to hospital; cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol may be used if history of immediate hypersensitivity reaction to penicillins or to cephalosporins
- Consider adjunctive treatment with dexamethasone (section 6.3.2) starting before or with first dose of antibacterial; avoid dexamethasone in septic shock, suspected meningococcal septicaemia, or if immunocompromised, or in meningitis following surgery
- In hospital, if aetiology unknown: *Neonate and Child 1–3 months*, cefotaxime + amoxicillin3
  *Child 3 months–18 years*, cefotaxime

Meningitis caused by group B streptococcus

Benzylpenicillin + gentamicin or cefotaxime alone
Treat for 14 days

Meningitis caused by meningococci

Benzylpenicillin or cefotaxime
Treat for at least 5 days; substitute chloramphenicol if history of anaphylaxis to penicillin or to cephalosporins. To eliminate nasopharyngeal carriage 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 early adjunctive treatment with dexamethasone (but may reduce penetration of vancomycin into cerebrospinal fluid; section 6.3.2)

Meningitis caused by *Haemophilus influenzae*

Cefotaxime
Treat for at least 10 days; substitute chloramphenicol if history of anaphylaxis to penicillin or to cephalosporins or if organism resistant to cefotaxime. Consider early adjunctive treatment with dexamethasone (section 6.3.2). For *H. influenzae* type b give rifampicin for 4 days before hospital discharge (see Table 2, section 5.1)

Meningitis caused by *Listeria*

Amoxicillin3 + gentamicin
Treat for at least 14 days. Consider stopping gentamicin after one week

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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.
Urinary tract

Urinary-tract infection

Child under 3 months of age, i/v amoxicillin\(^1\) + gentamicin or i/v cephalosporin alone

Child over 3 months of age with uncomplicated lower urinary-tract infection, trimethoprim or nitrofurantoin or oral cephalosporin (e.g. cefalexin) or amoxicillin\(^1\)

\(^1\) Treat for 3 days. Re-assess child if unwell 24–48 hours after initial assessment. Use amoxicillin only if organism sensitive

Child over 3 months of age with acute pyelonephritis, a cephalosporin or co-amoxiclav

Treat for 7–10 days

Genital system

Syphilis

Neonatal congenital syphilis, benzylpenicillin

Treat for 10 days. Also consider treating neonates with suspected congenital syphilis whose mothers were treated inadequately for syphilis, or whose mothers were treated for syphilis in the 4 weeks before delivery, or whose mothers were treated with non-penicillin antibacterials for syphilis

Other syphilis infections, benzathine benzylpenicillin [unlicensed] or doxycycline or erythromycin

Doxycycline is an option in children over 12 years. Treat early syphilis (infection of less than 2 years) with benzathine benzylpenicillin as a single dose (repeat dose after 7 days for females 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

Child under 12 years, ceftriaxone

Child 12–18 years, 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

Child under 12 years, erythromycin for 14 days

Child 12–18 years, single dose of azithromycin or doxycycline for 7 days

Contact tracing recommended

Pelvic inflammatory disease

Child 12–18 years, doxycycline + metronidazole + i/m ceftriaxone

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

Blood

Septicaemia: Initial empirical therapy

Neonate less than 48 hours old, benzylpenicillin + gentamicin or amoxicillin\(^1\) + cefotaxime

Neonate more than 48 hours old, flucloxacillin + gentamicin or amoxicillin\(^1\) + cefotaxime

Child 1 month–18 years, community-acquired septicaemia, aminoglycoside + amoxicillin\(^1\) or cefotaxime alone or ceftriaxone alone

Use aminoglycoside + broad spectrum antipseudomonal beta-lactam antibacterial if pseudomonas suspected; add metronidazole if anaerobic infection suspected; add flucloxacillin or vancomycin\(^2\) if Gram-positive infection suspected

Child 1 month–18 years, hospital-acquired septicaemia, a broad-spectrum antipseudomonal beta-lactam antibacterial (e.g. piperacillin with tazobactam, Timentin\(^c\), ceftazidime, imipenem [with cilastatin as Primaxin\(^c\) or meropenem] or meropenem)

Add aminoglycoside if pseudomonas suspected, or if multiple-resistant organisms suspected, or if severe sepsis; add vancomycin\(^2\) if meticillin-resistant Staphylococcus aureus suspected; add metronidazole to broad-spectrum cephalosporin if anaerobic infection suspected

\(^1\) Where amoxicillin is suggested ampicillin may be used.

\(^2\) Where vancomycin is suggested teicoplanin may be used.
Septicaemia related to vascular catheter
Vancomycin\(^1\)
Add a broad-spectrum antipseudomonal beta-lactam if Gram-negative sepsis suspected, especially in the immunocompromised. Consider removing vascular catheter, particularly if infection caused by *Staphylococcus aureus, pseudomonas,* or *candida*

Meningococcal septicaemia
Benzylenicillin or cefotaxime
If meningococcal disease suspected, general practitioners advised to give a single dose of benzylpenicillin before urgent transfer to hospital (see under Benzylenicillin, section 5.1.1.1); cefotaxime (section 5.1.2) may be an alternative in penicillin allergy; chloramphenicol may be used if history of immediate hypersensitivity to penicillin or to cephalosporins. To eliminate nasopharyngeal carriage give rifampicin or ciprofloxacin before hospital discharge (see Table 2, section 5.1)

**Musculoskeletal system**

Osteomyelitis
Flucloxacillin or clindamycin if penicillin-allergic (*or vancomycin*\(^1\) if resistant *Staphylococcus epidermidis* or metcillin-resistant *Staph. aureus*). Treat acute infection for 4–6 weeks and chronic infection for at least 12 weeks; if child under 5 years of age and not immunised against *Haemophilus influenzae*, add cefotaxime or ceftriaxone to flucloxacillin; combine vancomycin\(^1\) with either fusidic acid or rifampicin if prostheses present or if life-threatening condition

Septic arthritis
Flucloxacillin or clindamycin if penicillin-allergic (*or vancomycin*\(^1\) if resistant *Staphylococcus epidermidis* or metcillin-resistant *Staph. aureus*), and if patient under 5 years of age and not immunised against *Haemophilus influenzae*. Use cefotaxime + flucloxacillin or ceftriaxone + flucloxacillin. Combine vancomycin\(^1\) with either fusidic acid or rifampicin if prosthesis present or if life-threatening condition

**Eye**

Purulent conjunctivitis
*Neonate*, neomycin eye drops

*Child 1 month–18 years*, chloramphenicol or gentamicin eye-drops

Congenital chlamydial conjunctivitis
Erythromycin (by mouth)
Treat for 14 days

**Ear, nose, and oropharynx**

Pericoronitis
Metronidazole or amoxicillin
Antibacterial required only in presence of systemic features of infection or of trismus or persistent swelling despite local treatment; treat for 3 days or until symptoms resolve

Acute necrotising ulcerative gingivitis
Metronidazole or amoxicillin
Antibacterial required only if systemic features of infection; treat for 3 days or until symptoms resolve

Periapical or periodontal abscess
Amoxicillin or metronidazole
Antibacterial required only in severe disease with cellulitis or if systemic features of infection; treat for 5 days

Periodontitis
Metronidazole or doxycycline
Antibacterial required for severe disease or disease unresponsive to local treatment; doxycycline is an option in children over 12 years

Throat infections
Phenoxybenzin (or erythromycin\(^2\) if penicillin-allergic)
Most throat infections are caused by viruses and many do not require antibacterial therapy. Consider antibacterial if history of valvular heart disease, if marked systemic upset, if peritonsillar cellulitis or abscess, or if at increased risk from acute infection (e.g. in immunosuppression, cystic fibrosis); prescribe antibacterial for beta-haemolytic streptococcal pharyngitis; treat for 10 days. Avoid amoxicillin if possibility of glandular fever, see section 5.1.1.3. Initial parenteral therapy (in severe infection) with benzylpenicillin, then oral therapy with phenoxybenzin or amoxicillin\(^3\).

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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.
Sinusitis
Amoxicillin\(^1\) or erythromycin\(^2\)
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 immunosuppression, cystic fibrosis). Treat for 7 days. Consider oral co-amoxiclav if no improvement after 48 hours. Initial parenteral therapy with co-amoxiclav or cefuroxime may be required in severe infections

Otitis externa
Flucloxacillin (or erythromycin\(^4\) if penicillin-allergic)
Consider systemic antibacterial if spreading cellulitis or child systemically unwell. Use ciprofloxacin (or an aminoglycoside) if pseudomonas suspected, see section 12.1.1

Otitis media
Amoxicillin\(^1\) (or erythromycin\(^3\) 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); consider co-amoxiclav if no improvement after 48 hours; initial parenteral therapy in severe infection with co-amoxiclav or cefuroxime

Skin
Impetigo
Topical fusidic acid (or mupirocin if meticillin-resistant *Staphylococcus aureus*); oral flucloxacillin or erythromycin\(^4\) if widespread
Topical 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 phenoxymerpenicillin to flucloxacillin if streptococcal infection suspected

Erysipelas
Phenoxymerpenicillin (or erythromycin\(^3\) if penicillin-allergic)
Add flucloxacillin to phenoxymerpenicillin if staphylococcus suspected; substitute benzylpenicillin for phenoxymerpenicillin if parenteral treatment required

Cellulitis
Benzylpenicillin + flucloxacillin (or erythromycin\(^3\) alone if penicillin-allergic)
Substitute phenoxymerpenicillin for benzylpenicillin if oral treatment appropriate; discontinue flucloxacillin if streptococcal infection confirmed. Substitute treatment with broad-spectrum antibacterials if patients at risk from anaerobic or Gram-negative infections (e.g. use co-amoxiclav alone for facial infection, orbital infection, or infection caused by animal or human bites. Use ceftazidime + clindamycin in immunocompromised patients)

Animal and human bites
Co-amoxiclav alone (or clindamycin if penicillin-allergic)
Cleanse wound thoroughly; for tetanus-prone wound, give human tetanus immunoglobulin (with adsorbed diphtheria [low dose] and tetanus vaccine if necessary, according to immunisation history and risk of infection), see under Tetanus Vaccines, section 14.4; consider rabies prophylaxis (section 14.4) for bites from animals in endemic countries; assess risk of blood-borne viruses

Acne—see section 13.6
Paronychia or ‘septic spots’ in neonate
Flucloxacillin
Add aminoglycoside if systemically unwell

Surgical wound infection
Flucloxacillin or co-amoxiclav

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1. Where amoxicillin is suggested ampicillin may be used.
2. Where erythromycin is suggested another macrolide (e.g. azithromycin or clarithromycin) may be used.
**Prevention of secondary case of invasive group A streptococcal infection**

Phenoxymethylpenicillin by mouth

**Neonate** 12.5 mg/kg (max. 62.5 mg) every 6 hours for 10 days

**Child 1 month–1 year** 62.5 mg every 6 hours for 10 days

**Child 1–6 years** 125 mg every 6 hours for 10 days

**Child 6–12 years** 250 mg every 6 hours for 10 days

**Child 12–18 years** 250–500 mg every 6 hours for 10 days

If child penicillin allergic, either

- **erythromycin by mouth**
  - **Child 1 month–2 years** 125 mg every 6 hours for 10 days
  - **Child 2–8 years** 250 mg every 6 hours for 10 days
  - **Child 8–18 years** 250–500 mg every 6 hours for 10 days

- **azithromycin by mouth** [unlicensed indication]
  - **Child 6 months–12 years** 12 mg/kg (max. 500 mg) once daily for 5 days
  - **Child 12–18 years** 500 mg once daily for 5 days

**Prevention of secondary case of meningococcal meningitis**

Rifampicin by mouth

**Neonate** 5 mg/kg every 12 hours for 2 days

**Child 1 month–1 year** 5 mg/kg every 12 hours for 2 days

**Child 1–12 years** 10 mg/kg (max. 600 mg) every 12 hours for 2 days

**Child 12–18 years** 600 mg every 12 hours for 2 days

or

- **Ciprofloxacin by mouth** [unlicensed indication]
  - **Child 2–5 years** 125 mg as a single dose
  - **Child 5–12 years** 250 mg as a single dose
  - **Child 12–18 years** 500 mg as a single dose

or

- **Ceftriaxone by intramuscular injection** [unlicensed indication] (preferred if pregnant)
  - **Child 1 month–12 years** 125 mg as a single dose
  - **Child 12–18 years** 250 mg as a single dose

**Prevention of secondary case of Haemophilus influenzae type b disease**

Rifampicin by mouth

**Child 1–3 months** 10 mg/kg once daily for 4 days

**Child 3 months–12 years** 20 mg/kg (max. 600 mg) once daily for 4 days

**Child 12–18 years** 600 mg once daily for 4 days

**Prevention of secondary case of diphtheria in non-immune patient**

Erythromycin by mouth

**Child 1 month–2 years** 125 mg every 6 hours for 7 days

**Child 2–8 years** 250 mg every 6 hours for 7 days

**Child 8–18 years** 500 mg every 6 hours for 7 days

Treat for further 10 days if nasopharyngeal swabs positive after first 7 days’ treatment

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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.
Prevention of secondary case of pertussis in non-immune patient or partially immune patient
Erythromycin \(^1\) by mouth

- **Child 1 month–2 years**: 125 mg every 6 hours for 7 days
- **Child 2–8 years**: 250 mg every 6 hours for 7 days
- **Child 8–18 years**: 250–500 mg every 6 hours for 7 days

*Note*: Pertussis vaccine inappropriate for outbreak since 3 injections required for protection

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Prevention of pneumococcal infection in asplenia or in patients with sickle cell disease
Phenoxymethylpenicillin by mouth

- **Child 1 month–6 years**: 125 mg every 12 hours
- **Child 6–12 years**: 250 mg every 12 hours
- **Child 12–18 years**: 500 mg every 12 hours

If cover also needed for *H. influenzae* in child give amoxicillin instead

- **Child 1 month–5 years**: 125 mg every 12 hours
- **Child 5–12 years**: 250 mg every 12 hours
- **Child 12–18 years**: 500 mg every 12 hours

*Note*: Antibiotic prophylaxis is not fully reliable; for vaccines in asplenia see p. 727

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Prevention of *Staphylococcus aureus* lung infection in cystic fibrosis
Flucloxacillin by mouth

- **Child 1 month–18 years**: 12.5–25 mg/kg (max. 1 g) 4 times daily (total daily dose may alternatively be given in 2 divided doses)

*Use cefradine (section 5.1.2) if flucloxacillin cannot be used*

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Prevention of tuberculosis in susceptible close contacts or those who have become tuberculin positive\(^2\)
Isoniazid for 6 months

- **Neonate**: 5 mg/kg daily
- **Child 1 month–12 years**: 5 mg/kg daily (max. 300 mg daily)
- **Child 12–18 years**: 300 mg daily

*or* isoniazid + rifampicin for 3 months

- **Child 1 month–12 years**: isoniazid 5 mg/kg daily (max. 300 mg daily) + rifampicin 10 mg/kg daily (max. 450 mg daily if body-weight less than 50 kg; max. 600 mg daily if body-weight over 50 kg)
- **Child 12–18 years**: isoniazid 300 mg daily + rifampicin 600 mg daily (rifampicin 450 mg daily if body-weight less than 50 kg)

*or* (if isoniazid-resistant tuberculosis) rifampicin for 6 months

- **Child 1 month–12 years**: 10 mg/kg daily (max. 450 mg daily if body-weight less than 50 kg; max. 600 mg daily if body-weight over 50 kg)
- **Child 12–18 years**: 600 mg daily (450 mg daily if body-weight less than 50 kg)

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1. Where erythromycin is suggested another macroclide (e.g. azithromycin or clarithromycin) may be used.
2. 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
Prevention of gas-gangrene in high lower-limb amputations or following major trauma

i/v benzylpenicillin

Child 1 month–12 years 25 mg/kg (max. 600mg) every 6 hours for 5 days
Child 12–18 years 300–600 mg every 6 hours for 5 days
or if penicillin-allergic i/v or oral metronidazole

Child 1 month–12 years 7.5mg/kg (max. 500mg) every 8 hours for 5 days
Child 12–18 years 400–500 mg every 8 hours for 5 days

Prevention of infection in gastro-intestinal procedures

Operations on stomach or oesophagus
Single dose\(^1\) of i/v gentamicin or i/v cefuroxime

Open biliary surgery
Single dose\(^1\) of i/v cefuroxime + i/v metronidazole\(^2\) or i/v gentamicin + i/v metronidazole\(^2\)

Resections of colon and rectum, and resections in inflammatory bowel disease, and appendicectomy
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

Management of fractures
Single dose\(^1\) of i/v cefuroxime or i/v flucloxacillin
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 obstetric surgery

Termination of pregnancy
Single dose\(^4\) 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
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*

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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
Prevention of endocarditis

NICE Guidance

Antimicrobial prophylaxis against infective endocarditis in children and adults 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.

While 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.

Joint prostheses 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 antibacterial prophylaxis for dental treatment.

The Working Party considers that it is unacceptable to expose patients to the adverse effects of antibacterials when there is no evidence that such prophylaxis is of any benefit, but that those who develop any intercurrent infection require prompt treatment with antibacterials 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.

1. 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.

2. 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
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 antibacterial 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.

5.1.1 Penicillins

5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin

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

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. 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. Children 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 a child 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. 319).

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.

5.1.1.1 Benzylpenicillin and phenoxymethylpenicillin

Benzylpenicillin (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) in children. It is also used in combination with gentamicin for the empirical treatment of sepsis in neonates less than 48 hours old. 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 gastro-intestinal tract is low; therefore it must be given by injection.

**Benzathine benzylpenicillin** (available from ‘special-order’ manufacturers or specialist importing companies, see p. 943) is used for the treatment of early syphilis and late latent syphilis.

**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 infections 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 dentoalveolar abscess.

### BENZYLPENCILLIN SODIUM
(Penicillin G)

**Cautions**
- history of allergy; false-positive urinary glucose (if tested for reducing substances);
- interactions: Appendix 1 (penicillins)

**Renal impairment**
- neurotoxicity—high doses may cause convulsions. Estimated glomerular filtration rate 10–50 mL/minute/1.73 m², use normal dose every 8–12 hours; estimated glomerular filtration rate less than 10 mL/minute/1.73 m² use normal dose every 12 hours

**Pregnancy**
- not known to be harmful

**Breast-feeding**
- trace amounts in breast milk—not known to be harmful but be alert for hypersensitivity in infant

**Contra-indications**
- penicillin hypersensitivity

**Side-effects**
- hypersensitivity reactions including urticaria, fever, joint pains, rashes, angioedema, anaphylaxis, serum sickness-like reactions; 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)

### Indication and dose

#### Mild to moderate susceptible infections (including throat infections, otitis media, pneumonia, cellulitis, neonatal sepsis, Table 1, section 5.1)
- **By intramuscular injection or by slow intravenous injection or infusion** (intravenous route recommended in neonates and infants)

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm neonate and neonate under 7 days</td>
<td>25 mg/kg every 12 hours; dose doubled in severe infection</td>
</tr>
<tr>
<td>Neonate 7–28 days</td>
<td>25 mg/kg every 8 hours; dose doubled in severe infection</td>
</tr>
</tbody>
</table>

### Endocarditis (combined with another antibacterial if necessary, see Table 1, section 5.1)
- **By slow intravenous injection or infusion**
  - **Child 1 month–18 years** 25 mg/kg every 4–6 hours (max. 2.4 g every 4 hours) in severe infection

### Meningitis, meningococcal disease
- **By slow intravenous injection or infusion**
  - **Preterm neonate and neonate** 75 mg/kg every 8 hours
  - **Child 1 month–18 years** 50 mg/kg every 4–6 hours (max. 2.4 g every 4 hours)

### Treatment or prevention of neonatal group B streptococcal infection
- **By slow intravenous injection or infusion**
  - **Preterm neonate and neonate under 7 days** 50 mg/kg every 12 hours
  - **Neonate 7–28 days** 50 mg/kg every 8 hours

### Prophylaxis in limb amputation
- **Table 2, section 5.1**
### Administration

Intravenous route recommended in neonates and infants. For *intravenous infusion*, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–30 minutes. Longer administration time is particularly important when using doses of 50 mg/kg (or greater) to avoid CNS toxicity.

Safe practice: Intrathecal injection of benzylpenicillin is not recommended.

### Crystapen® (Genus)

Injection, powder for reconstitution, benzylpenicillin sodium (unbuffered), net price 600-mg vial = 46p; 2-vial 'GP pack' = £1.90; 1.2-g vial = 92p

Electrolytes: Na⁺ 1.68 mmol/600-mg vial; 3.36 mmol/1.2-g vial

### PHENOXYMETHYLpenicillin

(Penicillin V)

**Cautions** see under Benzylpenicillin; interactions: Appendix 1 (penicillins)

Renal impairment: no dose adjustment required

**Contra-indications** see under Benzylpenicillin

**Side-effects** see under Benzylpenicillin

**Indication and dose**

Susceptible infections including oral infections, tonsillitis, otitis media, erysipelas, cellulitis.

- **By mouth**
  - Child 1 month–1 year: 62.5 mg 4 times daily; increased in severe infection to ensure at least 12.5 mg/kg 4 times daily
  - Child 1–6 years: 125 mg 4 times daily; increased in severe infection to ensure at least 12.5 mg/kg 4 times daily
  - Child 6–12 years: 250 mg 4 times daily; increased in severe infection to ensure at least 12.5 mg/kg 4 times daily
  - Child 12–18 years: 500 mg 4 times daily; increased in severe infection up to 1 g 4 times daily

**Phenoxymethylpenicillin** (Non-proprietary)

- **Tablets**, phenoxymethylpenicillin (as potassium salt) 250 mg, net price 28-tab pack = £1.25. Label: 9, 23
- **Oral solution**, phenoxymethylpenicillin (as potassium salt) for reconstitution with water, net price 125 mg/5 mL, 100 mL = £1.90; 250 mg/5 mL, 100 mL = £2.59. Label: 9, 23

**Dental prescribing on NHS**

Phenoxymethylpenicillin Tablets and Oral Solution may be prescribed

### 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 main 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 cholestatic jaundice see under Flucloxacillin.

**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. *Clindamycin* alone or a combination of rifampicin and sodium fusidate can be used for *skin and soft-tissue infections* caused by MRSA; a *tetracycline* is an alternative in children over 12 years of age. A *glycopeptide* (e.g. vancomycin, section 5.1.7) can be used for severe skin and soft-tissue infections associated with MRSA. 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. *Linezolid* (section 5.1.7) or 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 children who cannot tolerate other antibacterials.
A glycopeptide can be used for pneumonia associated with MRSA. Linezolid or quinupristin and dalfopristin should be reserved for hospital-acquired pneumonia that has not responded to other antibacterials or for children who cannot tolerate other antibacterials.

Trimethoprim or nitrofurantoin can be used for urinary-tract infections caused by MRSA; a tetracycline is an alternative in children under 12 years of age. 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.

It is important that hospitals have infection control guidelines to minimise MRSA transmission, including policies on isolation and treatment of MRSA carriers and on hand hygiene. For eradication of nasal carriage of MRSA, see section 12.2.3.

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**FLUCLOXACILLIN**

**Cautions** see under Benzylpenicillin (section 5.1.1.1); also hepatic impairment (see CSM advice below)

**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.

**Renal impairment** use normal dose every 8 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

**Pregnancy** not known to be harmful

**Breast-feeding** trace amounts in breast milk—not known to be harmful but be alert for hypersensitivity in infant

**Contra-indications** see under Benzylpenicillin (section 5.1.1.1)

**Side-effects** see under Benzylpenicillin (section 5.1.1.1); also gastro-intestinal disturbances; very rarely hepatitis and cholestatic jaundice reported (see also CSM advice above)

**Indication and dose**

Infections due to beta-lactamase-producing staphylococci including otitis externa; adjunct in pneumonia, impetigo, cellulitis

- **By mouth**
  - Neonate under 7 days 25 mg/kg twice daily
  - Neonate 7–21 days 25 mg/kg 3 times daily
  - Neonate 21–28 days 25 mg/kg 4 times daily

- **By intramuscular injection**
  - Child 1 month–2 years 62.5–125 mg 4 times daily
  - Child 2–10 years 125–250 mg 4 times daily
  - Child 10–18 years 250–500 mg 4 times daily

- **By slow intravenous injection or by intravenous infusion**
  - Neonate under 7 days 25 mg/kg every 12 hours; may be doubled in severe infection
  - Neonate 7–21 days 25 mg/kg every 8 hours; may be doubled in severe infection
  - Neonate 21–28 days 25 mg/kg every 6 hours; may be doubled in severe infection

- **Child 1 month–18 years** 12.5–25 mg/kg every 6 hours (max. 1 g every 6 hours); may be doubled in severe infection

**Osteomyelitis** (Table 1, section 5.1), cerebral abscess, staphylococcal meningitis

- **By slow intravenous injection or by intravenous infusion**
  - Neonate under 7 days 50–100 mg/kg every 12 hours
  - Neonate 7–21 days 50–100 mg/kg every 8 hours
  - Neonate 21–28 days 50–100 mg/kg every 6 hours

- **Child 1 month–18 years** 50 mg/kg (max. 2 g) every 6 hours
Endocarditis (Table 1, section 5.1)

- By slow intravenous injection or by intravenous infusion
- Child 1 month–18 years: 50 mg/kg (max. 2 g) every 6 hours

Prevention of staphylococcal lung infection in cystic fibrosis

Table 2, section 5.1

Staphylococcal lung infection in cystic fibrosis

- By mouth
- Child 1 month–18 years: 12.5–25 mg/kg (max. 1 g) 4 times daily; total daily dose may alternatively be given in 3 divided doses

Administration for intermittent intravenous infusion, dilute reconstituted solution in Glucose 5% or Sodium Chloride 0.9% and give over 30–60 minutes; alternatively, may be given via drip tubing in Glucose 5% or Sodium Chloride 0.9% or Ringer’s Solution or Compound Sodium Lactate

Flucloxacillin (Non-proprietary)

Capsules, flucloxacillin (as sodium salt) 250 mg, net price 28 = £2.38; 500 mg, 28 = £4.30. Label: 9, 23
Brands include Floxapen®, Flucomox®, Ladoxpen®

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

Suspension (= syrup), flucloxacillin (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
Brands include Floxapen®

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

5.1.1.3 Broad-spectrum penicillins

Ampicillin is active against certain Gram-positive and Gram-negative organisms but is inactivated by penicillinases including those produced by Staphylococcus aureus and by common Gram-negative bacilli such as Escherichia coli. Ampicillin is also active against Listeria spp. and enterococci. 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 amoxicillin for the ‘blind’ treatment of infections; in particular, it should not be used for hospital patients without checking sensitivity.

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 gut. Ampicillin is well excreted in the bile and urine.

Amoxicillin (amoxycillin) is a derivative of ampicillin and has a similar antibacterial spectrum. It is better absorbed than ampicillin when given by mouth, producing higher plasma and tissue concentrations; unlike ampicillin, absorption is not affected by the presence of food in the stomach.

Amoxicillin or ampicillin are principally indicated for the treatment of community-acquired pneumonia 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). They are also used in the treatment of endocarditis and listerial meningitis. Amoxicillin may also be used for the treatment of Lyme disease [not licensed], see below.

Maculopapular rashes occur commonly with ampicillin (and amoxicillin) but are not usually related to true penicillin allergy. They often occur in children with glandular fever; broad-spectrum penicillins should not therefore be used for ‘blind’ treatment of a sore throat. Rashes are also common in children with acute or chronic lymphocytic leukaemia or in cytomegalovirus infection.

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 flucloxacillin (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. Amoxicillin [unlicensed indication], cefuroxime axetil or doxycycline are the antibacterials of choice for early Lyme disease or Lyme arthritis.
but doxycycline should only be used in children over 12 years of age. If these antibacterials are contra-indicated a macrolide (e.g. erythromycin) can be used for early Lyme disease. Intravenous administration of ceftriaxone, cefotaxime (section 5.1.2.1), or benzylpenicillin (p. 309) 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

**(Amoxycillin)**

**Cautions** see under Ampicillin; maintain adequate hydration with high doses (particularly during parenteral therapy)

**Renal impairment** risk of crystalluria with high doses (particularly during parenteral therapy) in mild to moderate impairment; reduce dose in severe impairment; rashes more common and risk of crystalluria

**Contra-indications** see under Ampicillin

**Side-effects** see under Ampicillin

**Indication and dose**

<table>
<thead>
<tr>
<th>Infection</th>
<th>By mouth</th>
<th>By intramuscular injection</th>
<th>By intravenous injection or infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptible infections including urinary-tract infections, sinusitis; <em>Haemophilus influenzae</em> infections</td>
<td><strong>Neonate under 7 days</strong> 30 mg/kg (max. 62.5 mg) twice daily; dose doubled in severe infection</td>
<td><strong>Neonate under 7 days</strong> 30 mg/kg every 12 hours; dose doubled in severe infection</td>
<td><strong>Neonate under 7 days</strong> 30 mg/kg every 12 hours; dose doubled in severe infection</td>
</tr>
<tr>
<td></td>
<td><strong>Neonate 7–28 days</strong> 30 mg/kg (max. 62.5 mg) 3 times daily; dose doubled in severe infection</td>
<td><strong>Neonate 7–28 days</strong> 30 mg/kg every 8 hours; dose doubled in severe infection</td>
<td><strong>Neonate 7–28 days</strong> 30 mg/kg every 8 hours; dose may be doubled in meningitis</td>
</tr>
<tr>
<td><strong>Child 1 month–1 year</strong> 62.5 mg 3 times daily; dose doubled in severe infection</td>
<td><strong>Child 1 month–1 year</strong> 62.5 mg 3 times daily</td>
<td><strong>Child 1 month–1 year</strong> 62.5 mg 3 times daily; dose doubled in severe infection</td>
<td><strong>Child 1 month–1 year</strong> 62.5 mg 3 times daily; dose doubled in severe infection</td>
</tr>
<tr>
<td><strong>Child 1–5 years</strong> 125 mg 3 times daily; dose doubled in severe infection</td>
<td><strong>Child 1–5 years</strong> 125 mg 3 times daily</td>
<td><strong>Child 1–5 years</strong> 125 mg 3 times daily; dose doubled in severe infection</td>
<td><strong>Child 1–5 years</strong> 125 mg 3 times daily</td>
</tr>
<tr>
<td><strong>Child 5–18 years</strong> 250 mg 3 times daily; dose doubled in severe infection</td>
<td><strong>Child 5–18 years</strong> 250 mg 3 times daily</td>
<td><strong>Child 5–18 years</strong> 250 mg 3 times daily; dose doubled in severe infection</td>
<td><strong>Child 5–18 years</strong> 250 mg 3 times daily</td>
</tr>
</tbody>
</table>

**Uncomplicated community-acquired pneumonia** (Table 1, section 5.1), invasive salmonellosis

<table>
<thead>
<tr>
<th>By mouth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child 1 month–1 year</strong> 125 mg 3 times daily</td>
<td><strong>Child 1 month–1 year</strong> 125 mg 3 times daily</td>
</tr>
<tr>
<td><strong>Child 1–5 years</strong> 250 mg 3 times daily</td>
<td><strong>Child 1–5 years</strong> 250 mg 3 times daily</td>
</tr>
<tr>
<td><strong>Child 5–18 years</strong> 500 mg 3 times daily</td>
<td><strong>Child 5–18 years</strong> 500 mg 3 times daily</td>
</tr>
</tbody>
</table>

**Listerial meningitis** (in combination with another antibacterial, Table 1, section 5.1), group B streptococcal infection, enterococcal endocarditis (in combination with another antibiotic)

<table>
<thead>
<tr>
<th>By intravenous infusion</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neonate under 7 days</strong> 50 mg/kg every 12 hours; dose may be doubled in meningitis</td>
<td><strong>Neonate under 7 days</strong> 50 mg/kg every 8 hours; dose may be doubled in meningitis</td>
</tr>
<tr>
<td><strong>Neonate 7–28 days</strong> 50 mg/kg every 8 hours; dose may be doubled in meningitis</td>
<td><strong>Child 1 month–18 years</strong> 50 mg/kg every 4–6 hours (max. 2 g every 4 hours)</td>
</tr>
</tbody>
</table>

**Otitis media**

<table>
<thead>
<tr>
<th>By mouth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child 1 month–18 years</strong> 40 mg/kg daily in 3 divided doses (max. 3 g daily in 3 divided doses)</td>
<td><strong>Child 1 month–18 years</strong> 40 mg/kg daily in 3 divided doses (max. 3 g daily in 3 divided doses)</td>
</tr>
</tbody>
</table>

**Cystic fibrosis** (treatment of asymptomatic *H. influenzae* carriage or mild exacerbations)

<table>
<thead>
<tr>
<th>By mouth</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child 1 month–1 year</strong> 125 mg 3 times daily</td>
<td><strong>Child 1–7 years</strong> 250 mg 3 times daily</td>
</tr>
<tr>
<td><strong>Child 7–18 years</strong> 500 mg 3 times daily</td>
<td><strong>Child 7–18 years</strong> 500 mg 3 times daily</td>
</tr>
</tbody>
</table>

**Helicobacter pylori eradication** section 1.3

**Administration** Displacement value may be significant when reconstituting injection, consult local guidelines. Dilute intravenous injection to a concentration of 50 mg/mL (100 mg/mL for neonates). May be further diluted with Glucose 5% or Glucose 10% or Sodium chloride 0.9% or 0.45% for intravenous infusion. Give intravenous infusion over 30 minutes when using doses over 30 mg/kg
Amoxicillin (Non-proprietary)

Capsules, amoxicillin (as trihydrate) 250 mg, net price 21 = £1.14; 500 mg, 21 = £1.56. Label: 9

Brands include Amix®, Amoramic®, Amoxicident®, Galenanamox®, 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®, Galenanamox®, 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 Capsules and Oral Suspension may be prescribed. Amoxicillin Sachets may be prescribed as Amoxicillin Oral Powder

AMPCILLIN

Cautions history of allergy; erythematous rashes common in glandular fever, cytomegalovirus infection, and acute or chronic lymphocytic leukaemia (see notes above); interactions: Appendix 1 (penicillins)

Renal impairment if estimated glomerular filtration rate less than 10 mL/minute/1.73 m² reduce dose or frequency—rashes more common

Pregnancy not known to be harmful

Breast-feeding trace amounts in breast milk—not known to be harmful but be alert for hypersensitivity in infant

Contra-indications penicillin hypersensitivity

Side-effects nausea, vomiting, diarrhoea; rashes (discontinue treatment); rarely, antibiotic-associated colitis; see also under Benzylpenicillin (section 5.1.1.1)

Indication and dose

Susceptible infections including urinary-tract infections, otitis media, sinusitis, oral infections (Table 1, section 5.1), Haemophilus influenzae infections, invasive salmonellosis

• By mouth

Neonate under 7 days 30 mg/kg (max. 62.5 mg) twice daily; dose doubled in severe infection

Neonate 7–21 days 30 mg/kg (max. 62.5 mg) 3 times daily; dose doubled in severe infection

Neonate 21–28 days 30 mg/kg (max. 62.5 mg) 4 times daily; dose doubled in severe infection

Child 1 month–1 year 62.5 mg 4 times daily; dose doubled in severe infection

Child 1–5 years 125 mg 4 times daily; dose doubled in severe infection

Child 5–12 years 250 mg 4 times daily; dose doubled in severe infection

Child 12–18 years 500 mg 4 times daily; dose doubled in severe infection

• By intramuscular injection

Child 1 month–18 years 25 mg/kg (max. 500 mg) every 6 hours

• By intravenous injection or infusion

Neonate under 7 days 30 mg/kg every 12 hours; dose doubled in severe infection

Neonate 7–21 days 30 mg/kg every 8 hours; dose doubled in severe infection

Neonate 21–28 days 30 mg/kg every 6 hours; dose doubled in severe infection

Child 1 month–18 years 25 mg/kg (max. 1 g) every 6 hours; dose doubled in severe infection

Uncomplicated community-acquired pneumonia (Table 1, section 5.1), invasive salmonellosis

• By mouth

Child 1 month–1 year 125 mg 4 times daily

Child 1–5 years 250 mg 4 times daily

Child 5–18 years 500 mg 4 times daily

• By slow intravenous injection or by intravenous infusion

Neonate under 7 days 50 mg/kg every 12 hours

Neonate 7–21 days 50 mg/kg every 8 hours

Neonate 21–28 days 50 mg/kg every 6 hours

Child 1 month–18 years 50 mg/kg (max. 1 g) every 6 hours

Excipients include sucrose 600 mg/1.25 mL

Sachets SF powder, sugar-free, amoxicillin (as trihydrate) 3 g/sachet, 2-sachet pack (peach-strawberry- and lemon-flavoured) = £2.99. Label: 9, 13

Injection, powder for reconstitution, amoxicillin (as sodium salt), net price 500-mg vial = 58p; 1-g vial = £1.16

Electrolytes Na⁺ 3.3 mmol/g

AMOXICILLIN (continued)

Amoxicillin (GSK)

Capsules, both maroon/gold, amoxicillin (as trihydrate) 250 mg, net price 21-cap pack = £3.59; 500 mg, 21-cap pack = £7.19. Label: 9

Paediatric suspension, amoxicillin 125 mg (as trihydrate)/1.25 mL when reconstituted with water, net price 20 mL (peach-strawberry- and lemon-flavoured) = £3.38. Label: 9, counselling, use of pipette

Sachets SF powder, sugar-free, amoxicillin (as trihydrate) 3 g/sachet, 2-sachet pack (peach-strawberry- and lemon-flavoured) = £2.99. Label: 9, 13

Injection, powder for reconstitution, amoxicillin (as sodium salt), net price 500-mg vial = 58p; 1-g vial = £1.16

Dental prescribing on NHS Amoxicillin Capsules and Oral Suspension may be prescribed. Amoxicillin Sachets may be prescribed as Amoxicillin Oral Powder

5.1.1 Penicillins
Ampicillin (continued)

**Cautions** see under Ampicillin and notes above; hepatic function; maintain adequate hydration with high doses (particularly during parenteral therapy)

**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-amoxiclav than with amoxicillin; these reactions have only rarely been reported in children. Jaundice is sometimes present in children; however, the risk of acute liver toxicity was about 6 times greater with co-amoxiclav. An epidemiological study has shown that the risk of acute liver toxicity was about 6 times greater with co-amoxiclav than with amoxicillin; these reactions have only rarely been reported in children.

**Side-effects** see under Ampicillin; hepatitis, cholestatic jaundice (see above); Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, vasculitis reported; rarely prolongation of bleeding time, dizziness, headache, convulsions (particularly with high doses or in renal impairment); superficial staining of teeth with suspension, phlebitis at injection site

**Injection**, powder for reconstitution, ampicillin (as sodium salt), net price 500-mg vial = £7.83

**Dental prescribing on NHS** Ampicillin Capsules and Oral Suspension may be prescribed

**Penbritin** (Chemidex) Capsules, both 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

**Excipients** include sucrose 3.6 g/5 mL.

**With fluocoxacillin**

**Co-fluampicil** (Non-proprietary) Capsules, co-fluampicil 250/250 (flucoxacin 250 mg as sodium salt, ampicillin 250 mg as trihydrate), net price 28-cap pack = £14.43. Label: 9, 22

**Brands include Flu-Amp.**

**Magnapen** (CP) Capsules, black/turquoise, co-fluampicil 250/250 (flucoxacin 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 (flucoxacin 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

**Excipients** include sucrose 3.14 g/5 mL.

**Injection** 500 mg, powder for reconstitution, co-fluampicil 250/250 (flucoxacin 250 mg as sodium salt, ampicillin 250 mg as sodium salt), net price per vial = £1.33

**Electrolytes Na⁺ 1.3 mmol/vial**

**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.

**Cautions** see under Ampicillin and notes above; also caution in hepatic impairment (monitor hepatic function); maintain adequate hydration with high doses (particularly during parenteral therapy)

**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-amoxiclav than with amoxicillin; these reactions have only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal. The duration of treatment should be appropriate to the indication and should not usually exceed 14 days.

**Hepatic impairment** monitor liver function in liver disease. See also Cholestatic Jaundice above

**Renal impairment** Oral: use normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m². Use half normal dose every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m². **Augmentin-Duo** not recommended if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

**Intravenous**: use normal initial dose and then use half normal dose every 12 hours if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; use normal initial dose and then use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

**Pregnancy** not known to be harmful

**Breast-feeding** trace amounts present in breast milk—not known to be harmful but be alert for hypersensitivity in the infant

**Contra-indications** penicillin hypersensitivity, history of co-amoxiclav-associated or penicillin-associated jaundice or hepatic dysfunction

**Side-effects** see under Ampicillin; hepatitis, cholestatic jaundice (see above); Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative dermatitis, vasculitis reported; rarely prolongation of bleeding time, dizziness, headache, convulsions (particularly with high doses or in renal impairment); superficial staining of teeth with suspension, phlebitis at injection site.
## Indication and dose

**Infections due to beta-lactamase-producing strains (where amoxicillin alone is not appropriate) including respiratory-tract infections, genito-urinary and abdominal infections, cellulitis, animal bites**

- By mouth, expressed as co-amoxiclav (see also under Augmentin-Duo® preparation below)

### Neonate

| 0.25 mL/kg of 125/31 suspension | 3 times daily |

### Child 1 month–1 year

| 0.25 mL/kg of 125/31 suspension | 3 times daily; dose doubled in severe infection |

### Child 1–6 years

| 5 mL of 125/31 suspension | 3 times daily or 0.25 mL/kg of 125/31 suspension | 3 times daily; dose doubled in severe infection |

### Child 6–12 years

| 5 mL of 250/62 suspension | 3 times daily or 0.15 mL/kg of 250/62 suspension | 3 times daily; dose doubled in severe infection |

### Child 12–18 years

| one 250/125 strength tablet | 3 times daily; increased in severe infections to one 500/125 strength tablet, 3 times daily |

- By intravenous injection over 3–4 minutes or by intravenous infusion, expressed as co-amoxiclav

### Severe dental infections (but not generally first-line, see notes above), expressed as co-amoxiclav

- By mouth

### Child 12–18 years

| one 250/125 strength tablet | every 8 hours for 5 days |

# Administration

For intermittent intravenous infusion

- Dilute reconstituted solution to a concentration of 10mg/mL with Sodium Chloride 0.9% or Water for Injections; give over 30–40 minutes and complete infusion within 4 hours of reconstitution.

### Co-amoxiclav (Non-proprietary) (GSK)

<table>
<thead>
<tr>
<th>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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dental prescribing on NHS Co-amoxiclav 250/125 Tablets may be prescribed</td>
</tr>
<tr>
<td>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</td>
</tr>
</tbody>
</table>

### 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-amoxiclav 500/100 (amoxicillin 500 mg as sodium salt, clavulanic acid 100 mg as potassium salt), net price per vial = £1.21

### Injection 1000/200, powder for reconstitution, co-amoxiclav 1000/200 (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt), net price per vial = £2.42

## 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 SP’, 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

### Suspension ‘250/62 SP’, 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

### Injection 600 mg, powder for reconstitution, co-amoxiclav 500/100 (amoxicillin 500 mg as sodium salt, clavulanic acid 100 mg as potassium salt). Net price per vial = £1.38

**Electrolytes Na⁺ 1.35 mmol, K⁺ 0.5 mmol/600-mg vial**

### Injection 1.2 g, powder for reconstitution, co-amoxiclav 1000/200 (amoxicillin 1 g as sodium salt, clavulanic acid 200 mg as potassium salt). Net price per vial = £2.76

**Electrolytes Na⁺ 2.7 mmol, K⁺ 1 mmol/1.2-g vial**

### Augmentin-Duo® (GSK)

### Suspension ‘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)

### Injection 2.5 mL twice daily, doubled in severe infections

### Injection 5 mL twice daily, doubled in severe infections

## Dose

- **Child 2 months–2 years** 0.15 mL/kg twice daily, doubled in severe infection
- **Child 2–6 years (13–21 kg)** 2.5 mL twice daily, doubled in severe infection
- **Child 7–12 years (22–40 kg)** 5 mL twice daily, doubled in severe infections
5.1.1.4 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 *Ps. aeruginosa*. The spectrum of activity of *Tazocin®* and *Timentin®* is comparable to that of the carbapenems, imipenem and meropenem (section 5.1.2).

These antipseudomonal penicillins may be used for the empirical treatment of septicaemia in immunocompromised children but otherwise should generally be reserved for serious infections resistant to other antibacterials. For pseudomonas septicaemias (especially in neutropenia or endocarditis) these antipseudomonal penicillins should be given with an aminoglycoside (e.g. gentamicin or netilmicin, section 5.1.4) since they have a synergistic effect.

*Tazocin®* is used in cystic fibrosis for the treatment of *Ps. aeruginosa* colonisation when ciprofloxacin and nebulised colistin have been ineffective, or in infective exacerbations, when it is combined with an aminoglycoside.

Owing to the sodium content of many of these antibiotics, high doses may lead to hypernatraemia.

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**PIPERACILLIN**

**Cautions** see under Benzylpenicillin (section 5.1.1.1)

**Contra-indications** see under Benzylpenicillin (section 5.1.1.1)

**Renal impairment** reduce dose if estimated glomerular filtration rate less than 40 mL/minute/1.73 m² (child under 12 years) or if estimated glomerular filtration rate less than 80 mL/minute/1.73 m² (child 12–18 years); consult product literature

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** present in milk—manufacturer advises use only if potential benefit outweighs risk

**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, pancypopenia, Stevens-Johnson syndrome, and toxic epidermal necrolysis

**Licensed use** *Tazocin®* not licensed for use in children under 12 years (except for children with neutropenia and complicated appendicitis)

**Indication and dose**

See preparations

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**With tazobactam**

**Tazocin®** (Lederle) (H)

**Injection** 2.25 g, powder for reconstitution, piperacillin 2 g (as sodium salt), tazobactam 250 mg (as sodium salt), Net price per vial = £7.96

Electrolytes Na⁺ 5.58 mmol/2.25-g vial

Injection 4.5 g, powder for reconstitution, piperacillin 4 g (as sodium salt), tazobactam 500 mg (as sodium salt). Net price per vial = £15.79

**Electrolytes** Na⁺ 11.16 mmol/4.5-g vial

**Dose**

(Expressed as a combination of piperacillin and tazobactam combined)

**Lower respiratory tract, urinary tract, intra-abdominal and skin infections, and bacterial septicaemia**

- By intravenous injection over 3–5 minutes or by intravenous infusion

**Neonate** 90 mg/kg every 8 hours

**Child 1 month–12 years** 90 mg/kg every 6–8 hours; (max 4.5 g every 6 hours)

**Child 12–18 years** 2.25–4.5 g every 6–8 hours, usually 4.5 g every 8 hours

**Infections in children with neutropenia** in combination with an aminoglycoside

- By intravenous injection over 3–5 minutes or by intravenous infusion

**Child 1 month–18 years** 90 mg/kg every 6 hours; (max 4.5 g every 6 hours)

**Complicated appendicitis**

- By intravenous injection over 3–5 minutes or by intravenous infusion

**Child 2–12 years** 112.5 mg/kg every 8 hours (max 4.5 g every 8 hours) for 5–14 days

**Administration** For intravenous infusion, dilute reconstituted solution to a concentration of 15–90 mg/mL with Glucose 5%, Sodium Chloride 0.9% or Compund Sodium Lactate, or to a concentration of 90 mg/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
**TICARCELLIN**

**Cautions** see under Benzylpenicillin (section 5.1.1.1)

**Hepatic impairment** cholestatic jaundice, see under Co-amoxiclav

**Renal impairment** reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²

**Pregnancy** not known to be harmful

**Breast-feeding** trace amounts present in breast milk—not known to be harmful but be alert for hypersensitivity in the infant

**Contra-indications** see under Benzylpenicillin (section 5.1.1.1)

**Side-effects** see under Benzylpenicillin (section 5.1.1.1); also nausea, vomiting, coagulation disorders, haemorrhagic cystitis (more frequent in children), injection-site reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, hypokalaemia, eosinophilia

**Indication and dose**

See under preparation

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**With clavulanic acid**

**Note** For a CSM warning on cholestatic jaundice possibly associated with clavulanic acid, see under Co-amoxiclav

**Timentin**

Timentin® (GSK) Injection 3.2 g, powder for reconstitution, ticarcillin 3 g (as sodium salt), clavulanic acid 200 mg (as potassium salt). Net price per vial = £5.66

Electrolytes Na⁺ 16 mmol, K⁺ 1 mmol /3.2-g vial

**Dose**

(Expressed as a combination of ticarcillin and clavulanic acid)

**Infections due to Pseudomonas and Proteus spp.** see notes above

- By intravenous infusion
  - Preterm neonate body-weight under 2 kg 80 mg/kg every 12 hours
  - Preterm neonate body-weight over 2 kg and neonate 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections

- Child 1 month–18 years and body-weight under 40 kg 80 mg/kg every 8 hours, increased to every 6 hours in more severe infections
  - Child under 18 years and body-weight over 40 kg 80 mg/kg (max 3.2 g) every 6–8 hours, increased to every 4 hours in more severe infections

**Administration** Displacement value may be important, consult local guidelines. For intermittent infusion, dilute reconstituted solution further to a concentration of 16–32 mg/mL with glucose 5% or to a concentration of 32 mg/mL with water for injections; infuse over 30–40 minutes.

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**5.1.1.5 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.

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**PIVMECILLINAM HYDROCHLORIDE**

**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); **interactions**: Appendix 1 (penicillins)

**Renal impairment** reduce dose

**Pregnancy** not known to be harmful

**Breast-feeding** trace amounts in milk

**Contra-indications** see under Benzylpenicillin (section 5.1.1.1); also carnitine deficiency, 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 carnitine (especially with long-term or repeated use)

**Licensed use** not licensed for use in children under 3 months

**Indication and dose**

**Acute uncomplicated cystitis**

- By mouth
  - Child body-weight over 40 kg initially 400 mg then 200 mg every 8 hours for 3 days

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**Chronic or recurrent bacteriuria**

Child body-weight over 40 kg 400 mg every 6–8 hours

**Urinary-tract infections**

Child body-weight under 40 kg 5–10 mg/kg every 6 hours; total daily dose may alternatively be given in 3 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**

Selexid® (LEO) Tablets, 100 mg, pivmecillinam hydrochloride 200 mg, net price 10-tab pack = £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, and ertaopenem.

5.1.2.1 Cephalosporins

The cephalosporins are broad-spectrum antibacterials 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 and ceftriaxone are suitable cephalosporins 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.

Cefradine (cephradine) 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 that 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.

Ceftazidime 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 septicaemia, 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 antibacterial is stopped. In neonates, ceftriaxone may displace bilirubin from plasma-albumin and should be avoided in neonates with unconjugated hyperbilirubinemia, hypoalbuminaemia, acidosis or impaired bilirubin binding.

Orally active cephalosporins The orally active ‘first generation’ cephalosporins, cefalexin (cephalexin), cefradine, and cefadroxil and the ‘second generation’ cephalosporin, cefaclor, 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 and needs to be given with food to maximise absorption.

Cefixime has a longer duration of action than the other cephalosporins that are active by mouth. It is presently 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 children who have had rheumatic fever and are on long-term penicillin therapy. Cefalexin and cefradine have been used in the treatment of oral infections.

## CEFACLOR

**Cautions** sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also notes above and p. 308); false positive urinary glucose (if tested for reducing substances) and false positive Coombs’ test; **interactions**: Appendix 1 (cephalosporins)

**Renal impairment** no dosage adjustment required, manufacturer advises caution

**Pregnancy** not known to be harmful

**Breast-feeding** present in milk in low concentration, considered compatible with breast-feeding

**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 disorders (including thrombocytopenia, leucopenia, agranulocytosis, aplastic anaemia and haemolytic anaemia); reversible interstitial nephritis, hyperactivity, nervousness, sleep disturbances, hallucinations, confusion, hypertonia, and dizziness

**Indication and dose**

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

- **By mouth**
  - Child 1 month–12 years 20 mg/kg daily in 3 divided doses, doubled for severe infection (usual max. 1 g daily)
  - Child 1 month–1 year 62.5 mg 3 times daily; dose doubled for severe infections
  - Child 1–5 years 125 mg 3 times daily; dose doubled for severe infections
  - Child 5–12 years 250 mg 3 times daily; dose doubled for severe infections

**CEFADROXIL**

**Cautions** see under Cefaclor

**Renal impairment** reduce dose if estimated glomerular filtration rate less than 26 mL/minute/1.73 m²

**Pregnancy** not known to be harmful

**Breast-feeding** present in milk in low concentrations

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Indication and dose**

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above

- **By mouth**
  - Child 12–18 years 250 mg 3 times daily; dose doubled for severe infections (max. 4 g daily)

**Asymptomatic carriage of Haemophilus influenzae or mild exacerbations in cystic fibrosis**

- **By mouth**
  - Child 1 month–1 year 125 mg every 8 hours
  - Child 1–7 years 250 mg 3 times daily
  - Child 7–18 years 500 mg 3 times daily

**Cefaclor** (Non-proprietary)

- **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 c*

- **Suspension**, cefaclor (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 c*

**Distaclor** (Flynn)

- **Capsules**, cefaclor (as monohydrate) 500 mg (violet/grey), net price 20 = £17.33. Label: 9
- **Suspension**, both pink, cefaclor (as monohydrate) for reconstitution with water, 125 mg/5 mL, net price 100 mL = £4.13; 250 mg/5 mL, 100 mL = £8.26. Label: 9

**Distaclor MR** (Flynn)

- **Tablets**, m/r, both blue, cefaclor (as monohydrate) 375 mg, Net price 14-tab pack = £6.93. Label: 9, 21, 25

**Dose**

**Susceptible infections**

- Child 12–18 years 375 mg every 12 hours with food, dose doubled for pneumonia

**Lower urinary-tract infections**

- Child 12–18 years 375 mg every 12 hours with food
CEFADROXIL (continued)

Cefadroxil (Non-proprietary) (BNF)
Capsules, cefadroxil (as monohydrate) 500 mg, net price $20-cap pack = £5.25. Label: 9

Baxan® (Bristol-Myers Squibb) (BNF)
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 (Cephalexin)

Cautions see under Cefaclor
Renal impairment reduce dose in moderate impairment
Pregnancy not known to be harmful
Breast-feeding present in milk in low concentrations, considered compatible with breast feeding
Contra-indications see under Cefaclor
Side-effects see under Cefaclor

Indication and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above
• By mouth
  Neonate under 7 days 25 mg/kg (max. 125 mg) twice daily
  Neonate 7–21 days 25 mg/kg (max. 125 mg) 3 times daily
  Neonate 21–28 days 25 mg/kg (max. 125 mg) 4 times daily

Child 1 month–12 years 12.5 mg/kg twice daily; dose doubled in severe infection; max. 25 mg/kg 4 times daily (max. 1 g 4 times daily) or
Child 1 month–1 year 125 mg twice daily
Child 1–5 years 125 mg 3 times daily
Child 5–12 years 250 mg 3 times daily
Child 12–18 years 500 mg 2–3 times daily, increased to 1–1.5 g 3–4 times daily for severe infection

Prophylaxis of recurrent urinary-tract infection
• By mouth
  Child 1 month–18 years 12.5 mg/kg at night (max. 125 mg at night)

CEFIXIME

Cautions see under Cefaclor
Renal impairment reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²
Pregnancy not known to be harmful
Breast-feeding manufacturer advises avoid—no information available
Contra-indications see under Cefaclor
Side-effects see under Cefaclor

Indication and dose

Acute infections due to sensitive Gram-positive and Gram-negative bacteria, but see notes above
• By mouth
  Child 6 months–1 year 75 mg daily
  Child 1–5 years 100 mg daily
  Child 5–10 years 200 mg daily
  Child 10–18 years 200–400 mg daily or 100–200 mg twice daily

Gonorrhoea [unlicensed indication, see also Table 1, section 5.1]
• By mouth
  Child 12–18 years 400 mg as a single dose
CEFOTAXIME

Cautions  see under Cefaclor

Renal impairment  usual initial dose, then use half normal dose if estimated glomerular filtration rate less than 5 mL/minute/1.73 m².

Pregnancy  not known to be harmful

Breast-feeding  present in milk in low concentration, considered compatible with breast-feeding

Contra-indications  see under Cefaclor

Side-effects  see under Cefaclor; rarely arrhythmias following rapid injection reported

Indication and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria, surgical prophylaxis, Haemophilus epiglottitis and meningitis (Table 1, section 5.1) see also notes above

• By intramuscular or by intravenous injection or intravenous infusion

Neonate under 7 days  25 mg/kg every 12 hours; dose doubled in severe infection and meningitis

Neonate 7–21 days  25 mg/kg every 8 hours; dose doubled in severe infection and meningitis

Neonate 21–28 days  25 mg/kg every 6–8 hours; dose doubled in severe infection and meningitis

Child 1 month–18 years  50 mg/kg every 8–12 hours; increase to every 6 hours in very severe infections and meningitis (max. 12 g daily)

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 Child under 12 years  50 mg/kg; Child over 12 years 1 g; chloramphenicol (section 5.1.7) may be used if there is a history of anaphylaxis to penicillins or cephalosporins

CEFPODOXIME

Cautions  see under Cefaclor

Renal impairment  increase dose interval to every 24 hours if estimated glomerular filtration rate 10–40 mL/minute/1.73 m². Increase dose interval to every 48 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².

Pregnancy  not known to be harmful

Breast-feeding  present in milk in low concentration

Contra-indications  see under Cefaclor

Side-effects  see under Cefaclor

Indication and dose

Upper respiratory-tract infections (but in pharyngitis and tonsillitis reserved for infections which are recurrent, chronic, or resistant to other antibiotics), lower respiratory-tract infections (including bronchitis and pneumonia), skin and soft tissue infections, uncomplicated urinary-tract infections

• By mouth

Child 15 days–6 months  4 mg/kg twice daily

Child 6 months–2 years  40 mg twice daily

Child 3–8 years  80 mg twice daily

Child 9–12 years  100 mg twice daily

Child 12–18 years  100 mg twice daily (increased to 200 mg twice daily in sinusitis, skin and soft tissue infections, uncomplicated upper urinary tract infections and if necessary in lower respiratory tract infections)
## Uncomplicated gonorrhoea

**By mouth**

- **Child 12–18 years** 200 mg as a single dose

### CEFPODOXIME (continued)

<table>
<thead>
<tr>
<th>Uncomplicated gonorrhoea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> 200 mg as a single dose</td>
</tr>
</tbody>
</table>

### CEFRADINE

(Cefradine)

**Cautions** see under Cefaclor

- **Renal impairment** reduce dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²
- **Pregnancy** not known to be harmful
- **Breast-feeding** present in milk in low concentrations

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Licensed use** not licensed for use in children for prophylaxis in urinary-tract infections or for prevention of *Staphylococcus aureus* lung infection in cystic fibrosis

**Indication and dose**

**Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above**

- **By mouth**
  - **Child 1 month–12 years** 12.5–25 mg/kg twice daily (total daily dose may alternatively be given in 3–4 divided doses)
  - **Child 12–18 years** 0.5–1 g twice daily or 250–500 mg 4 times daily; up to 1 g 4 times daily in severe infections
- **By deep intramuscular injection or by intravenous injection over 3–5 minutes or by intravenous infusion**
  - **Child 1 month–12 years** 12.5–25 mg/kg every 6 hours
  - **Child 12–18 years** 0.5–1 g every 6 hours, increased to 2 g every 6 hours in severe infection

**Surgical prophylaxis**

- **By deep intramuscular injection or by intravenous injection over 3–5 minutes**
  - **Child 12–18 years** 1–2 g at induction

### CEFTAZIDIME

**Cautions** see under Cefaclor

- **Renal impairment** reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²
- **Pregnancy** not known to be harmful
- **Breast-feeding** present in milk in low concentrations

**Contra-indications** see under Cefaclor

**Side-effects** see under Cefaclor

**Licensed use** nebulised route unlicensed

**Indication and dose**

**Infections due to sensitive Gram-positive and Gram-negative bacteria but see notes above**

- **By intravenous injection or infusion**
  - **Neonate under 7 days** 25 mg/kg every 24 hours; dose doubled in severe infection and meningitis
  - **Neonate 7–21 days** 25 mg/kg every 12 hours; dose doubled in severe infection and meningitis
  - **Neonate 21–28 days** 25 mg/kg every 8 hours; dose doubled in severe infection and meningitis
  - **Child 1 month–18 years** 25 mg/kg every 8 hours; dose doubled in severe infection, febrile neutropenia and meningitis (max. 6 g daily)

**Prevention of *Staphylococcus aureus* lung infection in cystic fibrosis**

- **By mouth**
  - **Child 1 month–1 year** 500 mg twice daily
  - **Child 1–7 years** 1 g twice daily
  - **Child 7–18 years** 2 g twice daily

**Prophylaxis in urinary-tract infection**

- **By mouth**
  - **Child 1 month–12 years** 3 mg/kg at night.

**Administration** Displacement value may be significant when reconstituting injections, consult local guidelines. For continuous or intermittent intravenous infusion dilute reconstituted solution further in Glucose 5% or Glucose 10% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate

**Cefradine (Non-proprietary) (NH)**

- **Capsules**, cefradine 250 mg, net price 20-cap pack = £3.97; 500 mg, 20-cap pack = £6.49. Label: 9
- **Brands include** Nicef (A)
- **Dental prescribing on NHS** Cefradine Capsules may be prescribed

**Velosef®** (Squibb) (NH)

- **Capsules**, cefradine 250 mg (orange/blue), net price 20-cap pack = £5.42; 500 mg (blue), 20-cap pack = £11.22. Label: 9
- **Syrup**, cefradine 250 mg/5 mL when reconstituted with water. Net price 100 mL = £4.22. Label: 9
- **Dental prescribing on NHS** Velosef® syrup may be prescribed as Cefradine Oral Solution
- **Injection**, powder for reconstitution, cefradine. Net price 500-mg vial = 99p; 1-g vial = £1.95

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5Infections
Pseudomonal lung infection in cystic fibrosis
- By intravenous injection or infusion or by deep intramuscular injection
  - **Child 1 month–18 years** 50 mg/kg every 8 hours (max. 9 g daily)

Chronic *Burkholderia cepacia* infection in cystic fibrosis
- By inhalation of nebulised solution
  - **Child 1 month–18 years** 1 g twice daily

**Administration**
For parenteral administration, intravenous route recommended in children. Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion dilute reconstituted solution further to a concentration of not more than 40 mg/mL in Glucose 5% or Glucose 10% or Sodium chloride 0.9% or Compound sodium lactate.

**CEFTRIAXONE**

**Cautions**
- see under Cefaclor; preterm 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
- **Hepatic impairment** if hepatic impairment is accompanied by severe renal impairment, reduce dose and monitor plasma concentration
- **Renal impairment** max. 50 mg/kg daily (max. 2 g daily) in severe renal impairment; also monitor plasma concentration if hepatic impairment accompanied by severe renal impairment
- **Pregnancy** not known to be harmful
- **Breast-feeding** present in milk in low concentration, considered compatible with breast-feeding

**Contra-indications**
- see under Cefaclor; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding; concomitant treatment with calcium—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

**Indication and dose**

**Infections due to sensitive Gram-positive and Gram-negative bacteria**
- **Neonate** 20–50 mg/kg once daily
- **By deep intramuscular injection, or by intravenous injection over 2–4 minutes, or by intravenous infusion**
  - **Child 1 month–12 years**
    - **Body-weight under 50 kg** 50 mg/kg once daily; up to 80 mg/kg daily in severe infections and meningitis; doses of 50 mg/kg and over by intravenous infusion only
  - **Body-weight 50 kg and over** dose as for child 12–18 years

**Uncomplicated gonorrhoea**
- **Child 12–18 years** 250 mg as a single dose

**Early syphilis** [unlicensed indication]
- **Child 12–18 years** 500 mg daily for 10 days

**Surgical prophylaxis**
- **Child 12–18 years**
  - 1 g at induction; colorectal surgery, 2 g at induction; intramuscular doses over 1 g divided between more than one site

**Prophylaxis of meningococcal meningitis** Table 2, section 5.1

**Administration**
Displacement value may be significant, consult local guidelines. For intravenous infusion, dilute reconstituted solution with Glucose 5% or 10% or Sodium Chloride 0.9%; give over at least 30 minutes (60 minutes in neonates). Not to be given with parenteral nutrition or infusion fluids containing calcium, even by different infusion lines. For intramuscular injection ceftriaxone may be mixed with 1% Lidocaine Hydrochloride Injection to reduce pain at intramuscular injection site; final concentration 250–350 mg/mL.
CEFTRIAXONE (continued)

Ceftriaxone (Non-proprietary)
Injection, powder for reconstitution, ceftriaxone (as sodium salt), net price 1-g vial = £10.17; 2-g vial = £20.36

Rocephin® (Roche)
Injection, powder for reconstitution, ceftriaxone (as sodium salt), net price 250-mg vial = £2.55; 1-g vial = £10.17; 2-g vial = £20.36

Electrolytes
Na+ 3.6 mmol /g

CEFROXIME

Cautions see under Cefaclor

Renal impairment reduce parenteral dose if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Pregnancy not known to be harmful

Breast-feeding present in milk in low concentration

Contra-indications see under Cefaclor

Side-effects see under Cefaclor

Indication and dose

Infections due to sensitive Gram-positive and Gram-negative bacteria

• By mouth (as cefuroxime axetil),
  Child 3 months–2 years 10 mg/kg (max. 125 mg) twice daily
  Child 2–12 years 15 mg/kg (max. 250 mg) twice daily
  Child 12–18 years 250 mg twice daily; dose doubled in severe lower respiratory-tract infections, or if pneumonia suspected; dose reduced to 125mg twice daily in lower urinary-tract infection

• By intravenous injection or infusion or by intramuscular injection

Neonate under 7 days 25 mg/kg every 12 hours; dose doubled in severe infection, intravenous route only

Neonate 7–21 days 25 mg/kg every 8 hours; dose doubled in severe infection, intravenous route only

Neonate 21–28 days 25 mg/kg every 6 hours; dose doubled in severe infection, intravenous route only

Child 1 month–18 years 20 mg/kg (max. 750 mg) every 8 hours; increase to 50–60 mg/kg (max. 1.5 g) every 6–8 hours in severe infection and cystic fibrosis

Lyme disease
• By mouth
  Child 12–18 years 500 mg twice daily for 20 days

Surgical prophylaxis
• By intravenous injection
  Child 1 month–18 years 50 mg/kg (max. 1.5 g) at induction, up to 3 further doses of 30 mg/kg (max. 750 mg) may be given by intramuscular or intravenous injection every 8 hours for high-risk procedures

Administration Single doses over 750mg should be administered by the intravenous route only. Displacement value may be significant when reconstituting injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9% or compound sodium lactate; give over 30 minutes.

Cefuroxime (Non-proprietary)
Tablets, cefuroxime (as axetil) 250 mg, net price 14-tab pack = £9.01. Label: 9, 21, 25

Zinacef® (GSK)
Injection, powder for reconstitution, cefuroxime (as sodium salt). Net price 250-mg vial = 94p; 750-mg vial = £2.34; 1.5-g vial = £4.70
Electrolytes Na+ 1.8 mmol/750-mg vial

Zinnat® (GSK)
Tablets, both f/c, cefuroxime (as axetil) 125 mg, net price 14-tab pack = £4.84; 250 mg, 14-tab pack = £9.67. Label: 9, 21, 25
Suspension, cefuroxime (as axetil) 125 mg/5 mL when reconstituted with water, net price 70 mL (tutti-frutti-flavoured) = £5.52. Label: 9, 21
Excipients include aspartame (section 9.4.1), sucrose 3.1 g/5 mL

5.1.2.2 Carbapenems

The carbapenems are beta-lactam antibacterials with a broad-spectrum of activity which includes many Gram-positive and Gram-negative bacteria, and anaerobes; imipenem and meropenem have good activity against Pseudomonas aeruginosa. The carbapenems are not active against meticillin-resistant Staphylococcus aureus and Enterococcus faecium.

Imipenem and meropenem are used for the treatment of severe hospital-acquired infections and polymicrobial infections caused by multiple-antibacterial resistant organisms (including sepsicaemia, hospital-acquired pneumonia, intra-abdominal infections, skin and soft-tissue infections, and complicated urinary-tract infections).
Ertapenem is licensed for treating abdominal and gynaecological infections and for community-acquired pneumonia, but it is not active against atypical respiratory pathogens and it has limited activity against penicillin-resistant pneumococci. Unlike the other carbapenems, ertapenem is not active against *Pseudomonas* or against *Acinetobacter* spp.

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 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. Meropenem has less seizure-inducing potential and can be used to treat central nervous system infection. Ertapenem has been associated with seizures uncommonly.

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### ERTAPENEM

**Cautions**
- hypersensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 308); renal impairment, CNS disorders—risk of seizures; **interactions:** Appendix 1 (ertapenem)
- Renal impairment—avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²
- Pregnancy—manufacturer advises avoid unless potential benefit outweighs risk

**Contra-indications**
- Breast-feeding—present in milk—manufacturer advises avoid

**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, melaena, antibiotic-associated colitis, hypotension, chest pain, oedema, pharyngeal discomfort, dyspnoea, dizziness, sleep disturbances, confusion, asthenia, seizures, vaginitis, raised glucose, petechiae; rarely dysphagia, cholecystitis, liver disorder (including jaundice), arthritism, increase in blood pressure, syncope, nasal congestion, cough, wheezing, hypersensitivity reactions, anxiety, depression, agitation, tremor, pelvic peritonitis, renal impairment, muscle cramp, scleral disorder, blood disorders (including neutropenia, thrombocytopenia, haemorrhage), hypoglycaemia, electrolyte disturbances; very rarely hallucinations

**Indication and dose**
- **Abdominal infections, acute gynaecological infections, community-acquired pneumonia**
- **By intravenous infusion**
  - **Child 3 months–13 years**
    - 15 mg/kg every 12 hours (max. 1 g daily)
  - **Child 13–18 years**
    - 1 g once daily

**Administration**
- reconstitute 1 g with 10 mL Water for Injections or Sodium Chloride 0.9%; for intermittent intravenous infusion, dilute requisite dose in Sodium Chloride 0.9% to a final concentration not exceeding 20 mg/mL; incompatible with glucose solutions

**invanz® (MSD)**

**Intravenous infusion**, powder for reconstitution, ertapenem (as sodium salt), net price 1-g vial = £31.65

**Electrolytes**
- Na⁺ 6 mmol/1-g vial

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### IMIPENEM WITH CILASTATIN

**Cautions**
- CNS disorders (e.g. epilepsy); hypersensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 308); **interactions:** Appendix 1 (imipenem with cilastatin)
- Renal impairment—not licensed for use in children with renal impairment. Reduce dose if estimated glomerular filtration rate less than 70 mL/minute/1.73 m²
- Pregnancy—manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies)
- Breast-feeding—present in milk but unlikely to be absorbed (however, manufacturer advises avoid)

**Side-effects**
- nausea, vomiting, diarrhoea (antibiotic-associated colitis reported), taste disturbances, tooth or tongue discoloration, hearing loss; blood disorders, positive Coombs’ test; allergic reactions (with rash, pruritus, urticaria, Stevens-Johnson syndrome, fever, anaphylactic reactions, rarely toxic epidermal necrolysis, exfoliative dermatitis); myoclonic activity, convulsions, confusion and mental disturbances reported; slight increases in liver enzymes and bilirubin reported, rarely hepatitis; increases in serum creatinine and blood urea; red coloration of urine in children reported; local reactions: erythema, pain and induration, and thrombophlebitis

**Licensed use**
- not licensed for use in children under 3 months
Indication and dose

**Aerobic and anaerobic Gram-positive and Gram-negative infections, hospital-acquired septicemia** Table 1, section 5.1; not indicated for CNS infections

- **By intravenous infusion**
  - expressed in terms of imipenem

<table>
<thead>
<tr>
<th>Neonate under 7 days</th>
<th>20 mg/kg every 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate 7–21 days</td>
<td>20 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Neonate 21–28 days</td>
<td>20 mg/kg every 6 hours</td>
</tr>
<tr>
<td>Child 1–3 months</td>
<td>20 mg/kg every 6 hours</td>
</tr>
<tr>
<td>Body-weight under 40 kg</td>
<td>15 mg/kg (max. 500 mg) every 6 hours</td>
</tr>
<tr>
<td>Body-weight over 40 kg</td>
<td>250–500 mg every 6 hours; less sensitive organisms up to 12.5 mg/kg (max. 1 g) every 6 hours; total daily dose may alternatively be given in 3 divided doses</td>
</tr>
<tr>
<td>Child 1 month–18 years</td>
<td>500 mg every 8 hours; dose doubled in hospital-acquired pneumonia, peritonitis, septicemia and infections in neutropenic patients</td>
</tr>
<tr>
<td>Body-weight under 50 kg</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Body-weight over 50 kg</td>
<td>dose as for child 12–18 years</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>2 g every 8 hours</td>
</tr>
</tbody>
</table>

**Cystic fibrosis**

- **By intravenous infusion**
  - Child 1 month–18 years
  - Body-weight under 40 kg 22.5 mg/kg every 6 hours
  - Body-weight over 40 kg 1 g every 6–8 hours

**Administration** for intermittent intravenous infusion dilute to a concentration of 5 mg (as imipenem)/mL in sodium chloride 0.9% or sodium chloride and glucose; give up to 500 mg over 20–30 minutes; give 1 g over 40–60 minutes

**Primaxin® (MSD)**

Intravenous infusion, powder for reconstitution, imipenem (as monohydrate) 500 mg with cilastatin (as sodium salt) 500 mg, net price per vial = £12.00

**Electrolytes**

- Na+ 1.72 mmol/vial

**MEROPENEM**

- **Cautions** hypersensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction, see also p. 308); **interactions**: Appendix 1 (meropenem)
- **Hepatic impairment** monitor transaminase and bilirubin concentrations
- **Renal impairment** use normal dose every 12 hours if estimated glomerular filtration rate 26–50 mL/minute/1.73 m²; use half normal dose every 12 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m²; use half normal dose every 24 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²
- **Pregnancy** manufacturer advises use only if potential benefit outweighs risk—no information available
- **Breast-feeding** unlikely to be absorbed (but manufacturer advises avoid unless potential benefit outweighs risk)
- **Side-effects** nausea, vomiting, diarrhoea (antibiotic-associated colitis reported), abdominal pain, disturbances in liver function tests; headache; thrombocythaemia, positive Coombs’ test; rash, pruritus, injection-site reactions; **less commonly** eosinophilia and thrombocytopenia; rarely convulsions; also reported paraesthesia, leucopenia, haemolytic anaemia, reduction in partial thromboplastin time, Stevens-Johnson syndrome, and toxic epidermal necrolysis
- **Licensed use** not licensed for use in children for infection in neutropenia; not licensed for use in children under 3 months
- **Indication and dose**
  - **Aerobic and anaerobic Gram-positive and Gram-negative infections, hospital-acquired septicemia** Table 1, section 5.1
  - **By intravenous injection over 5 minutes or by intravenous infusion**

<table>
<thead>
<tr>
<th>Neonate under 7 days</th>
<th>20 mg/kg every 12 hours, dose doubled in severe infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate 7–28 days</td>
<td>20 mg/kg every 8 hours; dose doubled in severe infection</td>
</tr>
<tr>
<td>Child 1 month–12 years</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Body-weight under 50 kg</td>
<td>10 mg/kg every 8 hours; dose doubled in hospital-acquired pneumonia, peritonitis, septicemia and infections in neutropenic patients</td>
</tr>
<tr>
<td>Body-weight over 50 kg</td>
<td>dose as for child 12–18 years</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>500 mg every 8 hours; dose doubled in hospital-acquired pneumonia, peritonitis, septicemia and infections in neutropenic patients</td>
</tr>
<tr>
<td>Body-weight under 50 kg</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Body-weight over 50 kg</td>
<td>dose as for child 12–18 years</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>2 g every 8 hours</td>
</tr>
</tbody>
</table>

**Meningitis**

- **By intravenous injection over 5 minutes or by intravenous infusion**

<table>
<thead>
<tr>
<th>Neonate under 7 days</th>
<th>40 mg/kg every 12 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate 7–28 days</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Child 1 month–12 years</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Body-weight under 50 kg</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Body-weight over 50 kg</td>
<td>dose as for child 12–18 years</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>2 g every 8 hours</td>
</tr>
</tbody>
</table>

**Exacerbations of chronic lower respiratory-tract infections in cystic fibrosis**

- **By intravenous injection over 5 minutes or by intravenous infusion**

<table>
<thead>
<tr>
<th>Neonate under 7 days</th>
<th>40 mg/kg every 8 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate 7–28 days</td>
<td>40 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Child 1 month–18 years</td>
<td>40 mg/kg every 8 hours (max. 2 g every 8 hours)</td>
</tr>
</tbody>
</table>

**Administration** Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion dilute reconstituted solution further in glucose 5% or glucose 10% or sodium chloride 0.9% and give over 15–30 minutes
328 5.1.3 Tetracyclines

5.1.3 Tetracyclines

The tetracyclines are broad-spectrum antibiotics whose value has decreased owing to increasing bacterial resistance. In children over 12 years of age they are useful 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 genital mycoplasma infections, in acne, in destructive (refractory) periodontal disease, in exacerbations of chronic respiratory diseases (because of their activity against Haemophilus influenzae), and for leptospirosis in penicillin hypersensitivity (as an alternative to erythromycin).

Microbiologically, there is little to choose between the various tetracyclines, the only exception being minocycline which has a broader spectrum; it is active

5.1.2.3 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

**Cautions** hypersensitivity to beta-lactam antibiotics; **interactions:** Appendix 1 (aztreonam)

**Hepatic impairment** experience limited, monitor liver function

**Renal impairment** usual initial dose, then half normal dose if estimated glomerular filtration rate 10–30 mL/minute/1.73 m², usual initial dose, then one-quarter normal dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

**Breast-feeding** present in milk in low concentration, considered compatible with breast-feeding

**Contra-indications** aztreonam hypersensitivity

**Pregnancy** manufacturer advises avoid—crosses placenta and no further information available

**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, halsitosis, and breast tenderness; very rarely antibiotic-associated colitis, gastro-intestinal bleeding, and toxic epidermal necrolysis

**Licensed use** not licensed for use in children under 7 days

**Indication and dose**

<table>
<thead>
<tr>
<th><strong>Gram-negative infections including Pseudomonas aeruginosa, Haemophilus influenzae, and Neisseria meningitidis</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>● <strong>By intravenous injection over 3–5 minutes or by intravenous infusion</strong></td>
</tr>
<tr>
<td>Neonate under 7 days</td>
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<tr>
<td>Neonate 7–28 days</td>
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<tr>
<td>Child 1 month–2 years</td>
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<tr>
<td>Child 2–12 years</td>
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<tr>
<td>Child 12–18 years</td>
</tr>
</tbody>
</table>

**Administration** Displacement value may be significant, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate to a concentration of less than 20 mg/mL; to be given over 20–60 minutes

Azactam® (Squibb)

Injection, powder for reconstitution, aztreonam.

Net price 500-mg vial = £5.00; 1-g vial = £9.98; 2-g vial = £19.98
against *Neisseria meningitidis* and has been used for meningococcal prophylaxis but is no longer recommended because of side-effects including dizziness and vertigo (see Table 2, section 5.1 for current recommendations). Compared to other tetracyclines, minocycline is associated with a greater risk of lupus-erythematosus-like syndrome. Minocycline sometimes causes irreversible pigmentation.

For the role of tetracyclines in the management of meticillin-resistant *Staphylococcus aureus* (MRSA) infections, see p. 310.

**Oral infections** In children over 12 years of age, 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 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).

**Hepatic impairment**: avoid (or use with caution); tetracycline and demeclocycline max. 1 g daily in divided doses.

**Renal impairment**: with the exception of doxycycline and minocycline, the tetracyclines may exacerbate renal failure and should not be given to patients with mild, moderate, or severe renal impairment. Doxycycline or minocycline may be used cautiously (avoid excessive doses).

**Pregnancy**: avoid in pregnancy. In the first trimester, effects on skeletal development in animal studies. In the second and third trimester, dental discoloration.

**Breast-feeding**: avoid (although absorption and therefore discoloration of teeth in infant probably usually prevented by chelation with calcium in milk)

**Contra-indications** Deposition 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 or breast-feeding women. However, doxycycline may be used in children for treatment and post-exposure prophylaxis of anthrax when an alternative antibacterial cannot be given [unlicensed indication]. Tetracyclines should not be given to children 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.

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**TETRACYCLINE**

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above; also reported, pancreatitis, acute renal failure, skin discoloration

**Indication and dose**

**Susceptible infections** see notes above

- **By mouth**
  - **Child 12–18 years** 250 mg 4 times daily, increased in severe infections to 500 mg 3–4 times daily

**Acne** section 13.6.2
**Non-gonococcal urethritis**

**By mouth**

**Child 12–18 years** 500 mg 4 times daily for 7–14 days (21 days if failure or relapse after first course)

**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**

**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

**Indication and dose**

**Susceptible infections** see notes above

**By mouth**

**Child 12–18 years** 150 mg 4 times daily or 300 mg twice daily

**Ledermycin®** (Goldshield)

Capsules, red, demeclocycline hydrochloride 150 mg, net price 28-cap pack = £13.73. Label: 7, 9, 11, 23

**DOXYCYCLINE**

**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, tinnitus

**Licensed use** not licensed for use in children under 12 years

**Indication and dose**

**Susceptible infections** see notes above

**By mouth**

**Child 12–18 years** 200 mg on first day, then 100 mg daily; severe infections (including refractory urinary-tract infections) 200 mg daily

**Early syphilis**

**By mouth**

**Child 12–18 years** 100 mg twice daily for 14 days

**Late latent syphilis**

**By mouth**

**Child 12–18 years** 100 mg twice daily for 28 days

**Uncomplicated genital chlamydia, non-gonococcal urethritis, pelvic inflammatory disease**

Table 1, section 5.1

**By mouth**

**Child 12–18 years** 100 mg twice daily for 7 days (14 days in pelvic inflammatory disease)

**LYMECYCLINE**

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Indication and dose**

**Susceptible infections** see notes above

**By mouth**

**Child 12–18 years** 408 mg twice daily, increased to 1.224–1.632 g daily in severe infections

**Anthrax (treatment or post-exposure prophylaxis)** see also section 5.1.12

**By mouth**

**Child under 12 years** (only if alternative antibacterial cannot be given) 2.5 mg/kg twice daily (max. 100 mg twice daily)

**Child 12–18 years** 100 mg twice daily

**Acne** section 13.6.2

**Adjunct to gingival scaling and root planing for periodontitis** section 12.3.1

**Counselling** Capsules should be swallowed whole with plenty of fluid during meals while sitting or standing

**Note** Doxycycline doses in BNF for Children may differ from those in product literature

**Doxycycline** (Non-proprietary)

Capsules, doxycycline (as hyclate) 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 Doxylar®

Dental prescribing on NHS Doxycycline Capsules 100 mg may be prescribed

**Vibramycin-D®** (Pfizer)

Dispersible tablets, yellow, scored, doxycycline 100 mg, net price 8-tab pack = £4.91. Label: 6, 9, 11, 13
Acne

**By mouth**

**Child 12–18 years** 408 mg daily for at least 8 weeks

**Tetralysal 300** (Galderma)®


**MINOCYCLINE**

**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

**Indication and dose**

**Susceptible infections** see notes above

- **By mouth**
  - **Child 12–18 years** 100 mg twice daily

**Minocycline** (Non-proprietary)®

**Capsules**

- minocycline (as hydrochloride) 50 mg, net price 56-cap pack = £21.14. Label: 6, 9, counselling, posture

Brands include **Aknemin**

**Tablets**

- minocycline (as hydrochloride) 50 mg, net price 28-tab pack = £3.96. Label: 6, 9, counselling, posture

**OXYTETRACYCLINE**

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Indication and dose**

**Susceptible infections** see notes above

- **By mouth**
  - **Child 12–18 years** 250–500 mg 4 times daily

**Oxytetracycline** (Non-proprietary)®

**Tablets**

- coated, oxytetracycline dihydrate 250 mg, net price 28-tab pack = £1.00. Label: 7, 9, 23

Brands include **Oxymycin**®

Dental prescribing on NHS Oxytetracycline Tablets may be prescribed

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 children 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 children 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 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 children with endocarditis or extensive burns of more than 20% of the total body surface area, or in children over 1 month of age with a creatinine clearance of less than 20 mL/minute/1.73m². The *extended interval dose regimen* is used in neonates to reflect the changes in renal function that occur with increasing gestational and postnatal age (see Neonates below).

**Serum concentrations**  
Serum concentration monitoring avoids both excessive and subtherapeutic concentrations thus preventing toxicity and ensuring efficacy. In children with normal renal function, aminoglycoside concentration should be measured initially after 3 or 4 doses for multiple daily dose regimens; children with renal impairment may require earlier and more frequent measurement of aminoglycoside concentration.

Blood samples should be taken approximately 1 hour after intramuscular or intravenous administration (‘peak’ concentration, not necessary for once daily dosing in children over 1 month) and also just before the next dose (‘trough’ concentration).

Serum-aminoglycoside concentration should be measured in all children and **must** be determined in infants, in neonates, in obesity, and in cystic fibrosis, or if high doses are being given, or if there is renal impairment.

**Cystic fibrosis**  
A higher dose of parenteral aminoglycoside is often required in children with cystic fibrosis because renal clearance of the aminoglycoside is increased. For the role of aminoglycosides in the treatment of pseudomonal lung infections in cystic fibrosis see Table 1, section 5.1. Nebulised tobramycin is used for chronic pseudomonal lung infection in cystic fibrosis; however, resistance may develop, and some children do not respond to treatment. Gentamicin can be used similarly [unlicensed use].

**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 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, children with cystic fibrosis or 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 slightly more active against Ps. aeruginosa but shows less activity against certain other Gram-negative bacteria. Tobramycin may be administered by nebuliser for the treatment of Ps. aeruginosa infection in cystic fibrosis (see Cystic Fibrosis, above).

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 in children with hepatic failure and, as these children may also be uraemic, cumulative may occur with resultant ototoxicity.

**Neonates** As aminoglycosides are eliminated principally via the kidney, neonatal treatment must reflect the changes in glomerular filtration that occur with increasing gestational and postnatal age. In patients on single daily dose regimens it may become necessary to prolong the dose interval to more than 24 hours if the trough concentration is high.

### NEOMYCIN

**Cautions** neonates, infants (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)

**Renal impairment** reduce dose frequency; monitor renal, auditory, and vestibular function; monitor serum-gentamicin concentrations; see notes above

**Pregnancy** second, third trimesters: 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)

**Contra-indications** myasthenia gravis

**Side-effects** vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis; also reported, nausea, vomiting, rash, blood disorders; see also notes above

**Licensed use** not licensed for nebulisation

**Pharmacokinetics** Extended interval dose regimen in neonates: pre-dose (‘trough’) concentration should be less than 2 mg/litre

**Once daily dose regimen**: pre-dose (‘trough’) concentration should be less than 1 mg/litre

**Multiple daily dose regimen**: one hour (‘peak’) serum concentration should be 5–10 mg/litre (3–5 mg/litre for endocarditis, 8–12 mg/litre in cystic fibrosis); pre-dose (‘trough’) concentration should be less than 2 mg/litre (less than 1 mg/litre for endocarditis)

Intrathecal/intraventricular injection: cerebrospinal fluid concentration should not exceed 10 mg/litre

**Indication and dose**

**Neonatal sepsis**

- **Extended interval dose regimen by slow intravenous injection or intravenous infusion**
  - Neonate less than 32 weeks postmenstrual age
    - 4–5 mg/kg every 36 hours
  - Neonate 32 weeks and over postmenstrual age
    - 4–5 mg/kg every 24 hours

- **Multiple daily dose regimen by slow intravenous injection**
  - Neonate less than 29 weeks postmenstrual age
    - 2.5 mg/kg every 24 hours
  - Neonate 29–35 weeks postmenstrual age
    - 2.5 mg/kg every 18 hours
  - Neonate over 35 weeks postmenstrual age
    - 2.5 mg/kg every 12 hours

- **Septicaemia, meningitis and other CNS infections, biliary-tract infection, acute pyelonephritis, endocarditis (see notes above), pneumonia in hospital patients, adjunct in listerial meningitis (Table 1, section 5.1)**
  - **Once daily dose regimen** (not for endocarditis or meningitis) by intravenous infusion
    - Child 1 month–18 years initially 7 mg/kg, then adjusted according to serum-gentamicin concentration
  - **Multiple daily dose regimen by intramuscular or by slow intravenous injection over at least 3 minutes**
    - Child 1 month–12 years 2.5 mg/kg every 8 hours
    - Child 12–18 years 2 mg/kg every 8 hours

### GENTAMICIN

**Cautions** neonates, infants (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)

**Renal impairment** reduce dose frequency; monitor renal, auditory, and vestibular function; monitor serum-gentamicin concentrations; see notes above

**Pregnancy** second, third trimesters: 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)

**Contra-indications** myasthenia gravis

**Side-effects** vestibular and auditory damage, nephrotoxicity; rarely, hypomagnesaemia on prolonged therapy, antibiotic-associated colitis; also reported, nausea, vomiting, rash, blood disorders; see also notes above

**Licensed use** not licensed for nebulisation

**Pharmacokinetics** Extended interval dose regimen in neonates: pre-dose (‘trough’) concentration should be less than 2 mg/litre

**Once daily dose regimen**: pre-dose (‘trough’) concentration should be less than 1 mg/litre

**Multiple daily dose regimen**: one hour (‘peak’) serum concentration should be 5–10 mg/litre (3–5 mg/litre for endocarditis, 8–12 mg/litre in cystic fibrosis); pre-dose (‘trough’) concentration should be less than 2 mg/litre (less than 1 mg/litre for endocarditis)

Intrathecal/intraventricular injection: cerebrospinal fluid concentration should not exceed 10 mg/litre
Pseudomonal lung infection in cystic fibrosis

- By slow intravenous injection over at least 3 minutes or by intravenous infusion
  - Child 1 month–18 years 3 mg/kg every 8 hours

- By inhalation of nebulised solution
  - Child 1 month–2 years 40 mg twice daily
  - Child 2–8 years 80 mg twice daily
  - Child 8–18 years 160 mg twice daily

Bacterial ventriculitis and CNS infection (supplement to systemic therapy)
- By intrathecal or intraventricular injection, seek specialist advice
  - Neonate
  - Child 1 month–18 years 1 mg daily (increased if necessary to 5 mg daily)

Note: only preservative-free, intrathecal preparation should be used

Eye section 11.3.1

Ear section 12.1.1

Note: Local guidelines may vary. See Pharmacokinetics above for serum-concentration monitoring. In obese or severely oedematous children use ideal weight for height to calculate the dose

GENTAMICIN (continued)

Administration for intravenous infusion, dilute in Glucose 5% or Sodium Chloride 0.9%; give over 30 minutes

For nebulisation, dilute preservative-free preparation in 3 mL sodium chloride 0.9%. Administer after physiotherapy and bronchodilators

For intrathecal or intraventricular injection, use preservative-free intrathecal preparations only

Gentamicin (Non-proprietary) *(56)*

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) *(56)*

Injection, gentamicin (as sulphate) 40 mg/mL. Net price 2-mL amp or vial = £1.48

Gentricin® (Amdipharm) *(56)*

Injection, gentamicin (as sulphate) 40 mg/mL. Net price 2-mL amp = £1.40

Isotonic Gentamicin Injection (Baxter) *(56)*

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

AMIKACIN

Cautions see under Gentamicin

Contra-indications see under Gentamicin

Side-effects see under Gentamicin

Pharmacokinetics Multiple dose regimen: one-hour (‘peak’) serum concentration should not exceed 30 mg/litre; pre-dose (‘trough’) concentration should be less than 10 mg/litre

Once daily dose regimen: pre-dose (‘trough’) concentration should be less than 5 mg/litre

Licensed use: dose for cystic fibrosis not licensed

Indication and dose

Neonatal sepsis
- Extended interval dose regimen by slow intravenous injection over 3–5 minutes or by intravenous infusion
- Neonate 15 mg/kg every 24 hours

- Multiple daily dose regimen by intramuscular or by slow intravenous injection or by infusion
- Neonate loading dose of 10 mg/kg then 7.5 mg/kg every 12 hours

Serious Gram-negative infections resistant to gentamicin
- By slow intravenous injection over 3–5 minutes
  - Child 1 month–12 years 7.5 mg/kg every 12 hours

Child 12–18 years 7.5 mg/kg every 12 hours, increased to 7.5 mg/kg every 8 hours in severe infections, max. 500 mg every 8 hours for up to 10 days (max. cumulative dose 15 g)

Once daily dose regimen (not for endocarditis or meningitis)
- By intravenous injection or infusion
  - Child 1 month–18 years initially 15 mg/kg, then adjusted according to serum-amikacin concentration

Pseudomonal lung infection in cystic fibrosis
- Multiple daily dose regimen by slow intravenous injection or infusion
  - Child 1 month–18 years 10 mg/kg every 8 hours (max. 500 mg every 8 hours)

Note: Local dosage guidelines may vary. For monitoring guidelines see Pharmacokinetics above. In obese or severely oedematous children use ideal weight for height to calculate the dose

Administration for intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9% or Compound Sodium Lactate; give over 30 minutes

Amikacin (Non-proprietary) *(56)*

Injection, amikacin (as sulphate) 250 mg/mL. Net price 2-mL vial = £10.14

Electrolytes Na+ 0.56 mmol/500-mg vial
TOBRAMYCIN

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, taste disturbances, voice alteration, cough, bronchospasm (see Cautions)

Pharmacokinetics  Intravenous extended interval dose regimen in neonates or multiple daily dose regimen: one-hour (‘peak’) serum concentration should not exceed 10 mg/litre (8–12 mg/litre in cystic fibrosis); pre-dose (‘trough’) concentration should be less than 2 mg/litre

Once daily dose regimen: pre-dose (‘trough’) concentration should be less than 1 mg/litre

Indication and dose

Neonatal sepsis

• Extended interval dose regimen by intravenous injection over 3–5 minutes or by intravenous infusion

Neonate less than 32 weeks postmenstrual age

4–5 mg/kg every 36 hours

Neonate 32 weeks and over postmenstrual age

4–5 mg/kg every 24 hours

• Multiple daily dose regimen by intramuscular injection or by slow intravenous injection or by intravenous infusion

Neonate under 7 days

2 mg/kg every 12 hours

Neonate 7–28 days

2–2.5 mg/kg every 8 hours

Septicaemia, meningitis and other CNS infections, biliary-tract infection, acute pyelonephritis, pneumonia in hospital patients

• Multiple daily dose regimen by slow intravenous injection over 3–5 minutes

Child 1 month–12 years

2–2.5 mg/kg every 8 hours

Child 12–18 years

1 mg/kg every 8 hours; in severe infections up to 5 mg/kg daily in divided doses every 6–8 hours (reduced to 3 mg/kg daily as soon as clinically indicated)

• Once daily dose regimen by intravenous infusion

Child 1 month–18 years

initially 7 mg/kg, then adjusted according to serum-tobramycin concentration

Pseudomonal lung infection in cystic fibrosis

• Multiple daily dose regimen by slow intravenous injection over 3–5 minutes

Child 1 month–18 years

8–10 mg/kg/daily in 3 divided doses

• Once daily dose regimen by intravenous infusion over 30 minutes

Child 1 month–18 years

initially 10 mg/kg (max. 660 mg), then adjusted according to serum-tobramycin concentration

Chronic pulmonary Pseudomonas aeruginosa infection in patients with cystic fibrosis

• By inhalation of nebulised solution

Child 6–18 years

300 mg every 12 hours for 28 days, subsequent courses repeated after 28-day interval without tobramycin nebuliser solution

Note: Local dosage guidelines may vary. In obese or severely oedematous children use ideal weight for height to calculate the dose. For serum concentration monitoring guidelines see Pharmacokinetics above

Administration for intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%; give over 20–60 minutes

Tobramycin (Non-proprietary) (Non-proprietary) (Non-proprietary) (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

Bramitob® (Chiesi) (Chiesi) (Chiesi) (Chiesi)

Nebuliser solution, tobramycin 75 mg/mL, net price 56 x 4-mL (300-mg) unit = £1187.00

Tobi® (Chiron) (Chiron) (Chiron) (Chiron)

Nebuliser solution, tobramycin 60 mg/mL, net price 56 x 5-mL (300-mg) unit = £1484.00

5.1.5 Macrolides

Erythromycin has an antibacterial spectrum that is similar but not identical to that of penicillin; it is thus an alternative in penicillin-allergic patients.

Indications for erythromycin include respiratory infections, whooping cough, legionnaires’ disease, and campylobacter enteritis. It is active against many penicillin-resistant staphylococci but some are now also resistant to erythromycin.

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mycin; it has poor activity against *Haemophilus influenzae*. Erythromycin is also active against chlamydia and mycoplasmas.

Erythromycin causes nausea, vomiting, and diarrhoea in some children; in mild to moderate infections this can be avoided by giving a lower dose or the total dose in 4 divided doses but if a more serious infection, such as Legionella pneumonia, is suspected higher doses are needed.

**Clarithromycin** is an erythromycin derivative with slightly greater activity than the parent compound. Tissue concentrations are higher than with erythromycin. It is given twice daily.

**Azithromycin** is a macrolide with slightly less activity than erythromycin against Gram-positive bacteria but enhanced activity against some Gram-negative organisms including *H. influenzae*. Plasma concentrations are very low but tissue concentrations are much higher. It has a long tissue half-life and once daily dosage is recommended. For treatment of Lyme disease, see section 5.1.1.3. Azithromycin is also used in the treatment of trachoma [unlicensed indication] (section 11.3.1).

Azithromycin and clarithromycin cause fewer gastro-intestinal side-effects than erythromycin.

**Spiramycin** is also a macrolide (section 5.4.7).

**Oral infections** Erythromycin is an alternative for oral infections in penicillin-allergic patients or where a beta-lactamase producing organism is involved. However, many organisms are now resistant to erythromycin or rapidly develop resistance; its use should therefore be limited to short courses. Metronidazole (section 5.1.11) may be preferred as an alternative to a penicillin.

### ERYTHROMYCIN

**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); acute porphyria (section 9.8.2); **interactions**: Appendix 1 (macrolides)

**Hepatic impairment** may cause idiosyncratic hepatotoxicity

**Renal impairment** reduce dose in severe renal impairment (ototoxicity)

**Pregnancy** not known to be harmful

**Breast-feeding** only small amounts in milk—not known to be harmful

**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; cholestatic jaundice, pancreatitis, cardiac effects (including chest pain and arrhythmias), myasthenia-like syndrome, Stevens-Johnson syndrome, and toxic epidermal necrolysis also reported

**Indication and dose**

<table>
<thead>
<tr>
<th>Susceptible infections in patients with penicillin hypersensitivity, oral infections (see notes above), campylobacter enteritis, respiratory tract infections (including legionnaires’ disease), skin infections, chlamydial ophthalmia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Child 8–18 years</strong> 250–500 mg 4 times daily; dose doubled in severe infections</td>
</tr>
<tr>
<td><strong>Note</strong> Total daily dose may be given in two divided doses</td>
</tr>
<tr>
<td><strong>By intermittent intravenous infusion</strong></td>
</tr>
<tr>
<td><strong>Neonate</strong> 10–12.5 mg/kg every 6 hours</td>
</tr>
<tr>
<td><strong>Child 1 month–18 years</strong> 12.5 mg/kg (max. 1 g) every 6 hours</td>
</tr>
<tr>
<td><strong>By continuous intravenous infusion</strong></td>
</tr>
<tr>
<td><strong>Child 1 month–18 years</strong> 50 mg/kg daily (max. 4 g daily); mild infections (oral treatment not possible) 25 mg/kg/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Early syphilis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> 500 mg 4 times daily for 14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Uncomplicated genital chlamydia, non-gonococcal urethritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Child 12–18 years</strong> 500 mg twice daily for 14 days</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Prophylaxis against pneumococcal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td><strong>Child 1 month–2 years</strong> 125 mg twice daily</td>
</tr>
<tr>
<td><strong>Child 2–8 years</strong> 250 mg twice daily</td>
</tr>
<tr>
<td><strong>Child 8–18 years</strong> 500 mg twice daily</td>
</tr>
</tbody>
</table>

**Gastric stasis** section 1.2
ERYTHROMYCIN (continued)

Acne vulgaris section 13.6

Diphtheria, whooping cough prophylaxis Table 2, section 5.1

Prevention of group A streptococcal infection Table 2, section 5.1

Administration Dilute reconstituted solution further in glucose 5% (neutralised with Sodium bicarbonate) or sodium chloride 0.9% 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. Concentration of up to 10 mg/mL may be used in fluid-restriction if administered via a central venous catheter.

Erythromycin (Non-proprietary) Capsules, enclosing e/c microgranules, erythromycin 250 mg, net price 28-cap pack = £5.95. Label: 5, 9, 25. Brands include Tiloryth.

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 100 mL = £1.71; 250 mg/5 mL, 100 mL = £2.36; 500 mg/5 mL, 100 mL = £3.82. Label: 9. Note: Sugar-free versions are available and can be ordered by specifying ’sugar-free’ on the prescription. Brands include Primacin.

Dental prescribing on NHS Erythromycin Ethyl Succinate Oral Suspension may be prescribed.

AZITHROMYCIN

Cautions see under Erythromycin; interactions: Appendix 1 (macrolides)

Pregnancy manufacturer advises use only if adequate alternatives not available.

Breast-feeding present in milk; use only if no suitable alternative.

Contra-indications Hepatic impairment avoid, jaundice reported.

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, asthenia, paraesthesia, hyperactivity, thrombocytopenia, haemolytic anaemia, interstitial nephritis, acute renal failure, photosensitivity, tooth and tongue discoloration.

Licensed use not licensed for typhoid fever or prophylaxis of group A streptococcal infection.

Indication and dose

Respiratory-tract infections, otitis media, skin and soft-tissue infections

- By mouth
  - Child over 6 months 10 mg/kg once daily (max. 500 mg 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
  - Body-weight over 45 kg 500 mg once daily for 3 days

Infection in cystic fibrosis

- By mouth
  - Child 6 months–18 years 10 mg/kg once daily (max. 500 mg once daily) for 3 days; course repeated after 1 week, then repeat as necessary.
### CLARITHROMYCIN

#### Cautions
see under Erythromycin; interactions: Appendix 1 (macrolides)

#### Hepatic impairment
hepatic dysfunction including jaundice reported

#### Renal impairment
use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; avoid Klaricid XL® if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

#### Pregnancy
manufacturer advises avoid unless potential benefit outweighs risk

#### Breast-feeding
manufacturer advises avoid unless potential benefit outweighs risk—present in milk

#### Side-effects
see under Erythromycin; also dyspepsia, tooth and tongue discolouration, smell and taste disturbances, stomatitis, glossitis, and headache; less commonly hepatitis, arthralgia, and myalgia; rarely tinnitus; very rarely pancreatitis, dizziness, insomnia, nightmares, anxiety, confusion, psychosis, paraesthesia, convulsions, hypoglycaemia, renal failure, leucopenia, and thrombocytopenia; on intravenous infusion, local tenderness, phlebitis

#### Licensed use
intravenous route not licensed for use in children

#### Indication and dose
Respiratory tract infections, mild to moderate skin and soft tissue infections, otitis media
- **By mouth**
  - Neonate 7.5 mg/kg twice daily
  - Child 1 month–12 years
    - Body-weight under 8 kg 7.5 mg/kg twice daily
    - Body-weight 8–11 kg 62.5 mg twice daily
    - Body-weight 12–19 kg 125 mg twice daily
    - Body-weight 20–29 kg 187.5 mg twice daily
    - Body-weight 30–40 kg 250 mg twice daily

#### Prevention of group A streptococcal infection
Table 2, section 5.1

### Azithromycin (continued)

#### Azithromycin (Non-proprietary)
Capsules, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £8.77, 6-cap pack = £13.16. Label: 5, 9, 23

#### 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 reconstituted with water. Net price 15-mL pack = £5.08, 22.5-mL pack = £7.62, 30-mL pack = £13.80. Label: 5, 9

#### Dental prescribing on NHS
May be prescribed as Azithromycin Oral Suspension 200 mg/5 mL

#### Administration for intermittent intravenous infu-
sion dilute reconstituted solution further in Glu-
cose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate to a concentra-
tion of 2 mg/mL; give into large proximal vein over 60 minutes

#### Helicobacter pylori eradication
section 1.3

#### Clarithromycin (Non-proprietary)
Tablets, clarithromycin 250 mg, net price 14-tab pack = £3.55; 500 mg, 14-tab pack = £7.02. Label: 9

#### Clarosip® (Grüenthal)
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. Label: 9, counselling, administration

#### Counselling
Place straw in cold or warm drink such as water, carbonated drink, or tea (but not full fat milk, milkshake, 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 = £12.00, 20-tab pack = £17.14. Label: 9

#### Paediatric suspension
clarithromycin for reconstituted with water 125 mg/5 mL, net price 70 mL

### Infections

#### 5.1.5 Macrolides

### Chronic Pseudomonas aeruginosa infection in cystic fibrosis
- **By mouth**
  - Child 6–18 years
    - Body-weight 25–40 kg 250 mg 3 times a week
    - Body-weight over 40 kg 500 mg 3 times a week

### Uncomplicated genitourinary infections
- **By mouth**
  - Child 12–18 years 1 g as a single dose

### Mild to moderate typhoid due to multiple-antimicrobial resistant organisms
- **By mouth**
  - Child 6 months–18 years 10 mg/kg once daily (max. 500 mg) for 7 days

### Prevention of group A streptococcal infection
Table 2, section 5.1

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#### Azithromycin (Non-proprietary)
Capsules, azithromycin (as dihydrate) 250 mg, net price 4-cap pack = £8.77, 6-cap pack = £13.16. Label: 5, 9, 23

#### 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 reconstituted with water. Net price 15-mL pack = £5.08, 22.5-mL pack = £7.62, 30-mL pack = £13.80. Label: 5, 9

#### Dental prescribing on NHS
May be prescribed as Azithromycin Oral Suspension 200 mg/5 mL

#### Administration for intermittent intravenous infusion dilute reconstituted solution further in Glucose 5% or Sodium chloride 0.9% or Ringer’s solution or Compound sodium lactate to a concentration of 2 mg/mL; give into large proximal vein over 60 minutes

#### Helicobacter pylori eradication
section 1.3

#### Clarithromycin (Non-proprietary)
Tablets, clarithromycin 250 mg, net price 14-tab pack = £3.55; 500 mg, 14-tab pack = £7.02. Label: 9

#### Clarosip® (Grüenthal)
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. Label: 9, counselling, administration

#### Counselling
Place straw in cold or warm drink such as water, carbonated drink, or tea (but not full fat milk, milkshake, 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 = £12.00, 20-tab pack = £17.14. Label: 9

#### Paediatric suspension
clarithromycin for reconstitution with water 125 mg/5 mL, net price 70 mL
Clindamycin

Clindamycin is active against Gram-positive cocci, including streptococci and penicillin-resistant staphylococci, and also against many anaerobes, especially *Bacteroides 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. It is also used in combination with other antibiotics for cellulitis in immunocompromised children. Clindamycin can also be used for infections associated with meticillin-resistant *Staphylococcus aureus* (MRSA) in bone and joint infections, and skin and soft-tissue infections.

Clindamycin has been associated with antibiotic-associated colitis (section 1.5), which may be fatal. Although it can occur with most antibacterials, antibiotic-associated colitis occurs more frequently with clindamycin. Children 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 bacteri.a. Clindamycin can be used for the treatment of dentoalveolar abscess that has not responded to penicillin or to metronidazole.

**Indications and dose**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcal bone and joint infections, peritonitis</td>
<td>See notes above</td>
</tr>
<tr>
<td><strong>By mouth</strong></td>
<td></td>
</tr>
<tr>
<td>Neonate under 14 days</td>
<td>3–6 mg/kg 3 times daily</td>
</tr>
<tr>
<td>Neonate 14–28 days</td>
<td>3–6 mg/kg 4 times daily</td>
</tr>
</tbody>
</table>

**Cautions**

- Discontinue immediately if diarrhoea or colitis develops; monitor liver and renal function on prolonged therapy and in neonates and infants; avoid rapid intravenous administration; avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (clindamycin)
- Pregnancy: Not known to be harmful
- Breast-feeding: Amount probably too small to be harmful; bloody diarrhoea reported in 1 infant
- 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, anaphylactoid reactions, Stevens-Johnson syndrome, toxic epidermal necrolysis, exfoliative and vesiculobullous dermatitis reported; pain, induration, and abscess after intramuscular injection; thrombophlebitis after intravenous injection

**Indication and dose**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Staphylococcal lung infection in cystic fibrosis</td>
<td><strong>By mouth</strong></td>
</tr>
<tr>
<td>Child 1 month–18 years</td>
<td>5–7 mg/kg (max. 600 mg) 4 times daily</td>
</tr>
</tbody>
</table>

**Administration**

For intravenous infusion, dilute to a concentration of not more than 18 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 10–60 minutes at a max. rate of 20 mg/kg/hour

**Treatment of falciparum malaria**

See p. 395
CLINDAMYCIN (continued)

**Clindamycin** (Non-proprietary)<br>Capsules, clindamycin (as hydrochloride) 150 mg, net price 24-cap pack = £24.87. Label: 9, 27, counselling, see above (diarrhoea)<br>Dental prescribing on NHS Clindamycin Capsules may be prescribed<br>**Liquid**, 75 mg/5 mL available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Dalacin C®** (Pharmacia)<br>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)<br>Dental prescribing on NHS May be prescribed as Clindamycin Capsules<br>**Injection**, clindamycin (as phosphate) 150 mg/mL, net price 2-mL amp = £6.20; 4-mL amp = £12.35<br>**Excipients** include benzyl alcohol (avoid in neonates, see Excipients, p. 3)

Some other antibacterials

Antibacterials discussed in this section include chloramphenicol, fusidic acid, glycopeptide antibiotics (vancomycin and teicoplanin), linezolid, the streptogramins (quinupristin and dalfopristin) and the polymyxin, colistin.

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 is also used in cystic fibrosis for the treatment of respiratory *Burkholderia cepacia* infection resistant to other antibacterials.

Grey baby syndrome may follow excessive doses in neonates with immature hepatic metabolism; monitoring of plasma concentrations is recommended.

Chloramphenicol eye drops (section 11.3.1) and chloramphenicol ear drops (section 12.1.1) are also available.

**CHLORAMPHENICOL**

**Cautions** avoid repeated courses and prolonged treatment; blood counts required before and periodically during treatment; monitor plasma-chloramphenicol concentration in neonates (see below); **interactions**: Appendix 1 (chloramphenicol)<br>Hepatic impairment avoid if possible—increased risk of bone-marrow depression; reduce dose and monitor plasma-chloramphenicol concentration<br>Renal impairment avoid in severe impairment unless no alternative; dose-related depression of haematopoiesis<br>**Contra-indications** acute porphyria (section 9.8.2)<br>Pregnancy neonatal grey-baby syndrome if used in third trimester<br>Breast-feeding use another antibiotic; may cause bone-marrow toxicity in infant; concentration in milk usually insufficient to cause ‘grey-baby syndrome’<br>**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 hae moglobinuria reported; grey syndrome (abdominal distension, pallid cyanosis, circulatory collapse) may follow excessive doses in neonates with immature hepatic metabolism (see Pharmacokinetics below)<br>**Pharmacokinetics** plasma concentration monitoring required in neonates and preferred in those under 4 years of age, and in hepatic impairment; recommended peak plasma concentration (approx. 1 hour after end of intravenous injection or infusion or 2 hours after oral administration) 15–25 mg/litre; pre-dose (‘trough’) concentration should not exceed 15 mg/litre<br>**Indication and dose**<br>See notes above<br>- **By intravenous injection**<br>Neonate up to 14 days 12.5 mg/kg twice daily<br>Neonate 14–28 days 12.5 mg/kg, 2–4 times daily<br>Note: Check dosage carefully; overdosage can be fatal (see also pharmacokinetics above)<br>- **By mouth or by intravenous injection or infusion**<br>Child 1 month–18 years 12.5 mg/kg every 6 hours; dose may be doubled in severe infections such as septicaemia, meningitis and epiglottitis providing plasma-chloramphenicol concentrations are measured and high doses reduced as soon as indicated<br>**Administration** Displacement value may be significant for injection, consult local guidelines. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%
Chloramphenicol (continued)

Kemicetine® (Pharmacia®)

Injection, powder for reconstitution, chloramphenicol (as sodium succinate). Net price 1-g vial = £1.39

Electrolytes Na⁺ 3.14 mmol/g

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 during treatment.

SODIUM FUSIDATE

Cautions monitor liver function with high doses, on prolonged therapy or in hepatic impairment; elimination may be reduced in hepatic impairment or biliary disease or biliary obstruction; interactions: Appendix 1 (fusidic acid)

Hepatic impairment impaired biliary excretion, avoid or reduce dose; possibly increased risk of hepatotoxicity, monitor liver function

Pregnancy not known to be harmful; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding present in milk; manufacturer advises caution

Side-effects nausea, vomiting, reversible jaundice, especially after high dosage or rapid infusion (withdraw therapy if persistent); rarely hypersensitivity reactions, acute renal failure (usually with jaundice), blood disorders

Indication and dose

Penicillin-resistant staphylococcal infection including osteomyelitis, staphylococcal endocarditis in combination with other antibiotics 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⁺ 3.1 mmol/vial when reconstituted with buffer

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 prophylaxis and treatment of serious infections caused by Gram-positive cocci. Vancomycin is principally excreted via the kidney and dose reduction is necessary in renal impairment.
Penetration into cerebrospinal fluid is poor; vancomycin may be administered by the intrathecal or intraventricular route for treatment of meningitis [unlicensed]. 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 for 7–10 days is effective in the treatment of *Clostridium difficile* infection (see also section 1.5); low doses (see below) are considered adequate (higher dose may be considered if the infection fails to respond or if it is severe). Vancomycin is also used by mouth in prophylaxis of neonatal necrotising enterocolitis. 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. Plasma concentration monitoring is not usually necessary, but may help optimise therapy. Unlike vancomycin, teicoplanin can be given by intramuscular as well as by intravenous injection; it is not given by mouth.

### VANCOMYCIN

**Cautions** avoid rapid infusion (risk of anaphylactoid reactions, see Side-effects); rotate infusion sites; 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 renal impairment; systemic absorption may follow oral administration especially in inflammatory bowel disorders or following multiple doses; **interactions:** Appendix 1 (vancomycin)

**Renal impairment** reduce dose—monitor plasma-vancomycin concentration and renal function regularly

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk—plasma-vancomycin concentration monitoring essential to reduce risk of fetal toxicity

**Breast-feeding** present in milk—significant absorption following oral administration unlikely

**Side-effects** after parenteral administration: nephrotoxicity including renal failure and interstitial nephritis; otoxicity (discontinue if tinnitus occurs); blood disorders including neutropenia (usually after 1 week or high cumulative dose), 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

**Pharmacokinetics** plasma concentration monitoring required; pre-dose (‘trough’) concentration should be 10–15 mg/litre (15–20 mg/litre for less sensitive strains of meticillin-resistant *Staphylococcus aureus*)

**Licensed use** not licensed for intraventricular use

### Indication and dose

**Infections due to Gram-positive bacteria including osteomyelitis, septicaemia and soft-tissue infections** see notes above

- **By intravenous infusion**
  - Neonate less than 29 weeks postmenstrual age 15 mg/kg every 24 hours
  - Neonate 29–35 weeks postmenstrual age 15 mg/kg every 12 hours
  - Neonate over 35 weeks postmenstrual age 15 mg/kg every 8 hours
  - Child 1 month–18 years 15 mg/kg every 8 hours (maximum daily dose 2 g), adjusted according to plasma concentration

**Clostridium difficile infection** (see also notes above)

- **By mouth**
  - Child 1 month–5 years 5 mg/kg 4 times daily for 7–10 days
  - Child 5–12 years 62.5 mg 4 times daily for 7–10 days
  - Child 12–18 years 125 mg 4 times daily for 7–10 days

**Prophylaxis of necrotising enterocolitis in neonates**

- **By mouth**
  - Neonate 15 mg/kg 3 times daily

**CNS infection e.g. ventriculitis**

- **By intraventricular administration, seek specialist advice**
  - Neonate 10 mg once every 24 hours
  - Child 1 month–18 years 10 mg once every 24 hours

*Note* for all children reduce to 5 mg daily if ventricular size reduced or increase to 15–20 mg once daily if ventricular size increased. Adjust dose according to CSF concentration after 3-4 days; aim for pre-dose (‘trough’) concentration less than 10 mg/litre. If CSF not draining freely reduce dose frequency to once every 2–3 days
VANCOMYCIN (continued)

Peritonitis associated with peritoneal dialysis
Add to each bag of dialysis fluid to achieve a concentration of 20–25 mg/litre

Note Vancomycin doses in BNFC for Children may differ from those in product literature

Administration Displacement value may be significant, consult product literature and local guidelines. For intermittent intravenous infusion, the reconstituted preparation should be further diluted in sodium chloride 0.9% or glucose 5% to a concentration of up to 5 mg/mL; 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 available (limited evidence); 10 mg/mL can be used if infused via a central venous line over at least 1 hour. Injection may be given orally; flavouring syrups may be added to the solution at the time of administration.

Safe Practice For intraventricular administration, seek specialist advice

TEICOPLANIN

Cautions vancomycin sensitivity; blood counts and liver and kidney function tests required—monitor renal and auditory function on prolonged administration during renal impairment or if other nephrotoxic or neurotoxic drugs given; monitor serum-teicoplanin concentration if severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), renal impairment, and in intravenous drug abusers; interactions: Appendix 1 (teicoplanin)

Renal impairment reduce dose on day 4: use half normal dose if estimated glomerular filtration rate is 40–60 mL/minute/1.73 m² and use one-third normal dose if estimated glomerular filtration rate is less than 40 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding no information available

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 alkaline phosphatase, bilirubin, and liver and kidney function tests required—monitor renal and auditory function on prolonged administration during renal impairment or if other nephrotoxic or neurotoxic drugs given; monitor serum-teicoplanin concentration if severe sepsis or burns, deep-seated staphylococcal infection (including bone and joint infection), renal impairment, and in intravenous drug abusers; interactions: Appendix 1 (teicoplanin)

Renal impairment reduce dose on day 4: use half normal dose if estimated glomerular filtration rate is 40–60 mL/minute/1.73 m² and use one-third normal dose if estimated glomerular filtration rate is less than 40 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Breast-feeding no information available

Pharmacokinetics plasma-teicoplanin concentration is not measured routinely because there is no clear relationship between plasma-teicoplanin concentration and toxicity. However, the plasma-teicoplanin concentration can be used to optimise treatment in some patients (see Cautions). Pre-dose (‘trough’) concentration should be greater than 10 mg/litre (greater than 15–20 mg/litre in endocarditis) but less than 60 mg/litre

Indication and dose

Potentially serious Gram-positive infections including endocarditis, and serious infections due to Staphylococcus aureus

● By intravenous injection or intravenous infusion over 30 minutes

Neonate initially 16 mg/kg for one dose followed 24 hours later by 8 mg/kg once daily (intravenous infusion only)

Child 1 month–18 years in moderate infections initially 10 mg/kg (max. 400 mg) every 12 hours for 3 doses, then 6 mg/kg (max. 200 mg) once daily; in severe infections or in neutropenia initially 10 mg/kg (max. 400 mg) every 12 hours for 3 doses then 10 mg/kg (max. 400 mg) once daily; after first 3 doses, subsequent doses can be given by intramuscular injection if necessary although intravenous route preferable for children

Administration For intermittent intravenous infusion, dilute reconstituted solution further in sodium chloride 0.9% or glucose 5% or compound sodium lactate intravenous infusion; give over 30 minutes. Intermittent intravenous infusion preferred in neonates

Targocid® (Aventis Pharma) (Non-proprietary)

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
Linezolid, an oxazolidinone antibacterial, is active against Gram-positive bacteria including meticillin-resistant *Staphylococcus aureus* (MRSA), and glycopeptide-resistant enterococci. Resistance to linezolid can develop with prolonged treatment or if the dose is less than that recommended. Linezolid should be reserved for infections caused by Gram-positive bacteria when the organisms are resistant to other antibacterials or when patients cannot tolerate other antibacterials. Linezolid is not active against common Gram-negative organisms; it must be given in combination with other antibacterials for mixed infections that also involve Gram-negative organisms. There is limited information on use in children and expert advice should be sought. A higher incidence of blood disorders and optic neuritis have been reported in patients receiving linezolid for more than the maximum recommended duration of 28 days.

**Cautions** monitor full blood count (including platelet count) weekly (see also CSM Advice below); unless close observation and blood-pressure monitoring possible, avoid in uncontrolled hypertension, phaeochromocytoma, carcinoid tumour, thyrotoxicosis, bipolar depression, schizophrenia, or acute confusional states; interactions: Appendix 1 (MAOIs)

**Hepatic impairment** no dose adjustment necessary but in severe hepatic impairment use only if potential benefit outweighs risk

**Renal impairment** no dose adjustment necessary but metabolites may accumulate if estimated glomerulat filtration rate less than 30 mL/minute/1.73 m²

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk—no information available

**CSM advice** 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.

**Contra-indications** see also Monoamine oxidase inhibition above

**Breast-feeding** manufacturer advises avoid—present in milk in animal studies

**Side-effects** diarrhoea (antibiotic-associated colitis reported), nausea, vomiting, taste disturbances, headache; less commonly thirst, dry mouth, glositis, 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 renal failure, pancytopenia and Stevens-Johnson syndrome; also reported, lactic acidosis; peripheral and optic neuropathy reported on prolonged therapy

**Licensed use** not licensed for use in children

**Indication and dose**

**Pneumonia, complicated skin and soft-tissue infections caused by Gram-positive bacteria (initiated under expert supervision)**

- By mouth or by intravenous infusion over 30–120 minutes

<table>
<thead>
<tr>
<th>Age</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate under 7 days</td>
<td>10 mg/kg every 12 hours, increase to every 8 hours if poor response</td>
</tr>
<tr>
<td>Neonate over 7 days</td>
<td>10 mg/kg every 8 hours</td>
</tr>
<tr>
<td>Child 1 month–12 years</td>
<td>10 mg/kg (max. 600 mg) every 8 hours</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>600 mg every 12 hours</td>
</tr>
</tbody>
</table>

**Zyvox® (Pharmacia) ▼ [UK] Tablets, 1/2, linezolid 600 mg, net price 10-tab pack = £445.00. Label: 9, 10, patient information leaflet**

**Suspension, yellow, linezolid 100 mg/5 mL when reconstituted with water, net price 150 mL (orange-
Quinupristin and dalfopristin

A combination of the streptogramin antibiotics, quinupristin and dalfopristin (as Synercid®) is licensed in adults for infections due to Gram-positive bacteria; there is limited information on use in children and expert advice should be sought. The combination should be reserved for treating infections which have failed to respond to other antibacterials (e.g. 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.

Cautions
- 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)

Hepatic impairment
- consider reducing dose to 5 mg/kg every 8 hours in moderate 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

Pregnancy
- manufacturer advises avoid unless potential benefit outweighs risk—no information available

Contra-indications
- plasma-bilirubin concentration greater than 3 times upper limit of reference range

Breast-feeding
- manufacturer advises avoid—present in milk in animal studies

Side-effects
- nausea, vomiting, diarrhoea, headache, arthralgia, myalgia, asthma, rash, pruritus, anaemia, leucopenia, eosinophilia, raised urea and creatinine; injection-site reactions on peripheral venous administration; less frequently oral candidiasis, stomatitis, constipation, abdominal pain, antibiotic-associated colitis, anorexia, peripheral oedema, hypotension, chest pain, arrhythmias, dyspnoea, hypersensitivity reactions (including anaphylaxis and urticaria), insomnia, anxiety, confusion, dizziness, paraesthesia, hypertonia, hepatitis, jaundice, pancreatitis, gout; also reported, thrombocytopenia, pancytopenia, electrolyte disturbances

Licensed use
- not licensed for use in children

Indication and dose

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. Dose expressed as a combination of quinupristin and dalfopristin (in a ratio of 3:7)

- By intravenous infusion into central vein
  - Child 1 month–18 years 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

Administration
- 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; for intravenous infusion dilute requisite dose with glucose 5% intravenous infusion to a concentration of 5 mg/mL and give over 60 minutes via central venous catheter. In an emergency, first dose may be diluted to 2 mg/mL and given over 60 minutes via peripheral line; flush line with glucose 5% before and after infusion; incompatible with sodium chloride solutions

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

Polymyxins

The polymyxin antibiotic, colistin, is active against Gram-negative organisms including Pseudomonas aeruginosa, Acinetobacter baumanii, and Klebsiella pneumoniae. It is not absorbed by mouth and is 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

**Cautions** acute porphyria (section 9.8.2); risk of bronchospasm on inhalation—may be prevented or treated with a selective beta₂ agonist; interactions: Appendix 1 (polymyxins)

**Renal impairment** monitor plasma-colistin concentration during parenteral treatment. Reduce parenteral dose in moderate to severe impairment

**Contra-indications** myasthenia gravis

**Pregnancy** avoid—possible risk of fetal toxicity especially in second and third trimesters

**Breast-feeding** present in milk but poorly absorbed from gut; manufacturers advise avoid (or use only if potential benefit outweighs risk)

**Side-effects** neurotoxicity reported especially with excessive doses (including apnoea, perioral and peripheral paraesthesia, 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

**Pharmacokinetics** see notes above; plasma concentration monitoring required for intravenous treatment in renal impairment and cystic fibrosis; recommended ‘peak’ plasma-colistin concentration (approx. 30 minutes after intravenous injection or infusion) 10–15 mg/litre (125–200 units/mL); colistin sulphate may be absorbed from the gastro-intestinal tract in infants under 6 months old

**Indication and dose**

- **Pseudomonas aeruginosa infection in cystic fibrosis**
  - **By slow intravenous injection into a totally implantable venous access device, or by intravenous infusion (but see notes above)**
  - **Child 1 month–18 years**
    - **Body-weight under 60 kg** 16 666–25 000 units/kg every 8 hours
    - **Body-weight over 60 kg** 1–2 million units every 8 hours
  - **Child 1 month–2 years** 500 000–1 million units twice daily
  - **Child 2–18 years** 1–2 million units twice daily

**Administration** For intravenous infusion, dilute to a concentration of 40 000 units/mL with Sodium Chloride 0.9%; give over 30 minutes

For slow intravenous injection into a totally implantable venous access device, dilute to a concentration of 90 000 units/mL for child under 12 years (200 000 units/mL for child over 12 years)

For nebulisation administer required dose in 2–4 mL of sodium chloride 0.9% (or water for injections). Colistin must not be mixed with tobramycin as they are chemically unstable together; it may be mixed with gentamicin if used immediately

**Colomycin®** (Forest)

**Injection, powder for reconstitution, colistimethate sodium (colistin sulphomethate sodium).** Net price 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 = £2.30

**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

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### 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 (see CSM recommendations below). Co-trimoxazole should be avoided in children less than 6 weeks of age (except for treatment and prophylaxis of *Pneumocystis pneumonia*) because of the risk of kernicterus. There is a risk of haemolytic anaemia if used in children with glucose-6-phosphate dehydrogenase (G6PD) deficiency (section 9.1.5).
CO-TRIMOXAZOLE

A mixture of trimethoprim and sulfamethoxazole in the proportions of 1 part to 5 parts

Cautions maintain adequate fluid intake; avoid in blood disorders (unless under specialist supervision); monitor blood counts on prolonged treatment; discontinue immediately if blood disorders or rash develop; predisposition to folate deficiency; asthma; G6PD deficiency (section 9.1.5); avoid in infants under 6 weeks (except for treatment or prophylaxis of pneumocystis pneumonia); interactions: Appendix 1 (trimethoprim, sulfamethoxazole)

Hepatic impairment manufacturer advises avoid in severe liver disease

Renal impairment use half normal dose if estimated glomerular filtration rate 15–30 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² and if plasma-sulfamethoxazole concentration cannot be monitored

Pregnancy teratogenic risk (trimethoprim a folate antagonist) in first trimester neonatal haemolysis and methaemoglobinaemia in 3rd trimester; fear of increased risk of kernicterus in neonates appears to be unfounded

Breastfeeding small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants (due to sulfamethoxazole)

Contra-indications acute porphyria (section 9.8.2)

Side-effects nausea, diarrhoea; headache, hyperkalaemia; rash (very rarely including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity)—discontinue immediately; less commonly vomiting; very rarely glossitis, stomatitis, anorexia, liver damage (including jaundice and hepatic necrosis), pancreatitis, antibiotic-associated colitis, myocarditis, cough and shortness of breath, pulmonary infiltrates, asceptic meningitis, depression, convulsions, peripheral neuropathy, ataxia, tinnitus, vertigo, hallucinations, hypoglycaemia, blood disorders (including leucopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia), hyponatraemia, renal disorders including interstitial nephritis, arthropathy, myalgia, vasculitis, systemic lupus erythematosus, and uveitis; rhadomyolysis reported in HIV-infected patients

Pharmacokinetics plasma concentration monitoring may be required with high doses or during moderate to severe renal impairment; seek expert advice

Licensed use not licensed for use in children under 6 weeks

Treatment of susceptible infections (but see notes above) dose expressed as co-trimoxazole

- By mouth
  - Child 6 weeks–12 years 24 mg/kg twice daily or
  - Child 6 weeks–6 months 120 mg twice daily
  - Child 6 months–6 years 240 mg twice daily
  - Child 6–12 years 480 mg twice daily
  - Child 12–18 years 960 mg twice daily

- By intravenous infusion
  - Child 6 weeks–18 years 18 mg/kg every 12 hours; increased in severe infection to 27 mg/kg (max. 1.44 g) every 12 hours

Treatment of Pneumocystis jiroveci (P. carinii) infections (undertaken where facilities for appropriate monitoring available—consult microbiologist and product literature)

- By mouth or by intravenous infusion
  - Child 1 month–18 years 60 mg/kg every 12 hours for 14 days; total daily dose may alternatively be given in 3–4 divided doses

Note oral route preferred

Prophylaxis of Pneumocystis jiroveci (P. carinii) infections

- By mouth
  - Child 1 month–18 years 450 mg/m² (max 960 mg) twice daily for three days of the week (either consecutively or on alternate days)

Note dose regimens may vary, consult local guidelines

Note 480 mg of co-trimoxazole consists of sulfamethoxazole 400 mg and trimethoprim 80 mg

Administration for intermittent intravenous infusion may be further diluted in glucose 5% and 10% or sodium chloride 0.9% or Ringer’s intravenous 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 the required dose infused over max. 60 minutes; check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

Co-trimoxazole (Non-proprietary) Tablets, co-trimoxazole 480 mg, net price 28-tab pack = £13.83; 960 mg, 20 = £4.69. Label: 9
Brands include Fectrim®, Fectrim® Forte
Paediatric oral suspension, co-trimoxazole 240 mg/5 mL, net price 100 mL = £1.12. Label: 9
Oral suspension, co-trimoxazole 480 mg/5 mL. Net price 100 mL = £4.41. Label: 9

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

Septrin® (GSK) Tablets, co-trimoxazole 480 mg. Net price 20 = £3.10. Label: 9
Forte tablets, scored, co-trimoxazole 960 mg. Net price 20 = £4.69. Label: 9
Adult suspension, co-trimoxazole 480 mg/5 mL. Net price 100 mL (vanilla-flavoured) = £4.41. Label: 9
Paediatric suspension, sugar-free, co-trimoxazole 240 mg/5 mL. Net price 100 mL (banana- and vanilla-flavoured) = £2.45. Label: 9
Intravenous infusion, co-trimoxazole 96 mg/mL. To be diluted before use. Net price 5-mL amp = £1.48
Excipients include propylene glycol, sulphites

TRIMETHOPRIM

Cautions predisposition to folate deficiency; manufacturer recommends blood counts on long-term therapy (but evidence of practical value unsatisfactory); neonates (specialist supervision required); acute porphyria (section 9.8.2);
interactions: Appendix 1 (trimethoprim)
Renal impairment use half normal dose after 3 days if estimated glomerular filtration rate 15–30 mL/minute/1.73 m²; use half normal dose immediately if estimated glomerular filtration rate less than 15 mL/minute/1.73 m² (monitor plasma-trimethoprim concentration if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²)
Breast-feeding present in milk—short-term use not known to be harmful
Blood disorders On long-term treatment, patients and 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, rash, mouth ulcers, purpura, bruising or bleeding develop
Contra-indications blood dyscrasias
Pregnancy teratogenic risk (folate antagonist) in first trimester; manufacturers advise avoid
Side-effects gastro-intestinal disturbances including nausea and vomiting, pruritus, rashes, hyperkalaemia, depression of haematopoiesis; rarely erythema multiforme, toxic epidermal necrolysis, photosensitivity and other allergic reactions including angioedema and anaphylaxis; aseptic meningitis reported
Licensed use not licensed for use in children under 6 weeks

Indication and dose
Urinary-tract infections; respiratory-tract infections
• By mouth
Neonate initially 3 mg/kg as a single dose then 1–2 mg/kg twice daily
Child 1 month–12 years 4 mg/kg (max. 200 mg) twice daily
Child 12 months–18 years 50 mg twice daily
Child 6–12 years 100 mg twice daily
Child 12–18 years 200 mg twice daily

Prophylaxis of urinary-tract infection
• By mouth
Neonate 2 mg/kg at night
Child 1 month–12 years 2 mg/kg (max. 100 mg) at night
Child 12–18 years 100 mg at night

Pneumocystis pneumonia see, p. 411

Trimethoprim (Non-proprietary) Tablets, trimethoprim 100 mg, net price 28 = 98p; 200 mg, 14-tab pack = 90p. Label: 9
Brands include Trimopan®
Suspension, trimethoprim 50 mg/5 mL, net price 100 mL = £1.62. Label: 9

5.1.9 Antituberculosis drugs

Tuberculosis is treated in two phases—an initial phase using 4 drugs and a continuation phase using two 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. Compliance with therapy is a major determinant of its success. Treatment needs to be carefully monitored in families in whom concordance may be problematic.

**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, provided the respective dose of each drug is appropriate, unless the child is unable to swallow the tablets or 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. 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). 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 although it may be used in the initial phase of treatment if resistance to isoniazid has been established before therapy is commenced and ethambutol is contra-indicated.

**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 those who are likely to take antituberculous drugs reliably without supervision. Children and families 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*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Child 1 month–18 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>5–10 mg/kg (max. 300 mg)</td>
<td>once daily</td>
</tr>
<tr>
<td><strong>Rifampicin</strong></td>
<td>10 mg/kg once daily (max. 450 mg if body-weight under 50 kg; if body-weight 50 kg and over max. 600 mg)</td>
<td>(for 2-month initial phase only)</td>
</tr>
<tr>
<td><strong>Pyrazinamide</strong></td>
<td>35 mg/kg once daily (max. 1.5 g if body-weight under 50 kg; if body-weight 50 kg and over max. 2 g)</td>
<td>(for 2-month initial phase only)</td>
</tr>
<tr>
<td><strong>Ethambutol</strong></td>
<td>15 mg/kg once daily</td>
<td>(for 2-month initial phase only)</td>
</tr>
</tbody>
</table>

Note: In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children.

The fixed-dose combination preparations (*Rifater®, Rifinah®*) are unlicensed for use in children. Consideration may be given to use of these preparations in older children, provided the respective dose of each drug is appropriate for the weight of the child.

**Pregnancy and breast-feeding**  The standard regimen (above) may be used during pregnancy and breast-feeding. Streptomycin should not be given in pregnancy.

**Neonates**  Congenital tuberculosis is acquired from maternal extrapulmonary sites at birth, particularly the genital tract; if infection is suspected, the baby will require treatment with isoniazid 10 mg/kg once daily, rifampicin 10 mg/kg once daily, pyrazinamide 35 mg/kg once daily, and ethambutol 15 mg/kg once daily. Isoniazid, rifampicin, pyrazinamide, and ethambutol are used for 2 months during the initial phase of treatment. After the initial phase, treatment is continued for a further 4 months with isoniazid and rifampicin.
**Supervised treatment** Drug administration needs to be **fully supervised** (directly observed therapy, DOT) in children or families 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)
  - Child 1 month–18 years, 15 mg/kg (max. 900 mg) 3 times a week

- **Rifampicin** (for 2-month initial and 4-month continuation phases)
  - Child 1 month–18 years, 15 mg/kg (max. 900 mg) 3 times a week

- **Pyrazinamide** (for 2-month initial phase only)
  - Child 1 month–18 years, 50 mg/kg (max. 2 g 3 times a week if body-weight under 50 kg; max. 2.5 g 3 times a week if body-weight 50 kg and over)

- **Ethambutol** (for 2-month initial phase only)
  - Child 1 month–18 years, 30 mg/kg 3 times a week

**Note** In general, doses should be rounded up to facilitate administration of suitable volumes of liquid or an appropriate strength of tablet. The exception is ethambutol due to the risk of toxicity. Doses may also need to be recalculated to allow for weight gain in younger children.

The fixed-dose combination preparations (Rifater®, Rifinah®) are unlicensed for use in children. Consideration may be given to use of these preparations in older children, provided the respective dose of each drug is appropriate for the weight of the child.

**Immunocompromised patients** Multi-resistant *Mycobacterium tuberculosis* may be present in immunocompromised children. 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, children 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** A corticosteroid should be given (in addition to antituberculosis therapy) for meningeal or pericardial tuberculosis.

**Prevention of tuberculosis** Chemoprophylaxis may be required in children who are close contacts of a case of smear-positive pulmonary tuberculosis and who are severely immunosuppressed (including congenital immunodeficiencies, cytotoxic or immunosuppressive therapy) and in those who have evidence of latent tuberculosis and require treatment with immunosuppressants; expert advice should be sought.

Chemoprophylaxis involves use of either isoniazid alone for 6 months or of isoniazid and rifampicin for 3 months (see Table 2, section 5.1).

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 and tuberculin testing, see section 14.4.

**Monitoring** Since isoniazid, rifampicin and pyrazinamide are associated with liver toxicity, hepatic function should be checked before treatment with these drugs. Those with pre-existing liver disease 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 antituberculous treatment on the one hand and to guard against serious liver damage on the other, children 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 antituberculous 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 child or their carer. Monthly tablet counts and urine examination (rifampicin imparts an orange-red coloration) may be useful indicators of compliance with treatment. Avoid both excessive and inadequate dosage. Treatment should be supervised by a specialist paediatrician.

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, chronic renal failure, malnutrition and HIV infection. In these circumstances, and in breast-fed infants treated with isoniazid, pyridoxine (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. Rifampicin induces hepatic enzymes which accelerate the metabolism of several drugs including oestrogens, corticosteroids, phenytoin, sulphonylureas, and anti-coagulants; 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 is indicated in adults for prophylaxis against M. avium complex infections in patients with a low CD4 count; it is also licensed in adults for the treatment of non-tuberculous mycobacterial disease and pulmonary tuberculosis. There is limited experience in children. As with rifampicin it induces hepatic enzymes and the effectiveness of hormonal contraceptives is reduced requiring alternative family planning methods.

Pyrazinamide is a bactericidal drug only active against intracellular dividing forms of Mycobacterium tuberculosis; it exerts its main effect only in the first two or three months. It is particularly useful in tuberculous meningitis because of good meningeal penetration. It is not active against M. bovis. Serious liver toxicity may occasionally occur (important: see Monitoring above).

Ethambutol is included in a treatment regimen if isoniazid resistance is suspected; it can be omitted if the risk of resistance is low. Side-effects of ethambutol are largely confined to visual disturbances in the form of loss of acuity, colour blindness, and restriction of visual fields. These toxic effects are more common where excessive dosage is used or if the child’s renal function is impaired. The earliest features of ocular toxicity are subjective and children and their carers should be advised to discontinue therapy immediately if deterioration in vision develops and promptly seek further advice. Early discontinuation of the drug is almost always followed by recovery of eyesight. Those who cannot understand warnings about visual side-effects should, if possible, be given an alternative drug. In particular, ethambutol should be used with caution in children until they are at least 5 years old and capable of reporting symptomatic visual changes accurately.
Where possible visual acuity should be tested by Snellen chart before treatment with ethambutol.

**Streptomycin** is now rarely used in the UK except for resistant organisms. Plasma-drug concentration should be measured in patients with impaired renal function in whom streptomycin must be used with great care. Side-effects increase after a cumulative dose of 100 g, which should only be exceeded in exceptional circumstances.

Drug-resistant tuberculosis should be treated by a specialist paediatrician with experience in such cases, and where appropriate facilities for infection-control exist. Second-line drugs available for infections caused by resistant organisms, or when first-line drugs cause unacceptable side-effects, include amikacin, capreomycin, cycloserine, newer macrolides (e.g. azithromycin and clarithromycin), quinolones (e.g. moxifloxacin) and protonamide (prothionamide; no longer on UK market). Availability of suitable formulations may limit choice in children.

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**CYCLOSERINE**

**Cautions** monitor haematological, renal, and hepatic function; **interactions**: Appendix 1 (cycloserine)

**Renal impairment** reduce dose; avoid in severe impairment

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk—crosses the placenta

**Breast-feeding** present in milk—amount too small to be harmful

**Contra-indications** 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

**Pharmacokinetics** blood concentration should not exceed a peak concentration of 30 mg/litre (measured 3–4 hours after the dose); penetrates CNS

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

Tuberculosis resistant to first-line drugs, used in combination with other drugs

- **By mouth**
  - **Child 2–12 years** initially 5 mg/kg twice daily, adjusted according to blood concentration and response
  - **Child 12–18 years** initially 250 mg twice daily for 2 weeks adjusted according to blood concentration and response to max. 500 mg twice daily

**Cycloserine**

Capsules, red/grey cycloserine 250 mg, net price 100-cap pack = £303.45. Label: 2, 8

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**ETHAMBUTOL HYDROCHLORIDE**

**Cautions** test visual acuity before treatment and warn patients to report visual changes—see notes above; young children (see notes above)—routine ophthalmological monitoring recommended

**Renal impairment** reduce dose; if creatinine clearance less than 30 mL/minute/1.73 m² monitor plasma-ethambutol concentration; risk of optic nerve damage

**Pregnancy** not known to be harmful; see notes above

**Breast-feeding** amount too small to be harmful

**Contra-indications** optic neuritis, poor vision

**Side-effects** optic neuritis, red/green colour blindness, peripheral neuritis, rarely rash, pruritus, urticaria, thrombocytopenia

**Pharmacokinetics** ‘peak’ concentration (2–2.5 hours after dose) should be 2–6 mg/litre (7–22 micromol/litre); ‘trough’ (pre-dose) concentration should be less than 1 mg/litre (4 micromol/litre); for advice on laboratory assay of ethambutol contact the Poisons Unit at New Cross Hospital (Tel (020) 7771 5360)

**Indication and dose**

Tuberculosis, used in combination with other drugs see notes above

**Ethambutol**

Tablets, ethambutol hydrochloride 100 mg (yellow), net price 56-tab pack = £11.51; 400 mg (grey), 56-tab pack = £42.74. Label: 8

*Extemporaneous formulations available see Extemporaneous Preparations, p. 8*

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**ISONIAZID**

**Cautions** slow acetylator status (increased risk of side-effects); epilepsy; history of psychosis; alcohol dependence, malnutrition, diabetes mellitus, HIV infection (risk of peripheral neuri-
isoniazid (continued)

Hepatic impairment use with caution; monitor liver function regularly and particularly frequently in the first 2 months
Renal impairment reduce dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²; risk of peripheral neuropathy
Pregnancy not known to be harmful; see notes above
Breast-feeding monitor infant for possible toxicity; theoretical risk of convulsions and neuropathy; prophylactic pyridoxine advisable in mother and infant
Hepatic disorders Children and 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; systemic lupus erythematosus-like syndrome, pellagra, hyperreflexia, difficulty with micturition, hyperglycaemia, and gynaecomastia reported; hearing loss and tinnitus (in children with end-stage renal impairment)

Indication and dose
Tuberculosis, used in combination with other drugs 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
Injection, isoniazid 25 mg/mL, net price 2-mL amp = £11.04

Pyrazinamide

Cautions diabetes; interactions: Appendix 1 (pyrazinamide)
Hepatic disorders Children and 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
Hepatic impairment monitor hepatic function—idiiosyncratic hepatotoxicity more common; avoid in severe hepatic impairment
Pregnancy manufacturer advises use only if potential benefit outweighs risk; see also notes above
Breast-feeding amount too small to be harmful
Contra-indications acute porphyria (section 9.8.2)
Side-effects hepatotoxicity including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure; nausea, vomiting, dysuria, arthralgia, sideroblastic anaemia, rash and occasionally photosensitivity
Licensed use not licensed

Indication and dose
Tuberculosis in combination with other drugs see notes above

Pyrazinamide (Non-proprietary)
Tablets, scored, pyrazinamide 500 mg. Label: 8
Available from 'special-order' manufacturers or specialist importing companies, see p. 943

Rifabutin

Cautions see under Rifampicin; acute porphyria (section 9.8.2)
Hepatic impairment reduce dose in severe hepatic impairment
Renal impairment use half normal dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²
Pregnancy manufacturer advises avoid—no information available
Breast-feeding manufacturer advises avoid—no information available

Side-effects nausea, vomiting; leucopenia, thrombocytopenia, anaemia, rarely haemolysis; 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
Licensed use not licensed for use in children

Indication and dose
Prophylaxis of Mycobacterium avium complex infections in immunosuppressed patients with low CD4 count (see product literature) Also see notes above
- By mouth
Child 1–12 years 5 mg/kg (max. 300 mg) once daily
Child 12–18 years 300 mg once daily
**RIFABUTIN (continued)**

**Treatment of non-tuberculous mycobacterial disease, in combination with other drugs**

- **By mouth**
  - **Child 1 month–12 years** 5 mg/kg once daily for up to 6 months after cultures negative
  - **Child 12–18 years** 450–600 mg once daily for up to 6 months after cultures negative

**Treatment of pulmonary tuberculosis, in combination with other drugs**

- **By mouth**
  - **Child 12–18 years** 150–450 mg once daily for at least 6 months

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**RIFAMPICIN**

**Indication and dose**

**Tuberculosis, in combination with other drugs**

see notes above

**Prophylaxis of meningococcal meningitis and Haemophilus influenzae (type b) infection**

Table 2, section 5.1

**Brucellosis, legionnaires disease, serious staphylococcal infections, in combination with other antibacterials**

- **By mouth or by intravenous infusion**
  - **Neonates** 5–10 mg/kg twice daily
  - **Child 1 month–1 year** 5–10 mg/kg twice daily
  - **Child 1–18 years** 10 mg/kg (max. 600 mg) twice daily

**Pruritus due to cholestasis**

- **By mouth**
  - **Child 1 month–18 years** 5–10 mg/kg (max. 600 mg) once daily

**Administration**

Owing to risk of contact sensitisation care must be taken to avoid contact during preparation and infusion. Displacement value may be significant, consult local reconstitution guidelines; reconstitute with solvent provided. May be further diluted with glucose 5% and 10% or sodium chloride 0.9% or Ringer’s solution to a final concentration of 1.2 mg/mL; in fluid restricted patients up to 6 mg/mL may be used. Infuse over 2–3 hours.

**Rifampicin (Non-proprietary)**

**Capsules**

- rifampicin 150 mg, net price 20 = £4.17; 300 mg, 20 = £10.44. Label: 8, 14, 22, counselling, see contact 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 contact lenses above

**Syrup**

- red, rifampicin 100 mg/5 mL (raspberry-flavoured). Net price 120 mL = £3.70. Label: 8, 14, 22, counselling, see contact lenses above

**Excipients** include sucrose

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**Cautions**

- liver function tests and blood counts in hepatic disorders, and on prolonged therapy, see also below; acute porphyria (section 9.8.2);
- important: advise those on hormonal contraceptives to use additional means (see also section 7.3.1); discoulours 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**

- Children and 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

**Hepatic impairment**

- impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily

**Pregnancy**

- manufacturers advise very high doses teratogenic in animal studies in 3rd trimester; risk of neonatal bleeding may be increased; see also notes above

**Breast-feeding**

- amount too small to be harmful

**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, disseminated intravascular coagulation and acute renal failure, thrombocytopenic purpura; alterations of liver function, jaundice; flushing, urticaria, and rashes; other side-effects reported include oedema, psychoses, adrenal insufficiency, muscular weakness and myopathy, exfoliative dermatitis, toxic epidermal necrolysis, Stevens-Johnson syndrome, pemphigoid reactions, leucopenia, eosinophilia, menstrual disturbances; urine, saliva, and other body secretions coloured orange-red; thrombophlebitis reported if infusion used for prolonged period

**Licensed use**

- not licensed for use in children for pruritus due to cholestasis

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**Mycobutin® (Pharmacia)**

**Capsules**, red-brown, rifabutin 150 mg. Net price 30-cap pack = £90.38. Label: 8, 14, counselling, lenses, see under Rifampicin

**Extemporaneous formulations available see Extemporaneous Preparations, p. 8**
RIFAMPICIN

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 contact lenses above

Combines preparations See notes above

STREPTOMYCIN

Cautions see under Aminoglycosides, section 5.1.4; measure plasma-concentration in renal impairment; 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
Pharmacokinetics 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)
Licensed use not licensed for use in children

Indication and dose
Tuberculosis, resistant to other treatment, in combination with other drugs
• By deep intramuscular injection
Child 1 month–18 years 15 mg/kg (max. 1 g) once daily

Adjunct to doxycycline in brucellosis, expert advice essential
• By deep intramuscular injection
Child 1 month–18 years 5–10 mg/kg every 6 hours; total daily dose may alternatively be given in 2–3 divided doses

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
Classification not used in BNF for Children.

5.1.11 Metronidazole

Metronidazole is an antimicrobial drug with high activity against anaerobic bacteria and protozoa. It is also used for surgical and gynaecological sepsis in which its activity against colonic anaerobes, especially Bacteroides fragilis, is important. 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. Metronidazole is well absorbed orally and the intravenous route is normally reserved for severe infections. 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.

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).

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 periocrinosis; suitable alternatives are amoxicillin (section 5.1.1.3) and erythromycin (section 5.1.5). For these purposes treatment with metronidazole 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**

**Cautions**

- disulfiram-like reaction with alcohol, clinical and laboratory monitoring advised if treatment exceeds 10 days; **interactions:** Appendix 1 (metronidazole)

**Hepatic impairment** in severe liver disease reduce total daily dose to one-third, and give once daily; use with caution in hepatic encephalopathy

**Pregnancy** manufacturer advises avoidance of high-dose regimens; use only if potential benefit outweighs risk

**Breast-feeding** significant amount in milk; manufacturer advises avoid large single doses though otherwise compatible; may give milk a bitter taste

**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, psychotic 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

**Licensed use** not licensed for use in neonates or children under 1 year

**Indication and dose**

**Protozoal infections** section 5.4.2

**Anaerobic infections** (usually treated for 7 days and for 7–10 days in *Clostridium difficile* infection)

- **By mouth**
  - Neonate: initially 15 mg/kg then 7.5 mg/kg twice daily
  - Child 1 month–12 years: 7.5 mg/kg (max. 400 mg) every 8 hours
  - Child 12–18 years: 400 mg every 8 hours

- **By rectum**
  - Child 1 month–1 year: 125 mg 3 times daily for 3 days, then twice daily thereafter
  - Child 1–5 years: 250 mg 3 times daily for 3 days, then twice daily thereafter
  - Child 5–12 years: 500 mg 3 times daily for 3 days, then twice daily thereafter
  - Child 12–18 years: 1 g 3 times daily for 3 days, then twice daily thereafter

- **By intravenous infusion over 20–30 minutes**

  - Neonate 15 mg/kg as a single loading dose, followed after 24 hours by 7.5 mg/kg every 12 hours thereafter
  - Child 1 month–18 years: 7.5 mg/kg (max. 500 mg) every 8 hours

**Pelvic inflammatory disease** (see also Table 1, section 5.1)

- **By mouth**
  - Child 12–18 years: 400 mg twice daily for 14 days

**Acute ulcerative gingivitis and other acute dental infections**

- **By mouth**
  - Child 1–3 years: 50 mg every 8 hours
  - Child 3–7 years: 100 mg every 12 hours
  - Child 7–10 years: 100 mg every 8 hours
  - Child 10–18 years: 200 mg every 8 hours

**Helicobacter pylori eradication** section 1.3

**Surgical prophylaxis**

- **By mouth or by intravenous infusion**
  - Child 1 month–12 years: 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
  - Child 12–18 years: 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

- **By rectum**
  - Child 5–10 years: 500 mg 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures

  - Child 10–18 years: 1 g 2 hours before surgery; up to 3 further doses of 1 g may be given every 8 hours for high-risk procedures

**Note** Metronidazole doses in BNF for Children 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 *Norzol*®

- **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) (NHSA)

- **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
**5.1.12 Quinolones**

Nalidixic acid is 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 is licensed in children over 1 year of age for pseudomonal infections in cystic fibrosis, for complicated urinary-tract infections, and for treatment and prophylaxis of inhalation anthrax. When the benefits of treatment outweigh the risks, ciprofloxacin is licensed in children over 1 year of age for severe infections of the respiratory tract and of the gastro-intestinal system (including typhoid fever). It is also used in the treatment of septicaemia caused by multi-resistant organisms (usually hospital acquired) and gonorrhoea (although resistance is increasing). Ciprofloxacin is also used in the prophylaxis of meningococcal disease.

Many staphylococci are resistant to quinolones and their use should be avoided in MRSA infections.

Ofloxacin eye drops are used in ophthalmic infections (section 11.3.1).

There is much less experience of the other quinolones in children; expert advice should be sought.

**Anthrax**  *Inhalation* or *gastro-intestinal anthrax* should be treated initially with either ciprofloxacin or, in children over 12 years, doxycycline [unlicensed indication] (section 5.1.3) combined with one or two other antibacterials (such as amoxicillin, benzylpenicillin, chloramphenicol, clarithromycin, clindamycin, 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 children with a history of epilepsy or conditions that predispose to seizures, in G6PD deficiency (section 9.1.5), myasthenia gravis (risk of exacerbation). 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).
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 is justified. Nalidixic acid is used for resistant urinary-tract infections in children over 3 months of age.

**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;
- 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, thrombocytopenia), 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, convulsions, psychoses, paraesthesia, renal failure, interstitial nephritis, tendon 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 (including severe rash) occur.

**CIPROFLOXACIN**

**Cautions** see notes above; avoid excessive alkalinity of urine and ensure adequate fluid intake (risk of crystalluria); **interactions:** Appendix 1 (quinolones)

**Skilled tasks** May impair performance of skilled tasks (e.g. driving)

**Renal impairment** reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²—consult product literature

**Breast-feeding** amount probably too small to be harmful but manufacturer advises avoid

**Contra-indications**

- **Pregnancy** avoid—arthropathy in animal studies; safer alternatives available

**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, vasculitis, and tenosynovitis

**Licensed use** licensed for use in children over 1 year for complicated urinary-tract infections, for pseudomonal lower respiratory-tract infections in cystic fibrosis, for prophylaxis and treatment of inhalational anthrax; licensed for use in children over 1 year for other infections where the benefit is considered to outweigh the potential risks; not licensed for use in children for gastro-intestinal anthrax; not licensed for use in children for prophylaxis of meningococcal meningitis; not licensed for use in children under 1 year of age

**Indication and dose**

- **Complicated urinary-tract infections**
  - **By mouth**
    - **Neonate** 7.5 mg/kg twice daily
  - **Child 1 month–1 year** 5–7.5 mg/kg twice daily; dose doubled in severe infection
  - **Child 1–18 years** 10 mg/kg twice daily; dose doubled in severe infection (max. 750 mg twice daily)

- **By intravenous infusion over 60 minutes**
  - **Neonate** 5 mg/kg every 12 hours
  - **Child 1 month–1 year** 4 mg/kg every 12 hours; dose doubled in severe infection
  - **Child 1–18 years** 6 mg/kg every 8 hours; increased to 10 mg/kg every 8 hours in severe infection (max. 400 mg every 8 hours)
CIPROFLOXACIN (continued)

Severe respiratory-tract infections, gastro-intestinal infections; see notes above
- **By mouth**
  - Neoneate 7.5 mg/kg twice daily
  - Child 1 month–1 year 5–7.5 mg/kg twice daily; dose doubled in severe infection
  - Child 1–18 years 20 mg/kg (max. 750 mg) twice daily
  - **By intravenous infusion over 60 minutes**
    - Neoneate 5 mg/kg every 12 hours
    - Child 1 month–1 year 4 mg/kg every 12 hours; dose doubled in severe infection
    - Child 1–18 years 10 mg/kg (max. 400 mg) every 8 hours

Pseudomonal lower respiratory-tract infection in cystic fibrosis
- **By mouth**
  - Child 1 month–1 year 15 mg/kg twice daily
  - Child 1–18 years 20 mg/kg (max. 750 mg) twice daily
  - **By intravenous infusion over 60 minutes**
    - Child 1 month–1 year 4–8 mg/kg every 12 hours
    - Child 1–18 years 10 mg/kg (max. 400 mg) every 8 hours

Gonorrhoea
- **By mouth**
  - Child 12–18 years 500 mg as a single dose

Anthrax (treatment and post-exposure prophylaxis, see notes above)
- **By mouth**
  - Child 1 month–18 years 15 mg/kg (max. 500 mg) twice daily
- **By intravenous infusion over 60 minutes**
  - Child 1 month–18 years 10 mg/kg (max. 400 mg) every 12 hours

Eye infections section 11.3.1

Prophylaxis of meningococcal meningitis Table 2, section 5.1

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 f/c, ciprofloxacin (as hydrochloride) 250 mg (scored), net price 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
- **Electrolytes** Na⁺ 15.4 mmol/100-mL bottle

NALIDIXIC ACID

Cautions see notes above; avoid in acute porphyria (section 9.8.2); 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)

Hepatic impairment manufacturer advises caution in liver disease

Renal impairment use with caution; avoid if estimated glomerular filtration rate less than 20 mL/minute/1.73 m²

Breast-feeding risk to infant very small but one case of haemolytic anaemia reported

Contra-indications

Pregnancy avoid—arthropathy in animal studies; safer alternatives available

Side-effects see notes above; also reported toxic psychosis, increased intracranial pressure, cranial nerve palsy, metabolic acidosis

Licensed use not licensed for use in children under 3 months of age

Indication and dose

Urinary tract infection resistant to other antibiotics
- **By mouth**
  - Child 3 months–12 years 12.5 mg/kg 4 times daily for 7 days, reduced to 7.5 mg/kg 4 times daily in prolonged therapy or 15 mg/kg twice daily for prophylaxis
  - Child 12–18 years 900 mg 4 times daily for 7 days, reduced in chronic infections to 600 mg 4 times daily

Uriben® (Rosemont)
- **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/5 mL
Urinary-tract infections

Urinary-tract infection is more common in adolescent girls than in boys; when it occurs in adolescent boys 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.

Whenever possible a specimen of urine should be collected for culture and sensitivity testing before starting antibacterial therapy. The antibacterial chosen should reflect current local bacterial sensitivity to antibacterials.

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, or amoxicillin for 3 days; children should be reassessed if they continue to be unwell 24–48 hours after the initial assessment.

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 intravenous 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 antibacterials such as ampicillin with gentamicin, or cefotaxime alone, until the infection responds; full doses of oral antibacterials are then given for a further period.

**Resistant infections** Widespread bacterial resistance, especially to amoxicillin, ampicillin, and trimethoprim has increased the importance of urine culture before therapy. Alternatives for resistant organisms include co-amoxiclav (amoxicillin with clavulanic acid), an oral cephalosporin, pivmecillinam, or a quinolone.

**Antibacterial prophylaxis** 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 is contraindicated in children under 3 months of age because of the theoretical possibility of haemolytic anaemia.

**Pregnancy** 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.

**Renal impairment** 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, methamine, and nitrofurantoin should be avoided altogether.

**NITROFURANTOIN**

**Cautions** anaemia; diabetes mellitus; electrolyte imbalance; vitamin B and folate deficiency; pulmonary disease; monitor lung and liver function on long-term therapy (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)

**Hepatic impairment** cholestatic jaundice and chronic active hepatitis reported

**Pregnancy** may produce neonatal haemolysis if used at term
NITROFURANTOIN (continued)

Contra-indications infants less than 3 months old, G6PD deficiency, acute porphyria (section 9.8.2)
Renal impairment avoid if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; risk of peripheral neuropathy; ineffective because of inadequate urine concentrations
Breast-feeding avoid; only small amounts in milk but enough to produce haemolysis in G6PD-deficient infants (section 9.1.5)

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, slialadenitis, 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

Indication and dose

Acute uncomplicated urinary tract infection
• By mouth
  Child 3 months–12 years 750 micrograms/kg 4 times daily for 3–7 days
  Child 12–18 years 50 mg 4 times daily for 3–7 days; increased to 100 mg 4 times daily in severe chronic recurrent infections

Prophylaxis of urinary tract infection (but see Cautions)
• By mouth
  Child 3 months–12 years 1 mg/kg at night

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 (oropharynx), 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 to treat aspergillosis. Itraconazole is an alternative for refractory infection or for patients who cannot tolerate amphotericin. Itraconazole is also used as an adjunct in the treatment of allergic bronchopulmonary aspergillosis. Caspofungin is licensed in children for invasive aspergillosis unresponsive to amphotericin or to itraconazole, or in children who cannot tolerate amphotericin or itraconazole; information on use in children is limited.

Candidiasis Many superficial candidal infections, including infections of the skin (section 13.10.2), are treated locally. Systemic antifungal treatment is required in widespread or intractable infection. Vaginal candidiasis can be treated
with locally acting antifungals (section 7.2.2); alternatively, fluconazole 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 reliably absorbed and is effective. Itraconazole can be used for fluconazole-resistant infections. Topical therapy may not be adequate in immunocompromised children 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 children 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 children intolerant of amphotericin. In refractory cases, flucytosine can be used with amphotericin.

Cryptococcosis Cryptococcosis is uncommon but infection in the immunocompromised, especially HIV-infected children, 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 with 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 infection 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 children. Itraconazole can be used for the treatment of immunocompetent children with indolent non-meningeal infection including chronic pulmonary histoplasmosis. Amphotericin by intravenous infusion is preferred in children 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; it is effective against infections caused by Trichophyton 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 children 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; they should be used under specialist advice. Although terbinafine is not licensed for use in children, it is considered to be the drug of choice for onychomycosis. 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 children Immunocompromised children 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 treatment of *Candida albicans* infection.

Caspofungin is licensed for the empirical treatment of systemic fungal infections (such as those involving *Candida* spp. or *Aspergillus* spp.) in children 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 *Amphocil*) are significantly less toxic and are recommended when the conventional formulation of amphotericin is contra-indicated 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 (section 13.10.2) and mucous membranes, including oesophageal and intestinal candidiasis.

**Imidazole antifungals** The imidazole antifungals include clotrimazole, econazole, 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. There is limited information available on use in children. 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 children with liver disease; fluconazole is less frequently associated with hepatotoxicity.

Voriconazole is a broad-spectrum antifungal drug which is licensed in adults for the treatment of life-threatening infections.

**Echinocandin antifungals** Caspofungin is active against *Aspergillus* spp. and *Candida* spp. It is given by intravenous infusion for invasive infection resistant to other antifungals. Micafungin is licensed for the treatment of candidiasis.

**Other antifungals** Flucytosine is used with amphotericin in a synergistic combination. Bone marrow depression can occur which limits its use, particularly in children with AIDS; 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. Griseofulvin is used in the treatment of tinea capitis. It is the drug of choice for
Infections

5 Infections

AMPHOTERICIN
(Amphoterin B)

Cautions when given parenterally, toxicity common (close supervision necessary and close observation required for at least 30 minutes after test dose; see Anaphylaxis below); hepatic and renal function tests, blood counts and plasma electrolyte (including plasma-potassium and magnesium concentration) monitoring required; corticosteroids (avoid except to control reactions); avoid rapid infusion (risk of arrhythmias); interactions: Appendix 1 (amphotericin)

Renal impairment use only if no alternative; nephrotoxicity may be reduced with use of lipid formulation

Pregnancy not known to be harmful; but manufacturers advise avoid unless potential benefit outweighs risk

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. Prophylactic antipyretics 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 (discontinue treatment), rash, anaphylactoid reactions (see Anaphylaxis, above); pain and thrombophlebitis at injection site

Licensed use intravenous conventional formulation of amphotericin (Fungizone®) is licensed for use in children (age range not specified by manufacturer); lipid formulations (Abelcet®, Amphocil®) are licensed for use in children (age range not specified by manufacturers), Ambisome® not licensed for use in children under 1 month

Indication and dose

Oral and peroral infections section 12.3.2

Systemic fungal infections

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) Intravenous infusion, powder for reconstitution, amphotericin (as sodium deoxycholate complex), net price 50-mg vial = £4.12

Electrolytes Na+ < 0.5 mmol/vial

Dose

Systemic fungal infection

By intravenous infusion

Neonate initial test dose of 100 micrograms/kg included as part of first dose of 1 mg/kg; then 1 mg/kg once daily (after 7 days, may be reduced to 1 mg/kg on alternate days)

Child 1 month–18 years initial test dose of 100 micrograms/kg (max. 1 mg) included as part of first dose of 250 micrograms/kg daily; increased over 2–4 days, if tolerated, to 1 mg/kg/day; in severe infection max. 1.5 mg/kg/day 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) 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

Severe invasive candidiasis; severe systemic fungal infections in children not responding to conventional amphotericin or to other antifungal drugs or where toxicity or renal impairment precludes conventional amphotericin, including invasive aspergillosis, cryptococcal meningitis and disseminated cryptococcosis in children with HIV

By intravenous infusion

Child 1 month–18 years initial test dose of 100 micrograms/kg (max. 1 mg) then 5 mg/kg once daily

Administration for intravenous infusion, 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 in Glucose 5% to a concentration of 2 mg/mL; preferably give via an infusion pump at a rate of 2.5 mg/kg/hour (initial test dose 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

Terbinafine is the drug of choice for fungal nail infections and is also used for ringworm infections where oral treatment is considered appropriate.
**5.2 Antifungal drugs**

**AMPHoterINc (continued)**

AmBisome® (Gilead) \[**BNFC 2009 5.2 Antifungal drugs 365**\]

**Intravenous infusion**, powder for reconstitution, amphotericin 50 mg encapsulated in liposomes, net price 50-mg vial = £196.69

**Electrolytes** Na⁺ < 0.5 mmol/vial

**Excipients** include sucrose 900 mg/vial

**Dose**

Severe systemic or deep mycoses where toxicity (particularly nephrotoxicity) precludes use of conventional amphotericin

- By intravenous infusion

**Neonate** initial test dose 100 micrograms/kg then 1 mg/kg once daily, increased if necessary to 3 mg/kg once daily, max. 5 mg/kg once daily

**Child 1 month–18 years** initial test dose 100 micrograms/kg then 1 mg/kg once daily, increased if necessary in steps of 1 mg/kg daily to 3 mg/kg once daily, max. 5 mg/kg once daily

Suspected or proven infection in febrile neutropenic patients unresponsive to broad-spectrum antibacterials

- By intravenous infusion

**Child 1 month–18 years** initial test dose 100 micrograms/kg then 1 mg/kg once daily, increased if necessary to 3 mg/kg once daily until afebrile for 3 consecutive days; max. period of treatment 42 days; max. 5 mg/kg once daily

**Visceral leishmaniasis** see section 5.4.5 and product literature

**Administration** for intravenous infusion, 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 Glucose 5% 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 given over 10 minutes); incompatible with sodium chloride solutions—flush existing intravenous line with Glucose 5% or use separate line

Amphotcil® (Beacon) \[**BNFC 2009 5.2 Antifungal drugs 365**\]

**Intravenous infusion**, powder for reconstitution, amphotericin as a complex with sodium cholesterol sulphate, net price 50-mg vial = £104.10, 100-mg vial = £190.05

**Electrolytes** Na⁺ < 0.5 mmol/vial

**Dose**

Severe systemic or deep mycoses where toxicity or renal failure precludes use of conventional amphotericin

- By intravenous infusion

**Child 1 month–18 years** initial test dose 100 micrograms/kg then 1 mg/kg once daily, increased if necessary to 3 mg/kg once daily; increased gradually if necessary to 3–4 mg/kg once daily; max. 6 mg/kg daily

**Administration** for intravenous infusion, initially reconstitute with Water for Injections (50 mg in 10 mL, 100 mg in 20 mL) shaking gently to dissolve (fluid may be opalescent) then dilute to a concentration of 625 micrograms/mL with Glucose 5% (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 (for initial test dose use a 100 microgram/mL solution and give over 10 minutes); incompatible with sodium chloride or other electrolyte solutions, flush existing intravenous line with Glucose 5% or use separate line

**C)ASPOFUNGIN**

**Cautions** interactions: Appendix 1 (caspofungin)

- Hepatic impairment usual initial dose, then use 70% of normal maintenance dose in moderate hepatic impairment; no information available for severe hepatic impairment

- Pregnancy manufacturer advises avoid unless essential—toxicity in animal studies

**Contra-indications**

- Breast-feeding present in milk in animal studies—manufacturer advises avoid

- Side-effects nausea, vomiting, abdominal pain, diarrhoea; tachycardia, flushing, hypotension; dyspnoea; fever, headache; anaemia, decrease in serum potassium, hypomagnesaemia; rash, pruritus, sweating; injection-site reactions; also reported, hepatic dysfunction, oedema, acute respiratory distress syndrome, hypersensitivity reactions (including anaphylaxis), and hypercalcaemia

**Indication and dose**

Invasive aspergillosis either unresponsive to amphotericin or itraconazole or in patients intolerant of amphotericin or itraconazole; invasive candidiasis (see notes above); empirical treatment of systemic fungal infections in patients with neutropenia

- By intravenous infusion

**Child 1–18 years** 70 mg/m² (max. 70 mg) on first day then 50 mg/m² (max. 70 mg) once daily; increased to 70 mg/m² (max. 70 mg) daily if lower dose tolerated but inadequate response

**Administration** for intravenous infusion, allow vial to reach room temperature; initially reconstitute 50 mg with 10.5 mL Water for Injections to produce a 5.2 mg/mL solution, or reconstitute 70 mg with 10.5 mL Water for Injections to produce a 7.2 mg/mL solution; mix gently to dissolve; dilute requisite dose to a final concentration not exceeding 500 micrograms/mL with Sodium Chloride 0.9% or Compound Sodium Lactate; give over 60 minutes; incompatible with glucose solutions

Cancidas® (MSD) \[**BNFC 2009 5.2 Antifungal drugs 365**\]

**Intravenous infusion**, powder for reconstitution, caspofungin (as acetate), net price 50-mg vial = £327.67; 70-mg vial = £416.78
**FLUCONAZOLE**

**Cautions** concomitant use with hepatotoxic drugs, monitor liver function with high doses or extended courses—discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis); susceptibility to QT interval prolongation; interactions: Appendix 1 (antifungals, triazole)

**Hepatic impairment** toxicity with related drugs

**Renal impairment** usual initial dose then halve subsequent doses if estimated glomerular filtration rate less than 50 mL/minute/1.73m²

**Pregnancy** manufacturer advises avoid—multiple congenital abnormalities reported with long-term high doses

**Breast-feeding** present in milk but amount probably too small to be harmful

**Contra-indications** acute porphyria (section 9.8.2)

**Side-effects** nausea, abdominal discomfort, diarrhoea, flatulence, headache, rash (discontinue treatment or monitor closely if infection invasive or systemic); less frequently dyspepsia, vomiting, taste disturbance, hepatic disorders, angioedema, anaphylaxis, dizziness, seizures, alopecia, pruritus, toxic epidermal necrolysis, Stevens-Johnson syndrome (severe cutaneous reactions more likely in AIDS patients), hyperlipidaemia, leucopenia, thrombocytopenia, and hypokalaemia reported

**Licensed use** not licensed for tinea infections in children, or for vaginal candidiasis in girls under 16 years, or for prevention of relapse of cryptococcal meningitis after completion of primary therapy in children with AIDS

**Indication and dose**

**Mucosal candidiasis (except genital)**

- **By mouth or by intravenous infusion**
  - **Neonate under 2 weeks** 3–6 mg/kg on first day then 3 mg/kg every 72 hours
  - **Neonate 2–4 weeks** 3–6 mg/kg on first day then 3 mg/kg every 48 hours
  - **Child 1 month–12 years** 3–6 mg/kg on first day then 3 mg/kg (max. 100 mg) daily for 7–14 days (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)
  - **Child 12–18 years** 50 mg daily (100 mg daily in unusually difficult infections) given for 7–14 days in oropharyngeal candidiasis (max. 14 days except in severely immunocompromised patients); for 14–30 days in other mucosal infections (e.g. oesophagitis, candiduria, non-invasive bronchopulmonary infections)

**Vaginal candidiasis (see also Recurrent Vulvovaginal Candidiasis, section 7.2.2)**

- **By mouth**
  - **Child under 16 years (post-puberty)** a single dose of 150 mg

**Candidal balanitis**

- **By mouth**
  - **Child 16–18 years** a single dose of 150 mg

**Tinea pedis, corporis, cruris, pityriasis versicolor, and dermal candidiasis**

- **By mouth**
  - **Child 1 month–18 years** 3 mg/kg (max. 50 mg) daily for 2–4 weeks (for up to 6 weeks in tinea pedis); max. duration of treatment 6 weeks

**Invasive candidal infections (including candidaemia and disseminated candidiasis) and cryptococcal infections (including meningitis)**

- **By mouth or by intravenous infusion**
  - **Neonate under 2 weeks** 6–12 mg/kg every 72 hours, treatment continued according to response (at least 8 weeks for cryptococcal meningitis)
  - **Neonate 2–4 weeks** 6–12 mg/kg every 48 hours, treatment continued according to response (at least 8 weeks for cryptococcal meningitis)
  - **Child 1 month–18 years** 6 mg/kg (max. 800 mg) daily, treatment continued according to response (at least 8 weeks for cryptococcal meningitis)

**Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy**

- **By mouth or by intravenous infusion**
  - **Child 1 month–18 years** 6 mg/kg (max. 200 mg) daily

**Prevention of fungal infections in immunocompromised patients**

- **By mouth or by intravenous infusion**
  - **Neonate under 2 weeks** according to extent and duration of neutropenia, 3–12 mg/kg every 72 hours
  - **Neonate 2–4 weeks** according to extent and duration of neutropenia, 3–12 mg/kg every 48 hours
  - **Child 1 month–18 years** according to extent and duration of neutropenia, 3–12 mg/kg every 48 hours

**Administration** for intravenous infusion, give over 10–30 minutes; do not exceed an infusion rate of 5–10 mL/minute
FLUCONAZOLE (continued)

Fluconazole (Non-proprietary) 

Capsules, fluconazole 50 mg, net price 7-cap pack = £9.8p; 150 mg, single-capule pack = £9.1p; 200 mg, 7-cap pack = £2.02. Label: 9. (50 and 200 mg)

Dental prescribing on NHS Fluconazole Capsules 50 mg may be prescribed

Intravenous infusion, fluconazole 2 mg/mL, net price 25-mL bottle = £7.32; 100-mL bottle = £29.28

Diflucan® (Pfizer) 

Capsules, fluconazole 50 mg (blue/white), net price 7-cap pack = £16.61; 150 mg (blue), single-capsule pack = £7.12; 200 mg (purple/white), 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

Dental prescribing on NHS May be prescribed as Fluconazole Oral Suspension 50 mg/5 mL.

Intravenous infusion, fluconazole 2 mg/mL in sodium chloride intravenous infusion 0.9%, net price 25-mL bottle = £7.32; 100-mL bottle = £29.28

Electrolytes Na+ 15 mmol/100-mL bottle

FLUCYTOSINE

Cautions blood disorders; liver- and kidney-function tests and blood counts required (weekly in renal impairment or blood disorders); interactions: Appendix 1 (flucytosine)

Renal impairment use normal dose every 12 hours if estimated glomerular filtration rate 20–40 mL/minute/1.73 m²; use normal dose every 24 hours if estimated glomerular filtration rate 10–20 mL/minute/1.73 m²; use initial normal dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m² and then adjust dose according to plasma-flucytosine concentration

Pregnancy teratogenic in animal studies; manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises avoid—although risk to infant probably small

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 including thrombocytopenia, leucopenia, and aplastic anaemia reported

Pharmacokinetics 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)

Licensed use tablets not licensed

Indication and dose

Systemic yeast and fungal infections, adjunct to amphotericin in severe systemic candidiasis and in other severe or long-standing infections

- By intravenous infusion or by mouth

Neonate 50 mg/kg every 12 hours

Child 1 month–18 years 50 mg/kg every 6 hours; extremely sensitive organisms, 25–37.5 mg/kg every 6 hours may be sufficient; treatment continued usually for not more than 7 days

Cryptococcal meningitis (adjunct to amphotericin, see Cryptococcosis, p. 362)

- By intravenous infusion or by mouth

Neonate 50 mg/kg every 12 hours

Child 1 month–18 years 25 mg/kg every 6 hours for 2 weeks

Administration for intravenous infusion, give over 20–40 minutes through a giving set with a 15-micron filter

Ancotil® (Valeant) 

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 may be available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

GRISEOFULVIN

Cautions interactions: Appendix 1 (griseofulvin)

Skilled tasks May impair performance of skilled tasks; effects of alcohol enhanced

Contra-indications systemic lupus erythematosus (risk of exacerbation); acute porphyria (section 9.8.2)

Hepatic impairment avoid in severe liver disease

Pregnancy avoid pregnancy during and for 1 month after treatment (fetotoxicity and teratogenicity in animals); effective contraception required during and for at least 1 month after administration

(important: effectiveness of oral contraceptives reduced); also males should avoid fathering a child during and for at least 6 months after treatment

Breast-feeding avoid—no information available

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

1. Capsules can be sold to the public for vaginal candidiasis and associated candidal balanitis in those aged 16–18 years, in a container or packaging containing not more than 150 mg and labelled to show a max. dose of 150 mg
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1 GRSEOFULVIN (continued)

Licensed use  tablets licensed for use in children
(age range not specified by manufacturer); suspen-
sion not licensed

Indication and dose

Dermatophyte infections where topical therapy has failed or is inappropriate

- By mouth
  
  Child 1 month–12 years 10 mg/kg (max.
  500 mg) once daily or in divided doses; in severe
  infection dose may be doubled, reducing when
  response occurs
  
  Child 12–18 years 500 mg once daily or in
  divided doses; in severe infection dose may be
doubled, reducing when response occurs

ITRACONAZOLE

Cautions  absorption reduced in AIDS and neutro-
penia (monitor plasma-itraconazole concen-
tration and increase dose if necessary); suscept-
ibility to congestive heart failure (see also CSM
advice, below); interactions: Appendix 1 (anti-
fungals, triazole)

Hepatotoxicity  Potentially life-threatening hepatotoxicity
reported very rarely—discontinue if signs of hepatitis
develop. Avoid or use with caution if history of hepato-
toxicity with other drugs or in active liver disease. 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  Children or their carers 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

Hepatic impairment  use only if potential benefit
outweighs risk of hepatotoxicity (see hepatotoxicity
above); dose reduction may be necessary

Renal impairment  risk of congestive heart fail-
ure; bioavailability of oral formulations possibly
reduced; use intravenous infusion with caution if
estimated glomerular filtration rate 30–80 mL/
minute/1.73 m² (monitor renal function); avoid
intravenous infusion if estimated glomerular filtra-
tion rate less than 30 mL/minute/1.73 m²

Pregnancy  manufacturer advises use only in life-
threatening situations (toxicity at high doses in
animal studies); ensure effective contraception
during treatment and until the next menstrual
period following end of treatment

CSM advice (heart failure)  Following rare reports of
heart failure, the CSM has advised caution when pre-
scribing itraconazole to patients at high risk of heart
failure. Those at risk include:
- patients receiving high doses and longer treatment
courses;
- those with cardiac disease;
- patients receiving treatment with negative inotropic
drugs, e.g. calcium channel blockers.

Contra-indications  acute porphyria (section
9.8.2)

Breast-feeding  small amounts present in milk—
may accumulate; manufacturer advises avoid

Side-effects  very rarely nausea, vomiting, dys-
pepsia, abdominal pain, diarrhoea, constipation,
jaundice, hepatitis (see also Hepatotoxicity
above), heart failure (see CSM advice above),
pulmonary oedema, headache, dizziness, periph-
eral neuropathy (discontinue treatment), men-
strual disorder, hypokalaemia, rash, pruritus,
Stevens-Johnson syndrome, and alopecia; with
intravenous injection, very rarely hypertension and
hyperglycaemia

Licensed use  Sporanox® capsules and Sporanox®
Pulse are not licensed for use in children under 12
years; Sporanox® liquid and Sporanox® infusion
are not licensed for use in children (age range not
specified by manufacturer)

Indication and dose

Oropharyngeal candidiasis

- By mouth
  
  Child 1 month–12 years 3–5 mg/kg once daily;
  max. 100 mg daily (200 mg daily in AIDS or
  neutropenia) for 15 days
  
  Child 12–18 years 100 mg once daily (200 mg
  once daily in AIDS or neutropenia) for 15 days

Pityriasis versicolor

- By mouth
  
  Child 1 month–12 years 3–5 mg/kg (max.
  200 mg) once daily for 7 days
  
  Child 12–18 years 200 mg once daily for 7 days

Tinea corporis and tinea cruris

- By mouth
  
  Child 1 month–12 years 3–5 mg/kg (max.
  100 mg) once daily for 15 days
  
  Child 12–18 years either 100 mg once daily for
  15 days or 200 mg once daily for 7 days

Tinea pedis and tinea manuum

- By mouth
  
  Child 1 month–12 years 3–5 mg/kg (max.
  100 mg) once daily for 30 days
  
  Child 12–18 years either 100 mg once daily for
  30 days or 200 mg twice daily for 7 days

Tinea capitis caused by Trichophyton tonsurans

- By mouth
  
  Child 1 month–12 years 15–20 mg/kg (max.
  1 g) once daily or in divided doses
  
  Child 12–18 years 1 g once daily or in divided
doses

Griseofulvin  (Non-proprietary) (SM)

Tablets, griseofulvin 125 mg, net price 20 = £6.76;
500 mg, 20 = £17.52. Label: 9, 21, counselling,
skilled tasks

Suspension, griseofulvin 125 mg/5 mL. Label: 9,
21, counselling, skilled tasks

Available via specialist importing companies
5.2 Antifungal drugs 369

<table>
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<th>ITRACONAZOLE (continued)</th>
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<td><strong>Onychomycosis</strong></td>
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<td>• By mouth</td>
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<td>Child 1–12 years</td>
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<tr>
<td>course (‘pulse’) of 5 mg/kg (max. 200 mg) daily for 7 days; subsequent courses repeated after 21 days; fingernails 2 courses, toenails 3 courses</td>
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<td>Child 12–18 years</td>
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<tr>
<td>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 intervals; fingernails 2 courses, toenails 3 courses</td>
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</table>

**Systemic aspergillosis, candidiasis and cryptococcosis including cryptococcal meningitis where other antifungal drugs inappropriate or ineffective** (limited information available)

• By mouth

Child 1 month–18 years
5 mg/kg (max. 200 mg) once daily; increased in invasive or disseminated disease and in cryptococcal meningitis to 5 mg/kg (max. 200 mg) twice daily

• By intravenous infusion

Child 1 month–18 years
2.5 mg/kg (max. 200 mg) every 12 hours for 2 days, then 2.5 mg/kg (max. 200 mg) once daily for max. 12 days

**Histoplasmosis**

• By mouth

Child 1 month–18 years
5 mg/kg (max. 200 mg) 1–2 times daily

**Maintenance in AIDS patients to prevent relapse of underlying fungal infection and prophylaxis in neutropenia when standard therapy inappropriate**

• By mouth

Child 1 month–18 years
5 mg/kg (max. 200 mg) once daily, increased to 5 mg/kg (max. 200 mg)

**Prophylaxis of deep fungal infections** when standard therapy inappropriate in patients with haematological malignancy or undergoing bone-marrow transplantation who are expected to become neutropenic

• By mouth (liquid preparation only)

Child 1 month–18 years
2.5 mg/kg twice daily starting before transplantation or before chemotherapy (taking care to avoid interaction with cytotoxic drugs) and continued until neutrophil count recovers

Administration

For intravenous infusion, dilute 250 mg with 50 mL Sodium Chloride 0.9% and give requisite dose through an in-line filter (0.2 micron) over 60 minutes

Sporanox® (Janssen-Cilag) [FRM]

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

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

• propylene glycol

**KETOCONAZOLE**

**Cautions** predisposition to adrenocortical insufficiency; **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 treatment, then on weeks 2 and 4 of treatment, then every 21-day intervals; fingernails 2 courses, toenails 3 courses.

**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, azospermia (with high doses), gynaecomastia, thrombocytopenia, photophobia, photosensitivity, and alopecia

**Indication and dose**

**Dermatophytooses 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; see also CSM recommendations, p. 363

• By mouth

Child body-weight 15–30 kg
100 mg once daily
**KETOCONAZOLE (continued)**

- **Child body-weight over 30 kg**: 200 mg once daily, increased if response inadequate to 400 mg once daily. Note: Treatment continued until symptoms have cleared and cultures negative, but see Cautions (max. duration of treatment 4 weeks for *Malassezia* infection).

**Nizoral** (Janssen-Cilag) Tablets, scored, ketoconazole 200 mg. Net price 30-tab pack = £14.59. Label: 5, 9, 21, Counselling, hepatotoxicity

- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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**MICAFUNGIN**

**Cautions** monitor renal function; **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) or if receiving other hepatotoxic drugs. Risk of hepatic side-effects greater in children under 1 year of age

**Renal impairment** use with caution; deterioration in renal function

**Pregnancy** manufacturer advises avoid unless essential—toxicity in animal studies

**Breast-feeding** manufacturer advises use only if potential benefit outweighs risk—present in milk in animal studies

**Side-effects** nausea, vomiting, diarrhoea, abdominal pain, hepatomegaly; blood pressure changes, tachycardia; headache, fever; hypokalaemia, hypomagnesaemia, hypocalcaemia, leucopenia, anaemia, thrombocytopenia, renal failure; rash, phlebitis; less commonly dyspepsia, constipation, hepatitis and cholestasis (see also Hepatotoxicity above), taste disturbances, anorexia, palpitation, bradycardia, flushing, dyspnoea, sleep disturbances, anxiety, confusion, dizziness, tremor, pancytopenia, eosinophilia, hyponatraemia, hyperkalaemia, hypophosphataemia, hyperhidrosis, and pruritus; rarely haemolytic anaemia

**Indication and dose**

- **Invasive candidiasis**
  - **Neonate**: 2 mg/kg once daily (increased to 4 mg/kg daily if inadequate response) for at least 14 days
  - **Child 1 month–18 years, body-weight over 40 kg**: 100 mg once daily (increased to 200 mg daily if inadequate response) for at least 14 days

**Prophylaxis of candidiasis in children undergoing bone-marrow transplantation or who are expected to become neutropenic for over 10 days**

- **By intravenous infusion**
  - **Neonate**: 1 mg/kg once daily; continue for at least 7 days after neutrophil count in desirable range
  - **Child 1 month–18 years, body-weight under 40 kg**: 1 mg/kg once daily; continue for at least 7 days after neutrophil count in desirable range
  - **Child 1 month–18 years, body-weight over 40 kg**: 50 mg once daily; continue for at least 7 days after neutrophil count in desirable range

**Administration** for intravenous infusion reconstitute each vial with 5 mL Glucose 5% or Sodium Chloride 0.9%; gently rotate vial, without shaking, to dissolve; dilute requisite dose to a concentration of 0.5–2 mg/mL with Glucose 5% or Sodium Chloride 0.9%; protect from light; give over 60 minutes

**Mycamine** (Astellas) Intravenous infusion, powder for reconstitution, micafungin (as sodium), net price 50-mg vial = £196.08; 100-mg vial = £341.00

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**NYSTATIN**

**Side-effects** nausea, vomiting, diarrhoea at high doses; oral irritation and sensitisation; rash (including urticaria) and rarely Stevens-Johnson syndrome reported

**Licensed use** suspension not licensed for treatment of intestinal candidiasis in neonates; suspension licensed for prophylaxis in neonates as once daily dose; tablets not licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

- **Treatment of intestinal candidiasis**
  - **By mouth**
    - **Neonate**: 100 000 units 4 times daily after feeds
  - **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)
  - **Child 12–18 years**: 500 000 units 4 times daily, doubled in severe infection

**Oral infection** section 12.3.2
**NYSTATIN (continued)**

**Skin infection** section 13.10.2

Nystan® (Squibb) Tablets, brown, s/c, nystatin 500 000 units, net price 56-tab pack = £4.37. Label: 9

**TERBINAFINE**

Cautions psoriasis (risk of exacerbation); autoimmune disease (risk of lupus-erythematosus-like effect) interactions: Appendix 1 (terbinafine)

Hepatic impairment manufacturer advises avoid—elimination reduced

Renal impairment use half normal dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if benefit outweighs risk—no information available

Breast-feeding present in milk—manufacturer advises avoid

Side-effects abdominal discomfort, anorexia, nausea, diarrhoea; headache; rash and urticaria occasionally with arthralgia or myalgia; less commonly taste disturbance; rarely with arthralgia or myalgia; less commonly psychiatric disturbances, blood disorders (including incidence of leucopenia higher and thrombocytopenia), lupus erythematosus-like effect, and exacerbation of psoriasis

Licensed use not licensed for use in children

**Indication and dose**

**Dermatophyte infections of the nails, ringworm infections (including tinea pedis, cruris, corporis, and capitis) where oral therapy appropriate (due to site, severity or extent)**

- **By mouth**
  - Child over 1 year; body-weight 10–20 kg 62.5 mg once daily
  - Child body-weight 20–40 kg 125 mg once daily
  - Child body-weight over 40 kg 250 mg once daily

**Note** treatment usually for 4 weeks in tinea capitis, 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)

**Fungal skin infections** section 13.10.2

Terbinafine (Non-proprietary) Tablets, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £2.70, 28-tab pack = £3.43. Label: 9

Lamisil® (Novartis) Tablets, off-white, scored, terbinafine (as hydrochloride) 250 mg, net price 14-tab pack = £23.16, 28-tab pack = £44.66. Label: 9

**VORICONAZOLE**

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; rare increased risk of hepatic reactions; monitor renal function; interactions: Appendix 1 (antifungals, triazole)

Hepatic impairment 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

Renal impairment excipient in intravenous infusion solution may accumulate if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²—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)

Pregnancy toxicity in animal studies—manufacturer advises avoid unless potential benefit outweighs risk; effective contraception required during treatment

**Contra-indications** acute porphyria (section 9.8.2)

Breast-feeding manufacturer advises avoid—no information available

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, 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 cholestatics, pancreatitis, hepatitis, constipation, arrhythmias (including QT interval prolongation), syncope, raised serum cholesterol, hypersensitivity reactions (including flushing), ataxia, nystagmus, hypoaesthesia, adrenocortical insuffi-
Voriconazole (continued)

- By mouth
  - Child 2–12 years (oral suspension recommended) 200 mg every 12 hours
  - Child 12–18 years, 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 12–18 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

- By intravenous infusion
  - 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
  - Child 12–18 years 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

Administration For intravenous infusion, reconstitute each 200 mg with 19 mL Water for Injections to produce a 10 mg/mL solution; dilute dose to concentration of 0.5–5 mg/mL with Glucose 5% or Sodium Chloride 0.9% or Compound Sodium Lactate and give at a rate not exceeding 3 mg/kg/hour

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 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 sulphobutylether 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.

The natural progression of HIV disease is different in children compared to adults; drug treatment should only be undertaken by specialists within a formal paediatric HIV clinical network. Guidelines and dose regimens are under constant review and for this reason specific dose recommendations have not been included in BNF for Children.

Further information on the management of children with HIV can be obtained from the Children’s HIV Association (CHIVA) www.chiva.org.uk; and further information on antiretroviral use and toxicity can be obtained from the Paediatric European Network for Treatment of AIDS (PENTA) website www.pentatrials.org.

Principles of treatment Treatment is aimed at suppressing viral replication 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

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.

5.3.3 Viral hepatitis

5.3.4 Influenza

5.3.5 Respiratory syncytial virus
many years are required; the regimen chosen should take into account convenience and the child’s tolerance of treatment. 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  Treatment is based on child’s age, CD4 cell count, viral load, and symptoms. Treatment is started in all HIV infected children under 1 year of age regardless of clinical and immunological parameters. The choice of antiviral treatment for children should take into account the method and frequency of administration, risk of side-effects, compatibility of drugs with food, palatability, and the appropriateness of the formulation. Initiating treatment with a combination of drugs (‘highly active antiretroviral therapy’ which includes 2 nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or a boosted protease inhibitor) is recommended. The metabolism of many antiretrovirals varies in young children; it may therefore be necessary to adjust the dose according to the plasma-drug concentration. Children who require treatment for both HIV and chronic hepatitis B should receive antivirals that are active against both diseases (section 5.3.3).

Switching therapy  Deterioration of the condition (including clinical, virological changes, and CD4 cell changes) may require a complete change of 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  Treatment of HIV infection in pregnancy aims to minimise the viral load and disease progression in the mother and reduce the risk of toxicity to the fetus (but the teratogenic potential of most antiretroviral drugs is unknown). Combination antiretroviral therapy represents optimal treatment but all options require careful assessment by a specialist. Combination antiretroviral therapy may be associated with a greater risk of preterm delivery. Consideration also needs to be given to preventing transmission of the infection to the neonate (see below).

Prevention of transmission to neonate  Zidovudine given in the perinatal period to the mother and the neonate reduces transmission to the baby. However, optimal treatment of the mother’s HIV infection with combination treatment maximises the chance of preventing transmission. Local protocols and national guidelines (www.bhiva.org) should be consulted for recommendations on treatment during pregnancy and the perinatal period.

Breast-feeding  Breast-feeding by HIV-positive mothers may cause HIV infection in the infant and should be avoided.

Post-exposure prophylaxis  Children exposed to HIV infection through needlestick injury or by another route should be sent to an accident and emergency department for post-exposure prophylaxis [unlicensed indication]. Antiretrovirals for prophylaxis are chosen on the basis of efficacy and potential for toxicity.

Drugs used 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 prodrug 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 for use in children over 2 years. 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 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. In adults, etravirine is licensed for use in regimens 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; it is given by subcutaneous injection.

**Maraviroc** is an antagonist of the CCR5 chemokine receptor. It is used in patients exclusively infected with CCR5–tropic HIV.

**Raltegravir** is an inhibitor of HIV integrase. It is used for the treatment of HIV infection resistant to multiple 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. Children should be encouraged to lead a healthy lifestyle that reduces their long-term cardiovascular risk. Plasma lipids and blood glucose should be measured before starting antiretroviral therapy, after 3–6 months of treatment, and then at least annually. Insulin resistance and hyperglycaemia occur only rarely in children.

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, and to a lesser extent zidovudine, are associated with a higher risk of lipoatrophy and should be used only if alternative regimens are not suitable.

Dyslipidaemia (with adverse effects on body lipids) is associated with antiretroviral treatment, particularly with protease inhibitors; in children, hypercholesterolaemia appears to be more common than hypertriglyceridaemia. Protease inhibitors are associated with insulin resistance and hyperglycaemia but they occur rarely in children. 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 children 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 children with hepatic impairment (greater risk of hepatic side-effects, see also Lactic Acidosis below). However, some nucleoside reverse transcriptase inhibitors are used in children who also have chronic hepatitis B. They should also be used with caution in renal impairment and in pregnancy (see also p. 373).

**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 children 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. 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 gastro-intestinal disturbances (such as nausea, vomiting, abdominal pain, flatulence and diarrhoea), anorexia, pancreatitis, liver damage (see also Lactic Acidosis, above), dyspnoea, cough, headache, insomnia, dizziness, fatigue, blood disorders (including anaemia, neutropenia, and thrombocytopenia), myalgia, arthralgia, rash, urticaria, and fever. See notes above for Lipodystrophy Syndrome (p. 374) and Osteonecrosis (p. 374).

ABACAVIR

Cautions see notes above; also test for HLA-B*5701 allele before treatment—risk of hypersensitivity reaction in presence of HLA-B*5701 allele; See Appendix 1 (abacavir)

Hepatic impairment avoid in moderate hepatic impairment unless essential; avoid in severe hepatic impairment

Renal impairment manufacturer advises avoid in end-stage renal disease

Hypersensitivity reactions Life-threatening hypersensitivity reactions reported (more common in Caucasians)—characterised by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache, and myalgia; less frequently mouth ulceration, oedema, hypotension, sore throat, acute respiratory distress syndrome, anaphylaxis, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia and renal failure (CSM has identified hypersensitivity reactions presenting as sore throat, influenza-like illness, cough, and breathlessness); rarely myelosy; laboratory abnormalities may include raised liver function tests (see Lactic Acidosis above) and creatine kinase; symptoms usually appear in the first 6 weeks, but may occur at any time; monitor for symptoms every 2 weeks; discontinue immediately if any symptom of hypersensitivity develops and do not rechallenge (risk of more severe hypersensitivity reaction); discontinue if hypersensitivity cannot be ruled out, even when other diagnoses possible—if rechallenge necessary it must be carried out in hospital setting; if abacavir is stopped for any reason other than hypersensitivity, exclude hypersensitivity reaction as the cause and rechallenge only if medical assistance is readily available; care needed with concomitant use of drugs which cause skin toxicity

Counselling Children and carers should be told the importance of regular dosing (intermittent therapy may increase the risk of sensitisation), how to recognise signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before re-starting treatment; children or their carers should be advised to keep Alert Card with them at all times

Contra-indications

Pregnancy manufacturer advises avoid (toxicity in animal studies); see also Pregnancy, p. 373

Breast-feeding avoid (see notes above)

Side-effects see notes above; also hypersensitivity reactions (see above); very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis; rash and gastro-intestinal disturbances more common in children

Licensed use Ziagen® not licensed for use in children under 3 months; Kivexa® not licensed for use in children under 12 years; Trizivir® not licensed for use in children

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Ziagen® (GSK) Tablets, yellow, f/c, scored, abacavir (as sulphate) 300 mg, net price 60-tab pack = £221.81. Counselling, hypersensitivity reactions

Kivexa® (GSK) Tablets, orange, f/c, abacavir (as sulphate) 600 mg, lamivudine 300 mg, net price 30-tab pack = £373.94. Counselling, hypersensitivity reactions

With lamivudine

Trizivir® (GSK) Tablets, 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

DIDANOSINE

(ddI, DDI)

Cautions see notes above; also history of pancreatitis (preferably avoid, otherwise extreme caution, see also below); peripheral neuropathy or hyperuricaraemia (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)

Renal impairment reduce dose if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²; consult product literature

Hepatic impairment insufficient information but monitor for toxicity

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Pancreatitis If symptoms of pancreatitis develop or if serum lipase is raised and pancreatitis is confirmed, discontinue treatment. Whenever possible avoid concomitant treatment with other drugs known to cause pan-
creatic toxicity (e.g. intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis monitor closely if triglycerides elevated

Contra-indications

Breast-feeding avoid (see notes above)

Side-effects see notes above; also pancreatitis (less common in children, see also under cautions), 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)

Licensed use tablets not licensed for use in children under 3 months; EC capsules not licensed for use in children under 6 years

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

EMTRICITABINE

Cautions see notes above; also on discontinuation, monitor patients with hepatitis B (risk of exacerbation of hepatitis); interactions: Appendix 1 (emtricitabine)

Renal impairment reduce dose or increase dosage interval if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; consult product literature

Pregnancy manufacturer advises use only if essential—no information available

Contra-indications

Breast-feeding avoid (see notes above)

Side-effects see notes above; also abnormal dreams, pruritus, and hyperpigmentation

Licensed use not licensed for use in children under 4 months

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

LAMIVUDINE (3TC)

Cautions see notes above; interactions: Appendix 1 (lamivudine)

Renal impairment reduce dose if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; consult product literature

Pregnancy manufacturer advises avoid during first trimester; see also p. 373

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 avoid (see notes above)

Side-effects see notes above; also peripheral neuropathy, muscle disorders including rhabdomyolysis, nasal symptoms, alopecia

Licensed use Epivir® not licensed for use in children under 3 months; Zeffix® not licensed for use in children

Indication and dose

See preparations, below


**LAMIVUDINE (continued)**

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 propylene glycol, sucrose 1 g/5 mL  
**Dose**  
HIV infection in combination with other antiretroviral drugs  
For dose, consult Guidelines (see notes above)  

Zeffix® (GSK)  
**Tablets**, brown, f/c, lamivudine 100 mg, net price 28-tab pack = £78.09  
**Oral solution**, banana and strawberry-flavoured, lamivudine 25 mg/5 mL, net price 240-mL pack = £22.79  
**Excipients** include propylene glycol, sucrose 1 g/5 mL  
**Dose**  
Chronic hepatitis B infection with either compensated liver disease (with evidence of viral replication and histology of active liver inflammation or fibrosis), or decompensated liver disease  
- By mouth  
  - Child 2–12 years: 3 mg/kg (max. 100 mg) once daily  
  - Child 12–18 years: 100 mg once daily  
**Note**: Children receiving lamivudine for concomitant HIV infection should continue to receive lamivudine in a dose appropriate for HIV infection  

With abacavir  
See under Abacavir  

With zidovudine  
See under Zidovudine  

With abacavir and zidovudine  
See under Abacavir  

**STAVUDINE**  
(d4T)  

**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)  

**Renal impairment** reduce dose to 50% if estimated glomerular filtration rate 25–50 mL/minute/1.73 m²; reduce dose to 25% if estimated glomerular filtration rate less than 25 mL/minute/1.73 m²  

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk  

**Contra-indications**  
Breast-feeding avoid (see notes above)  

**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  

**Licensed use** capsules not licensed for use in children under 3 months  

**Indication and dose**  
HIV infection in combination with other antiretroviral drugs  
For dose, consult Guidelines (see notes above)  

Zerit® (Bristol-Myers Squibb)  
**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  

**TENOFOVIR DISOPROXIL**  

**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)  

**Renal impairment** increase dose interval if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; avoid Atripla® if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²; avoid Truvada® if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²  

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk—no information available  

**Contra-indications**  
Breast-feeding avoid (see notes above)  

**Side-effects** see notes above; also hypophosphataemia; *rarely* renal failure; also reported nephrogenic diabetes insipidus, reduced bone density, hypokalaemia, myopathy, and rhabdomyolysis  

**Licensed use** not licensed for use in children  

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**5.3.1 HIV infection**
TENOFOVIR DISOPROXIL (continued)

Indication and dose
HIV infection in combination with other antiretroviral drugs
For dose, consult Guidelines (see notes above)

Viread® (Gilead) ▼ (HS)
Tablets, f/c, blue, tenofovir disoproxil (as fumarate) 245 mg, net price 30-tab pack = £255.00. Label: 21, counselling, administration
Counselling Children 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

ZIDOVUDINE
(Azidothymidine, AZT)
Note The abbreviation AZT which is sometimes used for zidovudine has also been used for another drug

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 12 deficiency (increased risk of neutropenia); if anaemia or myelosuppression occur, reduce dose or interrupt treatment according to product literature, or consider other treatment; interactions: Appendix 1 (zidovudine)
Hepatic impairment accumulation may occur
Renal impairment reduce dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²; consult product literature
Pregnancy limited information available; manufacturer advises use only if clearly indicated; see also p. 373
Contra-indications abnormally low neutrophil count 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 avoid (see notes above)
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
Licensed use Combivir® is not licensed for use in children with body-weight under 14 kg

Truvada® (Gilead) ▼ (HS)
Tablets, blue, f/c, tenofovir disoproxil (as fumarate) 245 mg, emtricitabine 200 mg, net price 30-tab pack = £418.50. Label: 21, Counselling, administration
Children with swallowing difficulties may disperse tablet in half a glass of water, orange juice, or grape juice (but bitter taste)

With efavirenz and emtricitabine
For cautions, contra-indications, and side-effects see under individual drugs

Atripla® (Gilead) ▼ (HS)
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

Protease inhibitors
Cautions Protease inhibitors should be used with caution in diabetes (see also Lipodystrophy Syndrome, p. 374). Caution is also needed in children with haemophilia who may be at increased risk of bleeding and in hepatic impairment; the risk of hepatic side-effects is increased in children with chronic hepatitis B or C. Atazanavir, darunavir, fosamprenavir, and tipranavir may be used at usual doses
in children with renal impairment, but other protease inhibitors should be used with caution in renal impairment. Indinavir is rarely used in children because of the risk of nephrolithiasis. Protease inhibitors should also be used with caution during pregnancy.

**Contra-indications** Protease inhibitors should not be given to patients with acute porphyria (section 9.8.2) or to women who are breast-feeding (see also Breast-feeding, p. 373).

**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 Lipodystrophy Syndrome (p. 374) and Osteonecrosis (p. 374).

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**ATAZANAVIR**

**Cautions** see notes above; 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)

**Hepatic impairment** use with caution in mild impairment; avoid in moderate to severe impairment

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk; theoretical risk of hyperbilirubinaemia in neonate if used at term

**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 hepatospleno-megaly, oedema, palpitation, and abnormal gait; also reported cholelithiasis, cholecystitis, and torsade de pointes

**Licensed use** not licensed for use in children

**Indication and dose** HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

**Reyataz®** (Bristol-Myers Squibb) 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

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**DARUNAVIR**

**Cautions** see notes above; also sulphonamide sensitivity; **interactions:** Appendix 1 (darunavir)

**Hepatic impairment** use with caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment—no information available

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk—no information available

**Contra-indications** see notes above

**Side-effects** see notes above; also haematemesis, myocardial infarction, chest pain, QT interval prolongation, syncope, tachycardia, bradycardia, palpitation, hypertension, flushing, peripheral oedema, dyspnoea, cough, peripheral neuropathy, anxiety, confusion, memory impairment, convulsions, depression, abnormal dreams, weight changes, pyrexia, hypothyroidism, osteoporosis, gynaecomastia, erectile dysfunction, reduced libido, dysuria, polyuria, nephrolithiasis, renal failure, arthralgia, visual disturbances, conjunctival hyperaemia, epistaxis, rhinorrhea, throat irritation, dry mouth, mouth ulcers, stomatitis, nail discoloration, acne, seborrhoic dermatitis, xeroderma, increased sweating, and alopecia

**Licensed use** not licensed for use in children

**Indication and dose** In combination with other antiretroviral drugs, for HIV infection resistant to other protease inhibitors

For dose, consult Guidelines (see notes above)

**Prezista®** (Janssen-Cilag) Tablets, f/c, darunavir (as ethanolate) 300 mg (orange), net price 120-tab pack = £446.70; 400 mg (light orange), 60-tab pack = £297.80; 600 mg (orange), 60-tab pack = £446.70. Label: 21
**FOSAMPRENAVIR**

*Note* Fosamprenavir is a pro-drug of amprenavir

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

**Hepatic impairment** Manufacturer advises caution in mild hepatic impairment; reduce dose in moderate to severe hepatic impairment

**Pregnancy** Toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk

**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)

**Licensed use** not licensed for use in children under 6 years and body-weight under 25 kg

**Indication and dose**

**HIV infection in combination with other antiretroviral drugs**

For dose, consult Guidelines (see notes above)

**Note** 700 mg fosamprenavir is equivalent to approx. 600 mg amprenavir

**Telzir** (GSK) ** 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-bubble-gum-and peppermint-flavoured) (with 10-mL oral syringe) = £73.31. Counselling, administration

**Excipients** include propylene glycol

**Administration** In children, oral suspension should be taken with food

**INDINAVIR**

**Cautions** see notes above; ensure adequate hydration (risk of nephrolithiasis); children at risk of nephrolithiasis (monitor for nephrolithiasis); **interactions:** Appendix 1 (indinavir)

**Hepatic impairment** increased risk of nephrolithiasis; reduce dose in mild to moderate impairment; not studied in severe impairment

**Pregnancy** 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

**Contra-indications** see notes above; also contra-indicated in neonates (risk of hyperbilirubinaemia)

**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), nephrolithiasis (may require interruption or discontinuation), dysuria, haematuria, crystalluria, pro-teinuria, pyuria, pylonephritis; haemolytic anaemia

**Licensed use** not licensed for use in children under 4 years

**Indication and dose**

**HIV infection in combination with nucleoside reverse transcriptase inhibitors**

For dose, consult Guidelines (see notes above)

**Crixivan** (MSD) ** tablets, indinavir (as sulphate), 200 mg, net price 360-cap pack = £226.28; 400 mg, 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 (may be mixed with apple sauce); in combination with didanosine tablets, allow 1 hour between each drug (antacids be mixed with apple sauce); 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)

**LOPINAVIR WITH RITONAVIR**

**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)

**Hepatic impairment** avoid oral solution—high propylene glycol content; manufacturer advises avoid capsules and tablets in severe impairment

**Renal impairment** avoid oral solution due to high propylene glycol content; use tablets with caution in severe renal impairment

**Pregnancy** avoid oral solution due to high propylene glycol content; manufacturer advises use capsules and tablets only if potential benefit outweighs risk (toxicity in animal studies)

**Pancreatitis** Signs and symptoms suggestive of pancreatitis (including raised serum lipase) should be evaluated—discontinue if pancreatitis diagnosed

**Contra-indications** see notes above

**Licensed use** not licensed for use in children under 6 years and body-weight under 25 kg

**Indication and dose**

**HIV infection in combination with other antiretroviral drugs**

For dose, consult Guidelines (see notes above)

**Note** 1 (lopinavir, ritonavir)

**Interactions:**

- Appendix 1 (indinavir)
- Appendix 1 (fosamprenavir)

**Dispense in original container** (contains desiccant)
LOPINAVIR WITH RITONAVIR (continued)

Licensed use not licensed for use in children under 2 years

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Kaletra® (Abbott) Tablets, yellow, f/c, lopinavir 100 mg, ritonavir 25 mg, net price 60-tab pack = £76.85. Label: 25

NELFINAVIR

Cautions see notes above; interactions: Appendix 1 (nelfinavir)

Hepatic impairment manufacturer advises caution—no information available

Renal impairment manufacturer advises caution—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk—no information available

Contra-indications see notes above

Side-effects see notes above; also reported, fever

Licensed use not licensed for use in children under 3 years

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Viracept® (Roche) Tablets, blue, f/c, nelfinavir (as mesilate) 250 mg, net price 300-tab pack = £273.16. Label: 21

RITONAVIR

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)

Hepatic impairment avoid in decompensated liver disease; in severe hepatic impairment without decompensation, use ‘booster’ doses with caution (avoid treatment doses)

Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies

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, hyperaesthesia, 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

Licensed use not licensed for use in children under 2 years

Indication and dose

HIV infection in combination with other antiretroviral drugs; low doses used to increase effect of some protease inhibitors

For dose, consult Guidelines (see notes above)

Norvir® (Abbott) Capsules, ritonavir 100 mg, net price 84-cap pack = £94.35. Label 21

Excipients 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

Excipients include alcohol, propylene glycol

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

Administration of ritonavir and didanosine should be separated by at least 2 hours

With lopinavir See under Lopinavir with ritonavir

SAQUINAVIR

Cautions see notes above; concomitant use of garlic (avoid garlic capsules—reduces plasma-saquinavir concentration); interactions: Appendix 1 (saquinavir)

Hepatic impairment manufacturer advises caution in moderate impairment; avoid in severe impairment

Renal impairment dose adjustment possibly required if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Contra-indications see notes above

Renal impairment dose adjustment possibly required if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Contra-indications see notes above

Licensed use not licensed for use in children under 2 years

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Tablets, yellow, f/c, lopinavir 200 mg, ritonavir 50 mg, net price 120-tab pack = £307.39. Label: 25

Oral solution, lopinavir 400 mg, ritonavir 100 mg/5 mL, net price 5 × 60-mL packs = £307.39. Label: 21

Excipients include propylene glycol 153 mg/mL (see Excipients, p. 3), alcohol 42%
SAQUINAVIR (continued)

Side-effects see notes above; also dyspnoea, increased appetite, peripheral neuropathy, convulsions, changes in libido, renal impairment, dry mouth, and alopecia

Licensed use not licensed for use in children under 16 years

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Tipranavir

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)

Hepatic impairment monitor liver function in mild hepatic impairment; avoid in moderate or severe hepatic impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies

Contra-indications see notes above

Side-effects see notes above; also dyspnoea, anorexia, peripheral neuropathy, influenza-like symptoms, renal impairment, and photosensitivity; rarely dehydration

Licensed use not licensed for use in children

Indication and dose

HIV infection resistant to other protease inhibitors, in combination with other antiretroviral drugs in children previously treated with antiretrovirals

For dose, consult Guidelines (see notes above)

Aptivus

Cautions chronic hepatitis B or C (greater risk of hepatic side-effects); history of mental illness or seizures; interactions: Appendix 1 (efavirenz)

Hepatic impairment in mild to moderate liver disease, monitor for dose-related side-effects (e.g. CNS effects) and liver function; avoid in severe hepatic impairment

Renal impairment manufacturer advises caution in severe renal failure—no information available

Pregnancy manufacturer advises avoid unless no alternative available

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 Children 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)

Breast-feeding avoid (see p. 373)

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. 374), gynaecomastia, photosensitivity; see also Osteonecrosis, p. 374

Licensed use capsules and oral solution not licensed for use in children under 3 years and body-weight under 13 kg; tablets not licensed for use in children with body-weight under 40 kg

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Sustiva

Cautions chronic hepatitis B or C (greater risk of hepatic side-effects); history of mental illness or seizures; interactions: Appendix 1 (efavirenz)

Hepatic impairment in mild to moderate liver disease, monitor for dose-related side-effects (e.g. CNS effects) and liver function; avoid in severe hepatic impairment

Renal impairment manufacturer advises caution in severe renal failure—no information available

Pregnancy manufacturer advises avoid unless no alternative available

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 Children 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)

Breast-feeding avoid (see p. 373)

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. 374), gynaecomastia, photosensitivity; see also Osteonecrosis, p. 374

Licensed use capsules and oral solution not licensed for use in children under 3 years and body-weight under 13 kg; tablets not licensed for use in children with body-weight under 40 kg

Indication and dose

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Sustiva® (Bristol-Myers Squibb) capsules, efavirenz 50 mg (yellow/white), net price 30-cap pack = £17.41; 200 mg (yellow), 90-cap pack = £208.40. Label: 23

Administration Capsules may be opened and contents added to food (contents have a peppery taste) [unlicensed use]

Tablets, f/c, yellow, efavirenz 600 mg, net price 30-tab pack = £208.40. Label: 23
ECTAVIRINE

Cautions chronic hepatitis B or C (greater risk of hepatic side-effects); interactions: Appendix 1 (etravirine)

Hepatic impairment use with caution in moderate hepatic impairment; avoid in severe hepatic impairment—no information available

Pregnancy manufacturer advises use only if potential benefit outweighs risk

Rash, usually in the second week, is the most common side-effect and appears more frequently in females; 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 avoid (see p. 373)

Side-effects rash (rarely including Stevens-Johnson syndrome; see also Rash above); gastrooesophageal reflux, nausea, vomiting, abdominal pain, flatulence, gastritis; hypertension; peripheral neuropathy; diabetes, hyperlipidaemia (see also Lipodystrophy Syndrome, p. 374); renal failure; thrombocytopenia; less commonly pancreatitis, haematemesis, stomatitis, hepatitis, myopathy, severe hepatic impairment; avoid in severe hepatic impairment; severe hepatic impairment—no information available

Administration for children with swallowing difficulties, tablets may be dispersed in a glass of water just before administration

Intolerance (Janssen-Cilag) Tablets, etravirine 100 mg, net price 120-tab pack £319.82. Label: 21

Note Dispense in original container (contains desiccant)

NEVIRAPINE

Cautions chronic hepatitis B or C, high CD4 cell count, and females (all at greater risk of hepatic side-effects); interactions: Appendix 1 (nevirapine)

Hepatic impairment manufacturer advises caution in moderate hepatic impairment; avoid in severe hepatic impairment; see also Hepatic Disease, below

Pregnancy although manufacturers advise avoid, may be appropriate to use if clearly indicated; see also p. 373

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 Children and carers 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); severe hepatic impairment; post-exposure prophylaxis

Breast-feeding avoid (see p. 373)

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; very rarely neuropsychiatric reactions; see also Osteonecrosis, p. 374

Licensed use tablets, not licensed for use in children weighing less than 50 kg or with body surface area less than 1.25 m²

With emtricitabine and tenofovir See under Tenofovir

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
**Indication and dose**

**NEVIRAPINE**

HIV infection in combination with other antiretroviral drugs

For dose, consult Guidelines (see notes above)

Note: If treatment interrupted for more than 7 days reintroduce using low dose and increase dose cautiously.

**Viramune** (Boehringer Ingelheim) [几十年]

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.

**Other antiretrovirals**

**ENFUVIRTIDE**

**Cautions**: chronic hepatitis B or C (possibly greater risk of hepatic side-effects)

**Hepatic impairment**: manufacturer advises caution—no information available

**Pregnancy**: manufacturer advises avoid

**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**: Children and carers should be told how to recognise signs of hypersensitivity, and advised to discontinue treatment and seek prompt medical attention if symptoms develop

**Contra-indications**

**Breast-feeding**: avoid (see p. 373)

**Side-effects**: injection-site reactions; pancreatitis, gastro-oesophageal reflux disease, anorexia, weight loss; hypertriglyceridaemia; peripheral neuropathy, asthenia, tremor, anxiety, nightmares, irritability, impaired 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. 374

**Licensed use**: not licensed for use in children under 6 years

**Indication and dose**

HIV infection in combination with other antiretroviral drugs for resistant infection or for children intolerant to other antiretroviral regimens

For dose, consult Guidelines (see notes above)

**Administration**: for subcutaneous injection, reconstitute with 1.1 mL Water for Injections and allow to stand (for up to 45 minutes) to dissolve; do not shake or invert vial

**Fuzeon** (Roche) [几十年]

Injection, powder for reconstitution, enfuvirtide 108 mg (= enfuvirtide 90 mg/mL when reconstituted with 1.1 mL Water for Injections), net price 108-mg vial = £19.13 (with solvent, syringe, and alcohol swabs). Counselling, hypersensitivity reactions.

**MARAVIROC**

**Cautions**: cardiovascular disease; chronic hepatitis B or C; interactions: Appendix 1 (maraviroc)

**Hepatic impairment**: use with caution

**Renal impairment**: if estimated glomerular filtration rate less than 80 mL/minute/1.73 m², consult product literature

**Pregnancy**: manufacturer advises use only if potential benefit outweighs risk—toxicity in animal studies

**Contra-indications**

**Breast-feeding**: avoid (see notes above, p. 373)

**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 pancreatitis, 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. 374

**Licensed use**: not licensed for use in children

**Indication and dose**

CCR5–tropic HIV infection in combination with other antiretroviral drugs in children previously treated with antiretrovirals

For dose, consult Guidelines (see notes above)

**Celsentri** (Pfizer) [几十年]

Tablets, blue, film coat, maraviroc 150 mg, net price 60-tab pack = £551.10; 300 mg, 60-tab pack = £551.10

**RALTEGRAVIR**

**Cautions**: risk factors for myopathy or rhabdomyolysis; chronic hepatitis B or C (greater risk of hepatic side-effects); interactions: Appendix 1 (raltegravir)

**Hepatic impairment**: use with caution in severe hepatic impairment—no information available

**Pregnancy**: manufacturer advises avoid—toxicity in animal studies

**Licensed use**: not licensed for use in children

**Indication and dose**

HIV infection in combination with other antiretroviral drugs in children previously treated with antiretrovirals

For dose, consult Guidelines (see notes above)
Contra-indications

Breast-feeding: avoid see p. 373

Side-effects

Abdominal pain, flatulence, constipation, lipodystrophy (see Lipodystrophy Syndrome, p. 374); 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. 374

Licensed use

Not licensed for use in children under 16 years

Indication and dose

In combination with other antiretroviral drugs for HIV infection resistant to multiple antiretrovirals

For dose, consult Guidelines (see notes above)

Isentress® (MSD)

Tablets, pink, f/c, raltegravir (as potassium salt) 400 mg, net price 60-tab pack = £647.29. Label: 25

5.3.2 Herpesvirus infections

5.3.2.1 Herpes simplex and varicella–zoster infection

The two most important herpesvirus pathogens are herpes simplex virus (herpesvirus hominis) and varicella–zoster virus.

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 child 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. Oral therapy is not recommended as absorption is variable.

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 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 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.

In pregnancy severe chickenpox may cause complications, especially varicella pneumonia. Specialist advice should be sought for the treatment of chickenpox during pregnancy.

Neonates and children 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. Immunocompromised 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 (postherpetic neuralgia) requires specific management (section 4.7.3).

**Choice**  
Aciclovir is active against herpesviruses but does not eradicate them. Uses of aciclovir include systemic treatment of varicella–zoster and the systemic and topical treatment of herpes simplex infections of the skin (section 13.10.3) and mucous membranes (section 7.2.2). It is used by mouth for severe herpetic stomatitis (see also p. 657). Aciclovir eye ointment (section 11.3.3) is used for herpes simplex infections of the eye; it is combined with systemic treatment for ophthalmic zoster.

Famciclovir, a prodrug of penciclovir, is similar to aciclovir and is licensed in adults for use in herpes zoster and genital herpes; there is limited information available on use in children. Penciclovir itself is used as a cream for herpes simplex labialis (section 13.10.3).

Valaciclovir is an ester of aciclovir, licensed in adults for herpes zoster and herpes simplex infections of the skin and mucous membranes (including genital herpes); it is also licensed in children over 12 years for preventing cytomegalovirus disease following renal transplantation. Valaciclovir may be used for the treatment of mild herpes zoster in immunocompromised children over 12 years; treatment should be initiated under specialist supervision. Valaciclovir once daily may reduce the risk of transmitting genital herpes to heterosexual partners—specialist advice should be sought.

### ACICLOVIR  
(Acyclovir)

**Cautions**  
- maintain adequate hydration (especially with infusion or high doses, or during renal impairment);  
- **interactions:** Appendix 1 (aciclovir)

**Renal impairment**  
- risk of neurological reactions increased; use normal intravenous dose every 12 hours if estimated glomerular filtration rate 25–50 mL/minute/1.73 m² (every 24 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m²); consult product literature for intravenous dose if estimated glomerular filtration rate less than 10 mL/minute/1.73 m².  
- For herpes zoster, use normal oral dose every 8 hours if estimated glomerular filtration rate 10–25 mL/minute/1.73 m² (every 12 hours if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²).

**Pregnancy**  
- not known to be harmful but manufacturers advise avoid unless potential benefit outweighs risk; limited absorption from topical preparations

**Breast-feeding**  
- significant amount in milk after systemic administration; not known to be harmful but manufacturers advise caution

**Side-effects**  
- nausea, vomiting, abdominal pain, diarrhoea, headache, fatigue, rash, urticaria, pruritus, photosensitivity; very rarely hepatitis, jaundice, dyspnoea, neurological reactions (including dizziness, confusion, hallucinations, convulsions, ataxia, dysarthria, and drowsiness), acute renal failure, anaemia, thrombocytopenia, and leucopenia; on intravenous infusion, severe local inflammation (sometimes leading to ulceration), and very rarely agitation, tremors, psychosis and fever

**Licensed use**  
- tablets and suspension not licensed for treatment of herpes zoster in children (age range not specified by manufacturer); intravenous infusion not licensed for herpes zoster in children under 18 years; tablets and suspension not licensed for attenuation of chickenpox (if varicella-zoster immunoglobulin not indicated) in children under 18 years

**Indication and dose**

#### Herpes simplex treatment

- **By mouth**
  - **Child 1 month–2 years** 100 mg 5 times daily, usually for 5 days (longer if new lesions appear during treatment or if healing incomplete); dose doubled if immunocompromised or if absorption impaired
  - **Child 2–18 years** 200 mg 5 times daily, usually for 5 days (longer if new lesions appear during treatment or if healing incomplete); dose doubled if immunocompromised or if absorption impaired

- **By intravenous infusion**
  - **Neonate** 20 mg/kg every 8 hours for 14 days (21 days if CNS involvement)
  - **Child 1–3 months with disseminated herpes simplex** 20 mg/kg every 8 hours for 14 days (21 days if CNS involvement)
  - **Child 3 months–12 years** 250 mg/m² every 8 hours usually for 5 days, dose doubled if CNS involvement
ACICLOVIR (continued)

Involvement (given for up to 21 days) or if immunosuppressed

Child 12–18 years 5 mg/kg every 8 hours usually for 5 days, dose doubled if CNS involvement (given for up to 21 days) or if immunosuppressed

Note To avoid excessive dose in obese patients parenteral dose should be calculated on the basis of ideal weight for height

Herpes simplex prophylaxis in the immunocompromised

- **By mouth**
  - Child 1 month–2 years 100–200 mg 4 times daily
  - Child 2–18 years 200–400 mg 4 times daily

Chickenpox and herpes zoster infection

- **By mouth**
  - Child 1 month–2 years 200 mg 4 times daily for 5 days
  - Child 2–6 years 400 mg 4 times daily for 5 days
  - Child 6–12 years 800 mg 4 times daily for 5 days
  - Child 12–18 years 800 mg 5 times daily for 7 days

- **By intravenous infusion**
  - Neonate 10–20 mg/kg every 8 hours for at least 7 days
  - Child 1–3 months 10–20 mg/kg every 8 hours for at least 7 days
  - Child 3 months–12 years 250 mg/m² every 8 hours usually for 5 days, dose doubled if immunocompromised
  - Child 12–18 years 5 mg/kg every 8 hours usually for 5 days, dose doubled if immunocompromised

Note To avoid excessive dose in obese patients parenteral dose should be calculated on the basis of ideal weight for height

Attenuation of chickenpox if varicella–zoster immunoglobulin not indicated

- **By mouth**
  - Child 1 month–18 years 10 mg/kg 4 times daily for 7 days starting 1 week after exposure

Herpesvirus eye infections section 11.3.3

**Administration** For intravenous infusion, reconstitute to 25 mg/mL with Water for Injections or Sodium Chloride 0.9% then dilute to concentration of 5 mg/mL with Sodium Chloride 0.9% or Sodium Chloride and Glucose or Compound Sodium Lactate and give over 1 hour; alternatively, may be administered in a concentration of 25 mg/mL using a suitable infusion pump and central venous access and given over 1 hour

Aciclovir (Non-proprietary) Tablets, aciclovir 200 mg, net price 25-tab pack = £4.01; 400 mg, 56-tab pack = £9.28; 800 mg, 35-tab pack = £11.42. Label: 9

Brands include Virovir®

Dental prescribing on NHS Aciclovir Tablets 200 mg or 800 mg may be prescribed

Dispersible tablets, aciclovir 200 mg, net price 25-tab pack = £2.21; 400 mg, 56-tab pack = £7.15; 800 mg, 35-tab pack = £6.54. Label: 9

Suspension, aciclovir 200 mg/5 mL, net price 125 mL = £29.56; 400 mg/5 mL, 100 mL = £33.02. Label: 9

Dental prescribing on NHS Aciclovir Oral Suspension 200 mg/5 mL may be prescribed

Intravenous infusion, powder for reconstitution, aciclovir (as sodium salt). Net price 250-mg vial = £9.13; 500-mg vial = £20.22.

Electrolytes Na⁺ 1.1 mmol/250-mg vial

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⁺ 1.16 mmol/250-mg vial

Zovirax® (GSK) Tablets, all dispersible, f/c, aciclovir 200 mg, net price 25-tab pack = £8.80; 800 mg (scored, Single Treatment Pack), 35-tab pack = £19.85. 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

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

VALACICLOVIR

Note Valaciclovir is a pro-drug of aciclovir

Cautions see under Aciclovir

Hepatic impairment manufacturer advises caution with high doses used for preventing cytomegalovirus disease—no information available in children

Renal impairment for herpes zoster, 1 g every 12 hours if estimated glomerular filtration rate 15–30 mL/minute/1.73 m² (every 24 hours if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²); for treatment of herpes simplex, 500 mg every 24 hours if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²; for suppression of herpes simplex, 250 mg (500 mg in immunocompromised) every 24 hours if estimated glomerular filtration rate less than 15 mL/minute/1.73 m²; reduce dose according to estimated glomerular filtration rate for cytomegalovirus prophylaxis following renal transplantation (consult product literature)
**5.3.2.2 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 under specialist supervision and only when the potential benefit outweighs the risks. Ganciclovir is administered by intravenous infusion for the *initial treatment* of CMV infection. The use of ganciclovir may also be considered for symptomatic congenital 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 (section 5.3.2.1) is licensed for use in children over 12 years for prevention of cytomegalovirus disease following renal transplantation.

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. There is limited information on its use in children.

For local treatment of CMV retinitis, see section 11.3.3.

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**GANCICLOVIR**

**Cautions** close monitoring of full blood count (severe deterioration may require correction and possibly treatment interruption); history of cytopenia; low platelet count; potential carcinogen and teratogen; radiotherapy; ensure adequate hydration during intravenous administration; vesicant—infuse into vein with adequate flow preferably using plastic cannula; possible risk of long-term carcinogenic or reproductive toxicity; interactions: Appendix 1 (ganciclovir)

**Renal impairment** reduce dose if estimated glomerular filtration rate less than 70 mL/minute/1.73 m²; consult product literature

**Contra-indications** hypersensitivity to ganciclovir or aciclovir; abnormally low haemoglobin, neutrophil, or platelet counts (consult product literature)

**Pregnancy** avoid—teratogenic risk (ensure effective contraception during treatment and barrier contraception for males during and for at least 90 days after treatment)

**Breast-feeding** avoid—no information available

**Side-effects** diarrhoea, nausea, vomiting, dyspepsia, abdominal pain, constipation, flatulence, dysphagia, hepatic dysfunction; dyspnoea, chest pain, cough; headache, insomnia, convulsions, dizziness, neuropathy, depression, anxiety, con-
Ganciclovir (continued)

- fusion, abnormal thinking, fatigue, weight loss, anorexia; infection, fever, night sweats; anaemia, leucopenia, 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, hypertension, anaphylactic reactions, psychosis, tremor, male infertility, haematuria, disturbances in hearing and vision, and alopecia.

Licensed use: not licensed for use in children.

Indication and dose

Life-threatening or sight-threatening cytomegalovirus infections in immunocompromised patients only; prevention of cytomegalovirus disease during immunosuppressive therapy following organ transplantation.

- By intravenous infusion

Child 1 month–18 years 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.

Congenital cytomegalovirus infection of the CNS

- By intravenous infusion

Neonate 6 mg/kg every 12 hours for 6 weeks.

Local treatment of CMV retinitis

Administration for intravenous infusion, reconstitute with Water for Injections (500 mg/10 mL) then dilute to a concentration of not more than 10 mg/mL with Glucose 5% or Sodium Chloride 0.9% or Compound Sodium Lactate and give over 1 hour.

Cymevene® (Roche) 

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

Cautions: 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).

Renal impairment: reduce dose; consult product literature.

Contra-indications

- Pregnancy: avoid.
- Breast-feeding: avoid—present in milk in animal studies.

Side-effects

- nausea, vomiting, diarrhoea (occasionally constipation and dyspepsia), abdominal pain, anorexia; changes in blood pressure and ECG; headache, fatigue, mood disturbances (including psychosis), asthenia, 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.

Licensed use: not licensed for use in children.

Indication and dose

CMV retinitis

- By intravenous infusion

Child 1 month–18 years 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

Child 1 month–18 years 40 mg/kg every 8 hours for 2–3 weeks or until lesions heal.

Administration for intravenous infusion, give undiluted solution via a central venous catheter; alternatively dilute to a concentration of 12 mg/mL with Glucose 5% or Sodium Chloride 0.9% for administration via a peripheral vein; give over at least 1 hour.

Foscavir® (AstraZeneca) 

Intravenous infusion, foscarnet sodium hexahydrate 24 mg/mL, net price 250-mL bottle = £34.49.
5.3.3 Viral hepatitis

Treatment for viral hepatitis should be initiated by a specialist in hepatology or infectious diseases. The management of uncomplicated acute viral hepatitis is largely symptomatic. 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** Interferon alfa (section 8.2.4), peginterferon alfa-2a, lamivudine (section 5.3.1), and adefovir dipivoxil have a role in the treatment of chronic hepatitis B in adults but their role in children has not been established. Specialist supervision is required for the management of chronic hepatitis B.

Tenofovir, 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 children who require treatment for both HIV and chronic hepatitis B. If children 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. Management of these children should be co-ordinated between HIV and hepatology specialists.

**Chronic hepatitis C** Treatment should be considered for children with moderate or severe liver disease. Specialist supervision is required and the regimen is chosen according to the genotype of the infecting virus and the viral load. A combination of ribavirin (section 5.3.5) and interferon alfa (section 8.2.4) is licensed for use in children over 3 years with chronic hepatitis C. A combination of peginterferon alfa (BNF Section 8.2.4) and ribavirin is preferred.

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; oseltamivir is licensed for use within 48 hours of the first symptoms while zanamivir is licensed for use within 36 hours of the first symptoms. In otherwise healthy individuals they reduce the duration of symptoms by about 1–1.5 days. For further information on the treatment of influenza, see NICE guidance, p. 391.

Oseltamivir and zanamivir are licensed for post-exposure prophylaxis of influenza when influenza is circulating in the community. Oseltamivir should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza (see also NICE guidance, p. 391). 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.

**Oseltamivir in children under 1 year of age** Safety data on the use of oseltamivir in children under 1 year of age is limited and it is not licensed for use in this age group. Furthermore, oseltamivir may be ineffective in neonates and very young infants because they may not be able to metabolise oseltamivir to its active form. In exceptional circumstances, oseltamivir can be used (under specialist supervision) for the treatment or post-exposure prophylaxis of influenza in children under 1 year of age. The Department of Health has advised (May 2009) that, during a pandemic, treatment with oseltamivir can be overseen by healthcare professionals experienced in assessing children.

Amanantadine is licensed for prophylaxis and treatment of influenza A in children over 10 years of age, but it is no longer recommended (see NICE guidance, p. 391).

Information on pandemic influenza, avian influenza, and swine influenza can 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).
NICE guidance
Osimertinib, zanamivir, and amantadine for prophylaxis and treatment of influenza (September 2008 and February 2009)

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 or treatment of influenza.
- Osimertinib or zanamivir are not recommended for seasonal prophylaxis against influenza.
- When influenza is circulating in the community, osimertinib or zanamivir is recommended (in accordance with UK licensing) for post-exposure prophylaxis in at-risk children 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. Osimertinib should be given within 48 hours of exposure to influenza while zanamivir should be given within 36 hours of exposure to influenza.
- When influenza is circulating in the community, osimertinib or zanamivir is recommended (in accordance with UK licensing) for the treatment of influenza in at-risk children who can start treatment within 48 hours (within 36 hours for zanamivir) of the onset of symptoms.
- During local outbreaks of influenza-like illness, when there is a high level of certainty that influenza is present, either osimertinib or zanamivir may be used for post-exposure prophylaxis or treatment in at-risk children (regardless of influenza vaccination) living in long-term residential or nursing homes.

At-risk children are those who have one or more of the following conditions:

- chronic respiratory disease (including asthma);
- chronic heart disease;
- chronic renal disease;
- chronic liver disease;
- chronic neurological disease;
- immunosuppression;
- diabetes mellitus.

This guidance does not cover the circumstances of a pandemic, an impending pandemic, or a widespread epidemic of a new strain of influenza to which there is little or no immunity in the community.

OSELTAMIVIR

Cautions
- Renal impairment: reduce dose by 50% if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²
- Pregnancy: avoid unless potential benefit outweighs risk
- Breast-feeding: avoid unless potential benefit outweighs risk; present in milk in animal studies

Side-effects
- nausea, vomiting, abdominal pain, diarrhoea; headache; conjunctivitis; less commonly rash; also reported hepatitis, arrhythmias, neuropsychiatric disorders, visual disturbances, Stevens-Johnson syndrome, and toxic epidermal necrolysis

Licensed use
- not licensed for use in children under 1 year

Indication and dose

Prevention of influenza
- By mouth
  - Child under 1 year (under specialist supervision, see notes above) 2 mg/kg once daily for 10 days for post-exposure prophylaxis
  - Child 1–13 years
    - Body-weight under 15 kg 30 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
    - Body-weight 15–23 kg 45 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
    - Body-weight 23–40 kg 60 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic
    - Body-weight over 40 kg 75 mg once daily for 10 days for post-exposure prophylaxis; for up to 6 weeks during an epidemic

1. National surveillance schemes, including those run by the Health Protection Agency, should be used to indicate when influenza is circulating in the community.
### OSERTAMIVIR (continued)

#### Treatment of influenza
- **By mouth**
  - **Child under 1 year** (see notes above) 2 mg/kg twice daily for 5 days
  - **Child 1–13 years**
    - Body-weight under 15 kg 30 mg twice daily for 5 days
    - Body-weight 15–23 kg 45 mg twice daily for 5 days
    - Body-weight 23–40 kg 60 mg twice daily for 5 days
    - Body-weight over 40 kg 75 mg twice daily for 5 days
  - **Child 13–18 years** 75 mg twice daily for 5 days

**Application**
- If suspension not available, capsules can be opened and the contents mixed with a small amount of sweetened food, such as yoghurt, just before administration.

**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.
- Excipients include sorbitol 1.7 g/5 mL

#### ZANAMIVIR

**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: only use if potential benefit outweighs risk—no information available.

**Contra-indications**
- Breast-feeding: avoid—present in milk in animal studies
- Side-effects: very rarely bronchospasm, respiratory impairment, angioedema, urticaria, and rash; also reported neuropsychiatric disorders

**Indication and dose**
- **Post-exposure prophylaxis of influenza**
  - **By inhalation of powder**
    - **Child 5–18 years** 10 mg once daily for 10 days
- **Prevention of influenza during an epidemic**
  - **By inhalation of powder**
    - **Child 5–18 years** 10 mg once daily for up to 28 days
- **Treatment of influenza**
  - **By inhalation of powder**
    - **Child 5–18 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

1. **Except** for the treatment and prophylaxis of influenza as indicated in the notes above and NICE guidance; endorse prescription ‘SLS’

### Respiratory syncytial virus

**Ribavirin** (tribavirin) inhibits a wide range of DNA and RNA viruses. It is licensed for administration by inhalation for the treatment of severe bronchiolitis caused by the respiratory syncytial virus (RSV) in infants, especially when they have other serious diseases. However, there is no evidence that ribavirin produces clinically relevant benefit in RSV bronchiolitis. Ribavirin is given by mouth with peginterferon alfa or interferon alfa for the treatment of chronic hepatitis C infection (see Viral Hepatitis, section 5.3.3). Ribavirin is also effective in Lassa fever and has also been used parenterally in the treatment of life-threatening RSV, parainfluenza virus, and adenovirus infections in immunocompromised children [unlicensed indications].

**Palivizumab** is a monoclonal antibody licensed for preventing serious lower respiratory-tract disease caused by respiratory syncytial virus in children at high risk of the disease; it should be prescribed under specialist supervision and on the basis of the likelihood of hospitalisation. Palivizumab should be considered for children under 6 months with haemodynamically significant left-to-right shunt congenital heart disease or who have pulmonary hypertension. It should also be considered for children under 2 years either with chronic lung disease who are using oxygen at home (or have been on prolonged oxygen treatment) or with...
severe congenital immunodeficiency. Palivizumab may also be used for the first 6–12 months of life in a child born at under 35 weeks gestation, if the child is considered by the specialist to be at special risk of hospitalisation. It is licensed for monthly use during the RSV season; the first dose should be administered before the start of the RSV season.

### Palivizumab

**Cautions** moderate to severe acute infection or febrile illness; thrombocytopenia; serum-palivizumab concentration may be reduced after cardiac surgery

**Contra-indications** hypersensitivity to humanised monoclonal antibodies

**Side-effects** fever, injection-site reactions, nervousness; *less commonly* diarrhoea, vomiting, constipation, haemorrhage, rhinitis, cough, wheeze, pain, drowsiness, asthma, hyperkinesia, leucopenia, and rash; *rarely* apnoea, hypersensitivity reactions (including anaphylaxis)

**Licensed use** not licensed in children with congenital immunodeficiency or in children born at 35 weeks gestation or less and older than 6 months (licensed in children under 6 months)

### Ribavirin

(Trivirin)

**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 systemic treatment: Exclude pregnancy before treatment in females of childbearing age; effective contraception essential during treatment and for 4 months after treatment in females and for 7 months after treatment in males of childbearing age; routine monthly pregnancy tests recommended; condoms must be used if partner of male patient is pregnant (ribavirin excreted in semen); cardiac disease (assessment including ECG recommended before and during treatment—discontinue if deterioration); determine full blood count, platelets, electrolytes, serum creatinine, liver function tests and uric acid before starting treatment and during season of risk; injection volume over 1 mL should be divided between 2 or more sites

**Indication and dose**

**Prevention of serious disease caused by respiratory syncytial virus infection (see notes above)**

- By intramuscular injection (preferably in anterolateral thigh)

**Neonate** 15 mg/kg once a month during season of RSV risk

**Child 1 month–2 years** 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 2 or more sites

**Synagis® (Abbott) ▼ (Palivizumab)**

**Injection** powder for reconstitution, palivizumab, net price 50-mg vial = £360.40; 100-mg vial = £663.11

**Contra-indications**

Pregnancy avoid (important teratogenic risk: see Cautions)

Breast-feeding avoid

Specific contra-indications for systemic treatment: Severe cardiac disease, including unstable or uncontrolled cardiac disease in previous 6 months; haemoglobinopa-thies; severe debilitating medical conditions; severe hepatic dysfunction or decompensated cirrhosis; autoimmune disease (including autoimmune hepatitis); history of severe psychiatric condition

**Side-effects** Specific side-effects for inhaled treatment: Worsening respiratory, bacterial pneumonia, and pneumothorax reported; rarely non-specific anaemia and haemolysis

Specific side-effects for systemic 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, flatulence, diarrhoea, constipation, colitis, pancreatitis, growth retardation (including decrease in height and weight), appetite changes, weight loss, pulmonary embolism, chest pain, tachycardia, palpitation, syncope, cerebrovascular disease, peripheral oedema, changes in blood pressure, flushing, Raynaud’s disease, hypertriglyceridaemia, dyspnoea, cough, interstitial pneumonitis, sleep disturbances, abnormal dreams, asthenia, impaired concentration and memory, psychoses, anxiety, depression, suicidal ideation, dizziness, hyperkinesia, tremor, hypertonia, seizures, ataxia, dysphonia, peripheral neuropathy, influenza-like symptoms, headache, hyperglycaemia, thyroid disorders, menstrual disturbances, virilism, testicular pain, micturition disorders, leucopenia, thrombocytopenia, aplastic anaemia, lymphopenopa-thy, hypocalcaemia, renal failure, hyperuricaemia, myalgia, arthralgia, systemic lupus erythematosus, vasculitis, sarcoidosis, eye changes (including blurred vision and retinopathy), rhinitis, tinnitus, hearing impairment, dry mouth, stomatitis, glossitis, taste disturbance, pharyngitis, gingivitis, tooth disorders, rash (including very rarely Stevens-Johnson syndrome and toxic epidermal necrolysis), pruritus, urticaria, photosensitivity, psoriasis, alopecia, dry skin, skin discoloration, increased sweating.
Licensed use

Inhalation licensed for use in children (age range not specified by manufacturer); intravenous preparation not licensed

Indication and dose

Bronchiolitis

- By aerosol inhalation or nebulisation (via small particle aerosol generator)
  - Child 1 month–2 years: inhale solution containing 20 mg/mL for 12–18 hours for at least 3 days; max. 7 days
  - Life-threatening RSV, parainfluenza virus, and adenovirus infection in immunocompromised children (seek expert advice)

- By intravenous infusion over 15 minutes
  - Child 1 month–18 years: 33 mg/kg as a single dose, then 16 mg/kg every 6 hours for 4 days, then 8 mg/kg every 8 hours for 3 days

Chronic hepatitis C (in combination with interferon alfa or peginterferon alfa) in previously untreated children without liver decompensation

- By mouth
  - Child over 3 years; body-weight under 47 kg: 15 mg/kg daily in 2 divided doses
  - Child body-weight 47–50 kg: 200 mg in the morning and 400 mg in the evening
  - Child body-weight 50–65 kg: 400 mg twice daily
  - Child body-weight 65–86 kg: 400 mg in the morning and 600 mg in the evening
  - Child body-weight 86–105 kg: 600 mg twice daily
  - Child body-weight over 105 kg: 600 mg in the morning and 800 mg in the evening

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

Oral solution, ribavirin 200 mg/5 mL, net price 100 mL (bubble-gum-flavoured) = £69.71. Label: 21

Virazole® (Valeant)

Inhalation, ribavirin 6 g for reconstitution with 300 mL water for injections. Net price 3 x 6-g vials = £349.00

Intravenous infusion, 100 mg/mL, 10-mL amp Available on a named-patient basis from Valeant

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

Advice on specific problems available from:

Advice for healthcare professionals

HPA (Health Protection Agency) Malaria Reference Laboratory
www.hpa.org.uk/infections/topics_az/malaria
(020) 7636 3924 (prophylaxis only)

National Travel Health Network and Centre
0845 602 6712

Travel Medicine Team, Health Protection, Scotland
www.travax.nhs.uk
(registered users of Travax only)
(0141) 300 1100 (weekdays 2–4 p.m. only)

Birmingham
(0121) 424 0357

Liverpool
(0151) 705 3100

London
0845 155 5000 (treatment)

Oxford
(01865) 225 430

Advice for travellers

Hospital for Tropical Diseases, Travel Healthline
www.fitfortravel.nhs.uk
020 7950 7799

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. Choice will depend on the age of the child (see below).

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 atovaquone), or *Riamet®* (artemether with lumefantrine). Falciparum malaria can progress rapidly in unprotected children 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 child 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 child is seriously ill or unable to take tablets. **Mefloquine** is now rarely used for treatment because of concerns about resistance.

**Oral. Quinine** is well tolerated by children although the salts are bitter.

- The dosage regimen for quinine by mouth is:
  - 10 mg/kg (of quinine salt; max. 600 mg) every 8 hours for 7 days together with or followed by either 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

If the parasite is likely to be sensitive, **pyrimethamine with sulfadoxine** as a single dose [unlicensed] may be given instead of either clindamycin or doxycycline together with or after a course of quinine.

- The dose regimen for pyrimethamine with sulfadoxine by mouth is:
  - Child up to 4 years and body-weight over 5 kg pyrimethamine 12.5 mg with sulfadoxine 250 mg as a single dose
  - Child 5–6 years pyrimethamine 25 mg with sulfadoxine 500 mg as a single dose
  - Child 7–9 years pyrimethamine 37.5 mg with sulfadoxine 750 mg as a single dose
  - Child 10–14 years pyrimethamine 50 mg with sulfadoxine 1 g as a single dose
  - Child 14–18 years pyrimethamine 75 mg with sulfadoxine 1.5 g as a single dose

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 is:
  - Child body-weight 5–8 kg, 2 ‘paediatric’ tablets once daily for 3 days
  - Child body-weight 9–10 kg, 3 ‘paediatric’ tablets once daily for 3 days
  - Child body-weight 11–20 kg, 1 ‘standard’ tablet once daily for 3 days
  - Child body-weight 21–30 kg, 2 ‘standard’ tablets once daily for 3 days
  - Child body-weight 31–40 kg, 3 ‘standard’ tablets once daily for 3 days
  - Child body-weight over 40 kg, 4 ‘standard’ tablets once daily for 3 days

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1. Valid for quinine hydrochloride, dihydrochloride, and sulphate; not valid for quinine bisulphate which contains a correspondingly smaller amount of quinine.
The dose regimen for Riamet® by mouth is:
Child 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)
Child 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)
Child 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)
Child 12–18 years and body-weight over 35 kg, 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 child is seriously ill or unable to swallow tablets, quinine should be given by intravenous infusion. The dose regimen for quinine by intravenous infusion is calculated on a mg/kg basis:

Neonates and children, loading dose\(^1,2\) of 20 mg/kg (up to maximum 1.4 g) of quinine salt\(^3\) infused over 4 hours then 8 hours after the start of the loading dose, maintenance dose of 10 mg/kg\(^4\) (up to maximum 700 mg) of quinine salt\(^3\) infused over 4 hours every 8 hours (until child can swallow tablets to complete the 7-day course together with or followed by either clindamycin or doxycycline as above).

Specialist advice should be sought in difficult cases (e.g. very high parasite count, deterioration on optimal doses of quinine, infection acquired in quinine-resistant areas of south-east Asia) because intravenous artemisate may be available for ‘named-patient’ use.

Pregnancy Falciparum malaria is particularly dangerous in pregnancy, especially in the last trimester. The treatment doses of oral and intravenous quinine given above (including the loading dose) can safely be given in pregnancy. Clindamycin [unlicensed indication] should be given for 7 days with or after quinine. Doxycycline should be avoided in pregnancy (affects teeth and skeletal development in fetus); 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\(^1\) is the drug of choice for the treatment of benign malarias (but chloroquine-resistant P. vivax infection has been reported from Indonesia, New Guinea and some adjacent islands).

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\(^6\) given after the chloroquine.

The dosage regimen of chloroquine by mouth for benign malaria in children is:
initial dose of 10 mg/kg of base (max. 620 mg) then
a single dose of 5 mg/kg of base (max. 310 mg) after 6–8 hours then
a single dose of 5 mg/kg of base (max. 310 mg) daily for 2 days
For a radical cure, primaquine\(^6\) [unlicensed] is then given to children over 6 months of age; specialist advice should be sought for children under 6 months of age. Primaquine is given in a dose of 250 micrograms/kg (max. 15 mg) daily for 14 days.

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1. In intensive care units the loading dose can alternatively be given as quinine salt\(^3\) 7 mg/kg infused over 30 minutes followed immediately by 10 mg/kg over 4 hours then (after 8 hours) maintenance dose as described.
2. 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.
3. Valid for quinine hydrochloride, dihydrochloride, and sulphate; not valid for quinine bisulphate which contains a correspondingly smaller amount of quinine.
4. Maintenance dose should be reduced to 5–7 mg/kg of quinine salt in children with severe renal impairment, severe hepatic impairment, or if parenteral treatment is required for more than 48 hours.
5. For the treatment of chloroquine-resistant benign malaria Malarone® [unlicensed indication], quinine, or Riamet® [unlicensed indication] can be used; as with chloroquine, primaquine should be given for radical cure.
6. Before starting primaquine, blood should be tested for glucose-6-phosphate dehydrogenase (G6PD) activity since the drug can cause haemolysis in G6PD-deficient patients. Specialist advice should be obtained in G6PD deficiency. In mild G6PD deficiency, primaquine in a dose of 750 micrograms/kg (max. 45 mg) once a week for 8 weeks, has been found useful and without undue harmful effects.
days in *P. ovale* infection or 500 micrograms/kg (max. 30 mg) daily for 14 days in *P. vivax* infection.

**Pregnancy** 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 10 mg/kg (max. 310 mg) each week during the pregnancy.

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**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 child 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).

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 obtain advice from specialist centre, see p. 394.

**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 (infants should sleep with a mosquito net stretched over the cot or baby carrier); 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 use 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 for 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 and carers of children 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.

**Epilepsy** Both chloroquine and mefloquine are unsuitable for malaria prophylaxis in children with a history of epilepsy. In areas without chloroquine resistance, proguanil alone is recommended; in areas with chloroquine resistance, doxycycline or **Malarone®** may be considered. The metabolism of doxycycline may be influenced by antiepileptics (see interactions: Appendix 1 (tetracyclines)).

**Asplenia** Asplenic children (or those with severe splenic dysfunction) are at particular risk of severe malaria. If travel to malarious areas is unavoidable, rigorous precautions are required against contracting the disease.
Renal impairment Avoidance (or dosage reduction) of proguanil is recommended since it is excreted by the kidneys. Malarone® should not be used for prophylaxis in children with estimated glomerular filtration rate less than 30 mL/minute/1.73 m². Chloroquine is only partially excreted by the kidneys and reduction of the dose for prophylaxis is not required except in severe impairment. Mefloquine is considered to be appropriate to use in renal impairment and does not require dosage reduction. Doxycycline is also considered to be appropriate.

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. 394 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.

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 and their carers (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

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 and child under 12 years) 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 Zaire), 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 northern third), Niger, Nigeria, Principe, Rwanda, São Tomé, Senegal, Sierra Leone, Somalia, South Africa (low-altitude areas of Mpumalanga and Limpopo Provinces, Kruger National Park, and north-east KwaZulu-Natal as far south as Jozi), Sudan, Swaziland, Tanzania, Togo, Uganda, Zambia, Zimbabwe (all year in Zambezi valley; November–June in other areas below 1200 m; risk negligible in Harare and Bulawayo):

- mefloquine or doxycycline (if child over 12) or Malarone®

**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 Agra], Haryana, Uttarakhand, 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):

- chemoprophylaxis not recommended but avoid mosquito bites and consider malaria if fever present

**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):

- chloroquine + proguanil hydrochloride or (if chloroquine + proguanil not appropriate) mefloquine or doxycycline or Malarone®

**High risk**  
Risk high and chloroquine resistance high in Bangladesh (only in Chittagong Hill Tracts; low risk in other areas, see above), India (Assam only; see also low risk and variable risk above):

- mefloquine or doxycycline (if child over 12) or Malarone® or (if mefloquine, doxycycline, or Malarone® not appropriate) chloroquine + proguanil hydrochloride
South-East Asia

**Very low risk**  
Risk very low in Bali, Brunei, main tourist areas of China (but substantial risk in Yunnan and Hainan, see below; chloroquine prophylaxis appropriate for other remote areas), Hong Kong, Korea (both North and South), Malaysia (both East and West including Cameron Highlands, but substantial risk in Sabah [except Kota Kinabalu], and variable risk in deep forests, see below), Singapore, Thailand (Bangkok, main tourist centres, Chang Ri, Kwai Bridge—important: regional risk exists, see under Great risk, below), Vietnam (cities, coast between Ho Chi Minh and 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):

chloroquine + 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 (if child over 12) 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 (if child over 12) or Malarone®

Oceania

**Risk**  
Risk high and chloroquine resistance high in Papua New Guinea (below 1800 m), Solomon Islands, Vanuatu:

doxycycline (if child over 12) 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 Pococí), Dominican Republic, El Salvador (Santa Ana province in west), Guatemala (below 1500 m), Haiti, Honduras, Mexico (states of Oaxaca and Chiapas), Nicaragua, Panama (west of Panama Canal but variable to high risk east of Panama Canal, see below), rural Paraguay:

chloroquine or (if chloroquine not appropriate) proguanil hydrochloride

**Variable to high risk**  
Risk variable to high and chloroquine resistance present in rural areas of Bolivia (below 2500 m; see below for Amazon basin area), Ecuador
(below 1500 m; no malaria in Galapagos Islands and Guayaquil; see below for Esmeraldas Province), Panama (east of Panama Canal), Peru (rural areas east of the Andes and west of the Amazon basin area below 1500 m; see below for Amazon basin area), Venezuela (north of Orinoco river; high risk south of and including Orinoco river and Amazon basin area, see below; Caracas free of malaria):

chloroquine + proguanil hydrochloride or (if chloroquine + proguanil not appropriate) mefloquine or doxycycline (if child over 12) or Malarone®

High risk  
Risk high and marked chloroquine resistance in Bolivia (Amazon basin area; see also variable to high risk above), Brazil (throughout ‘Legal Amazon’ area which includes the Amazon basin area, Mato Grosso and Maranhao only; elsewhere very low risk—no chemoprophylaxis), Colombia (most areas below 800 m), Ecuador (Esmeraldas Province; variable to high risk in other areas, see above), French Guiana, all interior regions of Guyana, Peru (Amazon basin area; see also variable to high risk above), Suriname (except Paramaribo and coast), Venezuela (Amazon basin area, areas south of and including Orinoco river; see also variable to high risk above):

mefloquine or doxycycline (if child over 12) or Malarone®

Standby treatment [unlicensed]

Children and their carers visiting remote, malarious areas for prolonged periods should carry standby treatment if they are likely to be more than 24 hours away from medical care. Self-medication should be avoided if medical help is accessible.

In order to avoid excessive self-medication, the traveller should be provided with written instructions that urgent medical attention should be sought if fever (38.8°C or more) develops 7 days (or more) after arriving in a malarious area and that self-treatment is indicated if medical help is not available within 24 hours of fever onset.

In view of the continuing emergence of resistant strains and of the different regimens required for different areas expert advice should be sought on the best treatment course for an individual traveller. A drug used for chemoprophylaxis should not be considered for standby treatment for the same traveller.

Artemether with lumefantrine

Artemether with lumefantrine is licensed for the treatment of acute uncomplicated falciparum malaria.

**ARTEMETHER WITH LUMEFANTRINE**

**Cautions**  
electrolyte disturbances, concomitant use with other drugs known to cause QT-interval prolongation; monitor patients unable to take food (greater risk of recrudescence); **interactions**: Appendix 1 (artemether with lumefantrine) **Hepatic impairment**  
manufacturer advises caution in severe impairment—monitor ECG and plasma potassium concentration **Renal impairment**  
manufacturer advises caution in severe impairment—monitor ECG and plasma potassium concentration **Pregnancy**  
toxicity in animal studies with arte- 

**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**  
Manufacturer advises avoid breast-feeding for at least 1 week after last dose; present in milk in animal studies **Side-effects**  
abdominal pain, anorexia, diarrhoea, vomiting, nausea; palpitation, prolonged QT interval; cough; headache, dizziness, sleep disturbances, asthenia, paraesthesia; arthralgia, myalgia; pruritus, rash; less commonly ataxia, hypoaesthesia, clonus
**ARTEMETHER WITH LUMEFANTRINE (continued)**

**Indication and dose**
- Treatment of acute uncomplicated falciparum malaria see p. 395
- Treatment of benign malaria see p. 396

**Administration**
- Tablets may be crushed just before administration

**Riamet**
- (Novartis)
- Tablets, yellow, artemether 20 mg, lumefantrine 120 mg, net price 24-tab pack = £22.50. Label: 21, counselling, skilled tasks

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**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. 398).

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. 395). It is still recommended for the treatment of benign malarias (for details, see p. 396).

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**CHLOROQUINE**

**Cautions**
- moderate or severe hepatic impairment; may exacerbate psoriasis, neurological disorders (avoid for prophylaxis if history of epilepsy, see notes above), may aggravate myasthenia gravis, severe gastro-intestinal disorders, G6PD deficiency (see section 9.1.5); ophthalmic examination with long-term therapy; avoid concurrent therapy with hepatotoxic drugs—other **interactions:** Appendix 1 (chloroquine and hydroxychloroquine)
- Renal impairment mild to moderate, reduce dose (but for malaria prophylaxis see, p. 398); severe, avoid (but for malaria prophylaxis see p. 398)
- Pregnancy
  - **first, third trimesters:** benefit of prophylaxis and treatment in malaria outweighs risk; **important:** see also Falciparum Malaria (Treatment), Benign Malarials (Treatment), and Prophylaxis Against Malaria
- Breast-feeding
  - amount probably too small to be harmful when used for malaria prophylaxis; inadequate for reliable protection against malaria in breast-fed infant, see p. 398; avoid breast-feeding when used for rheumatic diseases
- Side-effects
  - gastro-intestinal disturbances, headache; also hypotension, convulsions, visual disturbances, depigmentation or loss of hair, skin reactions (rashes, pruritus); rarely, bone-marrow suppression, hypersensitivity reactions such as urticaria and angioedema; other side-effects (not usually associated with malaria prophylaxis or treatment), see under Antimalarials, section 10.1.3; very toxic in **overdosage**—immediate advice from poisons centres essential (see also p. 41)

**Indication and dose**

**Prophylaxis of malaria**
- **By mouth**
  - Dose (expressed as chloroquine base) preferably started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above)
  - **Child up to 12 weeks, body-weight under 6 kg**
    - 37.5 mg once weekly
  - **Child 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
  - **Child 4–8 years, body-weight 16–25 kg**
    - 150 mg once weekly (or 155 mg once weekly if tablets used)
  - **Child 8–13 years, body-weight 25–45 kg**
    - 225 mg once weekly (or 232.5 mg once weekly if tablets used)
  - **Child over 13 years, body-weight over 45 kg**
    - 310 mg once weekly

**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

**Treatment of benign malaria** see p. 396

**Note**
- Chloroquine doses in BNFC may differ from those in product literature

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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.
1 CHLOROQUINE (continued)

1 Malarivon® (Wallace Mfg)  
Syrup, chloroquine phosphate 80 mg/5 mL (≡ chloroquine base 50 mg/5 mL), net price 75 mL = £3.35. Label: 5, counselling, prophylaxis, see above

2 Nivaquine® (Sanofi-Aventis)  
Syrup, golden, chloroquine sulphate 68 mg/5 mL (≡ chloroquine base 50 mg/5 mL), net price 100 mL = £5.15. Label: 5, counselling, prophylaxis, see above

With proguanil
For cautions and side-effects of proguanil see Proguanil; for dose see Chloroquine and Proguanil

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

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. 398).

Mefloquine is now rarely used for the treatment of falciparum malaria because of increased resistance. It is rarely used for the treatment of benign malarías 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

Cautions cardiac conduction disorders; epilepsy (avoid for prophylaxis); not recommended in infants under 3 months (5 kg); interactions: Appendix 1 (mefloquine); Hepatic impairment avoid for chemoprophylaxis in severe liver disease; Pregnancy (see Prophylaxis against Malaria, p. 398)—manufacturer advises avoid pregnancy during and for 3 months after (teratogenicity in animal studies); Breast-feeding present in milk but risk to infant minimal; Skilled tasks Dizziness or a disturbed sense of balance may affect performance of skilled tasks; 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 circulatory disorders (hypotension and hypertension), chest pain, tachycardia, palpitation, bradycardia, cardiac conduction disorders, dyspnoea, fatigue, fever, loss of appetite, neuropathic reactions (including sensory and motor neuropathies, tremor, ataxia, anxiety, depression, panic attacks, agitation, hallucinations, psychosis, convulsions), leucopenia or leucocytosis, thrombocytopenia, muscle weakness, myalgia, arthralgia, visual disturbances, tinnitus and vestibular disorders, rash (including Stevens-Johnson syndrome), urticaria, pruritus, alopecia; rarely suicidal ideation; very rarely AV block, pneumonitis, and encephalopathy; Licensed use not licensed for use in children under 5 kg body-weight and under 3 months; Indication and dose Prophylaxis of malaria preferably started 2½ weeks before entering endemic area and continued for 4 weeks after leaving (see notes above)

- By mouth
  - Child body-weight 5–16 kg 62.5 mg once weekly
  - Child body-weight 16–25 kg 125 mg once weekly
  - Child body-weight 25–45 kg 187.5 mg once weekly
  - Child body-weight over 45 kg 250 mg once weekly

Long-term chemoprophylaxis Mefloquine prophylaxis can be taken for up to 1 year. Counselling See CSM advice in notes above. Also warn travellers and carers of children travelling 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 BNFC may differ from those in product literature

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

CHLOROQUINE (continued)

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
**MEFLOQUINE (continued)**

**Administration**  Tablet may be crushed and mixed with food such as jam or honey just before administration

**Lariam** (Roche) Tablets, scored, mefloquine (as hydrochloride) 250 mg. Net price 8-tab pack = £14.53. Label: 21, 25, 27, counselling, skilled tasks, prophylaxis, see above

**Primaquine**

Primaquine is used to eliminate the liver stages of *P. vivax* or *P. ovale* following chloroquine treatment (for details, see p. 396).

**PRIMAQUINE**

**Cautions**  G6PD deficiency (test blood, see under Benign Malarias (treatment), p. 396); systemic diseases associated with granulocytopenia (e.g. juvenile idiopathic arthritis, lupus erythematosus); **interactions:** Appendix 1 (primaquine)  

**Pregnancy**  risk of neonatal haemolysis and methaemoglobinemia in third trimester; see also Benign Malarias (treatment)

**Side-effects**  nausea, vomiting, anorexia, abdominal pain; **less commonly** methaemoglobinemia, haemolytic anaemia especially in G6PD deficiency, leucopenia

**Licensed use**  not licensed

**Indication and dose**

Adjunct in the treatment of *Plasmodium vivax* and *P. ovale* malaria (eradication of liver stages) for dose see Benign Malarias, p. 396

**Primaquine** (Non-proprietary) Tablets, primaquine (as phosphate) 7.5 mg or 15 mg Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Proguanil**

Proguanil is used (usually with chloroquine, but occasionally alone) for the prophylaxis of malaria, (for details, see specific recommendations by country, p. 398).

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**

**Cautions**  interactions: Appendix 1 (proguanil)  

Renal impairment (see notes under Prophylaxis against malaria). Use half normal dose if estimated glomerular filtration rate 20–60 mL/minute/1.73 m². Use one-quarter normal dose on alternate days if estimated glomerular filtration rate 10–20 mL/minute/1.73 m². Use one-quarter normal dose once weekly if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²; increased risk of haematological toxicity.

**Pregnancy**  benefit of prophylaxis in malaria outweighs risk. Adequate folate supplements should be given to mother; see also Prophylaxis Against Malaria

**Breast-feeding**  amount probably too small to be harmful when used for malaria prophylaxis; inadequate for reliable protection against malaria in breast-fed infant

**Side-effects**  mild gastric intolerance, diarrhoea, and constipation; occasionally mouth ulcers and stomatitis; **very rarely** cholestasis, vasculitis, skin reactions and hair loss

**Indication and dose**

**Prophylaxis of malaria** preferably started 1 week before entering endemic area and continued for 4 weeks after leaving (see notes above)  

**By mouth**

- **Child up to 12 weeks**, body-weight under 6 kg 25 mg once daily  
- **Child 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  
- **Child 4–8 years**, body-weight 16–25 kg 100 mg once daily  
- **Child 8–13 years**, body-weight 25–45 kg 150 mg once daily

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1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed
PROGUANIL HYDROCHLORIDE (continued)

Child over 13 years, body-weight over 45 kg
200 mg once daily

Counselling Warn travellers and carers of children travelling 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 Proguanil doses in BNFC may differ from those in product literature.

Administration Tablets may be crushed and mixed with food such as milk, jam or honey just before administration.

PROGUANIL HYDROCHLORIDE WITH ATOVAQUONE

Cautions diarrhoea or vomiting (reduced absorption of atovaquone); efficacy not evaluated in cerebral or complicated malaria (including hyperparasitaemia, pulmonary oedema or renal failure); interactions: see Appendix 1 (proguanil, atovaquone).

Renal impairment avoid for malaria prophylaxis and, if possible for treatment, if estimated glomerular filtration rate less than 30 mL/minute/1.73 m².

Pregnancy manufacturer advises avoid unless essential.

Breast-feeding use only if no suitable alternative available; see also Breast-feeding, p. 398.

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, panic attacks, vasculitis, and Stevens-Johnson syndrome.

Indication and 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.

Malarone® Paediatric (GSK)

Paediatric tablets, pink, f/c proguanil hydrochloride 25 mg, atovaquone 25 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.

- By mouth
  - Child body-weight 11–21 kg: 1 tablet once daily
  - Child body-weight 21–31 kg: 2 tablets once daily
  - Child body-weight 31–40 kg: 3 tablets once daily
  - Child body-weight over 40 kg: 4 tablets once daily.

Malarone® (standard) tablets, see above.

Treatment of malaria

- By mouth
  - Child body-weight 5–9 kg: 2 tablets once daily
  - Child body-weight 9–11 kg: 3 tablets once daily
  - Child body-weight 11 kg and over: use Malarone® (standard) tablets, see above.

Administration 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 can be used in the treatment of falciparum malaria with (or following) quinine.

1. Drugs for malaria prophylaxis not prescribable on the NHS; health authorities may investigate circumstances under which antimalarials prescribed.
**PYRIMETHAMINE WITH SULFADOXINE**

**Cautions** see under Pyrimethamine (section 5.4.7) and under Co-trimoxazole (section 5.1.8); not recommended for prophylaxis (severe side-effects on long-term use); interactions: Appendix 1 (pyrimethamine, sulphonamides)

**Pregnancy** possible teratogenic risk in first trimester as pyrimethamine is a folate antagonist; in third trimester—risk of neonatal haemolysis and methaemoglobinemia; fears of increased risk of neonatal kernicterus appear unfounded

**Breast-feeding** small risk of neonatal kernicterus in jaundiced infants; risk of haemolysis in G6PD-deficient child due to sulfadoxine

**Contra-indications** see under Pyrimethamine (section 5.4.7) and under Co-trimoxazole (section 5.1.8); sulphonamide allergy

**Side-effects** see under Pyrimethamine (section 5.4.7) and under Co-trimoxazole (section 5.1.8); pulmonary infiltrates (e.g. eosinophilic or allergic alveolitis) reported—discontinue if cough or shortness of breath

**Licensed use** not licensed for use in children of body-weight under 5 kg

**Indication and dose**

Adjunct to quinine in treatment of *Plasmodium falciparum* malaria see p. 395

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

Also known as *Fansidar* Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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**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. 395).

**QUININE**

**Cautions** cardiac disease (including atrial fibrillation, conduction defects, heart block)—monitor ECG during parenteral treatment; monitor blood glucose and electrolyte concentration during parenteral treatment; G6PD deficiency (see section 9.1.5); interactions: Appendix 1 (quinine)

**Renal impairment** reduce parenteral maintenance dose for malaria treatment, see p. 396

**Pregnancy** risk of teratogenesis with high doses in first trimester; but in malaria benefit of treatment outweighs risk

**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. 41)

**Licensed use** injection not licensed

**Indication and dose**

Treatment of malaria see p. 395

**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

**Administration** for intravenous infusion, dilute to a concentration of 2 mg/mL (max. 30 mg/mL in fluid restriction) with Glucose 5% or Sodium Chloride 0.9% and give over 4 hours

**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. 943

**Note** Intravenous injection of quinine is so hazardous that it has been superseded by infusion

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**Tetracyclines**

**Doxycycline** (section 5.1.3) is used in children over 12 years 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. 398).

**Doxycycline** is also used as an adjunct to quinine in the treatment of *falciparum* malaria (for details see p. 395).
**DOXYCYCLINE**

Cautions section 5.1.3
Contra-indications section 5.1.3
Side-effects section 5.1.3
Licensed use not licensed for use in children under 12 years

**Indication and dose**

Prophylaxis of malaria preferably started 1–2 days before entering endemic area and continued for 4 weeks after leaving (see notes above)

- **By mouth**
  - Child over 12 years 100 mg once daily

Treatment of falciparum malaria see p. 395

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* which can cause ulceration of the large intestine. **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 large volume 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**

Contra-indications

- **Pregnancy** manufacturer advises avoid—no information available
- **Breast-feeding** manufacturer advises avoid—no information available

Side-effects flatulence, vomiting, urticaria, pruritus

Licensed use not licensed for use in children under 25 kg body-weight

**Indication and dose**

- **Chronic amoebiasis and as adjunct to metronidazole or tinidazole in acute amoebiasis**
  - **By mouth**
    - Child 1 month–12 years 6.6 mg/kg 3 times daily for 10 days
    - Child 12–18 years 500 mg 3 times daily for 10 days

Diloxanide (Sovereign) Tablets, diloxanide furoate 500 mg, net price 30-tab pack = £42.95. Label: 9

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
**METRONIDAZOLE**

**Cautions** section 5.1.11

**Side-effects** section 5.1.11

**Indication and dose**

**Anaerobic infections** section 5.1.11

**Invasive intestinal amoebiasis**
- **By mouth**
  - Child 1–3 years: 200 mg 3 times daily for 5 days
  - Child 3–7 years: 200 mg 4 times daily for 5 days
  - Child 7–10 years: 400 mg 3 times daily for 5 days
  - Child 10–18 years: 800 mg 3 times daily for 5 days

**Extra-intestinal amoebiasis (including liver abscess)**
- **By mouth**
  - Child 1–3 years: 100–200 mg 3 times daily for 5–10 days
  - Child 3–7 years: 100–200 mg 4 times daily for 5–10 days
  - Child 7–10 years: 200–400 mg 3 times daily for 5–10 days
  - Child 10–18 years: 400–800 mg 3 times daily for 5–10 days

**Urogenital trichomoniasis**
- **By mouth**
  - Child 1–3 years: 50 mg 3 times daily for 7 days
  - Child 3–7 years: 100 mg twice daily for 7 days
  - Child 7–10 years: 100 mg 3 times daily for 7 days
  - Child 10–18 years: 200 mg 3 times daily for 7 days or 400–500 mg twice daily for 5–7 days, or 2 g as a single dose

**Giardiasis**
- **By mouth**
  - Child 1–3 years: 500 mg once daily for 3 days
  - Child 3–7 years: 600–800 mg once daily for 3 days
  - Child 7–10 years: 1 g once daily for 3 days
  - Child 10–18 years: 2 g once daily for 3 days or 400 mg 3 times daily for 5 days or 500 mg twice daily for 7–10 days

**Preparations**

Section 5.1.11

**TINIDAZOLE**

**Cautions** see under Metronidazole (section 5.1.11); avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (tinidazole)

**Pregnancy** manufacturer advises avoid in first trimester

**Breast-feeding** present in milk—manufacturer advises avoid breast-feeding during and for 3 days after stopping treatment

**Side-effects** see under Metronidazole (section 5.1.11)

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

**Intestinal amoebiasis**
- **By mouth**
  - Child 1 month–12 years: 50–60 mg/kg (max. 2 g) once daily for 3 days
  - Child 12–18 years: 2 g once daily for 2–3 days

**Urogenital trichomoniasis and giardiasis**
- **By mouth**
  - Child 1 month–12 years: single dose of 50–75 mg/kg (max. 2 g) (repeated once if necessary)
  - Child 12–18 years: single dose of 2 g (repeated once if necessary)

**Amoebic involvement of liver**
- **By mouth**
  - Child 1 month–12 years: 50–60 mg/kg (max. 2 g) once daily for 5 days
  - Child 12–18 years: 1.5–2 g once daily for 3–6 days

**Fasigyn** (Pfizer)

Tablets, f/c, tinidazole 500 mg. Net price 20-tab pack = £13.80. Label: 4, 9, 21, 25

**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. Tinidazole (section 5.4.2) may be used as an alternative to metronidazole.
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 the treatment of choice for visceral leishmaniasis. The dose is 20 mg/kg daily (max. 850 mg) for at least 20 days by intramuscular or intravenous injection; the dosage varies with different geographical regions and expert advice should be obtained. Skin lesions can also be treated with sodium stibogluconate.

**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 isetionate** (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. 943.

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SODIUM STIBOGLUCONATE

**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** use with caution in hepatic disease

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** amount probably too small to be harmful

**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**

**Renal impairment** manufacturer advises avoid in severe impairment

**Side-effects** anorexia, nausea, vomiting, abdominal pain; ECG changes; coughing (see Cautions); headache, lethargy, arthralgia, myalgia; rarely jaundice, flushing, bleeding from nose or gum, substernal pain (see Cautions), vertigo, fever, sweating, and rash; also reported pancreatitis and anaphylaxis; pain and thrombosis on intravenous administration, intramuscular injection also painful

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

**Leishmaniasis** for dose, see notes above

**Administration** injection should be filtered immediately before administration using a filter of 5 microns or less; see also Cautions above

**Pentostam®** (GSK)

**Injection**, sodium stibogluconate equivalent to pentavalent antimony 100 mg/mL. Net price 100-mL bottle = £66.43

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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.

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5.4.7 Drugs for toxoplasmosis

Most infections caused by *Toxoplasma gondii* are self-limiting, and treatment is not necessary. Exceptions are children with eye involvement (toxoplasma chorioretinitis), 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 (folinic acid supplements (see p. 501) and weekly blood counts needed). Alternative regimens use combinations of pyrimethamine with clindamycin or clarithromycin 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; specialist advice should be sought on management. Spiramycin may reduce the risk of transmission of maternal infection to the fetus. When there is evidence of placental or fetal infection, pyrimethamine may be given with sulfadiazine and folinic acid after the first trimester.

In neonates without signs of toxoplasmosis, but born to mothers known to have become infected, spiramycin is given while awaiting laboratory results. If toxoplasmosis is confirmed in the infant, pyrimethamine and sulfadiazine are given for 12 months, together with folinic acid.

### PYRIMETHAMINE

**Cautions** blood counts required with prolonged treatment; history of seizures—avoid large loading doses; **interactions**: Appendix 1 (pyrimethamine)

- Hepatic impairment manufacturer advises caution
- Renal impairment manufacturer advises caution
- Pregnancy theoretical teratogenic risk in first trimester (folate antagonist); adequate folate supplement should be given to mother
- Breast-feeding present in milk—avoid breastfeeding during toxoplasmosis treatment; avoid other folate antagonists

**Side-effects** depression of haematopoiesis with high doses, rashes, insomnia

**Licensed use** not licensed for use in children under 5 years

**Indication and dose**

- Toxoplasmosis in pregnancy (in combination with sulfadiazine and folinic acid (section 8.1)), see notes above
  - By mouth
  - Child 12–18 years 50 mg once daily until delivery

### SPIRAMYCIN

**Cautions** cardiac disease, arrhythmias (including predisposition to QT interval prolongation)

- Hepatic impairment use with caution
- Breast-feeding present in breast milk

**Contra-indications** sensitivity to other macrolides

**Side-effects** gastro-intestinal disturbances including nausea, vomiting, diarrhoea; dizziness, headache; rash; hepatotoxicity; rarely, prolongation of QT interval, thrombocytopenia and vasculitis

**Licensed use** not licensed

**Indication and dose**

- Toxoplasmosis in pregnancy see notes above
  - By mouth
  - Child 12–18 years 1.5 g twice daily until delivery
**SULFADIAZINE**

**Cautions**  see under Co-trimoxazole, section 5.1.8

**Pregnancy**  risk of neonatal haemolysis and methaemoglobinemia in third trimester; fear of increased risk of kernicterus in neonates appears to be unfounded

**Breast-feeding**  small risk of kernicterus in jaundiced infants and of haemolysis in G6PD-deficient infants

**Contra-indications**  see under Co-trimoxazole, section 5.1.8

**Renal impairment**  use with caution; avoid in severe renal impairment; high risk of crystalluria

**Side-effects**  see under Co-trimoxazole, section 5.1.8

**Licensed use**  not licensed for use in toxoplasmosis

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**Indication and dose**

**Toxoplasmosis in pregnancy (in combination with pyrimethamine and folic acid (section 8.1)), see notes above**

- **By mouth**
  - **Child 12–18 years** 1 g 3 times daily until delivery

**Congenital toxoplasmosis (in combination with pyrimethamine and folic acid (section 8.1))**

- **By mouth**
  - **Neonate** 50 mg/kg twice daily for 12 months

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**Sulfadiazine**  *(Non-proprietary)*

- **Tablets**, sulfadiazine 500 mg, net price 56-tab pack = £57.15. Label: 9, 27
- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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5.4.8 Drugs for pneumocystis pneumonia

Pneumonia caused by *Pneumocystis jiroveci* *(Pneumocystis carinii)* occurs in immunosuppressed children; 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.

A combination of *dapsone* 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]* in children who cannot tolerate co-trimoxazole.

A combination of *clindamycin*  *(section 5.1.6)* and * primaquine*  *(section 5.4.1)* may be 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 children 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 pneumocystis infections associated with HIV infection, prednisolone  *(section 6.3.2)* is given by mouth in a dose of 2 mg/kg (max. 80 mg daily) for 5 days (alternatively, hydrocortisone may be given parenterally); the dose is then reduced over the next 16 days and then stopped. 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 children with a history of the infection. Prophylaxis against pneumocystis pneumonia should also be considered for severely immunocompromised children. Prophylaxis
should continue until immunity recovers sufficiently. It should not be discontinued if the child has oral candidiasis, continues to lose weight, or is receiving cytotoxic therapy or long-term immunosuppressant therapy.

Co-trimoxazole (section 5.1.8) by mouth is the drug of choice for prophylaxis against pneumocystis pneumonia. Co-trimoxazole may be used in infants born to mothers with a high risk of transmission of infection.

Intermittent inhalation of pentamidine isetionate is used for prophylaxis against pneumocystis pneumonia in children unable to tolerate co-trimoxazole. It is effective but children may be prone to extrapulmonary infection. Alternatively, dapsone can be used.

**PENTAMIDINE ISETIONATE**

**Indication and dose**

*Pneumocystis jiroveci (P. carinii)* pneumonia (in combination with trimethoprim)

- **By mouth**
  - Child 1 month–12 years: 2 mg/kg (max. 100 mg) once daily
  - Child 13–18 years: 100 mg once daily

*Pneumocystis jiroveci* prophylaxis

- **By mouth**
  - Child 1 month–18 years: 2 mg/kg (max. 100 mg) once daily

Dapsone (Non-proprietary) Tablets, dapsone 50 mg, net price 28-tab pack = £23.01; 100 mg 28-tab pack = £33.74. Label: 8

**DAPSONE**

**Cautions** cardiac or pulmonary disease; anaemia (treat severe anaemia before starting); susceptibility to haemolysis including G6PD deficiency (section 9.1.5); avoid in acute porphyria (section 9.8.2); **interactions:** Appendix 1 (dapsone)

**Pregnancy** neonatal haemolysis and methaemoglobinemia reported in third trimester; folic acid 5 mg daily should be given to mother throughout pregnancy

**Breast-feeding** haemolytic anaemia; although significant amount in milk, risk to infant very small unless infant is G6PD deficient

**Blood disorders** On long-term treatment, children and 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, rash, mouth ulcers, purpura, bruising or bleeding develop

**Side-effects** haemolysis, methaemoglobinemia, neuropathy, allergic dermatitis (rarely including toxic epidermal necrolysis and Stevens-Johnson syndrome), anorexia, nausea, vomiting, tachycardia, headache, insomnia, psychosis, hepatitis, agranulocytosis; dapsone syndrome (rash with fever and eosinophilia)—discontinue immediately (may progress to exfoliative dermatitis, hepatitis, hypoalbuminaemia, psychosis and death)

**Licensed use** not licensed for treatment of *P. jiroveci* pneumonia; monotherapy not licensed for children for prophylaxis of *P. jiroveci* pneumonia

**Indication and dose**

*Pneumocystis jiroveci (P. carinii)* pneumonia

- **By mouth**
  - Child 1 month–12 years: 2 mg/kg (max. 100 mg) once daily
  - Child 13–18 years: 100 mg once daily

Prophylaxis of *Pneumocystis jiroveci (P. carinii)* pneumonia

- **By mouth**
  - Child 1 month–18 years: 2 mg/kg (max. 100 mg) once daily

**Licensed use** nebuliser solution not licensed for use in children
5.5 Anthelmintics

5.5.1 Drugs for threadworms

Mebendazole is the drug of choice for treating threadworm infection in children over 6 months. 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.

Advice on prophylaxis and treatment of helminth infections is available from the following specialist centres:

- 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 advice only)

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

Visceral leishmaniasis (kala-azar, section 5.4.5)

- By deep intramuscular injection
  - Child 1–18 years: 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
  - Child 1–18 years: 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
  - Child 1–18 years: 4 mg/kg daily or on alternate days to total of 7–10 injections

Administration

Direct intravenous injection should be avoided whenever possible and never given rapidly; intramuscular injections should be deep and preferably given into the buttock. For intravenous infusion, reconstitute 300 mg with 3–5 mL Water for Injections (displacement value may be significant), then dilute required dose with 50–250 mL Glucose 5% or Sodium Chloride 0.9%; give over at least 60 minutes.

Pentacarinat® (Sanofi-Aventis) 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.

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. Washing 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 children over 6 months. 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

Cautions interactions: Appendix 1 (mebendazole)

Pregnancy manufacturer advises avoid—toxicity in animal studies

Breast-feeding amount present in milk too small to be harmful but manufacturer advises avoid

Note The patient information leaflet in the Vermox® pack includes the statement that it is not suitable for women known to be pregnant or for children under 2 years

Side-effects very rarely abdominal pain, diarrhoea; convulsions (in infants) and rash (including Stevens-Johnson syndrome and toxic epidermal necrolysis) reported

Licensed use not licensed for use in children under 2 years

Indication and dose

Threadworms
• By mouth
  Child 6 months—18 years 100 mg as a single dose; if reinfection occurs second dose may be needed after 2 weeks

Whipworms, roundworms (section 5.5.2), hookworms (section 5.5.4)
• By mouth
  Child 1—18 years 100 mg twice daily for 3 days

1 Mebendazole (Non-proprietary) Tablets, chewable, mebendazole 100 mg

1. Mebendazole tablets can be sold to the public if supplied for oral use in the treatment of enterobiasis in 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

PIPERAZINE

Cautions epilepsy; juvenile idiopathic arthritis; Sjögren’s syndrome

Hepatic impairment manufacturer advises avoid

Renal impairment use with caution; dose adjustment may be necessary

Pregnancy not known to be harmful but manufacturer advises avoid in first trimester

Breast-feeding present in milk—manufacturer advises avoid breast-feeding for 8 hours after dose (express and discard milk during this time)

Note Packs on sale to the general public carry a warning to avoid in epilepsy, liver or kidney disease, and to seek medical advice in pregnancy

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 inco-ordination (‘worm wobble’); drowsiness, nystagmus, vertigo, blurred vision, confusion and clonic contractions in children with neurological or renal abnormalities

Indication and 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
(Stirred into milk or water)

Threadworms
• By mouth
  Child 3 months–1 year 1 level 2.5-mL spoonful as a single dose in the morning, repeated after 14 days
  Child 1–6 years 1 level 5-mL spoonful as a single dose in the morning, repeated after 14 days
  Child 6–18 years content of 1 sachet as a single dose (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

LEVAMISOLE

Cautions epilepsy, juvenile idiopathic arthritis; Sjögren’s syndrome

Hepatic impairment use with caution—dose adjustment may be necessary

Pregnancy embryotoxic in animal studies, avoid if possible

Breast-feeding no information available

Contra-indications blood disorders

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.

Levamisole [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies, see p.943) is an alternative. It is very well tolerated; mild nausea or vomiting has been reported in about 1% of treated patients.

Piperazine may be given in a single 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.943) 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] is available from Merck (Cysticide®); it is as effective as niclosamide and is given to children over 4 years of age as a single dose of 5–10 mg/kg after a light breakfast (or as a single dose of 25 mg/kg for Hymenolepis nana).

Hydatid disease

Cysts caused by Echinococcus granulosus grow slowly and asymptomatic children 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.943 is used in conjunction with surgery to reduce the risk of recurrence or as primary treatment in inoperable cases. Albendazole is given to children over 2 years of age in a dose of 7.5 mg/kg twice daily (max. 400 mg twice daily) for 28 days followed by 14-day break and then repeated for up to 2–3 cycles. 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
(ankylostomiasis, 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. Albendazole [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies, see p.943 given as a single dose of 400 mg in children over 2 years, is an alternative. Levafoxadine is also effective (section 5.5.2).
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 mesentery. *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. In children over 4 years the dose is 20 mg/kg followed after 4–6 hours by a further dose of 20 mg/kg (20 mg/kg 3 times daily for 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.

5.5.6 Filaricides

Diethylcarbamazine [unlicensed] (available from ‘special-order’ manufacturers or specialist importing companies, see p. 943) is effective against microfilariae and adult worms of *Loa loa, Wuchereria bancrofti*, and *Brugia malayi*. To minimise reactions, treatment in children over 1 month is commenced with a dose of diethylcarbamazine citrate 1 mg/kg in divided doses on the first day and increased gradually over 3 days to 6 mg/kg daily (3 mg/kg daily if child under 10 years) in divided doses; length of treatment varies according to infection type, and usually gives a radical cure for these infections. 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. 943) is very effective in onchocerciasis and it is now the drug of choice. In children over 5 years, 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
(creeping 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. 943).

5.5.8 Drugs for strongyloidiasis

Adult forms of *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] in a dose of 200 micrograms/kg daily for 2 days is the treatment of choice for chronic *Strongyloides* infection in children over 5 years. Albendazole [unlicensed] is an alternative in children over 2 years given in a dose of 400 mg twice daily for 3 days, repeated after 3 weeks if necessary.

Both of these drugs are available from ‘special-order’ manufacturers or specialist importing companies, see p. 943.
6 Endocrine system

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For hormonal contraception, see section 7.3.
6.1 Drugs used in diabetes

6.1.1 Insulins

Insulin is a polypeptide hormone that plays a key role in the regulation of carbohydrate, fat, and protein metabolism. There are differences in the amino-acid sequence of animal insulins, human insulins, and the human insulin analo-
gues. 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).

Immunological resistance to insulin action is uncommon. Preparations of human sequence insulin should theoretically be less immunogenic than other insulin preparations, 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 thighs, buttocks, or abdomen; absorption from a limb site can 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 and is a factor in poor glycaemic control. Fat hypertrophy can be minimised by using different injection sites in rotation. Local allergic reactions are rare.

Insulin should be given to all children with type 1 diabetes; it may also be needed to treat type 2 diabetes either when other methods cannot control the condition or during periods of acute illness or peri-operatively. Insulin is required in all instances of ketoacidosis (section 6.1.3), which can develop rapidly in children.

Management of diabetes with insulin  The aim of treatment is to achieve the best possible control of blood-glucose concentration without making the child or carer obsessional and to avoid disabling hypoglycaemia; close co-operation is needed between the child or carer and the medical team to achieve good control and thereby reduce the risk of complications. Mixtures of insulin preparations may be required and appropriate combinations have to be determined for the individual child. Treatment should be started with several doses of short-acting insulin (soluble insulin or a rapid-acting insulin analogue) given throughout the day with a longer-acting insulin given once a day. Alternatively, for those who have difficulty with, or prefer not to use, multiple daily injection regimens or in whom such regimens fail to achieve adequate glycaemic control, a mixture of premixed short- and medium-acting insulins can be given twice daily. The dose of insulin is increased gradually taking care to avoid troublesome hypoglycaemia. The proportion of the short-acting soluble component can be increased in those with excessive postprandial hyperglycaemia.

Initiation of insulin may be followed by a partial remission phase or ‘honeymoon period’ when lower doses of insulin are required than are subsequently necessary to maintain glycaemic control.

Insulin preparations can be divided into 3 types:

- those of short duration which have a relatively rapid onset of action, namely soluble insulin and the rapid-acting insulin analogues, insulin aspart, insulin glulisine, and insulin lispro (section 6.1.1.1);
- those with an intermediate action, e.g. isophane insulin (section 6.1.1.2); and
- those whose action is slower in onset and lasts for long periods, e.g. protamine zinc insulin, insulin detemir, and insulin glargine (section 6.1.1.2)

The duration of action of a particular type of insulin can vary from one child to another, and needs to be assessed individually.

Examples of insulin regimens

- Multiple injection regimen: either soluble insulin or a rapid-acting insulin before meals and long–acting insulin at bedtime; suitable for those who wish to have flexibility. Long-acting insulin analogues (insulin detemir or insulin glargine) may be useful for this regimen;
- Three-times-daily combination of soluble insulin and isophane insulin in the morning, soluble insulin or a rapid-acting insulin analogue only before evening meal, and isophane insulin or long-acting insulin analogue only at bedtime; suitable for children who have at least 2 hours between the last 2 injections of the day;
- Twice-daily mixture of soluble insulin and isophane insulin: either mixed before administration or given as a pre-mixed combination e.g. 30:70 of soluble insulin: isophane insulin;
- Twice-daily isophane insulin: soluble insulin is added when necessary;
- Continuous subcutaneous insulin infusion (see below).
Insulin requirements Most prepubertal children require around 0.6–0.8 units/kg/day of insulin after the initial temporary remission phase. Unless the child has a very sedentary life-style, a requirement for higher doses may indicate poor compliance, poor absorption of insulin from the injection site (e.g. because of lipohypertrophic sites), or the beginning of puberty. During puberty up to 1.5–2 units/kg/day of insulin may be required, especially during growth spurts. Around 1 year after menarche or after the growth spurt in boys, the dose may need to be adjusted to avoid excessive weight gain. Insulin requirements can be increased by infection, stress, and accidental or surgical trauma. Insulin requirements can be reduced in very active individuals and in those with renal or hepatic impairment, some endocrine disorders (e.g. Addison’s disease, hypopituitarism) or coeliac disease. Insulin requirements should be assessed frequently in all these circumstances.

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 breast-feeding. The safety of long-acting insulin analogues in pregnancy has not been established, therefore isophane insulin is recommended where longer-acting insulins are needed.

Insulin administration Insulin is generally given by subcutaneous injection half-an-hour before a meal, except for rapid-acting insulins, which should be given immediately before, with, or even immediately after a meal (section 6.1.1.1). 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 less popular with children and carers, but may be 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 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 children who suffer recurrent hypoglycaemia or marked morning rise in blood-glucose concentration despite optimised multiple-injection regimens. Children on subcutaneous insulin infusion must be highly motivated, able to monitor their blood-glucose concentration or have it monitored by a carer, and have expert training, advice, and supervision from an experienced healthcare team.

Continuous subcutaneous insulin infusion is 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 e.g in diabetic ketoacidosis, and for fine control in serious illness and in the peri-operative period (see under Diabetes and Surgery, below).

Monitoring All carers and children need to be trained to monitor blood-glucose concentrations (section 6.1.6). Since blood-glucose concentrations vary substan-
tially throughout the day, ‘normoglycaemia’ cannot always be achieved throughout a 24-hour period without causing damaging hypoglycaemia. It is therefore best to recommend that children 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; efforts should be made to prevent the blood-glucose concentration from falling below 4 mmol/litre. Carers and children should be advised to look for ‘peaks’ and ‘troughs’ of blood glucose, and to adjust the insulin dosage only once or twice weekly. Overall it is ideal to aim for an HbA1c (glycosylated haemoglobin) concentration of 6.5–7.5% or less (reference range 4–6%) but this is not always possible without causing disabling hypoglycaemia. Measurement of serum-fructosamine concentration can also be used for assessment of control; this is simpler and cheaper but the measurement of HbA1c is generally more reliable.

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 blood 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 for all children using insulin, and they and their carers should be given careful instruction on how to avoid it.

Loss of warning of hypoglycaemia is common among insulin-treated children and can be a serious hazard, especially for cyclists and drivers. 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 child.

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.

**Diabetes and surgery**

Children with type 1 diabetes should undergo surgery in centres with facilities for the care of children with diabetes.

Children with type 1 diabetes who require surgery:
- should be admitted to hospital for general anaesthesia;
- should receive insulin, even if they are fasting, to avoid ketoacidosis;
- should receive glucose infusion when fasting before an anaesthetic to prevent hypoglycaemia.

**Elective surgery**

Surgery in children with diabetes is best scheduled early on the list, preferably in the morning. If glycaemic control is poor it is advisable to admit the child well in advance of surgery. On the evening before surgery, blood-glucose should be measured frequently, especially before meals and snacks and at bedtime; urine should be tested for ketones. The usual evening or bedtime insulin and bedtime snack should be given. Ketosis or severe hypoglycaemia require correction, preferably by overnight intravenous infusion (section 6.1.3 and section 6.1.4), and the surgery may need to be postponed.

For **surgery scheduled for the morning**, the usual morning dose of insulin should be omitted. Early on the day of the operation, intravenous infusion of fluids and insulin should be started (see Intravenous Fluids and Continuous Insulin Infusion below).

For **surgery scheduled for the afternoon**, one-third of the usual morning dose of insulin should be given in the morning as short-acting (or soluble) insulin. Intravenous fluids and insulin infusion should be started by midday.

For **emergency surgery**, intravenous fluids and an insulin infusion should be started immediately (see Intravenous Fluids and Continuous Insulin Infusion below). If ketoacidosis is present the recommendations for diabetic ketoacidosis should be followed (section 6.1.3).

For **minor procedures that require fasting**, a slight modification of the usual regimen may be all that is necessary e.g. for early morning procedures delay insulin and food until immediately after the procedure. In all cases the advice of a doctor or anaesthetist experienced in the management of children with diabetes should be sought.
Intravenous fluids and continuous insulin infusion: Blood-glucose and plasma-electrolyte concentrations must be measured frequently in a child receiving intravenous support. Intravenous infusion should be continued until after the child starts to eat and drink. The following infusions should be used and adjusted according to the child’s fluid and electrolyte requirements:

- Constant infusion of sodium chloride 0.45% and glucose 5% intravenous infusion together with potassium chloride 20 mmol/litre (provided that plasma-potassium concentration is not raised) at a rate determined by factors such as volume depletion and age; the amount of potassium chloride infused is adjusted according to plasma electrolyte measurements;

- Blood-glucose concentration should be maintained between 5 and 12 mmol/litre. If the glucose concentration falls below 5 mmol/litre, glucose 10% intravenous infusion may be required; conversely, if the glucose concentration persistently exceeds 15 mmol/litre, sodium chloride 0.9% intravenous infusion should be substituted;

- If the child develops overt hypoglycaemia (blood-glucose less than 3 mmol/litre) then the insulin infusion should be suspended for up to 30 minutes.

The usual subcutaneous insulin regimen should be started before the first meal (but the dose may need to be 10–20% higher than usual if the child is still bedbound or unwell) and the intravenous insulin infusion stopped 1 hour later. If glycaemic control is not adequately achieved, additional insulin can be given in the following ways:

- additional doses of soluble insulin at any of the 4 injection times (before meals or bedtime) or
- temporary addition of intravenous insulin infusion to subcutaneous regimen or
- complete reversion to intravenous insulin infusion (particularly if the child is unwell).

Neonatal diabetes: Neonatal diabetes is a rare condition that presents with acidosis, dehydration, hyperglycaemia and rarely ketosis; it responds to continuous insulin infusion (0.02 to 0.125 units/kg/hour); the dose should be adjusted according to blood glucose concentrations. When the neonate is stable, treatment can be switched to subcutaneous insulin given once or twice a day. Treatment is normally required for 4–6 weeks in transient forms but may be required permanently in some cases.

Neonatal hyperglycaemia: Newborn babies are relatively intolerant of glucose, especially in the first week of life and if premature. If intravenous glucose is necessary e.g. for total parenteral nutrition, infuse at a lower rate for 6–12 hours and the glucose intolerance should resolve. Insulin is not needed for such transient glucose intolerance, but may be needed if blood-glucose concentration is persistently high.

6.1.1.1 Short-acting insulins

Soluble insulin: 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 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 (10–20 minutes) and shorter duration of action (2–5 hours) than soluble insulin; as a result, compared with soluble insulin, fasting and preprandial blood-glucose concentrations are a little higher, postprandial blood-
glucose concentration is a little lower, and hypoglycaemia occurs slightly less frequently. There is no evidence to justify switching from conventional insulin to a human insulin analogue if glycaemic control is adequate; they should only be used in children in preference to soluble insulin when a fast onset of action is required, e.g. in very young children who refuse food and when timing of injections in relation to meals is difficult. They may also be useful in children susceptible to pre-lunch hypoglycaemia and those who eat late in the evening and are prone to nocturnal hypoglycaemia. Insulin aspart and insulin lispro can be administered by subcutaneous infusion (see Insulin Administration above). 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

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

**Renal impairment** may need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired

**Pregnancy** insulin requirements should be assessed frequently by an experienced diabetes physician; see also Pregnancy and Breast-feeding p. 420 above

**Side-effects** see notes above; transient oedema; local reactions and fat hypertrophy at injection site; rarely hypersensitivity reactions including urticaria, rash; overdose causes hypoglycaemia

**Indication and dose**

- **Hyperglycaemia, surgery in children with diabetes**
  - By intravenous infusion

- **Neonate** 0.01–0.1 units/kg/hour, adjusted according to blood-glucose concentration, see also notes above

- **Child 1 month–18 years** 0.025–0.1 units/kg/hour, adjusted according to blood-glucose concentration, see also notes above

**Diabetes mellitus**

- By subcutaneous injection
  - According to requirements (see notes above)
  - **Note** Rotate injection site to reduce local reactions and fat hypertrophy

**Administration** For intravenous infusion, dilute to a concentration of 1 unit/mL with Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

**Neonatal intensive care**, dilute 5 units to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/kg/hour provides a dose of 0.01 units/kg/hour

**Highly purified animal**

**Counselling** Show container to child or carer and confirm the expected version is dispensed

**Hypurin® Bovine Neutral (Wockhardt)**

Injection, soluble insulin (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £18.48; cartridges (for Autopen® Classic) 5 x 3 mL = £27.72

**Hypurin® Porcine Neutral (Wockhardt)**

Injection, soluble 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 child or carer and confirm the expected version is dispensed

**Actrapid® (Novo Nordisk)**

Injection, soluble insulin (human, pyr) 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)**

Injection, soluble insulin (human, prb) 100 units/mL. Net price 10-mL vial = £16.50; 5 x 3-mL cartridge (for Autopen® Classic or HumaPen®) = £28.12

**Insulan® Rapid (Aventis Pharma)**

Injection, soluble insulin (human, crb) 100 units/mL, net price 5 x 3-mL cartridge (for OptiPen® Pro I) = £23.43; 5 x 3-mL Insulan® 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)*

**Cautions** see under Insulin; use only if benefit likely compared to soluble insulin

**Pregnancy** see under Insulin;

**Side-effects** see under Insulin

**Indication and dose**

**Diabetes mellitus**

- 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
**INSULIN ASPART (continued)**

Administration for intravenous infusion, dilute to a concentration of 0.05–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

NovoRapid® (Novo Nordisk) Injection, insulin aspart (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £17.27; Penfill® cartridge (for Innovo® and NovoPen® devices) 5 x 3-mL = £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 child or carer and confirm the expected version is dispensed

Apidra® (Sanofi-Aventis) Injection, insulin glulisine (recombinant human insulin analogue) 100 units/mL, net price 10-mL vial = £17.27; 5 x 3-mL cartridge (for OptiPen® Pro 1 and AutoPen® 24) = £29.45; 5 x 3-mL OptiClik® cartridge (for OptiClik® Pen) = £31.50; 5 x 3-mL Apidra® Optiset® prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £29.45; 5 x 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. 4) has advised (October 2008) that Apidra® is accepted for restricted use within NHS Scotland for the treatment of children over 6 years with diabetes mellitus in whom the use of a short-acting insulin analogue is appropriate

**INSULIN GLULISINE**

(Recombinant human insulin analogue)

Cautions see under Insulin

Pregnancy see under Insulin

Side-effects see under Insulin

Licensed use not licensed for children under 6 years

Indication and dose

Diabetes mellitus

- By subcutaneous injection
  
  Immediately before meals or when necessary shortly after meals, according to requirements

- By subcutaneous infusion
  
  According to requirements

**INSULIN LISPRO**

(Recombinant human insulin analogue)

Cautions see under Insulin; children under 12 years (use only if benefit likely compared to soluble insulin)

Pregnancy see under Insulin;

Side-effects see under Insulin

Indication and dose

Diabetes mellitus

- 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

Administration For intravenous infusion, dilute to a concentration of 0.1–1 unit/mL with Glucose 5% or Sodium Chloride 0.9% and mix thoroughly; insulin may be adsorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin.

Humalog® (Lilly) Injection, insulin lispro (recombinant human insulin analogue) 100 units/mL. Net price 10-mL vial = £17.28; 5 x 3-mL cartridge (for AutoPen® Classic or HumaPen®) = £29.46; 5 x 3-mL Humalog®-Pen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46; 5 x 3-mL Humalog® KwikPen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £29.46

Counselling Show container to child or carer and confirm the expected version is dispensed

**6.1.1.2 Intermediate- and long-acting insulins**

When given by subcutaneous injection, intermediate- and long-acting insulins have an onset of action of approximately 1–2 hours, a maximal effect at 4–12 hours, and a duration of 16–35 hours. Some are given twice daily in conjunction with short-acting (soluble) insulin, and others are given once daily. Soluble insulin can be mixed with intermediate and long-acting insulins (except insulin detemir and insulin glargine), essentially retaining the properties of the two components, although there may be some blunting of the initial effect of the soluble insulin component (especially on mixing with protamine zinc insulin, see below).

Close monitoring of blood glucose is essential when introducing a change to the insulin regimen; the total daily dose as well as any concomitant treatment may need to be adjusted.
Isophane insulin is a suspension of insulin with protamine; it is of particular value for initiation of twice-daily insulin regimens. Isophane can be mixed with soluble insulin before injection but ready-mixed preparations may be more appropriate (biphasic isophane insulin, biphasic insulin aspart, or biphasic insulin lispro).

Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.

Protamine zinc insulin is usually given once daily with short-acting (soluble) insulin. It has the drawback of binding with the soluble insulin when mixed in the same syringe and is now rarely used.

Insulin detemir and insulin glargine are human insulin analogues with prolonged duration of action; insulin detemir is given once or twice daily and insulin glargine is given once daily. There is little evidence to justify switching from conventional intermediate- or long-acting insulin to a human insulin analogue if glycaemic control is adequate. NICE (December 2002) has recommended that insulin glargine should be available as an option for patients with type 1 diabetes.

NICE (May 2008) has recommended that, if insulin is required in patients with type 2 diabetes, insulin glargine may be considered for those:

- who require assistance with injecting insulin or
- whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemia or
- 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 DETEMIR**
(Recombinant human insulin analogue—long-acting)

Cautions see under Insulin (section 6.1.1.1)

Pregnancy see under Insulin; limited evidence of safety

Side-effects see under Insulin (section 6.1.1.1)

Licensed use not licensed for use in children under 6 years

Indication and dose

Diabetes mellitus

- By subcutaneous injection

- 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 child or carer and confirm the expected version is dispensed

**INSULIN GLARGINE**
(Recombinant human insulin analogue—long acting)

Cautions see under Insulin (section 6.1.1.1)

Pregnancy see under Insulin; limited evidence of safety

Side-effects see under Insulin (section 6.1.1.1)

Licensed use not licensed for use in children under 6 years

Indication and dose

Diabetes mellitus

- By subcutaneous injection

- 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. 4) 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 glycaemic 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 child or carer and confirm the expected version is dispensed
**INSULIN ZINC SUSPENSION**
(Insulin Zinc Suspension (Mixed)—long acting)
A sterile neutral suspension of bovine 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)

**Cautions** see under Insulin (section 6.1.1.1)

**Side-effects** see under Insulin (section 6.1.1.1)

**Indication and dose**

- **Diabetes mellitus**
  - By subcutaneous injection
  - According to requirements

**Mixed preparations**
See Biphasic Isophane Insulin (p. 427)

**ISOPHANE INSULIN**
(Isophane Insulin Injection; Isophane Protamine Insulin Injection; 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

**Cautions** see under Insulin (section 6.1.1.1)

**Side-effects** see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

**Indication and dose**

- **Diabetes mellitus**
  - By subcutaneous injection
  - According to requirements

**Highly purified animal**

- **Hypropurin® Bovine Lente** (Wockhardt)  
  Injection, insulin zinc suspension (bovine, highly purified) 100 units/mL. Net price 10-mL vial = £18.48
  
  **Counselling** Show container to child or carer and confirm the expected version is dispensed

- **Insulatard®** (Novo Nordisk)  
  Injection, isophane insulin (human, prb) 100 units/mL. Net price 10-mL vial = £16.50; 5 x 3 mL = £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)  
  Injection, isophane insulin (human, crb) 100 units/mL, net price 5-mL vial = £5.84; 5 x 3-mL Insuman® Basal OptiSet® prefilled disposable injection devices (range 2–40 units, allowing 2-unit dosage adjustment) = £26.40

**Mixed preparations**
See Biphasic Isophane Insulin (p. 427)
Biphasic insulins

Biphasic insulins are pre-mixed insulin preparations containing various combinations of short-acting (soluble) or rapid-acting (analogue) insulin and an intermediate-acting insulin.

The percentage of short-acting insulin varies from 10% to 50%. These preparations should be administered by subcutaneous injection up to 15 minutes before or soon after a meal.

**BIPHASIC INSULIN ASPART**
*(Intermediate-acting insulin)*

- **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

**Indication and dose**

- **Diabetes mellitus**
  - **By subcutaneous injection**
    - Up to 10 minutes before or soon after a meal, according to requirements

**BIPHASIC INSULIN LISPRO**
*(Intermediate-acting insulin)*

- **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

**Indication and dose**

- **Diabetes mellitus**
  - **By subcutaneous injection**
    - Up to 15 minutes before or soon after a meal, according to requirements

**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

- **Cautions**: see under Insulin (section 6.1.1.1)
- **Side-effects**: see under Insulin (section 6.1.1.1); protamine may cause allergic reactions

**Indication and dose**

- **Diabetes mellitus**
  - **By subcutaneous injection**
    - According to requirements

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**NovoMix® 30 (Novo Nordisk)**

- **Injection**, biphasic insulin aspart (recombinant human insulin analogue), 30% insulin aspart, 70% insulin aspart protamine, 100 units/mL, net price 5 x 3-mL Penfill® cartridges (for Innovio® and 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 child or carer and confirm the expected version is 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 x 3-mL cartridge (for Autopen® Classic or HumaPen®) = £29.46; 5 x 3-mL prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98; 5 x 3-mL Humalog® Mix50 KwikPen prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98

- **Counselling**: Show container to child or carer and confirm the expected version is 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)

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**Humalog® Mix25 (Lilly)**

- **Injection**, biphasic insulin lispro (recombinant human insulin analogue), 25% insulin lispro, 75% insulin lispro protamine, 100 units/mL, net price 5 x 3-mL cartridge (for Autopen® Classic or HumaPen®) = £29.46; 5 x 3-mL prefilled disposable injection devices (range 1–60 units, allowing 1-unit dosage adjustment) = £30.98; 5 x 3-mL Humalog® Mix25 KwikPen prefilled disposable injection

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**Highly purified animal**

- **Counselling**: Show container to child or carer and confirm the expected version is 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)

**Hypurin® 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 x 3 mL = £25.20

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**Human sequence**

- **Counselling**: Show container to child or carer and confirm the expected version is 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 insulin (human, prx), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £7.48; Mixtard 30 Penfill® cartridge (for Innova® or 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 insulin (human, prb), 30% soluble, 70% isophane, 100 units/mL. Net price 10-mL vial = £16.50; 5 × 3 mL cartridge (for Autopen® Classic or HumaPen®) = £28.12

Insulan® Comb 15 (Aventis Pharma) Injection, biphasic 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

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### 6.1.1.3 Hypodermic equipment

Carers and children 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

**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 = £24.60 (available in green and yellow); NovoPen 3 Demi (for 3-mL cartridges), allowing 0.5-unit dosage adjustment, max. 35 units, net price = £25.03; 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® 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 insulin adaptor, 1 10-mL insulin adaptor) = £147.83, 3-month consumables pack for 10-mL adaptor (7 nozzles, 5 × 10-mL insulin vial adaptors) = £18.08, for 3-mL adaptor (7 nozzles, 15 × 3-mL insulin cartridge adaptors) = £30.82; vial adaptor pack (6 insulin vial adaptors) = £7.66, cartridge adaptor pack (6 insulin cartridge adaptors) = £7.66; nozzle pack (6 nozzles) = £10.03

#### Lancets

Lancets—sterile, single use (Drug Tariff) BD Micro-Fine® = £3.16, 200 = £6.13; Cleanlet Fine® 100 = £3.19, 200 = £6.13; Finepoint® 100 = £3.48; 1FreeStyle® 200 = £6.89; 1Glucollet Fine 100 = £3.48, 200 = £6.74; Hypoguard Supreme® 100 = £2.75; 1Microlet® (formerly Ascensia Microlet®) 100 = £3.69, 200 = £7.03; 1Milward Steri-Let®, 23 gauge, 100 = £3.00, 200 = £5.70; 1Monolet® 100 = £3.28, 200 = £6.24; Monolet® Extra 100 = £2.28; MFP Ultra Thin®, 100 = £3.50, 200 = £6.50; MultiJet® 204 = £9.02; 1One Touch UltraSoft® 100 = £3.56; 2Softclix XL® 50 = £1.80; Thin Lancets, 200 = £7.02; 1Unilet ComforTouch® 100 = £3.60, 200 = £6.83; 1Unilet General Purpose Superlite® 100 = £3.67, 200 = £6.96; UniStik 3 Comfort®, 28-gauge, 100 = £6.24, 200 = £12.20; UniStik 3 Extra®, 21-gauge, 100 = £6.24, 200 = £12.20; UniStik 3 Normal®, 23-gauge, 100 = £6.24, 200 = £12.20; Universal®, 200 = £6.32, Vitrex Soft®, 23-gauge, 100 = £3.00, 200 = £5.70; Vitrex Gentle® 28-gauge, 100 = £3.19, 200 = £6.13; WaveSense Ultra Thin®, 28-gauge, 200 = £6.90, 33-gauge, 200 = £6.90 Compatible finger-pricking devices (unless indicated otherwise, see footnotes), all Softclix® B-D Optimus®, Glucollet®, Monolight®, Penlet II®, Soft Touch® 1. A Autopen® and A Autolet Impression® are also compatible finger-pricking devices 2. Use Softclix® finger-pricking device

#### Needles

Hypodermic Needle, Sterile single use (Drug Tariff) For use with reusable glass syringe, sizes 0.5 mm (25G), 0.45 mm (26G), 0.4 mm (27G). Net price 100-needle pack = £2.68 Brands include Microlance®, Monoject®
Needles for Prefilled and Reusable Pen Injectors (Drug Tariff)

**Screw on**, needle length 6.1 mm or less, net price 100-needle pack = £12.53; 6.2–9.9 mm, 100-needle pack = £8.69; 10 mm or more, 100-needle pack = £8.89

Brands include BD Micro-Fine®, Comfort Point®, NovoFine®, Novofine Autocover®, Unifine® Pentips

**Snap on**, needle length 6.1 mm or less, net price 100-needle pack = £12.02; 6.2–9.9 mm, 100-needle pack = £8.52; 10 mm or more, 100-needle pack = £8.52

Brands include Penfine®

**Syringes**

**Hypodermic Syringe** (Drug Tariff)
Calibrated glass with Luer taper conical fitting, for use with U100 insulin. Net price 0.5 mL and 1 mL = £15.18

Brands include Abcare®

**Pre-Set U100 Insulin Syringe** (Drug Tariff)
Calibrated glass with Luer taper conical fitting, supplied with dosage chart and strong box, for blind patients. Net price 1 mL = £21.99

U100 Insulin Syringe with Needle (Drug Tariff)
Disposable with fixed or separate needle for single use or single patient-use, colour coded orange. Needle length 8 mm, diameters 0.33 mm (29G), 0.3 mm (30G), net price 10 (with needle), 0.3 mL = £1.35, 0.5 mL = £1.40; needle length 12 mm, diameters 0.45 mm (26G), 0.4 mm (27G), 0.36 mm (28G), 0.3 mm (29G), net price 10 (with needle), 0.3 mL = £1.45; 0.5 mL = £1.30; 1 mL = £1.29

Brands include BD Micro-Fine®, Clinipak®, Insupak®, Monoject® Ultra, Omnikan®, Plastipak®

**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 1200 needles, not suitable for use with lancets. Net price = £1.92

Brands include BD Safe-Clip®

**Sharpsguard** (Drug Tariff)
Net price 1-litre sharpsbin = 85p

6.1.2 Oral 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 child fails to respond adequately to 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.

In children, type 2 diabetes does not usually occur until adolescence and information on the use of oral antidiabetic drugs in children is limited. Treatment with oral antidiabetic drugs should be initiated under specialist supervision only; the initial dose should be at the lower end of the adult dose range and then adjusted according to response.

Metformin (section 6.1.2.2) is the oral antidiabetic drug of choice because there is most experience with this drug in children. If dietary changes and metformin do not control the diabetes adequately, either a sulphonylurea (section 6.1.2.1) or insulin (section 6.1.1) can be added.

Alternatively, oral therapy may be substituted with insulin.

When insulin is added to oral therapy, it is generally given at bedtime as isophane insulin, and when insulin replaces an oral regimen it is generally given as twice-daily injections of a biphasic insulin (or isophane insulin mixed with soluble insulin). Weight gain and hypoglycaemia may be complications of insulin therapy but weight gain can 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 after giving birth. Metformin can be continued during breast-feeding for those with pre-existing diabetes.

Other oral hypoglycaemic drugs, including sulphonylureas, are contra-indicated in pregnancy and breast-feeding.

6.1.2.1 Sulphonylureas

The sulphonylureas are not the first choice oral antidiabetics in children. They 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 can cause hypoglycaemia but this is uncommon and usually indicates excessive dosage. Sulphonylurea-induced hypoglycaemia can persist for many hours and must always be treated in hospital.
Sulphonylureas are considered for children in whom metformin is contra-indicated or not tolerated. Several sulphonylureas are available but experience in children is limited; choice is determined by side-effects and the duration of action as well as the child’s age and renal function. The long-acting sulphonylureas chlorpropamide and glibenclamide are associated with a greater risk of hypoglycaemia and for this reason are generally avoided in children. Shorter-acting alternatives, such as tolbutamide, may be preferred.

Insulin therapy should be instituted temporarily during intercurrent illness (such as coma, infection, and trauma). Sulphonylureas should be omitted on the morning of surgery; insulin is often required because of the ensuing hyperglycaemia in these circumstances.

Sulphonylureas can be useful in the management of certain forms of maturity-onset diabetes of the young (MODY); there is most experience with gliclazide.

**Cautions** Sulphonylureas encourage weight gain and should be prescribed only if poor control and symptoms persist despite adequate attempts at dieting; metformin (section 6.1.2.2) is considered the drug of choice in children.

**Contra-indications** Sulphonylureas should be avoided where possible in acute porphyria (section 9.8.2). They should not be used while breast-feeding and insulin therapy should be substituted during pregnancy. Sulphonylureas are contra-indicated in the presence of ketoacidosis.

**Side-effects** Side-effects of sulphonylureas are generally mild and infrequent and include gastro-intestinal disturbances such as nausea, vomiting, diarrhoea and constipation.

Sulphonylureas can occasionally cause a disturbance in liver function, which rarely leads 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 or exfoliative dermatitis, fever, and jaundice; photosensitivity has rarely been reported with chlorpropamide and glipizide. Blood disorders are also rare but include leucopenia, thrombocytopenia, agranulocytosis, pancytopenia, haemolytic anaemia, and aplastic anaemia.

### GLIBENCLAMIDE

**Indication and dose**

Type 2 diabetes mellitus, maturity-onset diabetes of the young (specialist management only, see notes above)

- **By mouth**
  - **Child 12–18 years** initially 2.5 mg daily with or immediately after breakfast, adjusted according to response, max. 15 mg daily

**Glibenclamide** (Non-proprietary) (YH)

Tablets, glibenclamide 2.5 mg, net price 28-tab pack = 85p; 5 mg, 28-tab pack = 88p

### GLICLAZIDE

**Indication and dose**

Type 2 diabetes mellitus, maturity-onset diabetes of the young (specialist management only, see notes above)

- **By mouth**
  - **Child 12–18 years** initially 20 mg once daily with breakfast, adjusted according to response; up to 160 mg as a single dose; max. 160 mg twice daily

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

**Hepatic impairment** increased risk of hypoglycaemia in severe liver disease; avoid or use small dose; can produce jaundice

**Renal impairment** avoid in severe impairment

**Contra-indications** see notes above

**Side-effects** see notes above

**Licensed use** not licensed for use in children
6.1.2 Oral antidiabetic drugs

**Gliclazide (Non-proprietary)**

Tablets, scored, gliclazide 80 mg, net price 28-tab pack = £1.07, 60-tab pack = £1.71

Brands include **DIAGLYK**

**Diamicron® (Servier)**

Tablets, scored, gliclazide 80 mg, net price 60-tab pack = £4.56

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**TOLBUTAMIDE**

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

**Hepatic impairment** increased risk of hypoglycaemia in severe liver disease; avoid or use small dose; can produce jaundice

**Renal impairment** avoid if possible; if no alternative reduce dose and monitor closely

**Contra-indications** see notes above

**Side-effects** see notes above; also headache, tinnitus

**Licensed use** not licensed in children

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**Indication and dose**

**Type 2 diabetes mellitus** (see notes above), specialist management only

- **Child 12–18 years** 0.5–1.5 g (max. 2 g) daily in divided doses with or immediately after meals or as a single dose with or immediately after breakfast

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**Tolbutamide (Non-proprietary)**

Tablets, tolbutamide 500 mg. Net price 28-tab pack = £1.51

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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**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 children with type 2 diabetes, in whom strict dieting has failed to control diabetes. When the combination of strict diet and metformin treatment fails, other options to be considered under specialist management only, include:

- 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).

Insulin treatment is almost always required in medical and surgical emergencies; insulin should also be substituted before elective surgery (omit metformin on the morning of surgery and give insulin if required).

Hypoglycaemia does not usually occur with metformin; other advantages are the lower incidence of weight gain and lower plasma-insulin concentration. It does not exert a hypoglycaemic action in non-diabetic subjects unless given in overdose.

Gastro-intestinal side-effects are initially common with metformin, and may persist in some children, particularly when high doses are given. A slow increase in dose may improve tolerability.

Very rarely, metformin can provoke lactic acidosis which is most likely to occur in children with renal impairment, see Lactic Acidosis below.

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**METFORMIN HYDROCHLORIDE**

**Cautions** see notes above; determine renal function before treatment and once or twice annually during treatment; **interactions:** Appendix 1 (antidiabetics)

**Lactic acidosis** Metformin should be used cautiously in renal impairment because of the increased risk of lactic acidosis: it is contra-indicated in children with significant renal impairment. To reduce the risk of lactic acidosis, metformin should be stopped or 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

**Contra-indications** ketoacidosis, use of iodine-containing X-ray contrast media (do not restart metformin until renal function returns to normal) and use of general anaesthesia (suspend met-
formin on the morning of surgery and restart when renal function returns to normal

Hepatic impairment see Lactic Acidosis above

Renal impairment see Lactic Acidosis above

Pregnancy used in pregnancy for both pre-existing and gestational diabetes—see also Pregnancy and Breast-feeding, p. 429; manufacturer advises avoid

Breast-feeding may be used during breast-feeding—see also Pregnancy and Breast-feeding, p. 429; manufacturer advises avoid

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

Licensed use not licensed in children under 10 years

Indication and dose

Diabetes mellitus (see notes above) specialist supervision only

• By mouth
  
  Child 8–10 years initially 200 mg once daily adjusted according to response at intervals of at least 1 week; max. 2 g daily in 2–3 divided doses

  Child 10–18 years initially 500 mg once daily adjusted according to response at intervals of at least 1 week; max. 2 g daily in 2–3 divided doses

Metformin (Non-proprietary) Tablets, coated, metformin hydrochloride 500 mg, net price 28-tab pack = £1.37; 850 mg, 56-tab pack = £1.24. Label: 21

Oral solution, sugar-free, metformin hydrochloride 500 mg/5 mL, net price 100 mL = £62.41. Label: 21 Brands include Metsol c Glucophage c (Merck) Tablets, f/c, metformin hydrochloride 500 mg, net price 84-tab pack = £2.88; 850 mg, 56-tab pack = £3.20. Label: 21

Other antidiabetic drugs

There is little experience of the use of acarbose in children. It has been used in older children; therapy should be initiated by an appropriate expert.

The use of nateglinide in combination with a sulphonylurea is generally reserved for the management of some subtypes of maturity-onset diabetes of the young or other syndromes of diabetes and requires specialist management.

Diabetic ketoacidosis

The management of diabetic ketoacidosis involves the replacement of fluid and electrolytes and the administration of insulin. Guidelines for the Management of Diabetic Ketoacidosis, published by the British Society of Paediatric Endocrinology and Diabetes1, should be followed. Clinically well children who are dehydrated up to 5% usually respond to oral rehydration and subcutaneous insulin. For those who do not respond, or are clinically unwell, or are dehydrated by more than 5%, insulin and replacement fluids are best given by intravenous infusion.

To restore circulating volume, give 10 mL/kg sodium chloride 0.9% as a bolus, repeat as necessary up to a maximum of 30 mL/kg. Further fluid requirements should be given by intravenous infusion at a rate that corrects losses over 48 hours; usually use sodium chloride 0.9%, changing to sodium chloride 0.45% and glucose 5% after 6 hours if response is adequate and plasma sodium concentration is stable. Potassium chloride is included in the infusion unless anuria is suspected, adjust according to plasma-potassium concentration. Insulin infusion is necessary to switch off ketogenesis and reverse acidosis; it should not be started until at least 1 hour after the start of intravenous rehydration fluids.

Soluble insulin should be diluted (and mixed thoroughly) with sodium chloride 0.9% intravenous infusion to a concentration of 1 unit/mL and infused at a rate of 0.1 units/kg/hour. Insulin is continued until the metabolic disturbance is brought under control. Sodium bicarbonate infusion (1.26% or 2.74%) is rarely necessary and is used only in cases of extreme acidosis (blood pH less than 6.9) and shock since the acid-base disturbance is normally corrected by the insulin.

Blood glucose is expected to decrease by about 5 mmol/litre/hour; if the response is inadequate the insulin infusion rate can be increased. If the rate of decrease exceeds 5 mmol/litre/hour or blood glucose falls to 14–17 mmol/litre, glucose intravenous infusion 5% or 10% should be added to the replacement fluids.

1. Available at www.bsped.org.uk
The insulin infusion rate can be reduced to no less than 0.05 units/kg/hour when blood-glucose concentration is 14–17 mmol/litre and blood pH is greater than 7.3 and a glucose infusion has been started (see above); it is continued until the child is ready to take food by mouth. Subcutaneous insulin can then be started. The insulin infusion should not be stopped until 1 hour after starting subcutaneous soluble or long-acting insulin or 10 minutes after starting subcutaneous insulin aspart, or insulin glulisine, or insulin lispro.

Hyperosmolar hyperglycaemic state or hyperosmolar hyperglycaemic nonketotic coma occurs rarely in children. Treatment is similar to that of diabetic ketoacidosis, although lower rates of insulin infusion and slower rehydration may be required.

6.1.4 Treatment of hypoglycaemia

Prompt treatment of hypoglycaemia in children from any cause is essential as severe hypoglycaemia may cause subsequent neurological damage. Hyperinsulinism, fatty acid oxidation disorders and glycogen storage disease are less common causes of acute hypoglycaemia in children.

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, Glucogel® (formerly known as Hypostop® Gel, glucose 10 g/25 g tube, available from BBI Healthcare), and non-diет versions of Lucozade® Energy Original 55 mL, Coca-Cola® 100 mL, and Ribena® Blackcurrant 18 mL (to be diluted). If necessary this can be repeated in 10–15 minutes. After initial treatment, a snack providing sustained availability of carbohydrate (e.g. a sandwich, fruit, milk, or biscuits) or the next meal, if it is due, can prevent blood-glucose concentration from falling again.

Hypoglycaemia which causes unconsciousness or seizures is an emergency. Glucagon, a polypeptide hormone produced by the alpha cells of the islets of Langerhans, increases blood-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. Glucagon can be issued to parents or carers of insulin-treated children for emergency use in hypoglycaemic attacks. It is often advisable to prescribe it on an ‘if necessary’ basis for hospitalised insulin-treated children, so that it can be given rapidly by the nurses during a hypoglycaemic emergency. If not effective in 10 minutes intravenous glucose should be given.

Alternatively, 5 mL/kg of glucose intravenous infusion 10% (500 mg/kg of glucose) (section 9.2.2) can be given intravenously into a large vein through a large-gauge needle; care is required since this concentration is irritant especially if extravasation occurs. Glucose intravenous infusion 50% is not recommended, as it is very viscous and hypertonic. Close monitoring is necessary, particularly in the case of an overdose with a long-acting insulin because further administration of glucose may be required. Children whose hypoglycaemia is caused by an oral antidiabetic drug should be transferred to hospital because the hypoglycaemic effects of these drugs can persist for many hours.

Glucagon is not effective in the treatment of hypoglycaemia due to fatty acid oxidation or glycogen storage disorders.

Neonatal hypoglycaemia Neonatal hypoglycaemia at birth is treated with glucose intravenous infusion 10% given at a rate of 5 mL/kg/hour. An initial dose of 2.5 mL/kg over 5 minutes may be required if hypoglycaemia is severe enough to cause loss of consciousness or seizures. Mild asymptomatic persistent hypoglycaemia may respond to a single dose of glucagon. Glucagon has also been used in the short-term management of endogenous hyperinsulinism.

GLUCAGON

Cautions see notes above, insulinoma, glucagonoma; ineffective in chronic hypoglycaemia, starvation, and adrenal insufficiency; delayed hypoglycaemia when used as a diagnostic test—deaths reported (ensure a meal is eaten before discharge)

Contra-indications phaeochromocytoma

Side-effects nausea, vomiting, diarrhoea, hypokalaemia, rarely hypersensitivity reactions

Licensed use unlicensed for growth hormone test and hyperinsulinism
Indication and dose

**Hypoglycaemia associated with diabetes**
- By subcutaneous, intramuscular, or intravenous injection
  - **Neonate** 20 micrograms/kg
  - **Child 1 month–2 years** 500 micrograms
  - **Child 2–18 years, body-weight less than 25 kg** 500 micrograms; **body-weight over 25 kg** 1 mg

**Endogenous hyperinsulinism**
- By intramuscular or intravenous injection
  - **Neonate** 200 micrograms/kg (max. 1 mg) as a single dose
  - **Child 1 month–2 years** 1 mg as a single dose

**By continuous intravenous infusion**
- **Neonate** 1–18 micrograms/kg/hour, adjusted according to response (max. 50 micrograms/kg/hour)
- **Child 1 month–2 years** 1–10 micrograms/kg/hour, increased if necessary

**Administration**
- Do not add to infusion fluids containing calcium—precipitation may occur

Diagnosis of growth hormone secretion
- Specialist centre only (section 6.5.1)
- **By intramuscular injection**
  - **Child 1 month–18 years** 100 micrograms/kg (max. 1 mg) as a single dose; dose may vary, consult local guidelines

**Beta-blocker poisoning**, see p. 41

**Note**
1 unit of glucagon = 1 mg of glucagon

1 GlucaGen® HypoKit (Novo Nordisk)
2 For use in hypertensive crisis see section 2.5.1

GLUCAGON (continued)

**Indication and dose**

**Chronic intractable hypoglycaemia**
- **By mouth or by intravenous injection**
  - **Neonate** initially 5 mg/kg twice daily to establish response, adjust dose according to response; usual maintenance dose 1.5–3 mg/kg 2–3 times daily; up to 7 mg/kg 3 times daily may be required in some cases, higher doses unlikely to be beneficial
  - **Child 1 month–18 years** initially 1.7 mg/kg 3 times daily then adjusted according to response; usual maintenance dose 1.5–3 mg/kg 2–3 times daily; up to 5 mg/kg 3 times daily may be required in some cases, higher doses unlikely to be beneficial

**Diabetes**
- **Child 1 month–2 years** 1–10 micrograms/kg/hour, increased if necessary

**Administration**
- Do not add to infusion fluids containing calcium—precipitation may occur

**Diabetes**
- **Child 1 month–2 years** 1–10 micrograms/kg/hour, increased if necessary

**Endocrine system**

**DIAZOXIDE**

**Cautions**
- ischaemic heart disease; monitor blood pressure, during prolonged use monitor white cell and platelet count, and regularly assess growth, bone, and psychological development; avoid the intravenous route if possible; extravasation can cause tissue necrosis and single doses of 300 mg have been associated with angina and cerebral and myocardial infarction; **interactions**: Appendix 1 (diazoxide)

**Renal impairment**
- increased sensitivity to hypotensive and hyperglycaemic effect; dose reduction may be required

**Pregnancy**
- prolonged use in second or third trimesters may produce alopecia and impaired glucose tolerance in neonate; inhibits uterine activity

**Contra-indications**
- see section 2.5.1

**Side-effects**
- anorexia, nausea, vomiting, hyperuricaemia, sodium and water retention, hyperglycaemia, hypotension, oedema, tachycardia, arrhythmias, extrapyramidal effects; hypertrichosis on prolonged treatment

**Licensed use**
- chronic intractable hypoglycaemia (for use in hypertensive crisis see section 2.5.1)

**Indication and dose**

**Chronic intractable hypoglycaemia**
- **By mouth or by intravenous injection**
  - **Neonate** initially 5 mg/kg twice daily to establish response, adjust dose according to response; usual maintenance dose 1.5–3 mg/kg 2–3 times daily; up to 7 mg/kg 3 times daily may be required in some cases, higher doses unlikely to be beneficial
  - **Child 1 month–18 years** initially 1.7 mg/kg 3 times daily then adjusted according to response; usual maintenance dose 1.5–3 mg/kg 2–3 times daily; up to 5 mg/kg 3 times daily may be required in some cases, higher doses unlikely to be beneficial

Eudemine® (UCB Pharma)

- **Tablets**, diazoxide 50 mg. Net price 20 = £9.29
- **Injection**, see section 2.5.1

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
**OCTREOTIDE**

**Cautions**  
Avoid abrupt withdrawal of short-acting octreotide—see Side-effects below; in insulinoma (risk of increased depth and duration of hypoglycaemia—monitor closely when initiating treatment and changing doses); diabetes mellitus (antidiabetic requirements may be reduced); monitor thyroid function on long-term therapy; **interactions:** Appendix 1 (octreotide)  
**Pregnancy**  
Possible effect on fetal growth, avoid unless benefit outweighs risk  
**Breast-feeding**  
No information, avoid unless essential  
**Side-effects**  
Anorexia, nausea, vomiting, abdominal pain, bloating, flatulence, diarrhoea, and steatorrhoea; postprandial glucose tolerance may be impaired, rarely persistent hyperglycaemia with chronic administration; hypoglycaemia has also been reported; reduced gall bladder motility and bile flow; gallstones reported after long-term treatment; abrupt withdrawal of subcutaneous octreotide is associated with biliary colic and pancreatitis; pain and irritation at injection site—sites should be rotated; rarely, pancreatitis shortly after administration, altered liver function tests, hepatitis and transient alopecia  
**Licensed use**  
Not licensed in children  

### Indication and dose

**Persistent hyperinsulinaemic hypoglycaemia unresponsive to diazoxide and glucose**

- **By subcutaneous injection**

  **Neonate**  
  Initially 2–5 micrograms/kg every 6–8 hours, adjusted according to response; up to 7 micrograms/kg every 4 hours may rarely be required  
  **Child 1 month–18 years**  
  Initially 1–2 micrograms/kg every 4–6 hours, dose adjusted according to response; up to 7 micrograms/kg every 4 hours may rarely be required

**Bleeding from oesophageal or gastric varices**

- **By continuous intravenous infusion**

  **Child 1 month–18 years**  
  1 microgram/kg/hour, higher doses may be required initially; when no active bleeding reduce dose over 24 hours; usual max. 50 micrograms/hour

**Administration**  
Intravenous infusion, dilute with sodium chloride 0.9% to a concentration of 10-50%  

**Sandostatin** (Novartis)

*Injection*, octreotide (as acetate) 50 micrograms/mL, net price 1-mL amp = £3.72; 100 micrograms/mL, 1-mL amp = £6.99; 200 micrograms/mL 5-mL vial = £69.86; 500 micrograms/mL, 1-mL amp = £33.87

### 6.1.5 Treatment of diabetic nephropathy and neuropathy

**Diabetic nephropathy**

Regular review of diabetic children over 12 years of age should include an annual test for microalbuminuria (the earliest sign of nephropathy). If reagent strip tests (*Micral-Test II* or *Microbumintest*) are used and prove positive, the result should be confirmed by laboratory analysis of a urine sample. Microalbuminuria can occur transiently during puberty; if it persists (at least 3 positive tests) treatment with an ACE inhibitor (section 2.5.5.1) or an angiotensin-II receptor antagonist (section 2.5.5.2) under specialist guidance should be considered; 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 children with renal impairment.  

For the treatment of hypertension in diabetes, see section 2.5.

**Diabetic neuropathy**

Clinical neuropathy is rare in children whose diabetes is well controlled.

### 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. Carers and children should be properly trained in the use of blood glucose monitoring systems and the appropriate action to take on the
results obtained. Inadequate understanding of the normal fluctuations in blood glucose can lead to confusion and inappropriate action.

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 blood glucose level is high or if the child is unwell, blood ketones should be measured according to local guidelines in order to detect diabetic ketoacidosis (section 6.1.3). Children 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® strips only. Net price 50-strip pack = £14.76

**Advantage Plus®** (Roche Diagnostics)

Reagent strips, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Accu-Chek®

Advantage® strips only. Net price 50-strip pack = £14.76

**Ascensia® Autodi (Bayer Diabetes Care)**

Sensor discs, for blood glucose monitoring, range 0.6–33.3 mmol/litre, for use with Ascensia® Breeze® and Ascensia® Espri®

2 strips 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 Aviva® strips 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 AccuTrend®

BM-Accutest® strips 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®

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® strips only. Net price 50-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®

Net price 50-strip pack = £14.45

**GlucoMen®** (Menarini Diagnostics)

Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with GlucoMen®

GlucoMen® strips 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®

GlucoMen® LX strips only. Net price 50-strip pack = £14.33

**GlucoMen® Visio Sensor** (Menarini Diagnostics)

Reagent strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with GlucoMen® Visio®

GlucoMen® Visio® strips only. Net price 50-strip pack = £14.53

**Hypoguard® Supreme** (Hypoguard)

Reagent strips, for blood glucose monitoring, range 2.2–27.7 mmol/litre, for use with Hypoguard®

Hypoguard® strips only. Net price 50-strip pack = £12.00

**MediSense G2®** (Abbott)

Sensor strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with MediSense®

G2 strips 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®

Soft-Sense Plus® strips only. Net price 50-strip pack = £14.52

**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® Ultra2®, One Touch UltraSmart®

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

One Touch® Vita strips only. Net price 50-strip pack = £14.53

**Optium® β-ketone test strips** (Abbott)

Reagent Strips, for blood ketone monitoring, range 0–8.0 mmol/litre, for use with Optium®

Optium® strips 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®

Optium® strips only. Net price 50-strip pack = £14.53

**PocketScan** (LifeScan)

Reagent Strips, for blood glucose monitoring, range 1.1–33.3 mmol/litre, for use with PocketScan®

PocketScan® strips 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®

Prestige® strips only. Net price 50-strip pack = £14.25

**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

TRUEOne® strips only. Net price 50-strip and meter pack = £14.25
Tests for glucose range from reagent strips specific to glucose to reagent tablets which detect all reducing sugars. Clinistix® is rarely used now; Clinistix® is suitable for screening purposes only. It is rarely necessary for children to test themselves for ketones unless they become unwell—see also Blood Monitoring, p. 435.

Microalbuminuria can be detected with Micral-Test II® or Microbumintest® 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

Clinitek® (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 glucose 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

**Protein**

Albustix® (Bayer Diabetes Care)
Reagent strips, for detection of protein in urine. Net price 50-strip pack = £4.10

Medi-Test® Protein 2 (BHR)
Reagent strips, for detection of protein in urine. Net price 50-strip pack = £3.22

**Other reagent strips available for urinalysis include:**

Combun 1 Test® (glucose and protein—Roche Diagnostics), Clinitek Microalbumin® (albumin and...

**Oral glucose tolerance test**

The oral glucose tolerance test is now rarely needed for the diagnosis of diabetes when symptoms of hyperglycaemia are present. However, it is used for the investigation of insulin resistance, glycogen storage disease, and excessive growth hormone secretion. A dose of 1.75 g/kg (max. 75 g) of anhydrous glucose is used. It is also used to establish the presence of gestational diabetes; this generally involves giving anhydrous glucose 75 g (equivalent to Glucose BP 82.5 g) by mouth to the fasting patient, and measuring blood-glucose concentrations at intervals. The appropriate amount of glucose should be given with 200–300 mL fluid. Alternatively anhydrous glucose 75 g can be given as 113 mL *Polycal®* (Nutricia Clinical) with extra fluid to administer a total volume of 200–300 mL.

**6.2 Thyroid and antithyroid drugs**

**6.2.1 Thyroid hormones**

**Levothyroxine sodium** (thyroxine sodium) is the treatment of choice for maintenance therapy. Doses for congenital hypothyroidism and juvenile myxoedema should be titrated according to clinical response, growth assessment, and measurement of plasma thyroxine and thyroid-stimulating hormone concentrations. In congenital hypothyroidism higher initial doses (up to 15 micrograms/kg daily; max. 50 micrograms daily) may benefit mental development.

**Liothyronine sodium** has a similar action to levothyroxine but is more rapidly metabolised and has a more rapid effect; 20–25 micrograms is equivalent to approximately 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.

**LEVOTHYROXINE SODIUM** (Thyroxine sodium)

**Cautions** panhypopituitarism or predisposition to adrenal insufficiency (initiate corticosteroid therapy before starting levothyroxine), cardiovascular disorders (pre-therapy ECG may be valuable), long-standing hypothyroidism, diabetes insipidus, diabetes mellitus (dose of anti diabetic drugs including insulin may need to be increased); **interactions**: Appendix 1 (thyroid hormones)

**Pregnancy** dose adjustment may be necessary, monitor maternal serum thyrotrphin

**Breast-feeding** minimal amount present in breast milk; unlikely to affect tests for neonatal hypothyroidism

**Contra-indications** thyrotoxicosis

**Side-effects** usually at excessive dosage include diarrhoea, vomiting; 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; hypersensitivity reactions including rash, pruritus and oedema also reported
Indication and dose

Hypothyroidism (in cardiac disease reduce dose by 50% and increase more slowly)

**Note** Levothyroxine equivalent to 100 micrograms/m²/day can be used as a guide to the requirements in children.

- **By mouth**

**Neonate** initially 10–15 micrograms/kg once daily (max. 50 micrograms daily), adjusted in steps of 5 micrograms/kg every 2 weeks or as necessary; usual maintenance dose 20–50 micrograms daily

**Child 1 month–2 years** initially 5 micrograms/kg once daily (max. 50 micrograms daily) adjusted in steps of 10–25 micrograms daily every 2–4 weeks until metabolism normalised; usual maintenance dose 25–75 micrograms daily

**Child 2–12 years** initially 50 micrograms once daily adjusted in steps of 25 micrograms daily every 2–4 weeks until metabolism normalised; usual maintenance dose 75–100 micrograms daily

**Child 12–18 years** initially 50 micrograms once daily adjusted in steps of 25–50 micrograms daily every 3–4 weeks until metabolism normalised; usual maintenance dose 100–200 micrograms daily

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 = £42.75; 50 micrograms/5 mL, 100 mL = £44.90; 100 micrograms/5 mL, 100 mL = £52.75
  - Brands include Evotrox® (sugar-free)

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 are used for hyperthyroidism either to prepare children for thyroidectomy or for long-term management. In the UK carbimazole is the most commonly used drug. Propylthiouracil can be used in those 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.

Treatment in children should be undertaken by a specialist.
CSM warning (neutropenia and agranulocytosis)

Doctors are reminded of the importance of recognising bone marrow suppression induced by carbimazole and the need to stop treatment promptly.

1. Children and their carers should be asked to report symptoms and signs suggestive of infection, especially sore throat.
2. A white blood cell count should be performed if there is any clinical evidence of infection.
3. Carbimazole should be stopped promptly if there is clinical or laboratory evidence of neutropenia.

Carbimazole or propylthiouracil are initially given in large doses to block thyroid function. This dose is continued until the child becomes euthyroid, usually after 4 to 8 weeks, and is then gradually reduced to a maintenance dose of 30–60% of the initial dose. Alternatively high-dose treatment is continued in combination with levothyroxine replacement (blocking-replacement regimen); this is particularly useful when dose adjustment proves difficult or relapse is a problem. Treatment is usually continued for 12 to 24 months. The blocking-replacement regimen is not suitable during pregnancy. Hypothyroidism should be avoided particularly during pregnancy as it can cause fetal goitre.

When substituting, carbimazole 1 mg is considered equivalent to propylthiouracil 10 mg but the dose may need adjusting according to response.

Rashes and pruritus are common with carbimazole but they can be treated with antihistamines without discontinuing therapy; alternatively propylthiouracil can be substituted. If a child on carbimazole develops a sore throat it should be reported immediately because of the rare complication of agranulocytosis (see CSM warning, above).

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 ($^{131}$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 (section 2.4) is useful for rapid relief of thyrotoxic symptoms and can 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 atenolol (section 2.4) is also used.

Thyrotoxic crisis (‘thyroid storm’) requires emergency treatment with intravenous administration of fluids, propranolol and hydrocortisone as sodium succinate, as well as oral iodine solution and carbimazole or propylthiouracil which may need to be administered by nasogastric tube.

Neonatal hyperthyroidism is treated with carbimazole or propylthiouracil, usually for 8 to 12 weeks. In severe symptomatic disease iodine may be needed to block the thyroid and propranolol required to treat peripheral symptoms.

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 can 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 are present 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

Cautions

Hepatic impairment  manufacturers advise caution in mild to moderate hepatic impairment; avoid in severe hepatic impairment

Pregnancy  see notes above

Breast-feeding  see notes above

Side-effects  nausea, mild gastro-intestinal disturbances, taste disturbance, hepatic disorders (including hepatitis and jaundice), headache; fever, malaise; rash, pruritis, arthralgia; rarely myopathy, alopecia, bone marrow suppression (including pancytopenia and agranulocytosis, see CSM warning above), hypersensitivity reactions

Indication and dose

Hyperthyroidism (including Graves’ disease), thyrotoxic crisis, thyrotoxicosis

- By mouth

Neonate  initially 250 micrograms/kg 3 times daily until euthyroid then adjust as necessary (see notes above); higher initial doses occasionally required, particularly in thyrotoxic crisis

Child 1 month–12 years  initially 250 micrograms/kg (max. 10 mg) 3 times daily until euthyroid then adjusted as necessary (see notes above); higher initial doses occasionally required, particularly in thyrotoxic crisis

Counselling

Warn child and carers to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise, or non-specific illness develops

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®  (Amdipharm)  Tablets, both pink, carbimazole 5 mg, net price 100-tab pack = £5.15; 20 mg, 100-tab pack = £19.12. Counselling, blood disorder symptoms

Administration  tablets may be crushed in water and used immediately

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

IODINE AND IODIDE

Cautions  not for long-term treatment

Pregnancy  avoid if possible, neonatal goitre and hypothyroidism may occur

Contra-indications

Breast-feeding  possibly concentrated in milk—avoid; risk of neonatal goitre and hypothyroidism

Side-effects  hypersensitivity reactions including coryza-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

Indication and 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

Neonatal thyrotoxicosis  
- By mouth

Neonate  0.05–0.1 mL 3 times daily

Thyrotoxicosis (pre-operative)  
- By mouth

Neonate  0.1–0.3 mL 3 times daily

Child 1 month–18 years  0.1–0.3 mL 3 times daily

Thyrotoxic crisis  
- By mouth

Child 1 month–1 year  0.2–0.3 mL 3 times daily

Administration  Dilute well with milk or water

PROPYLTHIOURACIL

Cautions  see under Carbimazole

Hepatic impairment  consider dose reduction

Renal impairment  estimated glomerular filtration rate 10–50 mL/minute/1.73 m², use 75% of normal dose; estimated glomerular filtration rate less than 10 mL/minute/1.73 m², use 50% of normal dose

Pregnancy  see notes above

Breast-feeding  see notes above

Side-effects  see under Carbimazole; leucopenia; rarely cutaneous vasculitis, thrombocytopenia, aplastic anaemia, hypoprothrombinaemia, hepatitis, encephalopathy, hepatic necrosis, nephritis, lupus erythematosus-like syndromes

Licensed use  not licensed for use in children under 6 years of age

Indication and dose

Hyperthyroidism (including Graves’ disease), thyrotoxic crisis, thyrotoxicosis

- By mouth

Neonate  initially 2.5–5 mg/kg twice daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis
**PROPYLTHIOURACIL (continued)**

- **Child 1 month–1 year** initially 2.5 mg/kg 3 times daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis
- **Child 1–5 years** initially 25 mg 3 times daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis
- **Child 5–12 years** initially 50 mg 3 times daily until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis
- **Child 12–18 years** initially 100 mg 3 times daily administered until euthyroid then adjusted as necessary (see notes above); higher doses occasionally required, particularly in thyrotoxic crisis

**Propylthiouracil** (Non-proprietary) (Rx)

- **Tablets**, propylthiouracil 50 mg. Net price 56-tab pack = £34.85
- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

**PROPRANOLOL HYDROCHLORIDE**

- **Cautions** see section 2.4
- **Contra-indications** see section 2.4
- **Side-effects** see section 2.4
- **Licensed use** see section 2.4

**Indication and dose**

- **Hyperthyroidism with autonomic symptoms, thyrotoxicosis, thyrotoxic crisis**
  - **By mouth**
  - **Neonate** initially 250–500 micrograms/kg every 6–8 hours, adjusted according to response
  - **Child 1 month–18 years** initially 250–500 micrograms/kg every 8 hours, then adjusted according to response; doses up to 1 mg/kg every 8 hours occasionally required, max. 40 mg every 8 hours
  - **By intravenous injection over 10 minutes**
    - **Neonate** initially 20–50 micrograms/kg every 6–8 hours, adjusted according to response

**Preparations**

See section 2.4

### 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 by mouth is usually required. This is given in 2–3 divided 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.

In *acute adrenocortical insufficiency*, hydrocortisone is given intravenously (preferably as sodium succinate) 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 levothyroxine (section 6.2.1) and sex hormones (section 6.4) should be given as indicated by the pattern of hormone deficiency.
In congenital adrenal hyperplasia, the pituitary gland increases production of corticotropin to compensate for reduced formation of cortisol; this results in excessive adrenal androgen production. Treatment is aimed at suppressing corticotropin using hydrocortisone (section 6.3.2). Careful and continual dose titration is required to avoid growth retardation and toxicity; for this reason potent, synthetic glucocorticoids such as dexamethasone are usually reserved for use in adolescents. The dose is adjusted according to clinical response and measurement of adrenal androgens and 17-hydroxyprogesterone. Salt-losing forms of congenital adrenal hyperplasia (where there is a lack of aldosterone production) require mineralocorticoid replacement. Mineralocorticoid replacement may also be beneficial even when salt-losing symptoms are not evident.

FLUDROCORTISONE ACETATE

Cautions section 6.3.2; interactions: Appendix 1 (corticosteroids)
Contra-indications section 6.3.2
Side-effects section 6.3.2

Indication and dose
Mineralocorticoid replacement in adrenocortical insufficiency
• By mouth

Neonate initially 100 micrograms once daily, adjusted according to response; usual range 50–300 micrograms daily

Child 1 month–18 years initially 50–100 micrograms once daily; maintenance 50–300 micrograms once daily, adjusted according to response

Florinef® (Squibb)
Tablets, scored, fludrocortisone acetate 100 micrograms. Net price 100-tab pack = £5.36. Label: 10, steroid card

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

Note Bioavailability uncertain, tablets may result in more reliable absorption and may be dispersed in water

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 accompanied by relatively low mineralocorticoid activity (see Disadvantages of Corticosteroids below). The mineralocorticoid 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.

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. 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 children. 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 and section 1.7.2).

Use can be made of the mineralocorticoid activity of fludrocortisone to treat postural hypotension in autonomic neuropathy.

High-dose corticosteroids should be avoided for the management of septic shock. However, low-dose hydrocortisone can be used in septic shock (section 2.7.1) that is resistant to volume expansion and catecholamines, and is accompanied by suspected or proven adrenal insufficiency.

The suppressive action of glucocorticoids on the hypothalamic-pituitary-adrenal axis is greatest and most prolonged when they are given at night. In most adults 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 can be used in the management of raised intracranial pressure or cerebral oedema that occurs as a result of malignancy (see also p. 26); 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 may be required.

In the management of asthma, corticosteroids are preferably used by inhalation (section 3.2) but systemic therapy along with bronchodilators is required for the emergency treatment of severe acute asthma (section 3.1.1).

Dexamethasone should not be used routinely for the prophylaxis and treatment of chronic lung disease in neonates because of an association with adverse neurological effects.
Corticosteroids may be useful in conditions such as auto-immune hepatitis, rheumatoid arthritis, and sarcoidosis; they may also lead to remissions of acquired haemolytic anaemia (section 9.1.3) and thrombocytopenic purpura (section 9.1.4).

High doses of a corticosteroid (usually prednisolone) are used in the treatment of glomerular kidney disease, including nephrotic syndrome. The condition frequently recurs; a corticosteroid given in high doses and for prolonged periods may delay relapse but the higher incidence of adverse effects limits the overall benefit. Those who suffer frequent relapses may be treated with prednisolone given in a low dose (daily or on alternate days) for 3–6 months; the dose should be adjusted to minimise effects on growth and development. Other drugs used in the treatment of glomerular kidney disease include levamisole (section 5.5.2), cyclophosphamide and chlorambucil (section 8.1.1), and ciclosporin (section 8.2.2). Congenital nephrotic syndrome may be resistant to corticosteroids and immunosuppressants; indometacin (section 10.1.1) and an ACE inhibitor such as captopril (section 2.5.5.1) have been used.

Corticosteroids can improve the prognosis of serious conditions such as systemic lupus erythematosus 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 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 (p. 28), 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 re-introduction of corticosteroid treatment. To avoid a precipitous fall in blood pressure during anaesthesia or in the immediate post-operative period, anaesthetists must know whether a patient is taking or has been taking a corticosteroid. A regimen for corticosteroid replacement may be necessary before and after surgery.

Children on long-term corticosteroid treatment should carry a Steroid Treatment Card (see p. 449) 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, children 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 children 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**  Children taking corticosteroids, and their carers, should be advised to take particular care to avoid exposure to measles and to seek urgent 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) [in adults];
- 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 5 mg/m² 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 children 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. Children and their carers 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 cortico-
Advice to children and carers

A patient information leaflet should be supplied to every patient when a systemic corticosteroid is prescribed. Children and carers should especially be advised of the following (for details, see Infections, Adrenal Suppression, and Psychiatric Reactions above and Withdrawal of Corticosteroids below):

- **Immunosuppression** Prolonged courses of corticosteroids can increase susceptibility to infection and serious infections can go unrecognised. Unless already immune, children are at risk of severe chickenpox and should avoid close contact with people who have chickenpox or shingles. Similarly, precautions should also be taken against contracting measles;

- **Adrenal suppression** If the corticosteroid is given for longer than 3 weeks, treatment must not be stopped abruptly. Adrenal suppression can last for a year or more after stopping treatment and the child or carer must mention the course of corticosteroid when receiving treatment for any illness or injury;

- **Mood and behaviour changes** Corticosteroid treatment, especially with high doses, can alter mood and behaviour early in treatment—the child can become confused, irritable and suffer from delusion and suicidal thoughts. These effects can also occur when corticosteroid treatment is being withdrawn. Medical advice should be sought if worrying psychological changes occur;

- **Other serious effects** Serious gastro-intestinal, musculoskeletal, and ophthalmic effects which require medical help can also occur; for details see Side-effects of Corticosteroids, p. 448.

Steroid treatment cards (see p. 449) should be issued where appropriate. Doctors and pharmacists can obtain supplies of the card from:

**England and Wales**
3M Security Printing and Systems Limited
Gorse Street, Chadderton
Oldham, OL9 9QH.
Tel: (0161) 683 2189
Fax: (0161) 683 2188
Email: nhsforms@spsl.uk.com

**Scotland**
Banner Business Supplies Ltd
Unit 2, Kingsthorne Park, Nettlehill Road, Houstoun Industrial Estate
Livingston, EH54 5DB.
Tel: (01506) 448 440
Fax: (01506) 448 400
Email: cust.serv.scotland@bbslimited.co.uk

Pregnancy and breast-feeding

The benefit of treatment with corticosteroids during pregnancy and breast-feeding outweighs the risk; pregnant women with fluid retention should be monitored closely.

Following a review of the data on the safety of systemic corticosteroids used in pregnancy and breast-feeding the CSM 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.

**Other cautions and contra-indications**

Other cautions include: growth restriction—possibly irreversible, frequent monitoring required if history of tuberculosis (or X-ray changes), hypertension, congestive heart failure, hepatic impairment (side-effects more common), renal impairment, diabetes mellitus including family history, osteoporosis, 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, hypothyroidism, 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.

Corticosteroids suppress growth and can affect the development of puberty. It is important to use the lowest effective dose; alternate-day regimens may be appropriate and limit growth reduction. For the effect of corticosteroids given in pregnancy, see Pregnancy and Breast-feeding, p. 447.

**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 tetra-cosactide (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); 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 (the potential advantage of soluble or enteric-coated preparations to reduce the risk is speculative only). See also Psychiatric Reactions, p. 446.

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. 445).

Side-effects can be minimised by using the lowest effective dose for the minimum period possible.

**Other side effects include**: gastro-intestinal 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 papil-
loedema (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, urticaria, 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 1.5 (gastro-intestinal system), section 3.2 (asthma), section 11.4 (eye) and section 13.4 (skin).

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**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**

Cautions  see notes above

Pregnancy  transient effect on fetal movements and heart rate

Contra-indications  see notes above

Side-effects  see notes above

Licensed use  Betnesol® tablets not licensed for use as mouthwash

**Indication and dose**

Ear (section 12.1.1); eye (section 11.4.1); nose (section 12.2.1); mouth (section 12.3.1)

**Suppression of inflammatory and allergic disorders; congenital adrenal hyperplasia; see also notes above**

- By slow intravenous injection or by intravenous infusion
  
  Child 1 month–1 year initially 1 mg repeated up to 4 times in 24 hours according to response
  
  Child 1–6 years initially 2 mg repeated up to 4 times in 24 hours according to response
  
  Child 6–12 years initially 4 mg repeated up to 4 times in 24 hours according to response
  
  Child 12–18 years initially 4–20 mg repeated up to 4 times in 24 hours according to response

**Administration**  For intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%

Betnesol® (UCB Pharma)  
Injection, betamethasone 4 mg (as sodium phosphate)/mL. Net price 1-mL amp = £1.22. Label: 10, steroid card

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**DEFLAZACORT**

Cautions  see notes above

Contra-indications  see notes above

Side-effects  see notes above

**Indication and dose**

Inflammatory and allergic disorders

- By mouth
  
  Child 1 month–12 years 0.25–1.5 mg/kg once daily or on alternate days; up to 2.4 mg/kg (max. 120 mg) daily has been used in emergency situations
  
  Child 12–18 years 3–18 mg once daily or on alternate days; up to 2.4 mg/kg (max. 120 mg) daily has been used in emergency situations

Nephrotic syndrome

- By mouth
  
  Child 1 month–18 years initially 1.5 mg/kg once daily (max. 120 mg) reduced to lowest effective dose for maintenance

Calcort® (Shire)  
Tablets, deflazacort 6 mg, net price 60-tab pack = £16.46. Label: 5, 10, steroid card

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**DEXAMETHASONE**

Cautions  see notes above

Contra-indications  see notes above

Side-effects  see notes above; also perineal irritation may follow intravenous administration of the phosphate ester

Licensed use  not licensed for use in bacterial meningitis

**Indication and dose**

Croup (see p. 169); nausea and vomiting with chemotherapy (section 8.1); rheumatic disease (section 10.1.2); eye (see p. 625); see also notes above

Note  Dexamethasone 1 mg = dexamethasone phosphate 1.2 mg = dexamethasone sodium phosphate 1.3 mg

Inflammatory and allergic disorders

- By mouth (as dexamethasone)
  
  Child 1 month–18 years 10–100 micrograms/kg daily in 1–2 divided doses, adjusted according to response; up to 300 micrograms/kg daily may be required in emergency situations

Life-threatening cerebral oedema

- By intramuscular injection or slow intravenous injection or infusion (as dexamethasone phosphate)
  
  Child 1 month–12 years 100–400 micrograms/kg daily in 1–2 divided doses; max. 24 mg daily
  
  Child 12–18 years initially 0.5–24 mg daily

Child under 35 kg body-weight

- By intravenous injection (as dexamethasone phosphate)
  
  Child initially 20 mg, then 4 mg every 3 hours for 3 days, then 4 mg every 6 hours for 1 day, then 2 mg every 6 hours for 4 days, then decrease by 1 mg daily

Child over 35 kg body-weight

- By intravenous injection (as dexamethasone phosphate)
  
  Child initially 25 mg, then 4 mg every 2 hours for 3 days, then 4 mg every 4 hours for 1 day, then 4 mg every 6 hours for 4 days, then decrease by 2 mg daily

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**DEexamethasone (continued)**

Bacterial meningitis (see section 5.1)
- By slow intravenous injection (as dexamethasone phosphate)
  - Child 2 months–18 years 150 micrograms/kg every 6 hours for 4 days starting before or with first dose of antibacterial

Physiological replacement
- By mouth or by slow intravenous injection (as dexamethasone)
  - Child 1 month–18 years 250–500 micrograms/m² every 12 hours, adjusted according to response

Administration for administration by mouth tablets may be dispersed in water or injection solution given by mouth
For intravenous infusion dilute with Glucose 5% or Sodium Chloride 0.9%; give over 15–20 minutes

**HYDROCORTISONE**

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)

Indication and dose
Adrenocortical insufficiency (section 6.3.1); shock (section 2.7.1), see also notes above; hypersensitivity reactions e.g. anaphylactic shock, angioedema (section 3.4.3); inflammatory bowel disease (section 1.5.2); haemorrhoids (section 1.7.2); rheumatic disease (section 10.1.2); eye (section 11.4.1); skin (section 13.4)

Congenital adrenal hyperplasia (see also section 6.3.1)
- Neonate 6–7 mg/m² every 8 hours, adjusted according to response
  - Child 1 month–18 years 5–6.5 mg/m² every 8 hours, adjusted according to response; usual maintenance 4–5 mg/m² every 8 hours but higher doses may be needed

Acute adrenocortical insufficiency (Addisonian crisis) see also notes above and section 6.3.1
- Neonate initially 10 mg as a slow intravenous injection then 100 mg/m² daily as a continuous infusion or in divided doses every 6–8 hours; adjusted according to response; when stable reduce over 4–5 days to oral maintenance dose
  - Child 1 month–12 years initially 2–4 mg/kg as a slow intravenous injection or infusion then 2–4 mg/kg every 6 hours; adjusted according to response; when stable reduce over 4–5 days to oral maintenance dose
  - Child 12–18 years 100 mg every 6 to 8 hours by slow intravenous injection or infusion

Adrenal hypoplasia, Addison’s disease, chronic maintenance or replacement therapy
- By mouth
  - Neonate usual dose 4–5 mg/m² every 8 hours; higher doses may be needed
    - Child 1 month–18 years usual dose 4–5 mg/m² every 8 hours; higher doses may be needed
      - Note larger doses given in the morning and smaller doses in the evening

Inflammatory bowel disease—induction of remission (see also section 1.5)
- By intravenous injection
  - Child 2–18 years 2.5 mg/kg (max. 100 mg) every 6 hours
- By continuous intravenous infusion
  - Child 2–18 years 10 mg/kg daily (max. 400 mg daily)

Severe acute asthma (see p. 168)

Acute hypersensitivity reactions, angioedema
- By intramuscular or intravenous injection
  - Child under 6 months initially 25 mg 3 times daily, adjusted according to response
  - Child 6 months–6 years initially 50 mg 3 times daily, adjusted according to response
  - Child 6–12 years initially 100 mg 3 times daily, adjusted according to response
  - Child 12–18 years initially 200 mg 3 times daily, adjusted according to response

Dexamethasone (Non-proprietary) [TPH]
- Tablets, dexamethasone 500 micrograms, net price 20 = 70p; 2 mg, 20 = £1.75. Label: 10, steroid card, 21
  - Available from Chemidex and 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 Dexasol®
- 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

Adrenal hypoplasia, Addisonian crisis

Note larger doses given in the morning and smaller doses in the evening
Hypotension resistant to inotropic treatment and volume replacement (limited evidence).

By intravenous injection

Neonate initially 2.5 mg/kg repeated if necessary after 4 hours, then 2.5 mg/kg every 6 hours for 48 hours or until blood pressure recovers, then dose reduced gradually over at least 48 hours.

Child 1 month–18 years 1 mg/kg (max. 100 mg) every 6 hours.

Administration for intravenous administration, dilute with Glucose 5% or Sodium Chloride 0.9%; for intermittent infusion give over 20–30 minutes. For administration by mouth, injection solution may be swallowed [unlicensed use] but consider phosphate content; alternatively Corlan® pellets (section 12.3.1) may be swallowed [unlicensed use]—pellets should not be cut as may not provide appropriate dose.

Hydrocortisone® (Non-proprietary)

Tablets, scored, hydrocortisone 10 mg, net price 30-tab pack = £30.50; 20 mg, 30-tab pack = £32.00. Label: 10, steroid card, 21.

1 Effortesol® (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 Paraesthesia and pain (particularly in the perineal region) may follow intravenous injection of the phosphate ester.

1 Solu-Cortef® (Pharmacia) Injection, powder for reconstitution, hydrocortisone (as sodium succinate). Net price 100-mg vial = 92p, 100-mg vial with 2-mL amp water for injections = £1.16. Label: 10, steroid card

1. (ph) restriction does not apply where administration is for saving life in emergency

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

METHYLPREDNISOLONE

Cautions see notes above; rapid intravenous administration of large doses associated with cardiovascular collapse.

Contra-indications see notes above.

Side-effects see notes above.

Indication and dose

See also notes above; immunosuppression (section 8.2.2); rheumatic disease (section 10.1.2); skin (section 13.4).

Inflammatory and allergic disorders

• By mouth, slow intravenous injection or by intravenous infusion.

Child 1 month–18 years 0.5–1.7 mg/kg daily in 2–4 divided doses depending on condition and response.

Treatment of graft rejection reactions

• By intravenous injection.

Child 1 month–18 years 10–20 mg/kg or 400–600 mg/m² (max. 1 g) once daily for 3 days.

Severe erythema multiforme (Stevens-Johnson syndrome), lupus nephritis, systemic onset juvenile idiopathic arthritis (section 10.1.2.1).

• By intravenous injection.

Child 1 month–18 years 10–30 mg/kg (max. 1 g) once daily or on alternate days for up to 3 doses.

Administration intravenous injection given over 30 minutes; for intravenous infusion may be diluted with sodium chloride intravenous infusion 0.9% or 0.45%, or glucose intravenous infusion 5% or 10%.

Medrone® (Pharmacia) Tablets, scored, methylprednisolone 2 mg (pink), net price 30-tab pack = £3.23; 4 mg, 30-tab pack = £6.19; 16 mg, 30-tab pack = £17.17; 100 mg (blue), 20-tab pack = £48.32. Label: 10, steroid card, 21.

Solu-Medrone® (Pharmacia) Injection, powder for reconstitution, methylprednisolone (as sodium succinate) (all with solvent). Net price 40-mg vial = £1.58; 125-mg vial = £4.75; 500-mg vial = £9.60; 1-g vial = £17.30; 2-g vial = £32.86. Label: 10, steroid card.

Intramuscular depot

Depo-Medrone® (Pharmacia) 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. Label: 10, steroid card.

Dose

• By deep intramuscular injection into gluteal muscle seek specialist advice

PREDNISOLONE

Cautions see notes above.

Contra-indications see notes above.

Side-effects see notes above.

Indication and dose

See also notes above.

Asthma see p. 184.
**6.4 Sex hormones**

**6.4.1 Female sex hormones**

**6.4.2 Male sex hormones and antagonists**

**6.4.3 Anabolic steroids**

Sex hormone replacement therapy is indicated in children for the treatment of gonadotrophin deficiency, gonadal disorders, or delayed puberty that interferes with quality of life. Indications include constitutional delay in puberty, congenital or acquired hypogonadotropic hypogonadism, hypergonadotrophic hypogonadism (Turner’s syndrome, Klinefelter’s syndrome), endocrine disorders (Cushing’s syndrome or hyperprolactinaemia), and chronic illnesses, such as cystic fibrosis or sickle-cell disease, that may affect the onset of puberty.

Replacement therapy is generally started at the appropriate age for the development of puberty and should be managed by a paediatric endocrinologist. Patients with constitutional delay, chronic illness, or eating disorders may need only small doses of hormone supplements for 4 to 6 months to induce puberty and endogenous sex hormone production, which is then sustained. Patients with organic causes of hormone deficiency will require life-long replacement, adjusted to allow normal development.

Inadequate treatment may lead to poor bone mineralisation, resulting in fractures and osteoporosis.
6.4.1 Female sex hormones

6.4.1.1 Oestrogens

Oestrogens are necessary for the development of female secondary sexual characteristics. If onset of puberty is delayed because of organic pathology, puberty can be induced with ethinylestradiol in increasing doses, guided by breast staging and uterine scans. Cyclical progestogen replacement is added after 12–18 months of oestrogen treatment (see section 6.4.1.2). Once the adult dosage of oestrogen has been reached (20 micrograms ethinylestradiol daily), it may be more convenient to provide replacement either as a low-dose oestrogen containing oral contraceptive formulation [unlicensed indication] (see section 7.3.1) or as a combined oestrogen and progestogen hormone replacement therapy preparation [unlicensed indication] (see BNF section 6.4.1.2). There is limited experience in the use of transdermal patches or gels in children; compliance and skin irritation are sometimes a problem.

Ethinylestradiol is occasionally used, under specialist supervision, for the management of hereditary haemorrhagic telangiectasia (but evidence of benefit is limited), for the prevention of tall stature, and in tests of growth hormone secretion (see below). Side-effects include nausea and fluid retention.

Topical oestrogen creams are used in the treatment of labial adhesions (see section 7.2.1)

**ETHINYLESTRADIOL**

(Ethinylestradiol)

**Cautions** see Combined Hormonal Contraceptives (section 7.3.1); **interactions**: Appendix 1 (Oestrogens)

**Contra-indications** cardiovascular disease (sodium retention with oedema), personal or family history of thromboembolism, acute porphyria; see also Combined Hormonal Contraceptives (section 7.3.1)

**Hepatic impairment** contra-indicated in liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), and jaundice

**Pregnancy** contra-indicated

**Breast-feeding** contra-indicated

**Side-effects** nausea, vomiting, headache, breast tenderness, changes in body weight, fluid retention, depression, chorea, skin reactions, chloasma, hypertension, may irritate contact lenses, impairment of liver function, hepatic tumours, rarely photosensitivity; see also Combined Hormonal Contraceptives (section 7.3.1)

**Licensed use** unlicensed for use in children

**Indication and dose**

- **Induction of sexual maturation in girls**
  - By mouth
  - Initially 2 micrograms daily, increasing every 6 months to 5 micrograms, then to 10 micrograms, and then to 20 micrograms daily
  - Note after 12–18 months of treatment give progestogen for 7 days of each 28-day cycle

- **Maintenance of sexual maturation in girls**
  - By mouth
  - 20 micrograms daily with cyclical progestogen for 7 days of each 28-day cycle

- **Prevention of tall stature in girls**
  - By mouth
  - Girls 2–12 years 20–50 micrograms daily

- **Pituitary priming before growth hormone secretion test in girls**
  - By mouth
  - Girls with bone age above 10 years 100 micrograms daily for 3 days before test

**Ethinylestradiol** (Non-proprietary)

Tablets, ethinylestradiol (unlicensed) 10 micrograms, net price 21-tab pack = £15.55; 50 micrograms, 21-tab pack = £18.55; 1 mg, 28-tab pack = £34.53

**Note** 2 microgram tablets available from ‘special-order’ manufacturers or specialist-importing companies, see p. 943

6.4.1.2 Progestogens

There are two main groups of progestogen, **progesterone and its analogues** (dydrogesterone and medroxyprogesterone) and **testosterone analogues** (norethisterone and norgestrel). The newer progestogens (desogestrel, norgestimate, and gestodene) are all derivatives of norgestrel; levonorgestrel is the active isomer of
Norgestrel and has twice its potency. Progesterone and its analogues are less androgenic than the testosterone derivatives and neither progesterone nor dydrogesterone causes virilisation.

In delayed puberty cyclical progestogen is added after 12–18 months of oestrogen therapy (section 6.4.1.1) to establish a menstrual cycle; usually levonorgestrel 30 micrograms or norethisterone 5 mg daily are used for the last 7 days of each 28 day cycle.

Norethisterone is also used to postpone menstruation during a cycle; treatment is started 3 days before the expected onset of menstruation.

### NORETHISTERONE

**Cautions** conditions that may worsen with fluid retention e.g. epilepsy, hypertension, migraine, asthma, cardiac or renal dysfunction; susceptibility to thromboembolism (particular caution with high dose); history of depression; diabetes (monitor closely); **interactions**: Appendix 1 (progestogens)

Hepatic impairment caution; avoid if severe

Breast-feeding higher doses may suppress lactation and alter milk composition; use lowest effective dose

**Contra-indications** history of liver tumours, severe liver impairment; severe arterial disease, undiagnosed vaginal bleeding; acute porphyria (section 9.8.2); history during pregnancy of idiopathic jaundice, severe pruritus, or pemphigoid gestationis

Pregnancy contra-indicated

**Side-effects** menstrual disturbances, premenstrual-like syndrome (including bloating, fluid retention, breast tenderness), weight gain, nausea, headache, dizziness, insomnia, drowsiness, depression; skin reactions (including urticaria, pruritus, rash, and acne), hirsutism and alopecia; jaundice and anaphylactoid reactions also reported

**Licensed use** not licensed for use in children

### Indication and dose

**See notes above**

**Induction and maintenance of sexual maturation in females (combined with an oestrogen after 12–24 months oestrogen therapy)**

- **By mouth**
  - 5 mg once daily for the last 7 days of a 28-day cycle

**Postponement of menstruation**

- **By mouth**
  - 5 mg 3 times daily, starting 3 days before expected onset of menstruation

**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

**Utovlan** (Pharmacia)

Tablets, norethisterone 5 mg, net price 30-tab pack = £1.40, 90-tab pack = £4.21

### Male sex hormones and antagonists

Androgens cause masculinisation; they are used as replacement therapy in androgen deficiency, in delayed puberty, and in those who are hypogonadal due to either pituitary or testicular disease.

When given to patients with hypopituitarism androgens 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 stimulates spermatogenesis as well as androgen production.

Intramuscular depot preparations of testosterone esters are preferred for replacement therapy. Testosterone enantate or propionate or alternatively Sustanon®, which consists of a mixture of testosterone esters and has a longer duration of action, can be used. For induction of puberty, depot testosterone injections are given monthly and the doses increased every 6 to 12 months according to response. Single ester testosterone injections may need to be given more frequently. Testosterone enantate is unlicensed in children. Implants of testosterone can be used for hypogonadism; the implants are replaced every 4 to 5 months.

Oral testosterone undecanoate is used for induction of puberty. An alternative approach that promotes growth rather than sexual maturation uses oral oxandrolone (section 6.4.3).

Chorionic gonadotrophin (section 6.5.1) has also been used in delayed puberty in the male to stimulate endogenous testosterone production, but has little advantage over testosterone.
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.

Testosterone patches and topical gel are also available but experience of their use in children under 15 years is limited. Topical testosterone is applied to the penis in the treatment of microphallus; an extemporaneously prepared cream should be used because the alcohol in proprietary gel formulations causes irritation.

**TESTOSTERONE AND ESTERS**

**Cautions**
- cardiac impairment, hypertension, epilepsy, migraine, diabetes mellitus, skeletal metastases (risk of hypercalcaemia); interac-
tions: Appendix 1 (testosterone)
- Hepatic impairment avoid if possible—fluid retention and dose-related toxicity
- Renal impairment caution—potential for fluid retention

**Contra-indications**
- history of primary liver tumours, hypercalcaemia, nephrosis
- Pregnancy avoid; causes masculinisation of female fetus
- Breast-feeding avoid; may cause masculinisation in the female infant or precocious development in the male infant; high doses suppress lactation

**Side-effects**
- headache, depression, gastro-intestinal bleeding, nausea, cholestatic jaundice, changes in libido, gynaecomastia, polycystaemia, anxiety, asthenia, paraesthesia, hypertension, electrolyte disturbances including sodium retention with oedema and hypercalcaemia, weight gain; increased bone growth; androgenic effects such as hirsutism, male-pattern baldness, seborrhea, 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 males and virilism in females; rarely liver tumours; sleep apnoea also reported; with patches and gel, local irritation and allergic reactions

**Licensed use**
- Sustanon® and Virormone® licensed for use in children; Andropatch® licensed for use in children over 15 years

**Indication and dose**

- See also under preparations; specialist use only
- Induction and maintenance of sexual matura-
tion in males
  - By mouth (as testosterone undecanoate)
    - Child over 12 years 40 mg on alternate days increasing according to response up to 120 mg daily
  - By deep intramuscular injection of testo-
    steron enantate or propionate
    - Child over 12 years 25–50 mg/m² every month increasing dose every 6–12 months according to response
  - Patch
    - Child over 15 years 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 2.5–7.5 mg every 24 hours according to plasma-testosterone concentration

**Treatment of microphallus**
- **Topically**
  - Apply 3 times daily for 3 weeks
  - Note Use only specially manufactured preparation (see notes above)

**Oral**
- Restandol® Testocaps (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

**Intramuscular**
- Testosterone Enantate (Cambridge) Injection (oily), testosterone enantate 250 mg/mL. Net price 1-mL amp = £11.01
- Sustanon 100® (Organon) Injection (oily), testosterone propionate 20 mg, testosterone phenylpropionate 40 mg, and testosterone isocaproate 40 mg/mL. Net price 1-mL amp = £1.09
- Excipients include arachis (peanut) oil, benzyl alcohol (see Excipients p. 3)

**Dose**

- Delayed puberty in males
  - By intramuscular injection
    - 1 mL every month for 3 doses

**Pituitary priming prior to growth hormone secretion test**
- By deep intramuscular injection
  - 1 mL 3–5 days before test

- Sustanon 250® (Organon) Injection (oily), testosterone propionate 30 mg, testosterone phenylpropionate 60 mg, testosterone isocaproate 60 mg, and testosterone decanoate 100 mg/mL. Net price 1-mL amp = £2.55
- Excipients include arachis (peanut) oil, benzyl alcohol (see Excipients p. 3)

**Viormone® (Nordic)**
- Injection, testosterone propionate 50 mg/mL. Net price 2-mL amp = 45p
Implant

Testosterone (Organon)

**Implant**, testosterone 100 mg, net price = £7.40; 200 mg = £13.79

Dose

**Maintenance of sexual maturation in males**

Child over 16 years: 100–600 mg; 600 mg usually maintains plasma-testosterone concentration within the normal range for 4–5 months

Cream

Testosterone

Cream, testosterone 5% (other strengths available)

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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

Anti-androgens and precocious puberty

The gonadorelin stimulation test (section 6.5.1) is used to distinguish between gonadotrophin-dependent (central) precocious puberty and gonadotrophin-independent precocious puberty. Treatment requires specialist management.

Gonadorelin analogues, used in the management of gonadotrophin-dependent precocious puberty, delay development of secondary sexual characteristics and growth velocity.

Testolactone and cyproterone are used in the management of gonadotrophin-independent precocious puberty, resulting from McCune-Albright syndrome, familial male precocious puberty (testotoxicosis), hormone-secreting tumours, and ovarian and testicular disorders. Testolactone inhibits the aromatisation of testosterone, the rate limiting step in oestrogen synthesis. Cyproterone is a progestogen with anti-androgen properties.

Spironolactone (section 2.2.3) is sometimes used in combination with testolactone because it has some androgen receptor blocking properties.

High blood concentration of sex hormones may activate release of gonadotrophin releasing hormone, leading to development of secondary, central gonadotrophin-dependent precocious puberty. This may require the addition of gonadorelin analogues to prevent progression of pubertal development and skeletal maturation.

CYPROTERONE ACETATE

**Cautions**

- blood counts initially and throughout treatment; monitor adrenocortical function regularly; diabetes mellitus (see also Contra-indications)
- Skilled tasks: Fatigue and lassitude may impair performance of skilled tasks (e.g. driving)
- Hepatic impairment: monitor hepatic function regularly—dose-related toxicity, see side-effects below

**Contra-indications**

- hepatic disease, severe diabetes (with vascular changes); sickle-cell anaemia, malignant or wasting disease, severe depression, history of thrombo-embolic disorders

**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 oedema, inhibition of spermatogenesis (see notes above); hepatotoxicity reported (including jaundice, hepatitis and hepatic failure)

**Hepatotoxicity**

Direct hepatic toxicity including jaundice, hepatitis and hepatic failure have been reported (usually after several months) with cyproterone acetate 200–300 mg daily. Liver function tests should be performed before 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)

**Licensed use**

- unlicensed for use in children

**Indication and dose**

**Gonadotrophin-independent precocious puberty** (specialist use only; see also notes above)

- **By mouth**

  Initially 25 mg twice daily, adjusted according to response

Cyproterone Acetate (Non-proprietary)

Tablets, cyproterone acetate 50 mg, net price 56-tab pack = £31.54. Label: 21, counselling, driving

**Note**

10 mg tablets available from ‘special-order’ manufacturers or specialist-importing companies, see p. 943

Androcur® (Schering Health)

Tablets, scored, cyproterone acetate 50 mg. Net price 56-tab pack = £25.89. Label: 21, counselling, driving
### TESTOLACTONE

**Cautions**
- Interactions: Appendix 1 (testolactone)

**Contra-indications**
- Pregnancy: avoid
- Breast-feeding: no information available

**Side-effects**
- Nausea, vomiting, anorexia, diarrhoea; hypertension; peripheral neuropathy; weight changes; changes in hair pattern; rarely hypersensitivity reactions, rash

**Indication and dose**
- **Gonadotrophin-independent precocious puberty** (specialist use only; see also notes above)
  - **By mouth**
    - 5 mg/kg 3–4 times daily; up to 10 mg/kg 4 times daily may be required

**Testolactone**
- Tablets, testolactone 50 mg
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

### GOSERELIN

**Cautions**
- Monitor bone mineral density

**Contra-indications**
- Undiagnosed vaginal bleeding

**Pregnancy**
- Manufacturer advises avoid

**Breast-feeding**
- Manufacturer advises avoid

**Side-effects**
- Changes in blood pressure, headache, mood changes including depression, hypersensitivity reactions including urticaria, pruritus, rash, asthma and anaphylaxis; changes in scalp and body hair, weight changes, withdrawal bleeding, ovarian cysts (may require withdrawal), breast swelling and tenderness (males and females), visual disturbances, paraesthesia, local reactions at injection site

**Licensed use**
- Not licensed for use in children

**Indication and dose**
- **Gonadotrophin-dependent precocious puberty**
  - See notes above; for doses, see under preparations below
  - **Note:** Injections may be required more frequently in some cases

**Administration**
- Rotate injection site to prevent atrophy and nodule formation

**Zoladex®** (AstraZeneca)
- **Implant**, goserelin 3.6 mg (as acetate) in Safe-Sys-tem® syringe applicator. Net price each = £84.14

**Dose**
- **Implant, by subcutaneous injection into anterior abdominal wall**
  - 3.6 mg every 4 weeks

**Zoladex® LA** (AstraZeneca)
- **Implant**, goserelin 10.8 mg (as acetate) in Safe-System® syringe applicator. Net price each = £287.48

**Dose**
- **Implant, by subcutaneous injection into anterior abdominal wall**
  - 10.8 mg every 12 weeks

### LEUPRORELIN ACETATE

**Cautions**
- See Goserelin

**Contra-indications**
- See Goserelin

**Pregnancy**
- Avoid—teratogenic in animal studies

**Breast-feeding**
- Manufacturer advises avoid

**Side-effects**
- See Goserelin

**Licensed use**
- Not licensed for use in children

**Indication and dose**
- **Gonadotrophin-dependent precocious puberty**
  - See notes above; for doses, see under preparations below
  - **Note:** Injections may be required more frequently in some cases

**Administration**
- Rotate injection site to prevent atrophy and nodule formation

**Prostap® SR** (Wyeth)
- **Injection** (microsphere powder for reconstitution), leuprorelin acetate, net price 3.75-mg vial with 1-mL vehicle-filled syringe = £125.40

**Dose**
- **By subcutaneous or by intramuscular injection**
  - 3.75 mg every four weeks (half this dose is sometimes used in children with body-weight under 20 kg)

**Prostap® 3** (Wyeth)
- **Injection** (microsphere powder for reconstitution), leuprorelin acetate, net price 11.25-mg vial with 2-mL vehicle-filled syringe = £376.20

**Dose**
- **By subcutaneous or by intramuscular injection**
  - 11.25 mg every 12 weeks

### TRIPTORELIN

**Cautions**
- See Goserelin

**Contra-indications**
- See Goserelin

**Pregnancy**
- Manufacturer advises avoid

**Breast-feeding**
- Manufacturer advises avoid

**Side-effects**
- See Goserelin; also gastro-intestinal disturbances; asthenia; arthralgia
**Indication and dose**

**Gonadotrophin-dependent precocious puberty**

see notes above; for doses see under preparations below

**Administration**
rotate injection site to prevent atrophy and nodule formation

**Decapeptyl® SR (Ipsen)**

Injection, (powder for suspension), m/r, triptorelin (as acetate), net price 11.25-mg vial (with diluent) = £207.00

**Dose**

- By intramuscular injection
  - 11.25 mg every 3 months

**Note**
Each vial includes an overage to allow accurate administration of 11.25 mg dose

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**6.4.3 Anabolic steroids**

Anabolic steroids have some androgenic activity but in girls they cause less virilisation than androgens. They are used in the treatment of some aplastic anaemias (section 9.1.3). Oxandrolone is used to stimulate late pre-pubertal growth prior to induction of sexual maturation in boys with short stature and in girls with Turner’s syndrome; specialist management is required.

**OXANDROLONE**

**Cautions**
see Testosterone (section 6.4.2); interactions: Appendix 1 (oxandrolone)

**Contra-indications**
see Testosterone (section 6.4.2)

**Side-effects**
see Testosterone (section 6.4.2)

**Indication and dose**

- **Stimulation of late pre-pubertal growth in boys with short stature**
  - By mouth
    - Boys 10–18 years (or appropriate age) 1.25–2.5 mg daily for 3–6 months

**Stimulation of late pre-pubertal growth in girls with Turner’s syndrome**

- By mouth
  - Girls in combination with growth hormone 0.625–2.5 mg daily

**Oxandrolone**

Tablets, oxandrolone 2.5 mg
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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**6.5 Hypothalamic and pituitary hormones**

**6.5.1 Hypothalamic and anterior pituitary hormones including growth hormone**

**Posterior pituitary hormones and antagonists**

Use of preparations in these sections requires detailed prior investigation of the patient and should be reserved for specialist centres.

**6.5.1 Hypothalamic and anterior pituitary hormones including growth hormone**

**Anterior pituitary hormones**

**Corticotrophins**

Tetracosactide (tetracosactrin), an analogue of corticotropin (adrenocorticotropic hormone, ACTH), is used to test adrenocortical function; failure of plasma-cortisol concentration to rise after administration of tetracosactide indicates adrenocortical insufficiency. A low-dose test is considered by some clini-
TETRACOSACTIDE
(Tetracosactrin)

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)

Pregnancy avoid
Breast-feeding avoid

Side-effects as for corticosteroids, section 6.3.2

Licensed use not licensed for low-dose test for adrenocortical insufficiency or treatment of infantile spasms

Indication and dose
See notes above and under preparations below.

Synacthen® (Alliance) Injection, tetracosactide 250 micrograms (as acetate)/mL. Net price 1-mL amp = £2.93

Dose

Diagnosis of adrenocortical insufficiency (30-minute test)
- By intramuscular or intravenous injection
  Standard-dose test 145 micrograms/m² (max. 250 micrograms) as a single dose
  Low-dose test 300 nanograms/m² as a single dose

Administration may be diluted in sodium chloride 0.9% to 250 nanograms/mL

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. 3)

Dose

Infantile spasms
- By intramuscular injection
  Child 1 month–2 years initially 500 micrograms on alternate days, adjusted according to response

CORTICORELIN
(Corticotrophin-releasing hormone, CRH)

Contra-indications
- Pregnancy contra-indicated
- Breast-feeding contra-indicated

Side-effects flushing of face, neck and upper body, hypotension, mild sensation of taste or smell

Licensed use not licensed

Indication and dose
Test of anterior pituitary function
- By intravenous injection over 30 seconds
  Child 1 month–18 years 1 microgram/kg (max. 100 micrograms) as a single dose

CRH Ferring® (Shire) Injection, corticorelin 100 micrograms

Gonadotrophins

Gonadotrophins are occasionally used in the treatment of hypogonadotrophic hypogonadism and associated oligospermia. There is no justification for their use in primary gonadal failure.

Chorionic gonadotrophin is used in the investigation of testicular function in suspected primary hypogonadism and incomplete masculinisation. It has also been used in delayed puberty in boys to stimulate endogenous testosterone production, but it 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

Cautions cardiac or renal impairment, asthma, epilepsy, migraine; prepubertal boys (risk of pre-
mature epiphyseal closure or precocious puberty)

Contra-indications androgen-dependent tumours

Side-effects oedema (reduce dose), headache, tiredness, mood changes, gynaecomastia, local reactions

Licensed use unlicensed in children for test of testicular function

Indication and dose

Test of testicular function
- By intramuscular injection
  - Short stimulation test:
    - Child 1 month–18 years 1500–2000 units once daily for 3 days
  - Prolonged stimulation test:
    - Child 1 month–18 years 1500–2000 units twice weekly for 3 weeks

Hypogonadotrophic hypogonadism
- By intramuscular injection
  - Child 1 month–18 years 1000–2000 units twice weekly, adjusted to response

Growth hormone

Growth hormone is used to treat proven deficiency of the hormone, Prader-Willi syndrome, Turner’s syndrome, growth disturbance in children born small for gestational age, and chronic renal insufficiency (see NICE guidance below). Growth hormone is also used in Noonan syndrome and idiopathic short stature [unlicensed indications] under specialist management. 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.

Growth hormone of human origin (HGH; somatotrophin) 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 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.

Mecasermin, a human insulin-like growth factor-I (rhIGF-I), is licensed to treat growth failure in children with severe primary insulin-like growth factor-I deficiency (section 6.7.4).

SOMATROPIN
(Synthetic Human Growth Hormone)

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 epiphysis 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; interactions: Appendix 1 (somatropin) Breast-feeding no information available but absorption from milk unlikely

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 epiphyses (or near closure in Prader-Willi syndrome); severe obesity or severe respiratory syndrome in Prader-Willi syndrome

Pregnancy interrupt treatment if pregnancy occurs

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); 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


Indication and dose

Gonadal dysgenesis (Turner’s syndrome)
• By subcutaneous injection
  45–50 micrograms/kg daily or 1.4 mg/m² daily

Deficiency of growth hormone
• By subcutaneous or intramuscular injection
  23–39 micrograms/kg daily or 0.7–1 mg/m² daily

Prader-Willi syndrome
• By subcutaneous injection
  Children with growth velocity greater than 1 cm/year in combination with energy-restricted diet, 35 micrograms/kg daily or 1 mg/m² daily; max. 2.7 mg daily

Chronic renal insufficiency (renal function decreased to less than 50%)
• By subcutaneous injection
  45–50 micrograms/kg daily or 1.4 mg/m² daily (higher doses may be needed) adjusted if necessary after 6 months

Genotropin® (Pharmacons) (BNFC 2009) Injection, two-compartment cartridge containing powder for reconstitution, somatropin (rbe) and diluent, net price 5.3-mg (16-unit) cartridge = £122.87; 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) 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) (BNFC 2009) 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) SimpleXx 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® device (available free of charge from clinics). For subcutaneous injection

NutropinAq® (Ipsen) Injection, Somatropin (rbe), net price 10 mg (30 units) 2-mL cartridge = £230.00. For use with NutropinAq® Pen device (available free of charge from clinics). For subcutaneous injection

Omnitrope® (Sandoz) Injection, somatropin (rbe) 3.3 mg (10 units)/mL, net price 1.5-mL (5-mg, 15-unit) cartridge = £91.33; 6.7 mg (20 units)/mL, 1.5-mL (10-mg, 30-unit) cartridge = £182.66. For use with Omnitrope Pen 5® and Omnitrope Pen 10® devices respectively (available free of charge from clinics). For subcutaneous injection

Note Biosimilar medicine, see p. 2

Saizen® (Serono) (BNFC 2009) Injection, powder for reconstitution, somatropin (rmc), 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

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 3)

Growth disturbance in children born small for gestational age whose growth has not caught up by 4 years of age or later; Noonan syndrome • By subcutaneous injection
  35 micrograms/kg daily or 1 mg/m² daily

462 6.5.1 Hypothalamic and anterior pituitary hormones BNFC 2009
Hypothalamic hormones

**Gonadorelin** when injected intravenously in post-pubertal girls 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. It is used in the assessment of delayed or precocious puberty.

**Protirelin** is a hypothalamic releasing hormone which stimulates the release of thyrotrophin from the pituitary. It is indicated for the diagnosis of mild hyperthyroidism or hypothyroidism, but its use has been superseded by immunoassays for thyroid-stimulating hormone. Together with other tests protirelin may also be used to confirm hypopituitarism and hypothalamic disease in children with marginally lowered thyrotrphin.

Other growth hormone stimulation tests involve the use of insulin, glucagon, arginine, and clonidine [all unlicensed uses]. The tests should be carried out in specialist centres.

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**Gonadorelin**

(Gonadotrophin-releasing hormone; GnRH; LH–RH)

**Cautions** pituitary adenoma

**Contra-indications**
- Pregnancy avoid
- Breast-feeding avoid

**Side-effects** rarely nausea, headache, abdominal pain, increased menstrual bleeding; rarely, hypersensitivity reaction on repeated administration of large doses; irritation at injection site

**Licensed use** not licensed for use in children under 1 year

**Indication and dose**

Assessment of anterior pituitary function; assessment of delayed puberty

- **By subcutaneous or intravenous injection**
  - **Child 1–18 years** 2.5 micrograms/kg (max. 100 micrograms) as a single dose

**HRF** (Intrapharm)

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. 3)

**Protirelin**

(Thyrotrophin-releasing hormone; TRH)

**Cautions** severe hypopituitarism, myocardial ischaemia, bronchial asthma and obstructive airways disease

**Pregnancy** use with caution as limited information available

**Breast-feeding** breast enlargement and leakage of milk reported

**Side-effects** after rapid intravenous administration desire to micturate, flushing, dizziness, nausea, abnormal taste; transient increase in pulse rate and blood pressure; rarely bronchospasm

**Indication and dose**

Assessment of thyroid function and thyroid stimulating hormone reserve

- **By intravenous injection**
  - **Neonate** 1 microgram/kg as a single dose; dose may vary—consult local protocol

**Diagnosis of hypopituitarism and hypothalamic disease**

- **By intravenous injection**
  - **Neonate** 7 micrograms/kg as a single dose (unlicensed dose); dose may vary—consult local protocol

**Child 1 month–18 years** 7 micrograms/kg (max. 200 micrograms) as a single dose (unlicensed dose); dose may vary—consult local protocol

**Protirelin** (Cambridge)

Injection, protirelin 100 micrograms/mL. Net price 2-mL amp = £14.43
Posterior pituitary hormones

Diabetes insipidus

Diabetes insipidus is caused by either a deficiency of antidiuretic hormone (ADH, vasopressin) secretion (cranial, neurogenic, or pituitary diabetes insipidus) or by failure of the renal tubules to react to secreted antidiuretic hormone (nephrogenic diabetes insipidus).

Vasopressin (antidiuretic hormone, ADH) is used in the treatment of pituitary diabetes insipidus as is its analogue desmopressin. Dosage is tailored to produce a regular diuresis every 24 hours to avoid water intoxication. Treatment may be required permanently or 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 an intramuscular or intranasal dose, restoration of the ability to concentrate urine after water deprivation confirms a diagnosis of pituitary diabetes insipidus. Failure to respond suggests nephrogenic diabetes insipidus. Fluid input must be managed carefully to avoid hyponatraemia; this test is not usually recommended in young children.

In nephrogenic and partial pituitary diabetes insipidus benefit may be gained from the paradoxical antidiuretic effect of thiazides (section 2.2.1) e.g. chlorothiazide 10–20 mg/kg (max. 500 mg) twice daily.

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, before introducing more definitive treatment. Terlipressin, a derivative of vasopressin, and octreotide are used similarly but experience in children is limited.

VASOPRESSIN

Cautions

heart failure, hypertension, asthma, epilepsy, migraine or other conditions which might be aggravated by water retention; renal impairment (see also Contra-indications); avoid fluid overload

Pregnancy

oxytocic effect in third trimester

Breast-feeding

not known to be harmful

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

Licensed use

not licensed for use in children

Indication and dose

Adjunct in acute massive haemorrhage of gastro-intestinal tract or oesophageal varices (specialist use only)

- By continuous intravenous infusion (may also be infused directly into the superior mesenteric artery)

Child 1 month–18 years initially 0.3 units/kg (max. 20 units) over 20–30 minutes then 0.3 units/kg/hour, adjusted according to response (max. 1 unit/kg/hour); if bleeding stops, continue at same dose for 12 hours, then withdraw gradually over 24–48 hours; max. duration of treatment 72 hours

Administration

for intravenous infusion dilute with Glucose 5% or Sodium Chloride 0.9% to a concentration of 0.2–1 unit/mL

Synthetic vasopressin

Pitressin® (Goldshield). In.

Injection, argipressin (synthetic vasopressin)

20 units/mL. Net price 1-mL amp = £17.14 (hosp. only)

DESMOPRESSIN

Cautions

see under Vasopressin; less pressor activity, but still considerable caution in cardio-vascular disease and in hypertension (not indicated for nocturnal enuresis or nocturia in these
circumstances); also considerable caution in cystic fibrosis; in nocturia and nocturnal enuresis limit fluid intake from 1 hour before dose until 8 hours afterwards; in nocturia periodic blood pressure and weight checks needed to monitor for fluid overload; interactions: Appendix 1 (desmopressin)

Renal impairment use with caution, antidiuretic effect reduced

Pregnancy small oxytocic effect in third trimester; increased risk of pre-eclampsia

Breast-feeding concentration too low to be harmful

For cautions specifically relating to the use of desmopressin in nocturnal enuresis see section 7.4.2

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

Licensed use intranasal preparations not licensed for use in children for assessment of antidiuretic hormone secretion, for fibrinolytic response testing, or for haemophilia and von Willebrand’s disease; Desmomet® and Desmotab® not licensed for use in children for treatment of diabetes insipidus; Octim® preparations not licensed for use in children for renal function testing or for treatment or diagnosis of diabetes insipidus

Diabetes insipidus, treatment (specialist use only)

- By mouth (as desmopressin acetate)

Neonate initially 1–4 micrograms 2–3 times daily, adjusted according to response

Child 1 month–2 years initially 10 micrograms 2–3 times daily, adjusted according to response (range 30–150 micrograms daily)

Child 2–12 years initially 50 micrograms 2–3 times daily, adjusted according to response (range 100–800 micrograms daily)

Child 12–18 years initially 100 micrograms 2–3 times daily, adjusted according to response (range 0.2–1.2 mg daily)

- Sublingually (as desmopressin base)

Child 2–18 years initially 60 micrograms 3 times daily, adjusted according to response (range 40–240 micrograms 3 times daily)

- Intranasally (as desmopressin acetate)

Neonate initially 100–500 nanograms, adjusted according to response (range 1.25–10 micrograms daily in 1–2 divided doses)

Child 1 month–2 years initially 2.5–5 micrograms 1–2 times daily, adjusted according to response

Child 2–12 years initially 5–20 micrograms 1–2 times daily, adjusted according to response

Child 12–18 years initially 10–20 micrograms 1–2 times daily, adjusted according to response
6.5.2 Posterior pituitary hormones and antagonists

Desmopressin (continued)

- By subcutaneous or intramuscular injection
  
  **Neonate** initially 100 nanograms once daily, adjusted according to response (intramuscular route only)

  **Child 1 month–12 years** initially 400 nanograms once daily, adjusted according to response

  **Child 12–18 years** initially 1–4 micrograms once daily, adjusted according to response

- By intravenous injection over 20 minutes or by
  
  **Intranasally**

  **Sublingually** (as desmopressin base)

- By intravenous injection over 20 minutes or by subcutaneous injection
  
  **Child 2–18 years** 300 nanograms/kg as a single dose; blood sampled after 20 minutes for fibrinolytic activity

- By intravenous infusion over 20 minutes or by subcutaneous injection
  
  **Child 1 month–18 years** 300 nanograms/kg as a single dose immediately before surgery or after trauma; may be repeated at intervals of 12 hours if no tachycardia

- Intranasally
  
  **Child 1–18 years** 4 micrograms/kg as a single dose, for pre-operative use give 2 hours before procedure

- Intranasally
  
  **Child 1 month–1 year** 10 micrograms (empty bladder at time of administration and restrict fluid intake to 50% at next 2 feeds to avoid fluid overload)

  **Child 1–15 years** 20 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

  **Child 15–18 years** 40 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

- By subcutaneous or intramuscular injection
  
  **Child 1 month–1 year** 400 nanograms (empty bladder at time of administration and restrict fluid intake to 50% at next 2 feeds to avoid fluid overload)

  **Child 1–18 years** 2 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

Primary nocturnal enuresis (if urine concentrating ability normal) (specialist use only)

- By mouth
  
  (as desmopressin acetate)

- By intranasally
  
  **Child 5–18 years (preferably over 7 years)** 120 micrograms at bedtime, increased to 240 micrograms at bedtime only if lower dose not effective (important; see also Cautions); reassess after 3 months by withdrawing treatment for at least 1 week

- Sublingually
  
  (as desmopressin base)

- By intravenous injection over 20 minutes or by subcutaneous injection
  
  **Child 2–18 years** 300 nanograms/kg as a single dose; blood sampled after 20 minutes for fibrinolytic activity

Fibrinolytic response testing (specialist use only)

- By intravenous injection over 20 minutes or by subcutaneous injection
  
  **Child 2–18 years** 300 nanograms/kg as a single dose; blood sampled after 20 minutes for fibrinolytic activity

Mild to moderate haemophilia and von Willebrand’s disease (specialist use only)

- By intravenous infusion over 20 minutes or by subcutaneous injection
  
  **Child 1 month–18 years** 300 nanograms/kg as a single dose immediately before surgery or after trauma; may be repeated at intervals of 12 hours if no tachycardia

- Intranasally
  
  **Child 1–18 years** 4 micrograms/kg as a single dose, for pro-operative use give 2 hours before procedure

Renal function testing (specialist use only)

- Intranasally
  
  **Child 1 month–1 year** 10 micrograms (empty bladder at time of administration and restrict fluid intake to 50% at next 2 feeds to avoid fluid overload)

  **Child 1–15 years** 20 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

  **Child 15–18 years** 40 micrograms (empty bladder at time of administration and restrict fluid intake to 500 mL from 1 hour before until 8 hours after administration to avoid fluid overload)

Desmopressin acetate (Non-proprietary) [\textsuperscript{\textregistered}]

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 Presinex\textsuperscript{\textregistered}

Note Children requiring dose of less than 10 micrograms should be given DDAVP\textsuperscript{\textregistered} intranasal solution

DDAVP\textsuperscript{\textregistered} (Ferring) [\textsuperscript{\textregistered}]

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

Note Tablets may be crushed

Sublingual tablets, (DDAVP\textsuperscript{\textregistered} 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 notes above

Intranasal solution, desmopressin acetate 100 micrograms/mL. Net price 2.5-mL dropper bottle and catheter = £9.72. Counselling, fluid intake, see above

Administration May be diluted with sodium chloride 0.9% to a concentration of 10 micrograms/mL

Injection, desmopressin acetate 4 micrograms/mL. Net price 1-mL amp = £1.10

Administration May be administered orally [unlicensed]; for intravenous infusion, to be diluted to a concentration not less than 1 microgram/mL as adheres to surfaces if very dilute; for higher doses used in mild to moderate haemophilia and von Willebrand’s disease may be diluted with 30–50 mL sodium chloride 0.9% intravenous infusion

Desmotabs\textsuperscript{\textregistered} (Ferring) [\textsuperscript{\textregistered}]

Tablets, both scored, desmopressin acetate 200 micro- grams, net price 30-tab pack = £30.34. Counselling, fluid intake, see above

Note tablets may be crushed

Desmomelt\textsuperscript{\textregistered} (Ferring) [\textsuperscript{\textregistered}]

Sublingual 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\textsuperscript{\textregistered} (Ferring) [\textsuperscript{\textregistered}]

Nasal spray, desmopressin acetate 10 micrograms/ metered spray. Net price 6-mL unit (60 metered
**DESMOPRESSIN (continued)**

Sprays) = £26.04. Counselling, fluid intake, see above.

**Note** Children requiring dose of less than 10 micrograms should be given DDAVP intranasal solution.

Low dose Desmospray®

Nasal spray, desmopressin acetate 2.5 micrograms/metered spray

Available from Ferring on a named-patient basis.

Octim® (Ferring) POM

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.

Administration for intravenous infusion dilute with 50 mL of Sodium Chloride 0.9% and give over 20 minutes.

Glypressin® (Ferring) POM

Injection, terlipressin, powder for reconstitution. Net price 1-mg vial with 5 mL diluent = £19.44 (hosp. only).

**TERLIPRESSIN**

**Cautions** see under Vasopressin.

**Contra-indications** see under Vasopressin.

**Side-effects** see under Vasopressin, but effects milder.

**Licensed use** unlicensed for use in children.

**Indication and dose**

Adjunct in acute massive haemorrhage of gastro-intestinal tract or oesophageal varices (specialist use only)

- By intravenous injection

  Child 12–18 years initially 2 mg then 1–2 mg every 4–6 hours until bleeding is controlled; max. duration of treatment 72 hours.

**6.6 Drugs affecting bone metabolism**

**6.6.1 Calcitonin**

Calcitonin is involved with parathyroid hormone in the regulation of bone turnover and hence in the maintenance of calcium balance and homeostasis. 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).

**6.6.2 Bisphosphonates**

The two main disorders of bone metabolism that occur in children are rickets and osteoporosis. The two most common forms of rickets are Vitamin D deficiency rickets (section 9.6.4) and hypophosphataemic rickets (section 9.5.2). See also calcium (section 9.5.1.1).

**Osteoporosis**

Osteoporosis in children may be primary (e.g. osteogenesis imperfecta and idiopathic juvenile osteoporosis), or secondary (e.g. due to inflammatory disorders, immobilisation, or corticosteroids); specialist management is required.

**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.

**6.6.1 Calcitonin**

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**CALCITONIN (SALMON)/SALCATONIN**

**Cautions** history of allergy (skin test advised); renal impairment; heart failure; children—use for short periods only and monitor bone growth

**Pregnancy** avoid unless essential, toxicity in animal studies.

**Breast-feeding** avoid unless essential, may inhibit lactation.

**Contra-indications** hypocalcaemia.
6.6.2 Bisphosphonates

Bisphosphonates are adsorbed on to hydroxyapatite crystals in bone, slowing both their rate of growth and dissolution, and therefore reducing the rate of bone turnover.

A bisphosphonate such as disodium pamidronate is used in the management of severe forms of osteogenesis imperfecta and other causes of osteoporosis in children to reduce the number of fractures; the long-term effects of bisphosphonates in children have not been established. Single doses of bisphosphonates are also used to manage hypercalcaemia (section 9.5.1.2). Treatment should be initiated under specialist advice only.

**Osteonecrosis of the jaw** Osteonecrosis of the jaw has been reported in adult 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 children 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**

**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; 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)

**Renal impairment** avoid if estimated glomerular filtration rate is less than 35 mL/minute/1.73 m²

**Contra-indications** abnormalities of oesophagus and other factors which delay emptying (e.g. stricture or achalasia), hypocalcaemia,

**Pregnancy** manufacturer advises avoid

**Breast-feeding** no information available

**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 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
Contra-indications
oesophageal abnormalities and other
side-effects

Contra-indications
cardiac disease; previous thyroid sur-

Cautions
propylidenediphosphonate disodium (APD)

Licensed use
not licensed for use in children

Indication and dose
See notes above, specialist use only

Counselling
Swallow the tablets whole with a full glass of
water on an empty stomach at least 30 minutes
before breakfast (and any other oral medication); stand or sit
upright for at least 30 minutes and do not lie down until
after eating breakfast. Do not take the tablets at bedtime
or before rising.

Fosamax® (MSD) Tablets, alendronic acid (as sodium alendronate)
10 mg, 28-tab pack = £23.12. Counselling, admin-
istration

Fosamax® Once Weekly (MSD) Tablets, alendronic acid (as sodium alendronate)
70 mg, net price 4-tab pack = £22.80. Counselling, admin-
istration

DISODIUM PAMIDRONATE

Disodium pamidronate was formerly called aminohydroxy-
propylidenediphosphonate disodium (APD)

Cautions
cardiac disease; previous thyroid sur-
gery (risk of hypocalcaemia); monitor serum
electrolytes, calcium, and phosphate—possibility of
convulsions due to electrolyte changes; ensure
adequate hydration; 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)

Hepatic impairment
manufacturer advises caution in severe impairment—no information avail-
able

Renal impairment
monitor renal function in renal disease or predisposition to renal impairment
(e.g. in tumour-induced hypercalcaemia)

Skilled tasks
Patients should be warned against driving,
cycling, or performing skilled tasks immediately after
treatment (somnolence or dizziness can occur)

Contra-indications
Pregnancy
manufacturer advises avoid—toxicity in animal studies

Breast-feeding
manufacturer advises avoid

Side-effects
hypophosphataemia, transient rise in body temperature, fever and influenza-like
symptoms (sometimes accompanied by malaise, rigors, fatigue, and flushes); arthralgia, myalgia,
bone pain, nausea, vomiting, headache, lymphocytopenia, hypomagnesaemia; rarely muscle
cramps, anorexia, abdominal pain, diarrhea, constipation, dyspepsia, agitation, confusion,
dizziness, insomnia, somnolence, lethargy, anaemia, leucopenia, hypotension or hypertension,
rash, pruritus, symptomatic hypocalcaemia (paraesthesia, tetany), hyperkalaemia or hypo-
kalaemia, hypernatraemia; osteonecrosis (see
notes above); isolated cases of seizures, halluci-
nations, thrombocytopenia, haematuria, acute
renal failure, deterioration of renal disease, con-
nectivitis and other ocular symptoms; atrial fibrillation, and reactivation of herpes simplex
and zoster also reported; also local reactions at
injection site

Licensed use
not licensed for use in children

Indication and dose
See notes above, specialist use only

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® (Novartis) Injection, powder for reconstitution, disodium
pamidronate, for use as an infusion. Net price 15-
mg vial = £29.83; 30-mg vial = £59.66; 90-mg vial = £170.45 (all with diluent)

RISEDRONATE SODIUM

Cautions
oesophageal abnormalities and other factors which delay transit or emptying (e.g. stricture or achalasia—see also under Side-
effects); correct hypocalcaemia before starting, correct other disturbances of bone and mineral
metabolism (e.g. Vitamin-D deficiency) at onset of
treatment; consider preventive dental treat-
ment before initiating bisphosphonate (risk of
osteonecrosis of the jaw, see notes above);

interactions:

Appendix 1 (bisphosphonates)

Renal impairment
avoid if estimated glomerular filtration rate is less than 30 mL/minute/1.73 m²

Contra-indications
hypocalcaemia (see Cautions above)

Pregnancy
manufacturer advises avoid

Breast-feeding
manufacturer advises avoid

Side-effects
gastro-intestinal effects (including abdominal pain, diarrhea, constipation); dizziness, headache; influenza-like
symptoms, musculoskeletal pain; rarely oeso-
ophageal stricture, oesophagitis, oesophageal
ulcer, dysphagia, gastritis, duodenitis, glossitis,
peripheral oedema, weight loss, myasthenia,
arthralgia, apnoea, bronchitis, sinusitis, rash,
occuria, amblyopia, corneal lesion, dry eye, tin-
nitus, iritis, very rarely hypersensitivity reactions
including angioedema, osteonecrosis (see notes
above)

Licensed use
not licensed for use in children

Indication and dose
See notes above, specialist use only

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)

SODIUM CLODRONATE

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); interactions: Appendix 1 (bisphosphonates) Renal impairment use half normal dose if estimated glomerular filtration rate 10–30 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²

Contra-indications acute gastro-intestinal inflammatory conditions

Pregnancy manufacturer advises avoid

Breast-feeding no information available

Side-effects nausea, diarrhoea; skin reactions; bronchospasm; very rarely osteonecrosis (see notes above)

Licensed use not licensed for use in children

Indication and dose

See notes above, specialist use only

Counselling Avoid food for 1 hour before and after oral treatment, particularly calcium-containing products e.g. milk, also avoid iron and mineral supplements and antacids; maintain adequate fluid intake

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

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® tablets, f/c, scored, sodium clodronate 520 mg. Net price 60-tab pack = £161.99. Label: 10, patient information leaflet., Counselling, food and calcium

6.7 Other endocrine drugs

6.7.1 Bromocriptine and other dopaminergic drugs

Classification not used in BNF for Children

6.7.2 Drugs affecting gonadotrophins

Classification not used in BNF for Children. See section 6.4.3 for use in precocious puberty.

6.7.3 Metyrapone

Metyrapone is a competitive inhibitor of 11β-hydroxylation 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 is used as a test of anterior pituitary function.

Most types of Cushing’s syndrome are treated surgically. Metyrapone may be useful to control the symptoms of the disease or to prepare the child for surgery. The
dosages used are either low, and tailored to cortisol production, or high, in which case corticosteroid replacement therapy is also needed.

**Ketoconazole** (section 5.2) is also used by specialists for the management of Cushing’s syndrome [unlicensed indication].

**Metyrapone**

**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)

**Skilled tasks** Drowsiness may affect the performance of skilled tasks (e.g. driving)

**Contra-indications**
- adrenocortical insufficiency (see Cautions)
- Pregnancy contra-indicated
- Breast-feeding contra-indicated

**Side-effects**
- occasional nausea, vomiting, dizziness, headache, hypotension, sedation; rarely abdominal pain, allergic skin reactions, hypoadrenalism, hirsutism

**Licensed use**
- licensed for use in children

**Indication and dose**

**Differential diagnosis of ACTH-dependent Cushing’s syndrome**

- **By mouth**
  - **Child 1 month–18 years** 15 mg/kg (or 300 mg/m²) every 4 hours for 6 doses; minimum dose 250 mg every 4 hours, max. 750 mg every 4 hours

**Management of Cushing’s syndrome**

- **By mouth**
  - Range 250 mg–6 g daily, adjusted according to cortisol production; see notes above

**Metopirone** (Alliance)

Capsules, ivory, metyrapone 250 mg. Net price 100-tab pack = £41.44. Label: 21, counselling, driving

**Somatomedins**

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 with severe primary insulin-like growth factor-I deficiency.

**Mecasermin**

(Recombinant human insulin-like growth factor-I; rhIGF-I)

**Cautions**
- correct hypothyroidism before initiating treatment; diabetes mellitus (adjustment of anti-diabetic 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
  - manufacturer advises avoid unless essential; contraception advised in women of child-bearing potential

**Contra-indications**
- evidence of tumour activity (discontinue treatment)
- Breast-feeding
  - manufacturer advises avoid

**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); 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)

**Pregnancy**
- manufacturer advises avoid unless essential; contraception advised in women of child-bearing potential

**Contra-indications**
- evidence of tumour activity

**Indication and dose**

**Growth failure in children with severe primary insulin-like growth factor-I deficiency**

- **By subcutaneous injection**
  - **Child 2–18 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**
- 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. 3)
7 Obstetrics, gynaecology, and urinary-tract disorders

7.1 Drugs used in obstetrics

This section is not included in BNF for Children. See BNF for management of obstetrics.

For the management of ductus arteriosus, see section 2.14

7.2 Treatment of vaginal and vulval conditions

7.2.1 Preparations for vaginal and vulval changes

7.2.2 Vaginal and vulval infections

Pre-pubertal girls may be particularly susceptible to vulvovaginitis. Barrier preparations (section 13.2.2) applied after cleansing can be useful when the symptoms are due to non-specific irritation, but systemic drugs are required in the treatment of bacterial infection (section 5.1) or threadworm infestation (section 5.5.1). Intravaginal preparations, particularly those that require the use of an applicator, are not generally suitable for young girls; topical preparations may be useful in some adolescent girls.

In older girls symptoms are often restricted to the vulva, but infections almost invariably involve the vagina, which should also be treated; treatment should be as for adults (see BNF section 7.2).

7.2.1 Preparations for vaginal and vulval changes

Topical oestrogen creams containing estriol 0.01% (Ortho-Gynest®) are used in the treatment of labial adhesions (for details of preparation, see BNF section 7.2.1); treatment is usually restricted to symptomatic cases. Estriol cream should be applied to the adhesions once or twice daily for 2–6 weeks; adhesions may recur following treatment.
Vaginal and vulval infections

Effective specific treatments are available for the common vaginal infections.

Fungal infections

Vaginal fungal infections are not normally a problem in younger girls but can occur in adolescents. *Candidal vulvitis* can be treated locally with cream but is almost invariably associated with vaginal infection which should also be treated. *Vaginal candidiasis*, rare in girls before puberty, can be treated with antifungal pessaries or cream inserted high into the vagina (including during menstruation), however, these are not recommended for pre-pubertal girls and treatment with an external cream may be more appropriate. Single-dose intravaginal preparations offer an advantage when compliance is a problem. Local irritation can occur on application of vaginal antifungal products.

**Imidazole** drugs (clotrimazole, econazole, and miconazole) are effective against candida in short courses of 1 to 3 days according to the preparation used; treatment can be repeated if initial course fails to control symptoms or if symptoms recur. Vaginal applications may be supplemented with antifungal cream for vulvitis and to treat other superficial sites of infection.

Oral treatment of vaginal infection with fluconazole (section 5.2) may be considered for girls post-puberty.

**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. There is limited absorption of imidazoles from the skin and vagina. Oral antifungal treatment should be avoided during pregnancy.

**Recurrent vulvovaginal candidiasis** Recurrent vulvovaginal candidiasis is very rare in children, but can occur if there are predisposing factors such as antibiotic therapy, pregnancy, diabetes mellitus, and possibly oral contraceptive use. Reservoirs of infection can 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 sexual 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 suitable for older children [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.

**PREPARATIONS FOR VAGINAL AND VULVAL CANDIDIASIS**

*Note* Intravaginal preparations, particularly those that require use of an applicator, should be avoided in young girls unless there is no other alternative.

**Side-effects** occasional local irritation

**Licensed use** consult product literature for the licensing status of individual preparations

**Indication and dose** See notes above.

**Clotrimazole** (Non-proprietary)

| Cream (topical), clotrimazole 1% | net price 20 g = £1.92; 50 g = £3.84 |
| Condoms: effect on latex condoms and diaphragms not yet known |

**Pessary, clotrimazole 500 mg, net price 1 pessary with applicator = £3.16**

**Dose**

- Insert 1 pessary at night as a single dose; can be repeated once if necessary

**Canesten®** (Bayer Consumer Care)

| Cream (topical), clotrimazole 1% | Net price 20 g = £2.14; 50 g = £3.80 |
| Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates |
| Condoms: damages latex condoms and diaphragms |

**Dose**

- Apply to anogenital area 2–3 times daily
Thrush Cream (topical), clotrimazole 2%. Net price 20 g = £3.99  
**Excipients** include benzyl alcohol, cetostearyl alcohol, polysorbates  
**Condoms:** damages latex condoms and diaphragms  
**Dose**  
Apply to anogenital area 2–3 times daily

Vaginal cream (10% VC*) clotrimazole 10%. Net price 5-g applicator pack = £5.62  
**Excipients** include benzyl alcohol, cetostearyl alcohol, polysorbates  
**Condoms:** damages latex condoms and diaphragms  
**Dose**  
Insert 5 g at night as a single dose; may be repeated once if necessary  
**Note** Brands for sale to the public include Canesten®  
Internal Cream

Vaginal cream (10% VC®) clotrimazole 10%. Net price 5-g applicator pack = £5.62  
**Excipients** include benzyl alcohol, cetostearyl alcohol, polysorbates  
**Condoms:** damages latex condoms and diaphragms  
**Dose**  
Insert 5 g at night as a single dose; may be repeated once if necessary

**Note** Brands for sale to the public include Canesten®, Clotrimazole 10% Ointment

**Other infections**

Trichomonal infections commonly involve the lower urinary tract as well as the genital system and need systemic treatment with metronidazole (section 5.1.11) or tinidazole (section 5.4.2).

Bacterial infections with Gram-negative organisms are particularly common in association with gynaecological operations and trauma. Metronidazole is effec-
tive 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, famciclovir, 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 for systemic preparations, and section 13.10.3 for topical preparations.

**PREPARATIONS FOR OTHER VAGINAL INFECTIONS**

**Dalacin® (Pharmacia)**
- Cream, clindamycin 2% (as phosphate). Net price 40-g pack with 7 applicators = £10.86
- Excipients include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol
- Contraindications: damages latex condoms and diaphragms
- Side-effects: irritation, cervicitis and vaginitis; poorly absorbed into the blood—very low likelihood of systemic effects (section 5.1.6)
- Licensed use: Not licensed for use in pre-pubertal children

**Dose**
- **Bacterial vaginosis**
  - Insert 5-g applicatorful at night for 3–7 nights

**Zidoval® (3M)**
- Vaginal gel, metronidazole 0.75%. Net price 40-g pack with 5 applicators = £4.31
- Excipients include disodium edetate, hydroxybenzoates (parabens), propylene glycol
- Contraindications: 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
- Licensed use: Not licensed for use in pre-pubertal children

**Dose**
- **Bacterial vaginosis**
  - Insert 5-g applicatorful at night for 5 nights

### 7.3 Contraceptives

#### 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 dysmenorrhoea and menorrhagia;
- reduced incidence of premenstrual 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.

The Fraser Guidelines¹ should be followed when prescribing contraception for women under 16 years. The UK Medical Eligibility Criteria for Contraceptive Use (available at [www.ffprhc.org.uk](http://www.ffprhc.org.uk)) is published by The Faculty of Sexual and Reproductive Healthcare; it categorizes the risks of using contraceptive methods with pre-existing medical conditions.

**Hormonal contraception** is the most effective method of fertility control, but has major and minor side-effects, especially for certain groups of women. Hormonal contraception should only be used by adolescents after menarche.

**Intra-uterine devices** are a highly effective method of contraception but may produce undesirable local side-effects. They may be used in women of all ages irrespective of parity but are less appropriate 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.

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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](http://www.dh.gov.uk)
Combined oral contraceptives containing a fixed amount of 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 and a vaginal ring, both containing an oestrogen with a progestogen are 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.
- **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 norelgestromin is combined with ethinylestradiol in a transdermal patch.

The vaginal contraceptive ring contains the progestogen etonogestrel combined with ethinylestradiol.

**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 100 000 women per year of use. The absolute risk of venous thromboembolism in women using a combined oral contraceptive containing drospirenone is the same range as that for users of combined oral contraceptives containing other progestogens, including levonorgestrel. The risk of venous thromboembolism with vaginal ring use compared to the risk with other combined hormonal contraceptives is unknown.

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, or vaginal ring 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, reapply 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 contra-
ceptive 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’, the day after day 28; no
additional contraception is required.

**Expulsion, delayed insertion or removal, or broken vaginal ring**

If the vaginal ring is expelled for less than 3 hours, rinse the ring with cool water and reinser
immediately; no additional contraception is needed.

If the ring remains outside the vagina for more than 3 hours or if the user is not
aware when the ring was expelled, contraceptive protection may be reduced:

- if ring expelled during week 1 or 2 of cycle, rinse ring with cool water and
  reinser; use additional precautions (barrier methods) for next 7 days
- if ring expelled during week 3 of cycle, either insert a new ring to start a new
cycle or allow a withdrawal bleed and insert a new ring no later than 7 days
  after ring was expelled; latter option only available if ring was used continu-
osly for at least 7 days prior to expulsion

If insertion of a new ring at the start of a new cycle is delayed, contraceptive
protection is lost. A new ring should be inserted as soon as possible; additional precautions (barrier methods) should be used for the first 7 days of the new cycle. If intercourse occurred during the extended ring-free interval, pregnancy should be considered.

No additional contraception is required if the removal of the ring is delayed by up to 1 week (4 weeks of continuous use). The 7-day ring-free interval should be observed and subsequently a new ring should be inserted. Contraceptive protection may be reduced with continuous use of the ring for more than 4 weeks—pregnancy should be ruled out before inserting a new ring.

If the ring breaks during use, remove it and insert a new ring immediately; additional precautions (barrier methods) should be used for the first 7 days of the new cycle.

**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 and vaginal rings 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 or vaginal ring use, a new treatment cycle should be started immediately without a patch-free or ring-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. ampicillin, doxycycline) may reduce the efficacy of combined oral contraceptives by impairing the bacterial flora responsible for recycling ethinylestradiol 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 and vaginal rings. Additional contraceptive precautions are recommended during concomitant use and for 7 days after discontinuation of an antibacterial that is not enzyme-inducing (except tetracycline with contraceptive patch use, and amoxicillin or doxycycline with vaginal ring use). If concomitant administration runs beyond the 3 weeks of patch or vaginal ring use, a new treatment cycle should be started immediately without a patch-free or ring-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 or vaginal ring 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 should be stopped (pending investigation and treatment), if any of the following occur:

- 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;
- very high blood pressure;
- 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).

**COMBINED HORMONAL CONTRACEPTIVES**

**Cautions** see notes above; also risk factors for venous thromboembolism (see below and also notes above), arterial disease and migraine, see below; personal or family history of hypertriglyceridaemia (increased risk of pancreatitis); hyperprolactinaemia (seek specialist advice); history of severe depression especially if induced by hormonal contraceptive; undiagnosed breast mass; gene mutations associated with breast cancer (e.g. BRCA 1); sickle-cell disease; inflammatory bowel disease including Crohn’s disease; reduced efficacy of contraceptive patch in women with body-weight ≥ 90 kg; interactions: see above and Appendix 1 (oestrogens, progestogens)

**Risk factors for venous thromboembolism** See also notes above. Use with caution if any of 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 avoid if known prothrombotic coagulation abnormality e.g. factor V Leiden or antiphospholipid antibodies (including lupus anticoagulant));

- obesity—caution if overweight according to BMI (adjusted for age and gender), avoid if obese;

- long-term immobilisation e.g. in a wheelchair (avoid if confined to bed or leg in plaster cast);

- history of superficial thrombophlebitis;

- smoking.

**Risk factors for arterial disease** Use with caution if any one of 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);
7.3.1 Combined hormonal contraceptives (continued)

- diabetes mellitus (avoid if diabetes complications present);
- hypertension (avoid if blood pressure very high);
- smoking (avoid if smoking 40 or more cigarettes daily);
- obesity—caution if overweight according to BMI (adjusted for age and gender), avoid if obese;
- migraine without aura (avoid if migraine with aura (focal symptoms), or severe migraine frequently lasting over 72 hours despite treatment, or migraine treated with ergot derivatives).

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-indications see notes above; also 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 head- aches; systemic lupus erythematosus; acne por- phyrina (section 9.8.2); gallstones; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration); history of haemolytic uraemic syndrome or his- tory during pregnancy of chorea, pempigoid gestations; history of breast cancer but can be used after 5 years if no evidence of disease and non-hormonal methods unacceptable; undiag- nosed vaginal bleeding

Hepatic impairment avoid in active liver disease including disorders of hepatic excretion (e.g. Dubin-Johnson or Rotor syndromes), infective hepatitis (until liver function returns to normal), liver tumours, and if history of pruritus or chole- static jaundice during pregnancy

Pregnancy avoid but epidemiological evidence for combined oral contraceptives suggests no harmful effects on fetus

Breast-feeding avoid until weaning or for 6 months after birth (adverse effects on lactation)

Side-effects see notes above; also nausea, vomi- ting, abdominal cramps, changes in body-weight, liver impairment, hepatic tumours; fluid reten- tion, 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, chorea, nervousness, irritability; changes in libido, breast tenderness, enlargement, and secretion; reduced menstrual loss, ‘spotting’ in early cycles, absence of withdrawal bleeding, amenorrhoea after dis- continuation, changes in vaginal discharge, cer- vical erosion; contact lenses may irritate, visual disturbances; leg cramps; skin reactions, chloas- ma, photosensitivity; rarely gallstones and sys- temic 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 and vaginal rings 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 endo- metrium

Licensed use consult product literature for the licensing status of individual preparations

Indication and dose

Contraception, menstrual symptoms (section 6.4.1.2)

- 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) pre- parations, 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 differ- ent progestogen 21-day combined preparations: con- tinue 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.

Licensed use consult product literature for the licensing status of individual preparations

Indication and dose

Contraception, menstrual symptoms (section 6.4.1.2)

- 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) pre- parations, 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 differ- ent progestogen 21-day combined preparations: con- tinue 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.
COMBINED HORMONAL CONTRACEPTIVES (continued)

- **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 start immediately; no additional contraception required if started immediately. 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.

- **By vagina**
  Insert ring into vagina on day 1 of cycle and leave in for 3 weeks; remove ring on day 22; subsequent courses repeated after 7-day ring-free interval (during which withdrawal bleeding occurs).
  **Note**: If ring inserted later than day 1, additional precaution (abstinence or barrier methods) should be used for the next 7 days.

- **Changing from combined hormonal contraception**
  Insert the ring at the latest on the day after the usual tablet-free, patch-free, or placebo-tablet interval. If previous contraceptive used correctly and pregnancy unlikely, can switch to ring on any day of cycle.

- **Changing from progestogen-only method**
  From an implant or intra-uterine progestogen-only device, insert ring on the day implant or intra-uterine progestogen-only device removed; from an injection, insert ring when injection due; from oral preparation, first ring may be inserted on any day after stopping pill. For all methods additional precautions (barrier methods) should be used concurrently for first 7 days.

- **After first trimester abortion**
  Start immediately.

- **After childbirth (not breast-feeding) or second trimester abortion**
  Start 4 weeks after birth or abortion; if started later than 4 weeks after birth or abortion additional precautions (barrier methods) should be used for first 7 days.

**Low strength (oral)**

- **Ethinylestradiol with Norethisterone**
  **Loestrin 20** (Galen) (HWI)
  Tablets, blue, norethisterone acetate 1 mg, ethinylestradiol 20 micrograms. Net price 3 × 21-tab pack = £2.70.
  **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 Desogestrel**
  **Mercilon** (Organon) (HWI)
  **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 Gestodene**
  **Femodette** (Schering Health) (HWI)
  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) (HWI)
  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 (vaginal)**

- **Ethinylestradiol with Etonogestrel**
  **NuvaRing** (Organon) (HWI)
  Vaginal ring, releasing ethinylestradiol approx. 15 micrograms/24 hours and etonogestrel approx. 120 micrograms/24 hours, net price 3-ring pack = £27.00. Counselling, administration.
  **Dose**
  1 ring to be inserted into the vagina for 3 weeks, removed on day 22; subsequent courses repeated after 7-day ring-free interval (during which withdrawal bleeding occurs); for starting routines see under Dose above.

  **Counselling**
  The presence of the ring should be checked regularly. In case of expulsion see Expulsion, Delayed Insertion or Removal, or Broken Vaginal Ring, p. 477.

**Standard strength (oral)**

- **Ethinylestradiol with Levonorgestrel**
  **Logynon** (Schering Health) (HWI)
  6 light brown tablets, ethinylestradiol 30 micrograms, levonorgestrel 50 micrograms; 5 white tablets, ethinylestradiol 40 micrograms, levonorgestrel 75 micrograms;
### Combined Hormonal Contraceptives (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Logynon ED</strong></td>
<td>(Schering Health)</td>
<td>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.</td>
<td>£2.28</td>
</tr>
<tr>
<td><strong>Microgynon 30</strong></td>
<td>(Schering Health)</td>
<td>Tablets, s/c, levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms.</td>
<td>£3.80</td>
</tr>
<tr>
<td><strong>Microgynon 30 ED</strong></td>
<td>(Schering Health)</td>
<td>Tablets, beige, levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms, white inactive tablets.</td>
<td>£2.69</td>
</tr>
<tr>
<td><strong>Ovranette</strong></td>
<td>(Wyeth)</td>
<td>Tablets, levonorgestrel 150 micrograms, ethinylestradiol 30 micrograms.</td>
<td>£2.29</td>
</tr>
<tr>
<td><strong>Brevinor</strong></td>
<td>(Pharmacia)</td>
<td>Tablets, blue, norethisterone 500 micrograms, ethinylestradiol 35 micrograms.</td>
<td>£1.99</td>
</tr>
<tr>
<td><strong>Loestrin 30</strong></td>
<td>(Galen)</td>
<td>Tablets, pale green, norethisterone acetate 1.5 mg, ethinylestradiol 30 micrograms.</td>
<td>£3.90</td>
</tr>
<tr>
<td><strong>Norimin</strong></td>
<td>(Pharmacia)</td>
<td>Tablets, norethisterone 1 mg, ethinylestradiol 35 micrograms.</td>
<td>£2.28</td>
</tr>
<tr>
<td><strong>Ovysmen</strong></td>
<td>(Janssen-Cilag)</td>
<td>Tablets, norethisterone 500 micrograms, ethinylestradiol 35 micrograms.</td>
<td>£1.58</td>
</tr>
<tr>
<td><strong>Synphase</strong></td>
<td>(Pharmacia)</td>
<td>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.</td>
<td>£1.20</td>
</tr>
<tr>
<td><strong>TriNovum</strong></td>
<td>(Janssen-Cilag)</td>
<td>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.</td>
<td>£2.89</td>
</tr>
</tbody>
</table>

#### Ethinylestradiol with Norethisterone

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Dose</th>
<th>Price</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BiNovum</strong></td>
<td>(Janssen-Cilag)</td>
<td>7 white tablets, ethinylestradiol 35 micrograms, norethisterone 500 micrograms; 14 peach tablets, ethinylestradiol 35 micrograms, norethisterone 1mg.</td>
<td>£2.08</td>
</tr>
<tr>
<td><strong>Ovysmen</strong></td>
<td>(Janssen-Cilag)</td>
<td>Tablets, norethisterone 1 mg, ethinylestradiol 35 micrograms.</td>
<td>£2.29</td>
</tr>
<tr>
<td><strong>TriNovum</strong></td>
<td>(Janssen-Cilag)</td>
<td>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.</td>
<td>£2.89</td>
</tr>
</tbody>
</table>
7.3.1 Combined hormonal contraceptives

### Ethinylestradiol with Norgestimate

**Cilest** (Janssen-Cilag)

- Tablets, blue, norgestimate 250 micrograms, ethinylestradiol 35 micrograms. Net price 3 x 21-tab pack = £5.97, 6 x 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

**Marvelon** (Organon)

- Tablets, desogestrel 150 micrograms, ethinylestradiol 30 micrograms. Net price 3 x 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)

- Tablets, s/c, yellow, drospirenone 3 mg, ethinylestradiol 30 micrograms. Net price 3 x 21-tab pack = £14.70

**Cautions** use with care if increased concentration of plasma-potassium might be hazardous; renal impairment—avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

**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

**Katya 30/75** (Stragen)

- Tablets, s/c, gestodene 75 micrograms, ethinylestradiol 30 micrograms. Net price 3 x 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

### Mestranol with Norethisterone

**Norinyl-1** (Pharmacia)

- Tablets, norethisterone 1 mg, mestranol 50 micrograms. Net price 3 x 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)

### Standard Strength (Transdermal)

### Ethinylestradiol with Norelgestromin

**Eva** (Janssen-Cilag)

- Patches, self-adhesive (releasing ethinylestradiol approx. 33.9 micrograms/24 hours and norelgestromin approx. 203 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
7.3.2 Progestogen-only contraceptives

7.3.2.1 Oral progestogen-only contraceptives

Oral progestogen-only preparations may offer a suitable alternative when oestrogens are contra-indicated (including those patients with venous thrombosis or a past history or predisposition to venous thrombosis), but have a higher failure rate than combined preparations. They are suitable 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. 478 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 (12 hours for Cerazette® 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. 490) 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’)*

**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; interactions: see notes above and Appendix 1 (progestogens)

**Hepatic impairment** caution in active liver disease, recurrent cholestatic jaundice, and history of jaundice in pregnancy; avoid in liver tumour

**Breast-feeding** progestogen-only contraceptives do not affect lactation—start 3 weeks after birth or later

**Other conditions** The product literature advises caution in patients with history of thromboembolism, hypertension,
ORAL PROGESTOGEN-ONLY CONTRACEPTIVES

(continued)

Cerazette® (Organon) Tablets, f/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

Norgeston® (Bayer) Tablets, s/c, levonorgestrel 30 micrograms. Net price 35-tab pack = 98p

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; delaying the first injection until 6 weeks after the birth may minimise bleeding problems. 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). The manufacturer advises that in women who are breast-feeding, the first dose should be delayed until 6 weeks after the birth — however, evidence suggests no harmful effect to infant if given earlier; the benefits of using medroxyprogesterone acetate in breast-feeding women outweigh any risks

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 system 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.
Intra-uterine progestogen-only device

The progestogen-only intra-uterine system, Mirena®, releases levonorgestrel directly into the uterine cavity. It is used 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).

**INTRA-UTERINE PROGESTOGEN-ONLY SYSTEM**

**Cautions** see notes above; advanced uterine atrophy; not suitable for emergency contraception; **interactions:** see notes above and Appendix 1 (progestogens)

**Hepatic impairment** caution in active liver disease and liver tumour

**Pregnancy** remove system—teratogenicity cannot be excluded

**Breast-feeding** progestogen-only contraceptives do not affect lactation

**Contra-indications** see notes above

**Side-effects** see notes above; also abdominal pain; peripheral oedema; nervousness; salpingitis and pelvic inflammatory disease; pelvic pain, back pain; rarely hirsutism, hair loss, pruritus, migraine, rash

**Licensed use** not licensed for use in women under 18 years

**Indication and dose**

See under preparation

**Mirena®** (Bayer) 

**Intra-uterine system**, T-shaped plastic frame (impregnated with barium sulphate and with threads attached to base) with polydimethylsiloxane reservoir releasing levonorgestrel 20 micrograms/24 hours. Net price = £83.16. Counselling, see patient information leaflet

**Dose**

**Contraception and menorrhagia**

Insert into uterine cavity within 7 days of onset of menstruation (anytime if replacement) or immediately after first-trimester termination by curettage; post-partum insertions should be delayed until 6 weeks after delivery; effective for 5 years
7.3.3 Spermicidal contraceptives

Spermicidal contraceptives are useful additional safeguards but do not give adequate protection if used alone unless fertility is already significantly diminished. They have two components: a spermicide and a vehicle which itself may have some inhibiting effect on sperm activity. They are suitable for use with barrier methods, such as diaphragms or caps; however spermicidal contraceptives are not generally recommended for use with condoms, as there is no evidence of any additional protection compared with non-spermicidal lubricants.

Spermicidal contraceptives are not suitable for use in those with or at high risk of sexually transmitted diseases (including HIV); high frequency use of the spermicide nonoxinol ‘9’ has been associated with genital lesions, which may increase the risk of acquiring these infections.

CSM advice

Products such as petroleum jelly (Vaseline®), baby oil and oil-based vaginal and rectal preparations are likely to damage condoms and contraceptive diaphragms made from latex rubber, and may render them less effective as a barrier method of contraception and as a protection from sexually transmitted diseases (including HIV).

Gygel® (Marlborough)

Gel, nonoxinol ‘9’ 2%, net price 30 g = £4.25
Excipients include hydroxybenzoates (parabens), propylene glycol, sorbic acid
Condoms: No evidence of harm to latex condoms and diaphragms

7.3.4 Contraceptive devices

Intra-uterine devices

The intra-uterine device (IUD) is a suitable contraceptive for women of all ages; however it is less appropriate for those with an increased risk of pelvic inflammatory disease e.g. women under 25 years (see below).

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. 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 under 25 years are at a higher risk of sexually transmitted diseases, and pre-insertion screening (for chlamydia, and depending on sexual history and local prevalence of disease, Neisseria gonorrhoeae) should be performed. If results are unavailable at the time of fitting an intra-uterine device for emergency contraception, appro-
Intra-uterine contraceptive devices should be 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)

Contra-indications 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; 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).

Side-effects uterine or cervical perforation, displacement, expulsion; pelvic infection may be exacerbated, menorrhagia, dysmenorrhoea, allergy; on insertion: pain (alleviated by NSAID (FP)) and bleeding, occasionally epileptic seizure and allergy; exanthematous eruption, eczema, urticaria, urticarial rash, angioedema, anaphylactic shock, vasovagal attack.

Indication and dose

See notes above

Flexi-T 300® (FP)
Intra-uterine device, copper wire, surface area approx. 300 mm² 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 = £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 mm² 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 mm², 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 = £8.00
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 approx. 380 mm², impregnated with barium sulphate for radio-opacity, threads attached to base of vertical stem; easy-loading system, no capsule, net price = £11.70
For minimum uterine length 5 cm; replacement every 5 years (see also notes above)

Multiload® Cu375 (Organon)
Intra-uterine device, as Load® 375, with copper surface area approx. 375 mm² and vertical stem length 3.5 cm, net price = £9.24
For uterine length 6–9 cm; replacement every 5 years (see notes above)

Nova-T® 380 (Schering Health)
Intra-uterine device, copper wire with silver core, surface area approx. 380 mm² 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 = £13.50
For uterine length 6.5–9 cm; replacement every 5 years (see notes above)

T-Safe® CU 380 A (FP)
Intra-uterine device, copper wire, wound on vertical stem of T-shaped plastic carrier with copper collar on the distal portion of each arm, total surface area approx. 380 mm², 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)

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 approx. 380 mm², impregnated with barium sulphate for radio-opacity, thread attached to base of vertical stem; easy-loading system, no capsule, net price = £11.70
For uterine length 6.5–9 cm; replacement every 10 years (see also notes above)
INTRA-UTERINE CONTRACEPTIVE DEVICES (continued)

UT 380 Short® (Durbin)  
Intra-uterine device, copper wire wound on vertical stem of T-shaped plastic carrier, total surface area approx. 380 mm², impregnated with barium sulphate for radio-opacity, thread attached to base of vertical stem; net price = £10.53  
For uterine length 5–7 cm; replacement every 5 years (see also notes above)

UT 380 Standard® (Durbin)  
Intra-uterine device, copper wire, surface area approx. 380 mm², wound on vertical stem of T-shaped plastic carrier, impregnated with barium sulphate for radio-opacity, thread attached to base of vertical stem; net price = £10.53  
For uterine length 6.5–9 cm; replacement every 5 years (see also notes above)

Other contraceptive devices

Rubber contraceptive caps

Type A Contraceptive Pessary  
Opaque rubber, sizes 1 (50 mm), 2 (55 mm), 3 (60 mm), 4 (65 mm), 5 (75 mm), net price = £6.85

Type B Contraceptive Pessary  
Opaque rubber, sizes 22 to 31 mm (rising in steps of 3 mm), net price = £8.46

Type C Contraceptive Pessary  
Opaque rubber, sizes 1 to 3 (42, 48, and 54 mm), net price = £7.26

Silicone contraceptive caps

Silicone Contraceptive Pessary  
Silicone, sizes 22, 26, and 30 mm, net price = £15.00  
Brands include FemCap®

Rubber contraceptive diaphragms

Type A Diaphragm with Flat Metal Spring  
Transparent rubber with flat metal spring, sizes 55–95 mm (rising in steps of 5 mm), net price = £5.78  
Brands include Reflexions®

Type B Diaphragm with Coiled Metal Spring  
Opaque rubber with coiled metal spring, sizes 60–100 mm (rising in steps of 5 mm), net price = £6.59

Type C Arcing Spring Diaphragm  
Opaque rubber with arcing spring, sizes 60–95 mm (rising in steps of 5 mm), net price = £7.49

Silicone contraceptive diaphragms

Type B Diaphragm with Coiled Metal Spring  
Silicone with coiled metal spring, sizes 60–90 mm (rising in steps of 5 mm), net price = £8.35  
Brands include Milex Omniflex®

Type C Arcing Spring diaphragm  
Silicone with arcing spring, sizes 60–90 mm (rising in steps of 5 mm), net price = £8.35  
Brands include Milex Arcing Style®

7.3.5 Emergency 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 anti-emetic 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).

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

Cautions  
see notes above; past ectopic pregnancy; severe malabsorption syndromes; active trophoblastic disease (until return to normal of urine- and plasma-gonadotrophin concentration); interactions: see notes above and Appendix 1 (progestogens)

Pregnancy  
avoid but no evidence of harm to fetus; see also notes above

Breast-feeding  
progestogen-only contraceptives do not affect lactation

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

**Licensed use** consult product literature

**Indication and dose**

**Emergency contraception**
- **By mouth**
  - 1.5 mg as a single dose as soon as possible after coitus (preferably within 12 hours but no later than after 72 hours)

**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. Clean intermittent catheterisation may be considered. After the cause has been established and treated, drugs may be required to increase detrusor muscle tone.

Alpha-blockers such as doxazosin and tamsulosin can be used in some cases of dysfunctional voiding.

#### Alpha-blockers

The selective alpha-blockers **doxazosin** and **tamsulosin** can be used to improve bladder emptying in children with dysfunctional voiding where the post-void residual urine volume is significant; treatment should be under specialist advice only. Alpha-blockers can reduce blood pressure rapidly after the first dose and should be introduced with caution.

**DOXAZOSIN**

**Cautions** see under doxazosin (section 2.5.4)

**Contra-indications** see under doxazosin (section 2.5.4)

**Side-effects** see under doxazosin (section 2.5.4)

**Licensed use** not licensed for use in children

**Indication and dose**

**Dysfunctional voiding** (see notes above)
- **By mouth**
  - **Child 4–12 years** initially 0.5 mg daily increased at monthly intervals according to response; maximum 2 mg daily

**Hypertension** section 2.5.4

**Preparations** Section 2.5.4

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**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
TAMSULOSIN HYDROCHLORIDE

Cautions care with initial dose (postural hypotension); cataract surgery (risk of intra-operative floppy iris syndrome); interactions: Appendix 1 (alpha-blockers)
Renal impairment use with caution if estimated glomerular filtration rate less than 10 mL/minute/1.73 m²
Contra-indications history of postural hypotension
Hepatic impairment avoid in severe impairment
Side-effects dizziness, headache, asthenia; abnormal ejaculation; less commonly nausea, vomiting, constipation, diarrhoea, palpitation, postural hypotension, syncope, rhinitis, rash, pruritus, and urticaria; very rarely angioedema and priapism; also drowsiness, blurred vision, dry mouth, and oedema

Licensed use not licensed for use in children
Indication and dose Dysfunctional voiding (see notes above)
By mouth
Child 12–18 years 400 micrograms once daily

Tamsulosin hydrochloride (Non-proprietary) 
Capsules, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-cap pack = £6.11. Label: 25
Brands include Bazetham MR, Contiflo XL, Diffundox XL, Omnix MR, Stronazon MR, Tabphyen MR

Flomaxtra XL (Astellas)
Tablets, m/r, tamsulosin hydrochloride 400 micrograms, net price 30-tab pack = £17.55. Label: 25

OXYBUTYNIN HYDROCHLORIDE

Cautions see also notes above; also acute porphyria (section 9.8.2); interactions: Appendix 1 (antimuscarinics)
Renal impairment manufacturer advises caution

Pregnancy manufacturer advises avoid unless potential benefit outweighs risk
Breast-feeding present in milk—manufacturer advises avoid

Contra-indications see notes above

7.4.2 Drugs for urinary frequency, enuresis, and incontinence

Urinary incontinence
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. Oxybutynin can be considered first for children under 12 years. Side-effects limit the use of oxybutynin but they may be reduced by starting at a lower dose and then slowly titrating upwards; alternatively oxybutynin can be given by intravesicular instillation. Tolterodine is also effective for urinary incontinence: it can be considered for children over 12 years, or for younger children who have failed to respond to oxybutynin. Modified-release preparations of oxybutynin and tolterodine are available; they may have fewer side-effects. Antimuscarinic treatment should be reviewed soon after it is commenced, and then at regular intervals; a response generally occurs within 6 months but occasionally may take longer. Children with nocturnal enuresis may require specific additional measures if night-time symptoms also need to be controlled (see p. 493).

Cautions Antimuscarinic drugs should be used with caution in autonomic neuropathy and in hepatic or renal impairment. Antimuscarinics can worsen hyperthyroidism, congestive heart failure, arrhythmias, and tachycardia. For interactions see Appendix 1 (antimuscarinics).

Contra-indications Antimuscarinic drugs should be avoided in 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, gastrointestinal disturbances including constipation, blurred vision, dry eyes, dryness, 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 convulsions may occur. Antimuscarinic drugs may reduce sweating leading to heat sensations and fainting in hot environments or in patients with fever.
Side-effects see notes above; also dizziness; less commonly anorexia, facial flushing; rarely night terrors

Licensed use not licensed for use in children under 5 years; intravesical instillation not licensed

Indication and dose

**Urinary frequency, urgency and incontinence, neurogenic bladder instability**
- By mouth
  - Child 2–5 years 1.25–2.5 mg 2–3 times daily;
  - Child 5–12 years 2.5–3 mg twice daily, increased to 5 mg 2–3 times daily
  - Child 12–18 years 5 mg 2–3 times daily, increased if necessary to max. 5 mg 4 times daily
- By intravesical instillation
  - Child 2–18 years 5 mg 2–3 times daily

**Nocturnal enuresis associated with overactive bladder**
- By mouth
  - Child 7–18 years 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

Intravesical instillation, oxybutynin (as hydrochloride) 5 mg/30 mL. Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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

**Neurogenic bladder instability**
- By mouth
  - Child 6–18 years initially 5 mg once daily adjusted according to response in steps of 5 mg at weekly intervals; max. 15 mg once daily

Note Children taking immediate-release oxybutynin may be transferred to the nearest equivalent daily dose of Lyrinel® XL

Cautions see notes above; also history of QT-interval prolongation; concomitant use with other drugs known to prolong QT interval; interactions: see Appendix 1 (antimuscarinics)

Contra-indications see notes above

Hepatic impairment reduce dose; avoid Detrusitol® XL in hepatic impairment

Renal impairment reduce dose if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; avoid Detrusitol® XL if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Pregnancy manufacturer advises avoid—toxicity in animal studies

Breast-feeding manufacturer advises avoid—no information available

Side-effects see notes above; also chest pain, peripheral oedema; sinusitis, bronchitis; paraesthesia, fatigue, vertigo, weight gain; flushing also reported

Licensed use not licensed for use in children under 18 years

Indication and dose

**Urinary frequency, urgency, incontinence**
- By mouth
  - Child 2–18 years 1 mg once daily, increase according to response; max. 2 mg twice daily

Detrusitol® (Pharmacia) Tablets, f/c, tolterodine tartrate 1 mg, net price 56-tab pack = £29.03; 2 mg, 56-tab pack = £30.56

Modified release

Detrusitol® XL (Pharmacia) Capsules, blue, m/r, tolterodine tartrate 4 mg, net price 28-cap pack = £29.03. Label: 25

Note Children stabilised on immediate-release tolterodine 2 mg twice daily may be transferred to Detrusitol® XL 4 mg once daily

TOLTERODINE TARTRATE

Nocturnal enuresis

Nocturnal enuresis is common 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, well supported children aged over 7 years because alarms have a lower relapse rate than drug treatment when discontinued. Use of...
an alarm can be combined with drug therapy if either method alone is unsuccess-
ful.

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, for
example to cover periods away from home, or if the child and family are anxious
about the condition. 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 and treatment should not be continued for longer
than 3 months without interrupting treatment for one week for full reassessment.
When stopping treatment with desmopressin gradual withdrawal may be con-
sidered. 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 reassessed;
toxicity following overdosage with tricyclics is of particular concern.

Nocturnal enuresis associated with daytime symptoms (overactive bladder) can
be managed by antimuscarinic drugs (see Urinary incontinence, p. 492), with the addition of desmopressin if necessary.

7.4.3 Drugs used in urological pain

Lidocaine (lignocaine) gel is a useful topical application in urethral pain or to
relieve the discomfort of catheterisation (section 15.2).

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 infec-
tions.

POTASSIUM CITRATE

Cautions cardiac disease; interactions: Appendix
1 (potassium salts)
Renal impairment close monitoring required—
high risk of hyperkalaemia; avoid in severe
impairment
Side-effects hyperkalaemia on prolonged high
dosage, mild diuresis

Indication and dose

| Relief of discomfort in mild urinary-tract infec-
| tions, alkalisation of urine for dose see pre-
| parations below |

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 for-
| mula: potassium citrate 3 g, citric acid mono-
| hydrate 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. Label: 27

Dose

- By mouth
  - Child 1–6 years 5 mL 3 times daily well diluted with
    water
  - Child 6–18 years 10 mL 3 times daily well diluted with
    water

Note Proprietary brands of potassium citrate are on sale
to the public for the relief of discomfort in mild urinary-
tract infections

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 irritant.
**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.

**Maintenance of indwelling urinary catheters**  
The deposition which occurs in catheterised patients is usually chiefly composed of phosphate and to minimise this the catheter (if latex) should be changed at least as often as every 6 weeks. If the catheter is to be left for longer periods a silicone catheter should be used together with the appropriate use of catheter maintenance solutions. Repeated blockage usually indicates that the catheter needs to be changed.

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**CATHETER PATENCY SOLUTIONS**

**Chlorhexidine 0.02%**  
Brands include Uriflex C®, 100-mL sachet = £2.40; Uro-Tainer Chlorhexidine®, 100-mL sachet = £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 × 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 Solution R, 2 × 30-mL = £4.42

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**7.4.5 Drugs for erectile dysfunction**  
This section is not included in *BNF for Children*. Adolescents presenting with erectile dysfunction should be referred to a specialist.
The management of childhood cancer is complex and is generally confined to specialist regional centres, and some associated shared-care units, affiliated to the Children’s Cancer and Leukaemia Group (CCLG). The Group, together with other national and international organisations, develops and co-ordinates treatment protocols. In children, cytotoxic drugs are almost always administered in the context of a formal protocol.

Cytotoxic drugs have both anti-cancer activity and the potential for damage to normal tissue. In children, chemotherapy is almost always started with curative intent, but may be continued as palliation if the disease is refractory.

Chemotherapy with a combination of two or more cytotoxic drugs aims to reduce the development of resistance and to improve cytotoxic effect. Treatment protocols generally incorporate a series of treatment courses at defined intervals with clear criteria for starting each course, such as adequate bone-marrow recovery and renal or cardiac function. The principal component of treatment for leukaemias in children is cytotoxic therapy, whereas solid tumours may be managed with surgery or radiotherapy in addition to chemotherapy.

Guidelines on 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.
Only medical or nursing staff who have received appropriate training should administer parenteral cytotoxics. In most instances central venous access will be required for the intravenous administration of cytotoxics to children; care is required to avoid the risk of extravasation (see Side-effects of Cytotoxic Drugs and their Management).

Intrathecal chemotherapy
A Health Service Circular (HSC 2003/010) provides guidance on the introduction of safe practice in NHS Trusts where intrathecal chemotherapy is administered; written local guidance covering all aspects of national guidance must be available.
Copies, and further information may be obtained from:
Department of Health
PO Box 777
London SE1 6XH
Fax: 01623 724524
www.dh.gov.uk

Because of the complexity of dosage regimens in the treatment of malignant disease, dose statements have been omitted from many of the drug entries in this chapter.

Side-effects of cytotoxic drugs and their management
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 of individual drugs.

Extravasation of intravenous drugs A number of cytotoxic drugs will cause severe local tissue irritation and necrosis if leakage into the extravascular compartment occurs. For information on the prevention and management of extravasation injury, see section 10.3.

Gastro-intestinal effects Management of gastro-intestinal effects of cytotoxic drugs includes the use of antacids, H2-receptor antagonists, and proton pump inhibitors to protect the gastric mucosa, laxatives to treat constipation, and enteral and parenteral nutritional support.

Oral mucositis Good oral hygiene keeps the mouth clean and moist and helps to prevent mucositis; prevention is more effective than treatment of the complication. Good oral hygiene measures for children over 6 months include brushing teeth with a soft small brush with fluoride toothpaste 2–3 times daily, and rinsing the mouth frequently. Daily fluoride supplements (section 9.5.3) can be used on the advice of the child’s dental team. For children under 6 months or when it is not possible to brush teeth, carers should be instructed how to clean the mouth using an oral sponge moistened with water or with an antimicrobial solution such as diluted chlorhexidine. Mucositis related to chemotherapy can be extremely painful and may, in some circumstances, require opioid analgesia (section 4.7.2). Secondary infection with candida is frequent; treatment with a systemically absorbed antifungal, such as fluconazole (section 5.2), is effective.

Nausea and vomiting Nausea and vomiting cause considerable distress to many children who receive chemotherapy, and to a lesser extent abdominal radiotherapy, and may lead to refusal of further treatment; prophylaxis of nausea and vomiting is therefore extremely important. 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.
Susceptibility to nausea and vomiting may increase 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 the individual’s susceptibility to emetogenic stimuli.

Mildly emetogenic treatment—fluorouracil, etoposide, low doses of methotrexate, the vinca alkaloids, and abdominal radiotherapy.

Moderately emetogenic treatment—carboplatin, doxorubicin, intermediate and low doses of cyclophosphamide, mitoxantrone (mitozantrone), and high doses of methotrexate.

Highly emetogenic treatment—cisplatin, dacarbazine, and high doses of alkylating drugs.

Anti-emetic drugs, when given regularly, help prevent or ameliorate emesis associated with chemotherapy in children.

Prevention of acute symptoms For patients at low risk of emesis, pretreatment with metoclopramide (or less commonly domperidone) continued for up to 24 hours after chemotherapy, is often effective (section 4.6); a 5HT₁ antagonist (section 4.6) may also be of benefit.

For patients at high risk of emesis or when other treatment is inadequate, a 5HT₁ antagonist (section 4.6) is often highly effective. The addition of dexamethasone and other anti-emetics may also be required.

Prevention of delayed symptoms Dexamethasone, given by mouth, is the drug of choice for preventing delayed symptoms; it is used alone or with metoclopramide. The 5HT₁ antagonists may have a role in preventing uncontrolled symptoms.

Prevention of anticipatory symptoms Good symptom control is the best way to prevent anticipatory symptoms. Lorazepam can be helpful for its amnesiac, 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 melphalan. Peripheral blood counts must be checked before each treatment. The duration and severity of neutropenia can be reduced by the use of granulocyte-colony stimulating factors (section 9.1.6); their use should be reserved for children who have previously experienced severe neutropenia.

Infection in a child with neutropenia requires immediate broad-spectrum antibacterial treatment that covers all likely pathogens (Table 1, section 5.1). Antifungal treatment (section 5.2) may be required in a child with prolonged neutropenia or fever lasting longer than 4–5 days. Chickenpox and measles can be particularly hazardous in immunocompromised children. Varicella–zoster immunoglobulin (section 14.5) is indicated if the child does not have immunity against varicella and has had close contact with infectious chickenpox or herpes zoster. Antiviral prophylaxis (section 5.3.2.1) can be considered in addition to varicella–zoster immunoglobulin or as an alternative if varicella–zoster immunoglobulin is inappropriate. If an immunocompromised child has come into close contact with an infectious individual with measles, normal immunoglobulin (section 14.5) should be given.

Alopecia Reversible hair loss is a common complication, although it varies in degree between drugs and individual patients.

Pregnancy and reproductive function Before using cytotoxic drugs during pregnancy consideration should be given to both the prognosis of the patient and the fetal risk. The rapidly dividing cells of the fetus are potentially susceptible to the effects of cytotoxic drugs. Although antimetabolites are thought to be the strongest teratogens, specific risk assessment of individual cytotoxics is not possible with the available data. All of the long-term effects of cytotoxic exposure are not fully known.

The use of cytotoxic drugs during the first trimester is associated with the greatest risk of harm to the fetus; spontaneous abortion and teratogenicity are possible. If at all possible cytotoxic drugs should be avoided before week 10 of pregnancy.

In the second and third trimesters the risk of teratogenicity is negligible, but growth and developmental effects are possible. In the third trimester early
induction of delivery may be considered. If cytotoxic drugs are unavoidable in older girls with reproductive potential, contraceptive advice should be offered where appropriate. Regimens containing an alkylating drug carry the risk of causing permanent male sterility (but may not affect sexual potency).

**Long-term and delayed toxicity** Cytotoxic drugs may produce specific organ-related toxicity in children (e.g. cardiotoxicity with doxorubicin or nephrotoxicity with cisplatin and ifosfamide). Manifestations of such toxicity may not appear for several months or even years after cancer treatment. Careful follow-up of survivors of childhood cancer is therefore vital; national and local guidelines have been developed to facilitate this.

**Thromboembolism** Venous thromboembolism can be a complication of cancer itself, but chemotherapy can also increase the risk.

**Tumour lysis syndrome** Tumour lysis syndrome occurs secondary to spontaneous or treatment related rapid destruction of malignant cells. Features include hyperkalaemia, hyperuricaemia, and hyperphosphataemia with hypocalcaemia; renal damage and arrhythmias can follow. Early recognition of patients at risk and initiation of prophylaxis or therapy for tumour lysis syndrome is essential.

**Drugs for cytotoxic-induced side-effects**

**Anthracycline-induced cardiotoxicity**

The anthracycline cytotoxic drugs are associated with dose-related, cumulative, and potentially life-threatening cardiotoxic side-effects.

*Dexrazoxane*, an iron chelator, is licensed in adults 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. In practice, dexrazoxane is used for any patient receiving anthracycline therapy with evidence of subclinical cardiotoxicity thought to be secondary to anthracycline therapy, or for those children at risk of anthracycline-induced cardiotoxicity. Children receiving dexrazoxane should continue to be monitored for cardiac toxicity. The myelosuppressive effects of dexrazoxane may be additive to those of chemotherapy.

**DEXRAZOXANE**

**Cautions**

- monitor full blood count; heart failure, uncontrolled angina, symptomatic cardiac valvulopathy
- **Renal impairment** reduce dose by 50% if creatinine clearance less than 40 mL/minute/1.73 m²

**Contra-indications**

- **Pregnancy** manufacturer advises avoid unless essential; ensure effective contraception during and for 3 months after treatment in men and women
- **Breast-feeding** discontinue breast-feeding

**Side-effects**

- gastro-intestinal disturbances; blood disorders (including anaemia, leucopenia, and neutropenia); injection site reactions including phlebitis

**Licensed use** not licensed for use in children

**Indication and dose**

- Prevention of antracycline-induced cardiotoxicity (see notes above)
  - By intravenous infusion, 30 minutes prior to anthracycline administration
  - 10–20 times the doxorubicin-equivalent dose (depending on treatment protocol) or 10 times the epirubicin-equivalent dose

**Administration**

- for intravenous infusion reconstitute each vial with 25 mL Water for injections then dilute contents of each vial with 25–100 mL Compound sodium lactate. Give over 15 minutes

**Cardioxane® (Novartis)**

- Intravenous infusion, powder for reconstitution, dexrazoxane (as hydrochloride), net price 500-mg vial = £156.57

**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* is used routinely in children at low to moderate risk of hyperuricaemia. It should be started 24 hours before treatment; patients should be adequately hydrated (consideration should be given to omitting phosphate and potassium from hydration fluids). The dose of mercaptopurine or azathioprine should be reduced if allopurinol is given concomitantly (see Appendix 1).

*Rasburicase* is a recombinant urate oxidase used in children who are at high-risk of developing hyperuricaemia. It rapidly reduces plasma uric acid and may be of...
particular value in reducing complications following treatment of leukaemias or bulky lymphomas.

ALLOPURINOL

Cautions ensure adequate fluid intake; for hyperuricaemia associated with cancer therapy, allopurinol treatment should be started before cancer therapy; interactions: Appendix 1 (allopurinol)

Hepatic impairment reduce dose, monitor liver function

Renal impairment manufacturer advises reduce dose or increase dose interval in severe impairment; if monitoring possible, adjust dose to maintain plasma-oxipurinol concentration below 100 micromol/litre

Pregnancy toxicity not reported; manufacturer advises use only if no safer alternative and disease carries risk for mother or child

Breast-feeding present in milk—not known to be harmful

Side-effects rashes (withdraw therapy; if rash mild re-introduce cautiously but discontinue immediately 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); gastro-intestinal disorders; rarely malaise, headache, vertigo, drowsiness, visual and taste disturbances, hypertension, alopecia, hepatotoxicity, paraesthesia and neuropathy, blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia and aplastic anaemia)

Indication and dose

Prophylaxis of hyperuricaemia associated with cancer chemotherapy, prophylaxis of hyperuricaemic nephropathy, enzyme disorders causing increased serum urate e.g. Lesch-Nyhan syndrome

• By mouth
  Child 1 month–15 years 10–20 mg/kg daily (max. 400 mg daily), preferably after food
  Child 15–18 years initially 100 mg daily, increased according to response; max. 900 mg daily (doses over 300 mg daily given in divided doses); preferably after food

Allopurinol (Non-proprietary)

Tablets, allopurinol 100 mg, net price 28-tab pack = 97p; 300 mg, 28-tab pack = £1.10. Label: 8, 21, 27

Brands include Caplenal®, Cosuric®, Rimapurin®

Zyloric® (GSK)

Tablets, allopurinol 100 mg, net price 100-tab pack = £10.19; 300 mg, 28-tab pack = £7.31. Label: 8, 21, 27

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

RASBURICASE

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 manufacturer advises avoid—no information available

Breast-feeding manufacturer advises avoid—no information available

Side-effects fever; nausea, vomiting; less frequently diarrhoea, headache, hypersensitivity reactions (including rash, bronchospasm and anaphylaxis); haemolytic anaemia, methaemoglobinemia

Licensed use not licensed for use in children

Indication and dose

Prophylaxis and treatment of acute hyperuricemia with initial chemotherapy for haematological malignancy

• By intravenous infusion Consult local treatment protocol for details

Administration Consult local treatment protocol for details

For intravenous infusion, reconstitute with solvent provided then dilute requisite dose with Sodium Chloride 0.9% to 50 mL; give over 30 minutes; use immediately

Fasturtec (Sanofi-Synthelabo) Intravenous infusion, powder for reconstitution, rasburicase, net price 1.5-mg vial (with solvent) = £57.89; 7.5-mg vial (with solvent) = £241.20

Methotrexate-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.

The calcium salt of levofolinic acid, a single isomer of folinic acid, is also used following methotrexate administration. The dose of calcium levofolinate is generally half that of calcium folinate.

The efficacy of high dose methotrexate is enhanced by delaying initiation of folinic acid for at least 24 hours, local protocols define the correct time. Folinic
Acid is normally continued until the plasma-methotrexate concentration falls to 100–200 nanomol/litre (45–90 micrograms/mL).

In the treatment of methotrexate overdose, folinate should be administered immediately; other measures to enhance the elimination of methotrexate are also necessary.

**CALCIUM FOLINATE**
(Calcium leucovorin)

**Cautions** avoid simultaneous administration of methotrexate; not indicated for pernicious anaemia or other megaloblastic anaemias due to vitamin B12 deficiency; **interactions**: Appendix 1 (folates)

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** manufacturer advises caution—no information available

**Safe Practice** Intrathecal injection contra-indicated

**Side-effects** hypersensitivity reactions; rarely pyrexia after parenteral use

**Licensed use** not licensed for use in children for treatment of methotrexate overdose, megaloblastic anaemia due to folate deficiency or metabolic disorders leading to folate deficiency

**Indication and dose**

**Reduction of methotrexate-induced toxicity**
- By mouth, by intravenous injection over 2 minutes, or by intravenous infusion
  See notes above. Consult local treatment protocol for details

**Methotrexate overdose**
- By intravenous infusion
  See notes above. Consult local treatment protocol for details

**Megaloblastic anaemia due to folate deficiency**
- By mouth
  - Child up to 12 years 250 microgram/kg once daily
  - Child 12–18 years 15 mg once daily

**Metabolic disorders leading to folate deficiency**
- By mouth or by intravenous infusion
  - Child up to 18 years 15 mg once daily; larger doses may be required in older children

**Prevention of megaloblastic anaemia associated with pyrimethamine and sulfadiazine treatment of congenital toxplasmosis**
- By mouth
  - Neonate 5 mg 3 times a week (increased up to 20 mg 3 times a week if neutropenic)
  - Child 1 month-1 year 10 mg 3 times a week

**Administration** Consult local treatment protocol for details

For **intravenous infusion**, dilute with Glucose 5% or Sodium Chloride 0.9%, give over at least 30 minutes

For administration by mouth, the injection solution may be given orally

**Calcium Folate** (Non-proprietary)

**Tablets**, scored, folinic acid (as calcium salt) 15 mg, net price 10-tab pack = £39.20, 30-tab pack = £85.74

Brands include *Refolinon®*

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

**Injection**, powder for reconstitution, folinic acid (as calcium salt), net price 15-mg vial = £4.46; 30-mg vial = £8.36

**CALCIUM LEVOFOLINATE**
(Calcium levoleucovorin)

**Cautions** see Calcium Folate

**Side-effects** see Calcium Folate

**Indication and dose**

**Reduction of methotrexate-induced toxicity**
- By intramuscular injection, by intravenous injection over at least 3 minutes, or by intravenous infusion
  See notes above. Consult local treatment protocol for details

**Methotrexate overdose**
- By intramuscular injection, by intravenous injection over at least 3 minutes, or by intravenous infusion
  See notes above. Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For **intravenous infusion**, dilute with Glucose 5% or Sodium Chloride 0.9%

**Isovorin®** (Wyeth)

**Injection**, levofolinic 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

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Malignant disease and immunosuppression
### 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. Adequate hydration is essential to reduce the risk of urothelial toxicity. Mesna reacts specifically with acrolein in the urinary tract, preventing toxicity. Mesna is given for the same duration as cyclophosphamide or ifosfamide. It is generally given intravenously; the dose of mesna is equal to or greater than that of the oxazaphosphorine. For the role of nebulised mesna as a mucolytic in cystic fibrosis, see section 3.7.

### MESNA

**Cautions**

- **Pregnancy** not known to be harmful

**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)

**Licensed use** not licensed for use in children

**Indication and dose**

- **Urothelial toxicity following oxazaphosphorine therapy**
  - By intravenous injection or by continuous intravenous infusion

See notes above. Consult local treatment protocol for details

### Mucolytic in cystic fibrosis section 3.7

**Administration** Consult local treatment protocol for details

For intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%

**Mesna (Baxter)**

- Tablets, 1/2, 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), problems associated specifically with alkylating drugs include:

- an adverse effect on gametogenesis which may be reversible, particularly in females; amenorrhoea may also occur, which also may be reversible;
- a marked increase in the incidence of secondary tumours and leukaemia, particularly when alkylating drugs are combined with extensive irradiation;
- fluid retention with oedema and dilutional hyponatraemia in younger children; the risk of this complication is higher in the first 2 days and also when given with concomitant vinca alkaloids;
- urothelial toxicity with intravenous use; adequate hydration may reduce this risk; mesna (section 8.1) provides further protection against urotoxic effects of cyclophosphamide and ifosfamide.

### BUSULFAN

*(Busulphan)*

**Cautions** see section 8.1 and notes above; monitor full blood count regularly throughout treatment; monitor liver function; previous mediastinal or pulmonary radiography therapy; avoid in acute porphyria (section 9.8.2); **Interactions**: Appendix 1 (busulphan)

**Hepatic impairment** manufacturer advises monitor liver function—no information available

**Contra-indications**

- **Pregnancy** avoid (teratogenic in animals); manufacturers advise effective contraception during and for 6 months after treatment in men or women; see also section 8.1
- **Breast-feeding** discontinue breast-feeding

**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; rarely progressive pulmonary fibrosis, seizures, aplastic anaemia, visual disturbances, hypersensitivity reactions (including urticaria, erythema); very rarely myasthenia gravis, gynaecomastia

**Licensed use** Busilvex® not licensed for chronic granulocytic leukaemia
Indication and dose

Busilvex® (Fabre) Concentrate for intravenous infusion, busulfan 6 mg/mL, net price 10-mL vial = £201.25

Myleran® (GSK) Tablets, 1/c, busulfan 2 mg, net price 25-tab pack = £5.20

Busulfan Capsules, busulfan 25 mg Available from 'special-order' manufacturers or specialist importing companies, p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

CHLORAMBUCIL

Cautions see section 8.1 and notes above; monitor full blood count regularly throughout treatment; increased seizure risk in children with nephrotic syndrome or history of epilepsy; avoid in acute porphyria (section 9.8.2)

Hepatic impairment manufacturer advises consider dose reduction in severe hepatic impairment—limited information available

Contra-indications

Pregnancy avoid; manufacturer advises effective contraception during treatment in men or women; see also section 8.1

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; also less commonly skin rash (possible progression to Stevens-Johnson syndrome and toxic epidermal necrolysis); rarely seizures, hepatotoxicity and jaundice; very rarely irreversible bone-marrow suppression, pulmonary fibrosis, tremor, peripheral neuropathy, sterile cystitis, sterility in pre-pubertal and pubertal males

Licensed use not licensed for use in nephrotic syndrome

CYCLOPHOSPHAMIDE

Cautions see section 8.1 and notes above; avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (cyclophosphamide)

Hepatic impairment reduce dose—consult local treatment protocol for details

Renal impairment reduce dose—consult local treatment protocol for details

Contra-indications haemorrhagic cystitis

Pregnancy avoid; manufacturer advises effective contraception during and for at least 3 months after treatment in men or women; see also section 8.1

Breast-feeding discontinue breast-feeding during and for 36 hours after stopping treatment

Side-effects see section 8.1 and notes above; also anorexia; cardiotoxicity at high doses; interstitial pulmonary fibrosis; inappropriate secretion of anti-diuretic hormone; disturbances of carbohydrate metabolism; urothelial toxicity; pigmentation of palms, nails and soles; rarely hepatotoxicity

Licensed use not licensed for use in children

Indication and dose

Steroid-sensitive nephrotic syndrome see also section 6.3.2, p. 445

By mouth

Child 3 months–18 years 2–3 mg/kg once daily for eight weeks

1 Malignant disease and immunosuppression
**Cyclophosphamide (continued)**

- **By intravenous infusion**
  - **Child 3 months–18 years** 500 mg/m² once a month for six months

**Administration**
Consult local treatment protocol for details

For **intravenous infusion**, dilute with Glucose 5% or Sodium Chloride 0.9% or 0.18% with Glucose 4%; give over at least one hour

**Cyclophosphamide (Non-proprietary)**

- **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

**Cyclophosphamide (Baxter)**

- **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

- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

**Ifofamid**

**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); risk of urothelial toxicity (see notes above); interactions: Appendix 1 (ifosfamide)

**Renal impairment** avoid

**Contra-indications** bone marrow aplasia, myelosuppression; urinary tract obstruction; acute infection (including urinary-tract infection); urothelial damage

**Hepatic impairment** avoid

**Pregnancy** 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

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; also drowsiness, confusion, disorientation, restlessness, psychosis; urothelial toxicity causing haemorrhagic cystitis and dysuria, renal toxicity (see Cautions above); less commonly severe encephalopathy; rarely diarrhoea, constipation, convulsions, anorexia; very rarely jaundice, thrombophlebitis, syndrome of inappoprate antidiuretic hormone secretion

**Indication and dose**

- Rhabdomyosarcoma, soft-tissue sarcomas, Ewing tumour, germ cell tumour, osteogenic sarcoma
  - **By intravenous infusion**
  - Consult local treatment protocol for details

**Administration**
Consult local treatment protocol for details

For **intravenous infusion**, dilute reconstituted solution to a max. concentration of 40 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 30–120 minutes. Ensure adequate hydration and concurrent administration of mesna (see notes above and section 8.1).

**Ifosfamide (Baxter)**

- **Injection**, powder for reconstitution, ifosfamide. Net price 1-g vial = £27.03; 2-g vial = £45.49 (hosp. only)

**Melpalan**

**Cautions** see section 8.1 and notes above; monitor full blood count before and throughout treatment; for high-dose intravenous administration establish adequate hydration (see notes above), consider use of prophylactic anti-infective agents; haematopoietic stem cell transplantation essential for high dose treatment (consult local treatment protocol for details); interactions: Appendix 1 (melphalan)

**Renal impairment** reduce dose initially—consult product literature

**Contra-indications**

- **Pregnancy** avoid; manufacturer advises adequate contraception during treatment in men or women; see also section 8.1

- **Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above

- Licensed use childhood neuroblastoma; oral use not licensed in children

**Indication and dose**

- High intravenous dose with haematopoietic stem cell transplantation in the treatment of childhood neuroblastoma and some other advanced embryonal tumours
  - **By intravenous infusion**
  - Consult local treatment protocol for details

**Administration**

For **intravenous infusion** in Sodium Chloride 0.9%. Reconstitute with the solvent provided and inject slowly into the tubing of a fast running infusion; alternatively, reconstituted solution can be diluted in infusion fluid to a concentration not greater than 0.45 mg/mL. Max. 90 minutes between reconstitution and completion of administration. Incompatible with glucose infusion

**Alkeran (GSK)**

- **Injection**, powder for reconstitution, melphalan 50 mg (as hydrochloride). Net price 50-mg vial (with solvent-diluent) = £27.61
8.1.2 Cytotoxic antibiotics

Cytotoxic antibiotics are widely used. Many act as radiomimetics and simultaneous use of radiotherapy should be avoided as it may enhance toxicity markedly.

Daunorubicin, doxorubicin, and epirubicin are anthracycline antibiotics. Mitoxantrone (mitozantrone) is an anthracycline derivative.

All anthracycline antibiotics have been associated with varying degrees of cardiac toxicity—this may be idiosyncratic and reversible, but is commonly related to total cumulative dose and is irreversible. Cardiac function should be monitored before and at regular intervals throughout treatment and afterwards. Anthracycline antibiotics should not normally be used in children with left ventricular dysfunction. Epirubicin and mitoxantrone are considered less toxic, and may be suitable for children who have received high cumulative doses of other anthracyclines.

**BLEOMYCIN**

**Cautions** see section 8.1; ensure monitoring of pulmonary function—investigate any shortness of breath before initiation; caution in handling—irritant to tissues

Renal impairment reduce dose in renal impairment—consult local treatment protocol for details

**Contra-indications** acute pulmonary infection or significantly reduced lung function

**Pregnancy** avoid (teratogenic and carcinogenic in animal studies); see also section 8.1

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1, less bone marrow suppression; anorexia; pulmonary toxicity e.g. pulmonary fibrosis (usually dose-related and delayed); fever (directly following administration), fatigue; dermatological and mucous membrane toxicity, localised skin hyperpigmentation; rarely cardiorespiratory collapse and hyperpyrexia

**Licensed use** not licensed for use in children

**Indication and dose**

- Some germ cell tumours, Hodgkin’s lymphoma
  - By intravenous infusion
  - Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For intravenous infusion dilute with a suitable volume of Sodium Chloride 0.9% (e.g. up to 100 mL) into established intravenous line

**Bleomycin** (Non-proprietary) 

**Injection**, powder for reconstitution, bleomycin (as sulphate). Net price 15 000-unit vial = £15.56

**Note** To conform to the European Pharmacopoeia vials previously labelled as containing ‘15 units’ of bleomycin are now labelled as containing 15 000 units. The amount of bleomycin in the vial has not changed.

**Brands include** Bleo-Kyowa®

**DACTINOMYCIN**

(Actinomycin D)

**Cautions** see section 8.1 and notes above; caution in handling—irritant to tissues

Hepatic impairment consider dose reduction if raised serum bilirubin or biliary obstruction (consult local treatment protocol for details)

**Contra-indications**

- Pregnancy avoid (teratogenic in animal studies); see also section 8.1
- Breast-feeding discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; less commonly cheilitis, dysphagia; fever, malaise, lethargy; anaemia, hypoglycaemia; myalgia; acne; rarely hepatotoxicity (possibly dose-related)

**Licensed use** not licensed for use in children under 12 years

**Indication and dose**

- Wilms’ tumour, childhood rhabdomyosarcoma and other soft tissue sarcomas, Ewing’s sarcoma
  - By intravenous injection
  - Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For slow intravenous injection, give 500 micrograms/mL solution over 2–3 minutes

**Cosmegen Lyovac®** (Ovation)

**Injection**, powder for reconstitution, dactinomycin, net price 500-microgram vial = £6.75

**DAUNORUBICIN**

**Cautions** see section 8.1 and notes above; caution in handling—irritant to tissues

Hepatic impairment reduce dose according to serum bilirubin concentration (consult local treatment protocol for details)

**Contra-indications**

- Pregnancy avoid (teratogenic and carcinogenic in animal studies), see also section 8.1
- Breast-feeding discontinue breast-feeding

**Side-effects** see section 8.1 and notes above, leucopenia, less commonly mucositis; cardiac
DAUNORUBICIN (continued)

Toxicity (usually 1–6 months after initiation of therapy): fever; red urine discoloration

Licensed use Liposomal preparation not licensed for use in children

Indication and dose

Acute myelogenous leukaemia, acute lymphocytic leukaemia
- By intravenous infusion

Consult local treatment protocol for details

DOXORUBICIN HYDROCHLORIDE

Cautions See section 8.1 and notes above; caution in handling—irritant to tissues; interactions: Appendix 1 (doxorubicin)

Hepatic impairment Reduce dose according to bilirubin concentration, consult local treatment protocol for details

Contra-indications

Pregnancy 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

Breast-feeding Discontinue breast-feeding

Side-effects See section 8.1 and notes above; red urine discoloration; thrombophlebitis over injection site; less commonly bronchospasm, fever, amenorrhoea, and skin rash

Licensed use Not licensed for use in children

Indication and dose

Paediatric malignancies including Ewing’s sarcoma, osteogenic sarcoma, Wilms’ tumour, neuroblastoma, retinoblastoma, some liver tumours, acute lymphoblastic leukaemia, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma
- By intravenous infusion

Consult local treatment protocol for details

Administration Consult local treatment protocol for details

For intravenous infusion, dilute with Sodium Chloride 0.9%; give preferably through a central venous catheter

Doxorubicin

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

Injection, doxorubicin hydrochloride 2 mg/mL, net price 5-mL vial = £20.60, 25-mL vial = £103.00, 100-mL vial = £412.00

EPIRUBICIN HYDROCHLORIDE

Cautions See section 8.1 and notes above; caution in handling—irritant to tissues

Hepatic impairment Reduce dose according to bilirubin concentration (consult local treatment protocol for details)

Contra-indications

Pregnancy Avoid (carcinogenic in animal studies); see also section 8.1

Breast-feeding Discontinue breast-feeding

Side-effects See section 8.1 and notes above; red urine discoloration; anaphylaxis

Licensed use Not licensed for use in children

Indication and dose

Recurrent acute lymphoblastic leukaemia, rhabdomyosarcoma, other soft tissue tumours of childhood
- Intravenous infusion

Consult local treatment protocol for details

Administration Consult local treatment protocol for details

For intravenous infusion, dilute with Sodium Chloride 0.9%; give preferably through a central venous catheter

Pharmorubicin® Rapid Dissolution (Pharmacia)

Injection, powder for reconstitution, epirubicin hydrochloride. Net price 50-mg vial = £96.54

Pharmorubicin® Solution for Injection (Pharmacia)

Injection, epirubicin hydrochloride 2 mg/mL, net price 5-mL vial = £19.31, 25-mL vial = £96.54, 100-mL vial = £386.16

Daunorubicin (Non-proprietary)

Infection, powder for reconstitution, daunorubicin (as hydrochloride), net price 20-mg vial = £44.76

Administration Dilute with Sodium Chloride 0.9% and give into the tubing or side-arm of a fast flowing infusion—consult local treatment protocol for details

Lipid formulation

DaunoXome® (Diatos)

Concentrate for intravenous infusion, daunorubicin encapsulated in liposomes. For dilution before use. Net price 50-mg vial = £137.67

Administration Consult local treatment protocol for details

Licensed use Liposomal preparation not licensed for use in children

Indication and dose

Acute myelogenous leukaemia, acute lymphocytic leukaemia.

By intravenous infusion

Consult local treatment protocol for details

Licensed use Liposomal preparation not licensed for use in children

Indication and dose

Acute myelogenous leukaemia, acute lymphocytic leukaemia
- By intravenous infusion

Consult local treatment protocol for details
**Antimetabolites**

Antimetabolites are incorporated into new nuclear material or they combine irreversibly with vital cellular enzymes and prevent normal cellular division. Cytarabine, fludarabine, mercaptopurine, methotrexate, and tioguanine are commonly used in paediatric chemotherapy.

**Methotrexate** inhibits the enzyme dihydrofolate reductase, essential for the synthesis of purines and pyrimidines. It is given by mouth, intravenously, intramuscularly, or intrathecally. 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 and myelosuppression.

**Cytarabine** acts by interfering with pyrimidine synthesis. It is given subcutaneously, intravenously, or intrathecally. It is a potent myelosuppressant and requires careful haematological monitoring. A liposomal formulation of cytarabine for intrathecal use is available for lymphomatous meningitis.

**Fludarabine** is generally well tolerated but does cause myelosuppression, which may be cumulative.

**Fludarabine** has a potent and prolonged immunosuppressive effect. Children treated with fludarabine are more prone to serious bacterial, opportunistic fungal, and viral infections, and prophylactic therapy is recommended in children 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 children 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 children 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 events is strongly recommended—discontinue treatment if neurotoxicity occurs.

Mercaptopurine is used as maintenance therapy for acute lymphoblastic leukaemia and in the management of ulcerative colitis and Crohn’s disease (section 1.5). 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 child is receiving allopurinol since it interferes with their metabolism. For the role of thiopurine methyltransferase (TPMT) in the metabolism of azathioprine see section 8.2.1.

Tioguanine (thioguanine) is given by mouth for the treatment of acute lymphoblastic leukaemia; it is given at various stages of treatment in short-term cycles. Tioguanine has a lower incidence of gastro-intestinal side-effects than mercaptopurine. Long-term therapy with tioguanine is no longer recommended because of the high risk of liver toxicity.

CLOFARABINE

Cautions see section 8.1

Hepatic impairment manufacturer advises caution in mild to moderate impairment; avoid in severe impairment

Renal impairment manufacturer advises caution in mild to moderate impairment; avoid in severe impairment

Contra-indications

Pregnancy manufacturer advises avoid (teratogenic in animal studies); see also section 8.1

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1; also jaundice, tachycardia, flushing, hypotension, pericardial effusion, haematoma, dyspnoea, cough, anxiety, agitation, dizziness, drowsiness, headache, paraesthesia, peripheral neuropathy, restlessness, rash, pruritus, increased sweating

Licensed use not licensed for use in children under 1 year

Indication and dose

Relapsed or refractory acute lymphoblastic leukaemia

• By intravenous infusion

Consult local treatment protocol for details

Administration Consult local treatment protocol for details

For intravenous infusion, filter requisite dose through a 0.2-micron filter and dilute with Sodium Chloride 0.9%; give over 2 hours

Evoltra (Bioenvision) ▼ (Ph)

Concentrate for intravenous infusion, clofarabine 1 mg/mL, net price 20-mL vial = £1200.00

Electrolytes Na⁺ 3.08 mmol/vial

Note Based on weight or body-surface area, children may tolerate higher doses of cytarabine than adults

CYTARABINE

Cautions see section 8.1 and notes above; interactions: Appendix 1 (cytarabine)

Hepatic impairment reduce dose

Renal impairment reduce dose for high dose regimens or avoid, consult local treatment protocol for details

Contra-indications

Pregnancy avoid (teratogenic in animal studies); see also section 8.1

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; ‘cytarabine syndrome’—6–12 hours after intravenous administration—characterised by fever and malaise, myalgia, bone pain, maculopapular rash, and occasionally chest pain; less commonly conjunctivitis (consider prophylactic corticosteroid eye drops), neurotoxicity, renal and hepatic dysfunction, jaundice; rarely severe spinal cord toxicity following intrathecal administration

Licensed use DepoCyt® intrathecal injection not licensed for use in children

Indication and dose

Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin’s lymphoma

• By intravenous injection, by intravenous infusion, or by subcutaneous injection

Consult local treatment protocol for details

Meningeal leukaemia, meningeal neoplasms

• By intrathecal injection

Consult local treatment protocol for details

Administration Consult local treatment protocol for details

For intravenous injection or intravenous infusion dilute with Water for Injections or Sodium Chloride 0.9% or Glucose 5%; do not give high strength (100 mg/mL) intrathecally

Cytarabine (Non-proprietary) ▼ (Ph)

Injection (for intravenous, subcutaneous or intrathecal use), cytarabine 20 mg/mL, net price 5-mL vial = £4.00

Injection (for intravenous or subcutaneous use), cytarabine 20 mg/mL, net price 5-mL vial = £3.90, 25-mL vial = £19.50

Injection (for intravenous or subcutaneous use), cytarabine 100 mg/mL, net price 1-mL vial = £4.00; 5-mL vial = £20.00; 10-mL vial = £39.00; 20-mL vial = £77.50

Lipid formulation for intrathecal use

DepoCyt® (Napp) ▼ (Ph)

Intrathecal injection, cytarabine encapsulated in liposomes, net price 50-mg vial = £1223.75
**FLUDARABINE PHOSPHATE**

**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; **interactions:** Appendix 1 (Fludarabine)

**Renal impairment** reduce dose by up to 50% if creatinine clearance 30–70 mL/minute/1.73 m²; avoid if creatinine clearance less than 30 mL/minute/1.73 m²

**Contra-indications** haemolytic anaemia

**Pregnancy** avoid (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

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; also diarrhoea, anorexia; oedema; pneumonia, cough; peripheral neuropathy, visual disturbances; chills, fever, malaise, weakness, rash; *less commonly* gastro-intestinal haemorrhage, pulmonary toxicity (including pulmonary infiltrates, pneumonitis, and fibrosis), and confusion; *rarely* heart failure, arrhythmia, coma, seizures, agitation, myelodysplastic syndrome, acute myeloid leukaemia, optic neuropathy, blindness, Stevens-Johnson syndrome, toxic epidermal necrolysis, skin cancer, and haemorrhagic cystitis

**Licensed use** not licensed for use in children

**Indication and dose**

**Poor prognosis or relapsed acute myeloid leukaemia, relapsed acute lymphoblastic leukaemia, conditioning before bone marrow transplantation**

- By mouth, by intravenous injection, or by intravenous infusion

Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

Reconstitute each 50 mg powder with 2 mL Water for Injections

For *intravenous injection*, dilute requisite dose with 10 mL Sodium Chloride 0.9%

For *intravenous infusion*, dilute requisite dose with 100–125 mL Sodium Chloride 0.9%; give over 30 minutes

**Fludara®** (Bayer) Tablets, f/c, pink, fludarabine phosphate 10 mg, net price 15-tab pack = £279.00, 20-tab pack = £372.00

**Injection**, powder for reconstitution, fludarabine phosphate. Net price 50-mg vial = £156.00

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**MERCAPTOPURINE**

**Cautions** see section 8.1 and notes above; monitor liver function; **interactions:** Appendix 1 (mercaptopurine)

**Hepatic impairment** may need dose reduction; avoid if jaundice or hepatomegaly; consult local treatment protocol for details

**Renal impairment** manufacturer advises considering reducing dose

**Contra-indications**

- **Pregnancy** avoid (teratogenic); see also section 8.1
- **Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; also gastro-intestinal effects less common; hepatotoxicity (more frequent at higher doses); rarely intestinal ulceration, pancreatitis, fever, crystalluria with haematuria, rash, and hyperpigmentation

**Licensed use** not licensed for use in children for acute lymphoblastic lymphoma or T-cell non-Hodgkin’s lymphoma

**Indication and dose**

**Acute lymphoblastic leukaemia, lymphoblastic lymphomas**

- By mouth

Consult local treatment protocol for details

**Severe ulcerative colitis and Crohn’s disease section 1.5.3**

**Puri-Nethol®** (GSK) Tablets, yellow, scored, mercaptopurine 50 mg. Net price 25-tab pack = £18.78

**Mercaptopurine Capsules**, mercaptopurine 10 mg Available from ‘special-order’ manufacturers or specialist importing companies, p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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**METHOTREXATE**

**Cautions** see section 8.1 and section 10.1.3; monitor renal and hepatic function; peptic ulceration, ulcerative colitis, diarrhoea, and ulcerative stomatitis; porphyria (section 9.8.2); **interactions:** Appendix 1 (methotrexate)

**Hepatic impairment** consult local treatment protocol for details; avoid for all indications in severe hepatic impairment

**Renal impairment** reduce dose; risk of nephrotoxicity at high doses (reduced if adequate hydration and urinary pH of 6.5–7); manufacturers advise avoid in severe renal impairment

**Contra-indications**

- **Pregnancy** 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
- **Breast-feeding** discontinue breast-feeding
**Side-effects** see section 8.1; also anorexia, abdominal discomfort, dyspepsia, gastro-intestinal ulceration and bleeding, diarrhoea, toxic megacolon, hepatotoxicity (see Cautions above); hypotension, pericarditis, pericardial tamponade, thrombosis; pulmonary oedema, pleuritic pain, pulmonary fibrosis, interstitial pneumonitis (see also Pulmonary Toxicity, p. 611); anaphylactic reactions, urticaria; dizziness, fatigue, chills, fever, drowsiness, malaise, headache, mood changes, abnormal cranial sensations, neurotoxicity, confusion, psychosis, paraesthesia, cerebral oedema; precipitation of diabetes; menstrual disturbances, vaginitis, cystitis, reduced libido, impotence; haematuria, dysuria, renal failure; osteoporosis, arthralgia, myalgia, vasculitis; conjunctivitis, blepharitis, visual disturbances; rash, pruritus, Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity, changes in nail and skin pigmentation, telangiectasia, acne, furunculosis, ecchymosis; injection-site reactions

**Indication and dose**

**Maintenance and remission of acute lymphoblastic leukaemia, lymphoblastic lymphoma**

- **By mouth**
  Consult local treatment protocol for details

**Safe Practice** To avoid error with low-dose methotrexate, it is recommended that:

- the child or their carer 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 child or their carer 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).

**Indications and dose**

**Treatment of early stage Burkitt’s lymphoma, non-Hodgkin’s lymphoma, osteogenic sarcoma, some CNS tumours including infant brain tumours, acute lymphoblastic leukaemia**

- **By intravenous injection or infusion**
  Consult local treatment protocol for details

**Meningeal leukaemia, treatment and prevention of CNS involvement of leukaemia**

- **By intrathecal injection**
  Consult local treatment protocol for details

**Severe Crohn’s disease** section 1.5.3

**Rheumatic disease** section 10.1.3

**Psoriasis** section 13.5.3

**Administration** Consult local treatment protocol for details

For **intravenous infusion**, dilute with Glucose 5% or Sodium Chloride 0.9% For **intrathecal injection**, use low-volume preservative-free preparation

**Methotrexate** (Non-proprietary) 

**Injection**, methotrexate (as sodium salt) 2.5 mg/mL, net price 2-mL vial = £1.68

**Injection**, methotrexate (as sodium salt) 25 mg/mL, net price 2-mL vial = £2.62, 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**

**Cautions** see section 8.1 and notes above; previous or concurrent intrathecal chemotherapy or craniospinal irradiation (increased risk of neurotoxicity)

**Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. cycling or driving)

**Contra-indications**

**Pregnancy** avoid (teratogenic 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

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; also constipation, diarrhoea; confusion, seizures, drowsiness, peripheral neurological disorders, demyelination, hypoaesthesia, paraesthesia, ataxia, tremor, headache, asthenia, fatigue; pyrexia; hypoglycaemia, electrolyte disturbances; arthralgia; benign and malignant tumours also reported

**Indication and dose**

**T-cell acute lymphoblastic leukaemia, T-cell lymphoblastic lymphoma**

- **By intravenous infusion**
  Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For **intravenous infusion**, give over 1–2 hours

**Atriance® (GSK)**

**Intravenous infusion**, nelarabine 5 mg/mL, net price 50-mL vial = £222.00

**Electrolytes** Na+ 3.75 mmol/vial
**8.1.4 Vinca alkaloids and etoposide**

The vinca alkaloids, **vinblastine** and **vincristine** are used to treat a variety of cancers including leukaemias, lymphomas, and some solid tumours.

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 vinblastine. Children with neurotoxicity commonly have peripheral paraesthesia, loss of deep tendon reflexes, abdominal pain, and constipation; otoxicity has been reported. If symptoms of neurotoxicity are severe, doses should be reduced, but children generally tolerate vincristine better than adults. Motor weakness can also occur and dose reduction or discontinuation of therapy may be appropriate if motor weakness increases. Recovery from neurotoxic effects is usually slow but complete.

Myelosuppression is the dose-limiting side-effect of vinblastine; vincristine causes negligible myelosuppression. The vinca alkaloids may cause reversible alopecia. They cause severe local irritation and care must be taken to avoid extravasation. Constipation is common with vinblastine and vincristine; prophylactic use of laxatives may be considered.

**Safe Practice**

Vinblastine and vincristine are for **intravenous administration only**. Inadvertent intrathecal administration can cause severe neurotoxicity, which is usually fatal.

The National Patient Safety Agency has advised (August 2008) that teenage patients treated in an adolescent unit should receive their vinca alkaloid dose in a 50 mL minibag. Teenagers and children treated in a child unit may receive their vinca alkaloid dose in a syringe.

**ETOPOSIDE**

**Cautions** see section 8.1 and notes above; interactions: Appendix 1 (etoposide)

**Renal impairment** consult specialist literature and local treatment protocol for details

**Contra-indications** see section 8.1

**Hepatic impairment** avoid in severe impairment

**Pregnancy** avoid (teratogenic in animal studies); see also section 8.1

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1, dose limiting myelosuppression, mucositis more common if given with doxorubicin; anaphylaxis associated with concentrated infusions; hypotension associated with rapid infusion; irrigant to tissues if extravasated

**Licensed use** not licensed for use in children

**Indication and dose**

**Stage 4 neuroblastoma, germ-cell tumours, intracranial germ-cell tumours, rhabdomyosarcoma, soft-tissue sarcomas, neuroectodermal tumours (including medulloblastoma), relapsed Hodgkin’s disease, non-Hodgkin’s lymphoma, Ewing tumour, acute lymphoblastic leukaemia, acute myeloid leukaemia**

*By mouth or by intravenous infusion*

Consult local treatment protocol for details

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**Side-effects** see section 8.1; also stomatitis and hepatotoxicity; rarely intestinal necrosis and perforation

**Indication and dose**

**Infant acute lymphoblastic leukaemia**

*By mouth*

Consult local treatment protocol for details

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**Lanvis** (GSK) Tablets, yellow, scored, tioguanine 40 mg. Net price 25-tab pack = £45.41

**Extemporaneous formulations available see Extemporaneous Preparations, p. 8**
Administration Consult local treatment protocol for details.

For intravenous infusion, dilute with Sodium Chloride 0.9%. Use nylon filters and PVC bags or glass bottles. Inspect solution regularly for precipitate.

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 Eposin®.

Indication and dose

Hodgkin’s disease and other lymphomas

- By intravenous injection
  Consult local treatment protocol for details.

Administration Consult local treatment protocol for details.

For intravenous injection, dilute solution containing 1 mg/mL with Sodium Chloride 0.9%; give into the tubing of a fast-running Sodium Chloride 0.9% infusion.

For child over 10 years, dilute to at least 20 mL to avoid inadvertent intrathecal use.

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

Cautions see section 8.1 and notes above; caution in handling; interactions: Appendix 1 (vinblastine).

Hepatic impairment dose reduction may be necessary, consult local treatment protocol for details.

Contra-indications see section 8.1 and notes above.

Pregnancy avoid (limited experience suggests fetal harm; teratogenic in animal studies); see also section 8.1.

Breast-feeding discontinue breast-feeding.

Indication and dose

Acute leukaemias, lymphomas, paediatric solid tumours

- By intravenous injection
  Consult local treatment protocol for details.

Administration Consult local treatment protocol for details.

For intravenous injection, dilute solution containing 1 mg/mL with Sodium Chloride 0.9%; give into the tubing of a fast-running Sodium Chloride 0.9% infusion.

For child over 10 years, dilute to at least 20 mL to avoid inadvertent intrathecal use.

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.

VINCIRISTINE SULPHATE

Cautions see section 8.1 and notes above; neuromuscular disease; ileus; caution in handling; interactions: Appendix 1 (vincristine).

Hepatic impairment dose reduction may be necessary, consult local treatment protocol for details.

Contra-indications see section 8.1 and notes above.

Pregnancy avoid (teratogenicity and fetal loss in animal studies); see also section 8.1.

Breast-feeding discontinue breast-feeding.

Indication and dose

Acute leukaemias, lymphomas, paediatric solid tumours

- By intravenous injection
  Consult local treatment protocol for details.

Administration Consult local treatment protocol for details.

For intravenous injection, dilute solution containing 1 mg/mL with Sodium Chloride 0.9%; give into the tubing of a fast-running Sodium Chloride 0.9% infusion.

For child over 10 years, dilute to at least 20 mL to avoid inadvertent intrathecal use.

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

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.

AMSA CRINE

Cautions see section 8.1 and notes above; consider monitoring cardiac function; monitor electrolytes (fatal arrhythmias possible if hypokalaemia); previous treatment with anthracyclines; also caution in handling—irritant to skin and tissues

Hepatic impairment reduce dose—25% initially, up to 50% in severe impairment

Renal impairment manufacturer advises reduce initial dose by 20–30%

Pregnancy avoid (teratogenic and toxic in animal studies); may reduce fertility; see also section 8.1

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 mucositis, phlebitis; less commonly diarrhoea, cardiotoxicity, haematuria, renal impairment, hepatotoxicity, skin rash; rarely acute renal failure, grand mal seizures

Licensed use not licensed for use in children

Indication and dose

Acute myeloid leukaemia

• By intravenous infusion

Consult local treatment protocol for details

Administration Consult local treatment protocol for details

For intravenous infusion, dilute with Glucose 5%; give over 60–90 minutes through central venous catheter

Amsidine® (Goldshield)

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

Asparaginase

Asparaginase is used almost exclusively in the treatment of acute lymphoblastic leukaemia. Hypersensitivity reactions may occur and facilities for the management of anaphylaxis should be available. A number of different preparations of asparaginase exist and only the product specified in the treatment protocol should be used. Crisantaspase is the enzyme asparaginase produced by Erwinia chrysanthemi. Preparations of asparaginase derived from Escherichia coli are also available. Children who are hypersensitive to asparaginase derived from one organism may tolerate asparaginase derived from another organism but cross-sensitivity occurs in about 20–30% of individuals.

CRISANTASPASE

Cautions see section 8.1 and notes above

Pregnancy avoid; see also section 8.1

Breast-feeding discontinue breast-feeding

Side-effects see section 8.1 and notes above; fever, CNS depression, neurotoxicity; hyperglycaemia, liver dysfunction, coagulation disorders, altered plasma lipid concentration, pancreatitis

Indication and dose

Acute lymphoblastic leukaemia, acute myeloid leukaemia, non-Hodgkin’s lymphoma

• By intravenous, intramuscular or subcutaneous injection

Consult local treatment protocol for details

Erwinase® (EUSA Pharma)

Injection, powder for reconstitution, crisantaspase. Net price 10 000-unit vial = £194.77

Preparations

Preparations of asparaginase derived from Escherichia coli are available but they are not licensed, they include: Medac® asparaginase, Elspar® asparaginase, and Oncaspar® pegaspargase.

Dacarbazine and temozolomide

Dacarbazine is a component of a commonly used combination for Hodgkin’s disease (ABVD—doxorubicin [previously Adriamycin®], bleomycin, vinblastine, and dacarbazine). It is given intravenously.

Temozolomide is structurally related to dacarbazine and is used in children for second-line treatment of malignant glioma.
**DACARBAZINE**

**Cautions** see section 8.1; caution in handling

**Hepatic impairment** dose reduction may be required in combined hepatic and renal impairment; avoid in severe impairment

**Renal impairment** dose reduction may be required in combined renal and hepatic impairment; manufacturer advises avoid in severe renal impairment

**Contra-indications**

**Pregnancy** 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

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1; also anorexia; less commonly facial flushing, confusion, headache, seizures, facial paraesthesia, influenza-like symptoms, blurred vision, renal impairment, rash; rarely diarrhoea, hepatotoxicity including liver necrosis and hepatic vein thrombosis, photosensitivity, irritant to skin and tissues, injection-site reactions

**Indication and dose**

Hodgkin’s disease, paediatric solid tumours

- By intravenous injection or by intravenous infusion

Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For slow intravenous injection, reconstitute vial with Water for Injections to produce solution containing 10 mg/mL; give over 2–3 minutes. For intravenous infusion, further dilute reconstituted solution in 125–250 mL Glucose 5% or Sodium Chloride 0.9%; give over 15–30 minutes. Protect infusion set from light throughout administration to reduce pain

**Dacarbazine** (Non-proprietary)

Injection, powder for reconstitution, dacarbazine (as citrate), net price 100-mg vial = £5.05; 200-mg vial = £7.16; 500-mg vial = £16.50; 600-mg vial = £22.50; 1-g vial = £31.80

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**TEMZOLOMIDE**

**Cautions** see section 8.1; interactions: Appendix 1 (temozolamide)

**Hepatic impairment** use with caution in severe impairment

**Renal impairment** use with caution in severe impairment

**Contra-indications**

**Pregnancy** 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

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1

**Licensed use** not licensed for treatment of malignant gliomas in children under 3 years

**Indication and dose**

Treatment of malignant gliomas

- By mouth

Consult local treatment protocol for details

**Temodal** (Schering-Plough) (TM)

Capsules, temozolomide 5 mg (green/white), net price 5-cap pack = £17.30; 20 mg (yellow/white), 5-cap pack = £69.20; 100 mg (pink/white), 5-cap pack = £346.00; 140 mg (blue/white), 5-cap pack = £484.40; 180 mg (orange/white), 5-cap pack = £622.80; 250 mg (white), 5-cap pack = £865.00. Label: 23, 25

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**Imatinib**

Imatinib, a tyrosine kinase inhibitor, has recently been licensed in children for the treatment of newly diagnosed Philadelphia-chromosome-positive chronic myeloid leukaemia when bone marrow transplantation is not considered first line treatment, and for Philadelphia-chromosome-positive chronic myeloid leukaemia in chronic phase after failure of interferon alfa, or in accelerated phase, or in blast crisis.

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**IMATINIB**

**Cautions** see section 8.1; cardiac disease; monitor for fluid retention; monitor liver function (see also Hepatic Impairment, below); interactions: Appendix 1 (imatinib)

**Hepatic impairment** start with minimum recommended dose; reduce dose further if not tolerated; consult local treatment protocol

**Renal impairment** start with minimum recommended dose; reduce dose further if not tolerated; consult local treatment protocol

**Contra-indications**

**Pregnancy** manufacturer advises avoid unless potential benefit outweighs risk; see also section 8.1

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1; also abdominal pain, appetite changes, constipation, diarrhoea, flu-like symptoms, gastro-oesophageal reflux, taste disturbance, weight changes, dry mouth; oedema (including pulmonary oedema, pleural effusion, and ascites), flushing, haemorrhage; cough, dys-
pnoea; dizziness, headache, insomnia, hypoaesthesia, paraesthesia, fatigue; influenza-like symptoms; cramps, arthralgia; visual disturbances, 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, arhythmia, 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

**Indication and dose**

**Chronic phase and advanced phase chronic myeloid leukaemia**

- By mouth
  - Consult local treatment protocol for details

**Glivec** (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

**Mitotane**

Mitotane is used in children 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. Neuro-psychological impairment can occur, possibly secondary to hypothyroidism, and growth retardation has also been reported in children treated with mitotane.

**Cautions** see notes above; risk of accumulation in overweight patients; monitor plasma-mitotane concentration—consult product literature; interactions: Appendix 1 (mitotane)

**Skilled tasks** Central nervous system toxicity may affect performance of skilled tasks

**Counselling** Children and their carers should be warned to contact doctor immediately if injury, infection, or illness occurs (because of the risk of acute adrenal insufficiency)

**Hepatic impairment** manufacturer advises caution in mild to moderate impairment—monitoring of plasma-mitotane concentration recommended; avoid in severe impairment

**Renal impairment** manufacturer advises caution in mild to moderate renal impairment—monitoring of plasma-mitotane concentration recommended; avoid in severe renal impairment

**contra-indications**

- Pregnancy manufacturer advises avoid—effective contraception should be used during and after treatment; see also section 8.1
- Breast-feeding discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; also gastro-intestinal disturbances (including nausea, vomiting, diarrhoea, epigastric discomfort), anorexia, liver disorders; hypercholesterolaemia, hypertriglyceridaemia; ataxia, confusion, asthenia, myasthenia, paraesthesia, drowsiness, neuropathy, cognitive impairment, movement disorder, dizziness, headache; gynaecomastia; prolonged bleeding time, leucopenia, thrombocytopenia, anaemia; rash; rarely hypersalivation, hypertension, postural hypotension, flushing, pyrexia, haematuria, proteinuria, haemorrhagic cystitis, hypouricaemia, visual disturbances and ocular disorders

**Licensed use** not licensed for use in children

**Indication and dose**

**Symptomatic treatment of advanced or inoperable adrenocortical carcinoma**

- By mouth
  - Consult local treatment protocol for details

**Lysodren** (HRA Pharma) Tablets, scored, mitotane 500 mg, net price 100-tab pack = £460.40. Label: 2, 10, 21, counselling, skilled tasks, adrenal suppression

**Platinum compounds**

Carboplatin is used in the treatment of a variety of paediatric malignancies; it is given by intravenous infusion. Carboplatin can be given in an outpatient setting and is better tolerated than cisplatin; nausea and vomiting are less severe and nephrotoxicity, neurotoxicity, and ototoxicity are much less of a problem. Carboplatin is, however, more myelosuppressive than cisplatin.
Cisplatin is of value in children with a variety of malignancies; it is given by intravenous infusion. Cisplatin requires intensive intravenous hydration; routine use of intravenous fluids containing potassium or magnesium may also be required to help control hypokalaemia and hypomagnesaemia. Treatment may be complicated by severe nausea and vomiting; delayed vomiting may occur and is difficult to control. Cisplatin has dose-related and potentially cumulative side-effects including nephrotoxicity, neurotoxicity, and ototoxicity. Baseline testing of renal function and hearing is required; for children with pre-existing renal or hearing impairment or marked bone-marrow suppression, consideration should be given to withholding treatment or using another drug.

**CARBOPLATIN**

**Cautions** see section 8.1 and notes above; consider therapeutic drug monitoring; **interactions:** Appendix 1 (platinum compounds)

**Renal impairment** reduce dose and monitor haematological parameters and renal function; avoid if creatinine clearance is less than 20 mL/minute/1.73 m²

**Contra-indications**

* Pregnancy avoid (teratogenic and embryotoxic in animal studies); see also section 8.1
* Breast-feeding discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; less commonly nephrotoxicity and ototoxicity

**Licensed use** not licensed for use in children

**Indication and dose**

Stage 4 neuroblastoma, germ cell tumours, low-grade gliomas (including astrocytomas), neuroectodermal tumours (including medulloblastoma), rhabdomyosarcoma (metastatic and non-metastatic disease), soft-tissue sarcomas, retinoblastoma, high risk Wilms’ tumour, some liver tumours

- By intravenous infusion
  Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9% or Sodium Chloride 0.45% and Glucose 2.5%; give over at least 24 hours (48 hours for infant brain tumours). Do not refrigerate (risk of precipitation). Ensure adequate intravenous hydration and urinary output, at least 3 hours before, during, and for at least 24 hours after administration. Mannitol routinely used to aid diuresis.

**Carboplatin** (Non-proprietary) [BNF]

**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 = £260.00

**Paraplatin** (Bristol-Myers Squibb) [BNF]

Concentrate for intravenous infusion, carboplatin 10 mg/mL, net price 5-mL vial = £21.26, 60-mL vial = £244.88

**CISPLATIN**

**Cautions** see section 8.1 and notes above; monitor full blood count, renal function, audiometry, and plasma electrolytes; **interactions:** Appendix 1 (platinum compounds)

**Renal impairment** avoid if possible—nephrotoxic and neurotoxic

**Contra-indications**

* Pregnancy avoid (teratogenic and toxic in animal studies); see also section 8.1
* Breast-feeding discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; ototoxicity (may be particularly severe in children); nephrotoxicity: hypomagnesaemia, hypokalaemia, hypophosphataemia, hypocalcaemia, hyperuricaemia; less commonly peripheral neuropathy

**Licensed use** not licensed for use in children

**Indication and dose**

Osteogenic sarcoma, stage 4 neuroblastoma, some liver tumours, infant brain tumours, intracranial germ-cell tumours

- By intravenous infusion
  Consult local treatment protocol for details

**Administration** Consult local treatment protocol for details

For intravenous infusion, dilute in Sodium Chloride 0.9% or Sodium Chloride 0.45% and Glucose 2.5%; give over at least 24 hours (48 hours for infant brain tumours). Do not refrigerate (risk of precipitation). Ensure adequate intravenous hydration and urinary output, at least 3 hours before, during, and for at least 24 hours after administration. Mannitol routinely used to aid diuresis.

**Cisplatin** (Non-proprietary) [BNF]

**Injection**, cisplatin 1 mg/mL, net price 10-mL vial = £5.85, 50-mL vial = £24.50, 100-mL vial = £50.22

**Brands include** Platinex®

**Injection**, powder for reconstitution, cisplatin, net price 50-mg vial = £17.00
**Procarbazine**

Procarbazine is most often used in Hodgkin’s disease. It is given *by mouth*. It is a weak monoamine-oxidase inhibitor and dietary restriction is rarely considered necessary. Alcohol ingestion may cause a disulfiram-like reaction.

**PROCARBAZINE**

**Cautions** see section 8.1 and notes above; interactions: Appendix 1 (procarbazine)

**Hepatic impairment** consider dose reduction; avoid in severe impairment

**Renal impairment** manufacturer advises use with caution; avoid in severe renal impairment

**Contra-indications**

**Pregnancy** avoid (teratogenic in animal studies and isolated reports in humans); see also section 8.1

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; hypersensitivity rash (discontinue treatment)

**Indication and dose**

Hodgkin’s lymphoma, gliomas

- **By mouth**
  - Consult local treatment protocol for details

**Procarbazine (Cambridge)**

Capsules, ivory, procarbazine (as hydrochloride) 50 mg, net price 50-cap pack = £181.04. Label: 4

- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

**Tretinoin**

Tretinoin is licensed for the induction of remission in acute promyelocytic leukaemia. It is used in previously untreated children 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

**Cautions** monitor full blood count and coagulation profile, liver function, serum calcium and plasma lipids before and during treatment; increased risk of thrombo-embolism during first month of treatment; interactions: Appendix 1 (retinoids)

**Hepatic impairment** reduce dose; consult local treatment protocol for details

**Renal impairment** mild impairment—reduce dose; consult local treatment protocol for details

**Contra-indications**

**Pregnancy** teratogenic; exclude pregnancy before starting treatment; 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 sufficiently effective); see also section 8.1

**Breast-feeding** discontinue breast-feeding

**Side-effects** retinoic acid syndrome (fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural effusion, hyperleukocytosis, hypotension, oedema, weight gain, hepatic, renal and multi-organ failure) requires immediate treatment—consult product literature; gastrointestinal disturbances, pancreatitis; arrhythmias, flushing, oedema; headache, benign intracranial hypertension (children particularly susceptible—consider dose reduction if intractable headache), shivering, dizziness, confusion, anxiety, depression, insomnia, paraesthesia, visual and hearing disturbances (children particularly susceptible to nervous system effects); raised liver enzymes, serum creatinine and lipids; bone and chest pain, alopecia, erythema, rash, pruritus, sweating, dry skin and mucous membranes, cheilitis; thromboembolism, hypercalcaemia, and genital ulceration reported

**Indication and dose**

Acute promyelocytic leukaemia

- **By mouth**
  - Consult treatment protocol for details

**Vesanoid** (Roche)

Capsules, yellow/brown, tretinoin 10 mg. Net price 100-cap pack = £170.52. Label: 21, 25

**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**

**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 calcineurin inhibitor
(ciclosporin or tacrolimus), combined with an antiproliferative drug (azathioprine or mycophenolate mofetil) and a corticosteroid. Specialist management is required and other immunomodulators may be used to initiate treatment or to treat rejection.

**Bioavailability**
Different formulations of the same immunosuppressant 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**
Infections in the immunocompromised child can be severe and show atypical features. Specific local protocols should be followed for the management of infection. Corticosteroids may suppress clinical signs of infection and allow diseases such as sepsicaemia or tuberculosis to reach an advanced stage before being recognised. Children should be up-to-date with their childhood vaccinations before initiation of immunosuppressant therapy (e.g. before transplantation); vaccination with varicella-zoster vaccine (section 14.4) is also necessary during this period—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 birthweight 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.

### 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 (see section 10.1.3), usually when corticosteroid therapy alone provides inadequate control. It is metabolised to mercaptopurine, and doses should be reduced to one quarter of the original dose 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 used in combination with a corticosteroid and either ciclosporin or tacrolimus for the prophylaxis of acute rejection in transplant recipients. Compared with similar regimens incorporating azathioprine, mycophenolate mofetil may reduce the risk of acute rejection episodes; the risk of opportunistic infections (particularly due to tissue-invasive cytomegalovirus) and the occurrence of blood disorders such as leucopenia may be higher. Children may suffer a high incidence of side-effects, particularly gastrointestinal effects, calling for temporary reduction in dose or interruption of treatment.

**NICE guidance (immunosuppressive therapy for renal transplantation in children and adolescents)**
See p. 521

Cyclophosphamide (section 8.1.1) is less commonly prescribed as an immunosuppressant.
AZATHIOPRINE

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; interactions: Appendix 1 (azathioprine)

Bone marrow suppression Children and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. inexplicable bruising or bleeding, infection

Hepatic impairment may need dose reduction

Renal impairment reduce dose and monitor full blood count

Pregnancy see section 8.2; treatment should not normally be initiated during pregnancy

Breast-feeding teratogenic metabolite present in milk in low concentration but no evidence of harm in small studies—consider if potential benefit outweighs risk

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—called 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

Indication and dose

Suppression of transplant rejection
• By mouth, or (if oral route not possible) by intravenous infusion (see also note below)
Consult local treatment protocol for details

Child 1 month–18 years maintenance, 1–3 mg/kg once daily, adjusted according to response;

MYCOPHENOLATE MOFETIL

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 neutropaenia develops); active gastrointestinal disease (risk of haemorrhage, ulceration and perforation); delayed graft function; increased susceptibility to skin cancer (avoid exposure to strong sunlight); possible decreased effectiveness of vaccination—avoid live vaccines; interactions: Appendix 1 (mycophenolate mofetil)

Bone marrow suppression Children and their carers should be warned to report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding

Renal impairment manufacturer advises consider dose reduction if estimated glomerular filtration rate less than 25 mL/minute/1.73 m²

Contra-indications Pregnancy manufacturer advises avoid—congenital malformations reported; effective contra-
Licensed use  by mouth, in combination with a corticosteroid and ciclosporin, for children 2 years and older for the prophylaxis of acute transplant rejection in renal transplantation

Indication and dose

Prophylaxis of acute rejection in renal transplantation in combination with a corticosteroid and ciclosporin
• By mouth or by intravenous infusion
  Consult local treatment protocol for details

Child 1 month–18 years  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

Prophylaxis of acute rejection in hepatic transplantation in combination with a corticosteroid and ciclosporin or tacrolimus
• By mouth or by intravenous infusion
  Consult local treatment protocol for details

Child 1 month–18 years  10 mg/kg twice daily, increased to 20 mg/kg twice daily (max. 2 g daily)

Administration  For intravenous infusion, dilute reconstituted solution to a concentration of 6 mg/mL in Glucose 5%; infuse over 2 hours

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
Oral suspension, mycophenolate mofetil 1 g/5 mL when reconstituted with water, net price 175 mL = £122.25
Intravenous infusion, powder for reconstitution, mycophenolate mofetil (as hydrochloride), net price 500-mg vial = £9.69

8.2.2 Corticosteroids and other immunosuppressants

The corticosteroids prednisolone and dexamethasone are widely used in paediatric oncology; they have a marked antitumour effect. Dexamethasone is preferred for acute lymphoblastic leukaemia whilst prednisolone may be used for Hodgkin’s disease, non-Hodgkin’s lymphoma, and B-cell lymphoma and leukaemia.

Dexamethasone is the corticosteroid of choice in paediatric supportive and palliative care. For children who are not receiving a corticosteroid as a component of their chemotherapy, dexamethasone may be used to reduce raised intracranial pressure (see p. 28), or to help control emesis when combined with an appropriate anti-emetic (see p. 27). For more information on glucocorticoid therapy, including the disadvantages of treatment, see section 6.3.2.

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-myelotoxic but markedly nephrotoxic. It may be used 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. Ciclosporin also has a role in steroid-sensitive and steroid-resistant nephrotic syndrome; in corticosteroid-sensitive nephrotic syndrome it may be given with prednisolone (section 6.3).

Tacrolimus is also a calcineurin inhibitor. Although not chemically related to ciclosporin it has a similar mode of action and side-effects.

Both ciclosporin and tacrolimus may affect glucose metabolism in children. Hypertrichosis may be a concern with ciclosporin.

Sirolimus is a potent non-calcineurin inhibiting immunosuppressant.

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 immunosuppression regimens; its use should be confined to specialist centres.
Antithymocyte immunoglobulin (rabbit) is used 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.

NICE guidance

Immunosuppressive therapy for renal transplantation in children and adolescents (April 2006)

NICE has recommended that for induction therapy in the prophylaxis of organ 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 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.

Mycophenolic acid is not recommended as part of an immunosuppressive regimen for renal transplantation in children or adolescents.

Sirolimus [not licensed for use in children] 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)

Cautions
see notes above; monitor blood count

Pregnancy
manufacturer advises use only if potential benefit outweighs risk—no information available

Contra-indications
infection

Breast-feeding
manufacturer advises avoid—no information available

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

Indication and dose

Heart transplantation
- By intravenous infusion over at least 6 hours
  Child 1 month–18 years 1–2.5 mg/kg daily for 3–5 days starting the day of transplantation
  Note To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight

Renal transplantation
- By intravenous infusion over at least 6 hours
  Child 1–18 years 1–1.5 mg/kg daily for 3–9 days starting the day of transplantation
  Note To avoid excessive dosage in obese patients, calculate dose on the basis of ideal body weight

Corticosteroid-resistant renal graft rejection
- By intravenous infusion over at least 6 hours
  Child 1–18 years 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

Administration
For continuous intravenous infusion reconstitute each vial with 5 mL water for injection to produce a solution of 5 mg/mL; gently rotate to dissolve. Dilute requisite dose with Glucose 5% or Sodium Chloride 0.9% to an approx. concentration of 0.5 mg/mL; begin infusion immediately after dilution; give through an in-line filter (pore size 0.22 micron); incompatible with heparin and hydrocortisone glucose infusion—precipitation reported

Thymoglobuline® [Genzyme] 
Intravenous infusion, powder for reconstitution, rabbit anti-human thymocyte immunoglobulin, net price 25-mg vial = £168.18
**Basiliximab**

**Contra-indications**

- **Pregnancy** avoid; adequate contraception must be used during treatment and for 16 weeks after last dose
- **Breast-feeding** avoid

**Side-effects** severe hypersensitivity reactions and cytokine release syndrome reported

**Indication and dose**

Prophylaxis of acute rejection in allogeneic renal transplantation used in combination with ciclosporin and corticosteroid-containing immunosuppression regimens

- By intravenous injection or by intravenous infusion
  
  Consult local treatment protocol for details

**Child over 1 year, body-weight under 35 kg**

- 10 mg within 2 hours before transplant surgery and 10 mg 4 days after surgery

**Note** withhold second dose if severe hypersensitivity or graft loss occurs

**Administration** For **intravenous infusion**, dilute reconstituted solution to a concentration not exceeding 400 micrograms/mL, with Glucose 5% or Sodium Chloride 0.9%; give over 20–30 minutes

**Simulect®** (Novartis) **(Nov)**

**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)

**Cautions** monitor kidney function (see also below); monitor liver function (see also below); 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; acute porphyria (section 9.8.2); monitor whole blood ciclosporin concentration (trough level dependent on indication—consult local treatment protocol for details); 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; in long-term management, perform renal biopsies every 1–2 years

**Additional cautions** Atopic Dermatitis and Psoriasis, section 13.5.3; Rheumatoid Arthritis, section 10.1.3

**Hepatic impairment** dosage adjustment based on bilirubin and liver enzymes may be needed

**Renal impairment** dose as in normal renal function but dose dependent increase in serum creatinine and urea during first few weeks may necessitate discontinuation (exclude rejection if kidney transplant); in nephrotic syndrome reduce dose by 25–50% if serum creatinine more than 30% above baseline on more than one measurement

**Pregnancy** see section 8.2; crosses placenta

**Breast-feeding** present in milk—manufacturer advises avoid

**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, hyperlipidaemia, hypercholesterolaemia; muscle cramps, myalgia; hypertrichosis; less commonly oedema, weight gain, encephalopathy, anaemia, thrombocytopenia, rash; rarely pancreatitis, motor polyneuropathy, menstrual disturbances, gynaecomastia, micro-angiopathic haemolytic anaemia, haemolytic uraemic syndrome, hyperglycaemia, muscle weakness, myopathy; visual disturbances secondary to benign intracranial hypertension (discontinue), also anaphylaxis reported with infusion

**Indication and dose**

Prevention of graft rejection following bone-marrow, kidney, liver, pancreas, heart, lung, and heart-lung transplantation, prophylaxis and treatment of graft-versus-host disease

- By mouth or by intravenous infusion
  
  Consult local treatment protocols for details

**Nephrotic syndrome** see also section 6.3.2, p. 445

- By mouth
  
  **Child 1 month–18 years** 3 mg/kg twice daily, increase if necessary in corticosteroid-resistant disease; for maintenance reduce to lowest effective dose according to whole blood-ciclosporin concentrations, proteinuria, and renal function

**Severe psoriasis, severe eczema** section 13.5.3

**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; Sandimmun® capsules and oral solution and SangCya® oral solution are available on named-patient basis only for children who cannot be transferred to another brand of oral ciclosporin

Because of differences in bioavailability, the brand of ciclosporin to be dispensed should be specified by the prescriber
CICLOSPORIN (continued)

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

Sandimmun® (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 polyoxyl castor oil (risk of anaphylaxis, see Excipients, p. 3)

Administration For intravenous infusion, dilute to a concentration of 0.5–2.5 mg/mL with Glucose 5% or Sodium Chloride 0.9%; give over 2–6 hours; not to be used with PVC equipment; observe patient for signs of anaphylaxis for at least 30 minutes after starting infusion and at frequent intervals thereafter.

SIROLIMUS

Cautions monitor kidney function when given with ciclosporin; Afro-Caribbean patients may require higher doses; interactions: Appendix 1

Hepatic impairment monitor blood-sirolimus trough concentration

Contra-indications

Pregnancy manufacturer advises avoid (toxicity in animal studies); effective contraception must be used during treatment and for 12 weeks after stopping

Breast-feeding discontinue breast-feeding

Side-effects abdominal pain, diarrhoea, stomatitis, abnormal liver-function tests (elevated transaminases); oedema, tachycardia, hypercholesterolaemia, hypertriglyceridaemia, venous thromboembolism; pneumonitis; pyrexia, increased susceptibility to infection (especially urinary-tract infection); proteinuria, haemolytic uraemic syndrome; anaemia, thrombocytopenia, thrombotic thrombocytopenic purpura, leucopenia, neutropenia, hypokalaemia, hypophosphataemia, hyperglycaemia, lymphocele; arthralgia, osteonecrosis; epistaxis; acne, rash, impaired healing; less commonly pancreatitis, pulmonary embolism, pulmonary haemorrhage, pericardial effusion, nephrotic syndrome, increased susceptibility to lymphoma and other malignancies particularly of the skin, and pancytopenia; rarely interstitial lung disease, hepatic necrosis, lymphoedema, and hypersensitivity reactions including anaphylactic reactions, angioedema, exfoliative dermatitis, and hypersensitivity vasculitis

Licensed use not licensed for use in children

Indication and dose

See NICE guidance, p. 521

• By mouth

Consult local treatment protocols for details

RAPAMUNE® (Wyeth) Tablets, coated, sirolimus 1 mg (white), net price 30-tab pack = £90.00; 2 mg (yellow), 30-tab pack = £180.00

Oral solution, sirolimus 1mg/mL, net price 60 mL = £169.00. Counselling, administration

Administration food may affect absorption (give at the same time with respect to food). Mix solution with at least 60 mL water or orange juice in a glass or plastic container immediately before taking; refill container with at least 120 mL of water or orange juice and drink immediately (to ensure total dose). Do not mix with any other liquids

TACROLIMUS

Cautions see under Ciclosporin; also monitor ECG (important: also echocardiography, see CSM warning below), visual status, blood glucose, haematological and neurological parameters; monitor whole blood ‘trough’ concentration of tacrolimus (especially during episodes of diarrhoea)—consult local treatment protocol for details; interactions: Appendix 1 (tacrolimus)

Skilled tasks May affect performance of skilled tasks (e.g. driving)

Hepatic impairment reduce dose in severe impairment

Contra-indications hypersensitivity to macro-lides; avoid concurrent administration with ciclosporin (care if patient has previously received ciclosporin)

Pregnancy crosses placenta; association with pre-term delivery and intra-uterine growth retardation; contra-indicated by manufacturer; exclude pregnancy before starting—if contraception needed non-hormonal methods should be used

BREAST-FEEDING avoid—present in milk following systemic administration

Side-effects include 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, leucopenia, thrombocytopenia, coagulation disorders; altered acid-base balance and glucose metabolism, electrolyte disturbances including hyperkalaemia (less frequently hypo-kalaemia); altered renal function including
increased serum creatinine; hypophosphataemia, hypercalcaemia, hyperuricaemia; muscle cramps, arthralgia; pruritus, alopecia, rash, sweating, acne, photosensitivity; susceptibility to lymphoma and other malignancies particularly of the skin; less commonly ascites, pancreatitis, asteatosis, kidney damage and renal failure, myasthenia, hirsutism, rarely Stevens-Johnson syndrome

CSM warning Cardiomyopathy has been reported in children given tacrolimus after transplantation. Children should be monitored carefully by echocardiography for hypertrophic changes; dose reduction or discontinuation should be considered if these occur

Licensed use Advagraf® not licensed for use in children

Indication and dose
See under preparation

Administration
For continuous intravenous infusion over 24 hours, dilute to a concentration of 4–100 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%, to a total volume between 20–500 mL; incompatible with PVC

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 = £84.22, 100-cap pack = £168.87; 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 polyoxyl castor oil (risk of anaphylaxis, see Excipients, p. 3)

Dose
Prophylaxis of graft rejection following liver transplantation, commencing 12 hours after completion of surgery
- By mouth
  Consult local treatment protocol for details
  Child 1 month–18 years initially 150 micrograms/kg/kg twice daily, adjusted according to whole blood concentration
- By continuous intravenous infusion (only if oral route inappropriate)
  Consult local treatment protocol for details
  Child 1 month–18 years 75–100 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole blood concentration

Allograft rejection resistant to conventional immunosuppressive regimen following liver transplantation
Consult local treatment protocol for details

Prophylaxis of graft rejection following heart transplantation, commencing within 24 hours of completion of surgery
- By mouth
  Consult local treatment protocol for details
  Child 1 month–18 years initially 150 micrograms/kg/kg twice daily, adjusted according to whole blood concentration
- By continuous intravenous infusion (only if oral route inappropriate)
  Consult local treatment protocol for details
  Child 1 month–18 years 75–100 micrograms/kg over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole blood concentration

Prophylaxis of graft rejection following heart transplantation without antibody induction
- By mouth
  Consult local treatment protocol for details
  Child 1 month–18 years initially 30–50 micrograms/kg/kg daily over 24 hours for up to 7 days (then transfer to oral therapy), adjusted according to whole blood concentration
- By continuous intravenous infusion (only if oral route inappropriate)
  Consult local treatment protocol for details
  Child 1 month–18 years 150 micrograms/kg/kg twice daily as soon as clinically possible (give 8–12 hours after discontinuation of intravenous infusion), adjusted according to whole blood concentration

Prophylaxis of graft rejection following heart transplantation following antibody induction
- By mouth
  Consult local treatment protocol for details
  Child 1 month–18 years 50–150 micrograms/kg/kg twice daily, adjusted according to whole blood concentration

Allograft rejection resistant to conventional immunosuppressive regimen following heart transplantation
Consult local treatment protocol for details

Important Prograf® and Advagraf® are not interchangeable (see MHRA/CHM advice, above); tacrolimus trough levels should be measured before conversion and within 2 weeks of conversion to Advagraf®, and if necessary dose adjustment made to maintain similar systemic exposure

Modified release Advagraf® is not licensed for use in children

Advagraf® (Astellas) Capsules, m/r, tacrolimus 500 micrograms (yellow/orange), net price 50-cap pack = £44.22; 1 mg (white/orange), 50-cap pack = £84.43, 100-cap pack = £168.87; 5 mg (red/orange), 50-cap pack = £442.17. Label: 23, 25, counselling, driving

Dose Prograf® and Advagraf® are not interchangeable (see MHRA/CHM advice, above); tacrolimus trough levels should be measured before conversion and within 2 weeks of conversion to Advagraf®, and if necessary dose adjustment made to maintain similar systemic exposure

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
8.2.3 Rituximab and alemtuzumab

**Rituximab**, a monoclonal antibody which causes lysis of B lymphocytes, has been used as a component of the treatment of post-transplantation lymphoproliferative disease, non-Hodgkin’s lymphoma, Hodgkin’s lymphoma, and severe cases of resistant immune modulated disease including idiopathic thrombocytopenia purpura, haemolytic anaemia, and systemic lupus erythematosus. Full resuscitation facilities should be at hand and as with other cytotoxics, treatment should be undertaken under the close supervision of a specialist.

Rituximab should be used with caution in children receiving cardiotoxic chemotherapy or with a history of cardiovascular disease; in adults 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.

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. Children 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 or local treatment protocol 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. Children 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).

**Alemtuzumab**, another monoclonal antibody that causes lysis of B lymphocytes, has been used in children for conditioning therapy before allogeneic bone marrow transplantation. 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.

### ALEMTUZUMAB

**Cautions** see notes above—for full details (including monitoring) consult product literature or local treatment protocol

**Contra-indications** for full details consult product literature or local treatment protocol

**Pregnancy** avoid; manufacturer advises effective contraception for 6 months after treatment in men or women

**Breast-feeding** avoid; manufacturer advises avoid breast-feeding during treatment and for at least 4 weeks after treatment

**Side-effects** see notes above—for full details (including monitoring and management of side-effects) consult product literature

### Licensed use

not licensed for use in children under 17 years

### Indication and dose

See notes above

- By intravenous infusion
  Consult local treatment protocol for details

### Administration

For intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%. Add requisite dose through a low protein binding 5-micron filter to 100-mL infusion fluid; infuse over 2 hours

**MabCampath® (Bayer)**

Concentrate for intravenous infusion, alemtuzumab 30 mg/mL, net price 1-mL amp = £274.83

### RITUXIMAB

**Cautions** see notes above—but for full details (including monitoring) consult product literature or local treatment protocol

**Contra-indications**

**Pregnancy** avoid unless potential benefit to mother outweighs risk of B-lymphocyte depletion in fetus—effective contraception (in both sexes) required during and for 12 months after treatment

**Breast-feeding** avoid breast-feeding during and for 12 months after treatment

**Side-effects** see notes above—but for full details (including monitoring and management of side-effects) consult product literature
Licensed use  not licensed for use in children

Indication and dose

See notes above
• By intravenous infusion
  Consult local treatment protocol for details

Administration  For intravenous infusion, dilute to a concentration of 1–4 mg/mL with Glucose 5% or Sodium Chloride 0.9%; gently invert bag to avoid foaming

MabThera® (Roche) [Roche]
Concentrate for intravenous infusion, rituximab 10 mg/mL, net price 10-mL vial = £174.63, 50-mL vial = £873.15

8.2.4 Other immunomodulating drugs

Interferon alfa

Interferon alfa has shown some antitumour effect and may have a role in inducing early regression of life-threatening corticosteroid-resistant haemangiomas of infancy. 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). Interferon alfa should always be used under the close supervision of a specialist. 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 and monitoring of hepatic function is recommended. 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, and reversible motor problems in young children. Rarely pulmonary infiltrates, pneumonitis, and pneumonia have occurred; respiratory symptoms should be investigated and if pulmonary infiltrates are suspected or lung function is impaired the discontinuation of interferon alfa should be considered.

INTERFERON ALFA

Cautions  consult product literature and local treatment protocol for details; interactions: Appendix 1 (interferons)

Hepatic impairment  close monitoring in mild to moderate impairment; avoid if severe
Renal impairment  close monitoring required; manufacturers advise avoid in severe impairment

Contra-indications  consult product literature and local treatment protocol for details; avoid injections containing benzyl alcohol in neonates (see under preparations below)

Pregnancy  manufacturers recommend avoid unless compelling reasons; effective contraception required in both sexes if receiving treatment

Breast-feeding  manufacturers advise avoid

Side-effects  see notes above, consult product literature and local treatment protocols for details

Licensed use  not licensed for use in children for chronic active hepatitis B; Roferon-A® not licensed for use in children

Indication and dose

Induction of early regression of life-threatening corticosteroid resistant haemangiomas of infancy
• By subcutaneous injection
  Consult local treatment protocol for details

Chronic active hepatitis B infection  see under preparations below

Chronic active hepatitis C infection  see under preparations below

IntronA® (Schering-Plough) [Schering-Plough]
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, 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 = £35.70.

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

Dose

Chronic active hepatitis B
• By subcutaneous injection
  Child 2–18 years 5–10 million units/m² 3 times weekly

Chronic active hepatitis C (in combination with oral ribavirin, see p.393)
• By subcutaneous injection
  Child 3–18 years 3 million units/m² 3 times weekly

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 mil-
l lion units/mL, 0.5-mL (6 million-unit) prefilled syringe = £30.12; 18 million 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 intramuscular injection (cartridges and vials)

**Excipients** include benzyl alcohol (avoid in neonates, see Excipients, p. 3)

**Dose**

- **Chronic active hepatitis B**
  - By subcutaneous injection
  - **Child 2–18 years** 2.5–5 million units/m² 3 times weekly; up to 10 million units/m² has been used 3 times weekly

**Interferon gamma**

**Interferon gamma-1b** is used to reduce the frequency of serious infection in chronic granulomatous disease and in severe malignant osteopetrosis.

**INTERFERON GAMMA-1b**

*(Immune interferon)*

**Cautions** 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); **interactions**: Appendix 1 (interferons)

**Driving** May impair ability to perform skilled tasks; effects may be enhanced by alcohol

**Hepatic impairment** manufacturer advises caution in severe liver disease

**Renal impairment** manufacturer advises caution in severe impairment—risk of accumulation

**Pregnancy** manufacturer recommends avoid unless compelling reasons; effective contraception should be used by men and women

**Breast-feeding** manufacturer advises avoid—no information available

**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

**Indication and dose**

See notes above and under Preparations below

**Immukin®** (Boehringer Ingelheim)

Injection, recombinant human interferon gamma-1b 200 micrograms/mL, net price 0.5-mL vial = £88.00

**Dose**

- By subcutaneous injection
  - **Body surface area 0.5 m² or less** 1.5 micrograms/kg 3 times a week
  - **Body surface area greater than 0.5 m²** 50 micrograms/m² 3 times a week

Not recommended for infant under 6 months with chronic granulomatous disease

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**8.3 Sex hormones and hormone antagonists in malignant disease**

Classification not used in BNF for Children.
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

Treatments with an iron preparation is justified only in the presence of a demonstrable iron-deficiency state. Before starting treatment, it is important to exclude any serious underlying cause of the anaemia (e.g. gastrointestinal bleeding). The possibility of thalassaemia should be considered in children of Mediterranean or Indian subcontinent descent.

Prophylaxis with an iron preparation may be appropriate in those with a poor diet, malabsorption, menorrhagia, pregnancy, in haemodialysis patients, and in the management of low birth-weight infants such as preterm neonates.

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 formulation, palatability, incidence of side-effects and cost.

**Treatment of iron-deficiency anaemia**

The oral dose of elemental iron to treat deficiency is 3–6 mg/kg (max. 200 mg) daily given in 2–3 divided doses. Iron supplementation may also be required to produce an optimum response to erythropoietins in iron-deficient children with chronic renal failure or in preterm neonates. (See also Prophylaxis of iron deficiency, below.)

Prescribing Express the dose in terms of elemental iron and iron salt and select the most appropriate preparation; specify both the iron salt and formulation on the prescription. The iron content of artificial formula feeds should also be considered.

<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>
<tr>
<td>Sodium feredetate</td>
<td>190 mg</td>
<td>27.5 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 normal 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. The most common reason for lack of response in children is poor compliance; poor absorption is rare in children.

**Prophylaxis of iron deficiency**

In neonates, haemoglobin and haematocrit concentrations change rapidly. These changes are not due to iron deficiency and cannot be corrected by iron supplementation. Similarly, neonatal anaemia resulting from repeated blood sampling does not respond to iron therapy.

All babies, including preterm neonates, are born with substantial iron stores but these stores can become depleted unless dietary intake is adequate. All babies require an iron intake of 400–700 nanograms daily to maintain body stores. Iron in breast milk is well absorbed but that in artificial feeds or in cow’s milk is less so. Most artificial formula feeds are sufficiently fortified with iron to prevent deficiency and their iron content should be taken into account when considering further iron supplementation.

**Dose**

Prophylactic iron supplementation (elemental iron 5 mg daily) may be required in babies of low birth-weight who are solely breast-fed; supplementation...
is started 4–6 weeks after birth and continued until mixed feeding is established. Infants with a poor diet may become anaemic in the second year of life, particularly if cow’s milk, rather than fortified formula feed, is a major part of the diet.

**Compound preparations** 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 p. 534.

**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 can exacerbate diarrhoea in patients with inflammatory bowel disease.

Iron preparations taken orally can be constipating 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 content of elemental iron. The incidence of side-effects due to ferrous sulphate is no greater than with other iron salts when compared on the basis of equivalent amounts of elemental iron.

Iron preparations are an important cause of accidental overdose in children and as little as 20 mg/kg of elemental iron can lead to symptoms of toxicity. For the treatment of iron overdose, see Emergency Treatment of Poisoning, p. 42.

**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.

### Ferrous Sulphate

**Cautions** interactions: Appendix 1 (iron)

**Side-effects** see notes above

**Indication and dose**

Iron-deficiency anaemia, prophylaxis of iron deficiency See notes above and preparations

Ferrous Sulphate (Non-proprietary)

**Tablets**, coated, dried ferrous sulphate 200 mg (65 mg iron), net price 28-tab pack = £1.44

**Dose**

Child 6–18 years prophylactic, 1 tablet daily; therapeutic, 1 tablet 2–3 times daily, see notes above

**Ironorm® Drops** (Wallace Mfg)

Oral drops, ferrous sulphate 625 mg (125 mg iron)/5 mL. Net price 15 mL = £3.35

**Dose**

Child 1 month–6 years prophylactic 0.3 mL daily, but see notes above

Child 6–18 years prophylactic 0.6 mL daily

### Ferrous Fumarate

**Cautions** interactions: Appendix 1 (iron)

**Side-effects** see notes above

**Indication and dose**

Iron-deficiency anaemia, prophylaxis of iron deficiency See notes above and preparations

Fersaday® (Goldshield)

**Tablets**, brown, f/c, ferrous fumarate 322 mg (100 mg iron). Net price 28-tab pack = 79p

**Dose**

Child 12–18 years 1–2 tablets 3 times daily, but see notes above

Fersamal® (Goldshield)

**Tablets**, brown, ferrous fumarate approx. 140 mg (45 mg iron)/5 mL. Net price 200 mL = £3.11

**Dose**

Preterm neonate see notes above

Neonate see notes above

Child 1 month–6 years 2.5–5 mL twice daily, but see notes above

Child 6–18 years 10 mL twice daily, but see notes above
**FERROUS FUMARATE (continued)**

*Galfer®* (Thornton & Ross)  
**Capsules**, red/green, ferrous fumarate 305 mg (100 mg iron). Net price 20 = 36p

**Dose**  
**Child 12–18 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**  
**Preterm neonate and body-weight up to 3 kg** prophylactic, 0.5 mL daily; therapeutic, 0.25 mL/kg twice daily (total daily dose may alternatively be given in 3 divided doses), see notes above

**Neonate** prophylactic and therapeutic, 0.25 mL/kg twice daily (total daily dose may alternatively be given in 3 divided doses); max 20 mL daily, see notes above

**Child 12–18 years** prophylactic, 10 mL once daily; therapeutic, 10 mL 1–2 times daily

**FERROUS GLUCONATE**

**Cautions** interactions: Appendix 1 (iron)  
**Side-effects** see notes above

**Indication and dose**  
**Iron-deficiency anaemia** See notes above and preparation

**Ferrous Gluconate** *(Non-proprietary)*  
**Tablets**, red, coated, ferrous gluconate 300 mg (35 mg iron). Net price 20 = 73p

**Dose**  
**Child 6–12 years** prophylactic and therapeutic, 1–3 tablets daily  
**Child 12–18 years** prophylactic, 2 tablets daily; therapeutic, 4–6 tablets daily in divided doses

**POLYSACCHARIDE-IRON COMPLEX**

**Cautions** interactions: Appendix 1 (iron)  
**Side-effects** see notes above

**Indication and dose**  
**Iron-deficiency anaemia, prophylaxis of iron deficiency** See notes above and preparation

*Niferex®* *(Tillomed)*  
**Elixir**, brown, sugar-free, polysaccharide-iron complex equivalent to 100 mg of iron/5 mL. Net price 240-mL pack = £6.06; 30-mL dropper bottle for paediatric use = £2.16. Counselling, use of dropper

**Child 1 month–2 years** (from dropper bottle) 1 drop (approx. 500 micrograms iron) per 450 g body-weight 3 times daily, see notes above

**Child 2–6 years** therapeutic, 2.5 mL daily  
**Child 6–12 years** therapeutic, 5 mL daily  
**Child 12–18 years** prophylactic, 2.5 mL daily; therapeutic, 5 mL 1–2 times daily (5 mL once daily if required during second and third trimester of pregnancy)

**Sytron®** *(Link)*  
**Elixir**, sugar-free, sodium feredetate 190 mg equivalent to 27.5 mg of iron/5 mL. Net price 100 mL = 89p

**Dose**  
**Neonate** (from dropper bottle) 1 drop (approx. 500 micrograms iron) per 450 g body-weight 3 times daily, see notes above  
**Neonate** prophylactic, 1 mL daily, see notes above; therapeutic, up to 2.5 mL twice daily (smaller doses should be used initially), see notes above  
**Child 1 month–1 year** prophylactic, 1 mL daily, see notes above; therapeutic, up to 2.5 mL twice daily (smaller doses should be used initially), see notes above  
**Child 1–5 years** therapeutic, 2.5 mL 3 times daily  
**Child 5–12 years** therapeutic, 5 mL 3 times daily  
**Child 12–18 years** therapeutic, 5 mL increasing gradually to 10 mL 3 times daily

**SODIUM FEREDETATE**  
*(Sodium ironedetate)*  
**Cautions** interactions: Appendix 1 (iron)  
**Side-effects** see notes above

**Licensed use** not licensed for prophylaxis of iron deficiency

**Indication and dose**  
**Iron-deficiency anaemia, prophylaxis of iron deficiency** See notes above and preparation

**Sodium Feredetate** *(Sodium ironedetate)*  
**Elixir**, sugar-free, sodium feredetate 190 mg equivalent to 27.5 mg of iron/5 mL. Net price 100 mL = 89p

**Dose**  
**Neonate** prophylactic, 1 mL daily, see notes above; therapeutic, up to 2.5 mL twice daily (smaller doses should be used initially), see notes above  
**Child 1 month–1 year** prophylactic, 1 mL daily, see notes above; therapeutic, up to 2.5 mL twice daily (smaller doses should be used initially), see notes above  
**Child 1–5 years** therapeutic, 2.5 mL 3 times daily  
**Child 5–12 years** therapeutic, 5 mL 3 times daily  
**Child 12–18 years** therapeutic, 5 mL increasing gradually to 10 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 child cannot tolerate oral iron, or does not take it reliably, or if there is continuing blood loss, or in malabsorption.

Many children 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 children 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 iron complexes; depending on the preparation, a small test dose may be required, see preparations for details; facilities for cardiopulmonary resuscitation must be available. If children complain of acute symptoms particularly nausea, back pain, breathlessness, or develop hypotension, the infusion should be stopped.

**FERRIC CARBOXYMALTOSE**

A ferric carboxymaltose complex containing 5% (50 mg/mL) of iron

**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; infection (discontinue if ongoing bacteraemia)

**Hepatic impairment** use with caution; avoid in conditions where iron overload increases risk of impairment

**Pregnancy** avoid in first trimester, crosses the placenta in animal studies; may influence skeletal development

**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

**Licensed use** not licensed for use in children under 14 years

**Indication and dose** Iron-deficiency anaemia see notes above.

- By slow intravenous injection or by intravenous infusion
  Calculated according to body-weight and iron deficit, consult product literature

**Ferinject** (Syner-Med)

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 sucrose containing 5% (50 mg/mL) of iron

**Cautions** oral iron not to be given until 5 days after last injection

**Pregnancy** avoid in first trimester, crosses the placenta in animal studies; may influence skeletal development

**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. 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 and eczema; infection; active rheumatoid arthritis

**Hepatic impairment** avoid in severe impairment

**Renal impairment** avoid in acute renal failure

**Side-effects** less commonly nausea, vomiting, abdominal pain, flushing, dyspnoea, anaphylactic reactions (see Anaphylaxis above), numbness, cramps, blurred vision, pruritus, and rash; rarely diarrhoea, chest pain, hypotension, angioedema, arrhythmias, tachycardia, dizziness, restlessness, fatigue, seizures, tremor, impaired consciousness, myalgia, arthralgia, sweating, and injection-site reactions; very rarely hypertension, palpitation, headache, paraesthesia, haemolysis, and transient deafness

**Licensed use** not licensed for use in children under 14 years

**Indication and dose** Iron-deficiency anaemia see notes above.

- By slow intravenous injection or by intravenous infusion
  Calculated according to body-weight and iron deficit, consult product literature

**Cosmofer** (Vitaline)

Injection, iron (as iron dextran) 50 mg/mL, net price 2-mL amp = £7.97; 10-mL amp = £39.85

**Electrolytes** Na⁺ 0.24 mmol/mL
IRON SUCROSE

A complex of ferric hydroxide with sucrose containing 2% (20 mg/mL) of iron

Cautions oral iron therapy should not be given until 5 days after last injection; infection (discontinue if ongoing bacteraemia)

Pregnancy avoid in first trimester

Hepatic impairment use with caution; avoid in conditions where iron overload increases risk of impairment

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, asthenia, and paraesthesia; confusion, arthralgia, and increased sweating also reported

Licensed use not licensed for use in children

Indication and dose Iron-deficiency anaemia see notes above.

- By slow intravenous injection or by intravenous infusion

Calculated according to body-weight and iron deficit, consult product literature

Venofer (Syner-Med) Injection, iron (as iron sucrose) 20 mg/mL, net price 5-mL amp = £7.08

9.1.2 Drugs used in megaloblastic anaemias

Megaloblastic anaemias are rare in children; they may result from a lack of either vitamin B\textsubscript{12} 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.

Vitamin B\textsubscript{12} is used in the treatment of megaloblastosis caused by prolonged nitrous oxide anaesthesia, which inactivates the vitamin, and in the rare disorders of congenital transcobalamin II deficiency, methylmalonic acidemia and homocystinuria (see section 9.8.1).

Vitamin B\textsubscript{12} should be given prophylactically after total ileal resection.

Apart from dietary deficiency, all other causes of vitamin B\textsubscript{12} deficiency are attributable to malabsorption. There is little place for the use of low-dose vitamin B\textsubscript{12} orally and none for vitamin B\textsubscript{12} intrinsic factor complexes given by mouth. Vitamin B\textsubscript{12} in large oral doses [unlicensed] may be effective.

Hydroxocobalamin has completely replaced cyanocobalamin as the form of vitamin B\textsubscript{12} 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\textsubscript{12} 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\textsubscript{12} is administered concurrently otherwise neuropathy may be precipitated (see above).

In folate-deficient megaloblastic anaemia (e.g. because of poor nutrition, pregnancy, or treatment with antiepileptics), daily folic acid supplementation for 4 months brings about haematological remission and replenishes body stores; higher doses may be necessary in malabsorption states. In pregnancy, folic acid 5 mg daily is continued to term.

For prophylaxis in chronic haemolytic states, malabsorption or in renal dialysis, folic 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.

Folic acid is actively excreted in breast milk and is well absorbed by the infant. It is also present in cow’s milk and artificial formula feeds but is heat labile. Serum and
red cell folate concentrations fall after delivery and urinary losses are high, particularly in low birth-weight neonates. Although symptomatic deficiency is rare in the absence of malabsorption or prolonged diarrhoea, it is common for neonatal units to give supplements of folic acid to all preterm neonates from 2 weeks of age until full-term corrected age is reached, particularly if heated breast milk is used without an artificial formula fortifier.

Folinic acid is also effective in the treatment of folate-deficient megaloblastic anaemia but it is normally only 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 4.8.1).

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 B₁₂ or folic acid.

**HYDROXOCOBALAMIN**

**Cautions**  should not be given before diagnosis fully established but see also notes above; **interactions** Appendix 1 (hydroxocobalamin)

**Side-effects**  itching, exanthema; fever, chills, hot flushes; nausea, dizziness; initial hypokalaemia; rarely acniform and bullous eruptions; anaphylaxis

**Licensed use**  licensed for use in children (age not specified by manufacturers); not licensed for use in inborn errors of metabolism

**Indication and dose**

**Macrocystic anaemia without neurological involvement**

- By intramuscular injection
  **Child 1 month–18 years** initially 250 micrograms–1 mg 3 times a week for 2 weeks then 250 micrograms once weekly until blood count normal, then 1 mg every 3 months

**Macrocystic anaemia with neurological involvement**

- By intramuscular injection
  **Child 1 month–18 years** initially 1 mg on alternate days until no further improvement, then 1 mg every 2 months

**Prophylaxis of macrocystic anaemias associated with vitamin B₁₂ deficiency**

- By intramuscular injection
  **Child 1 month–18 years** 1 mg every 2–3 months

**Leber’s optic atrophy**

- By intramuscular injection
  initially 1 mg daily for 2 weeks, then 1 mg twice weekly until no further improvement, thereafter 1 mg every 1–3 months

**Congenital transcobalamin II deficiency**

- By intramuscular injection
  **Neonate** 1 mg 3 times a week, reduce after 1 year to 1 mg once weekly or as appropriate
  **Child 1 month–18 years** 1 mg 3 times a week, reduce after 1 year to 1 mg once weekly or as appropriate

**Methylmalonic acidaemia and homocystinuria**

- By intramuscular injection
  **Child 1 month–18 years** initially 1 mg daily for 5–7 days, reduce according to response to maintenance dose of up to 1 mg once or twice weekly
Methylmalonic acidaemia, maintenance once intramuscular response established

By mouth
Child 1 month–18 years 5–10 mg once or twice weekly

Note Some children do not respond to the oral route

Hydroxocobalamin (Non-proprietary) (HY)
Injection, hydroxocobalamin 1 mg/mL. Net price 1-mL amp = £2.46
Brands include Cobalin-H®, Neo-Cytamen®

Injection, hydroxocobalamin 2.5 mg/mL, 2 mL Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
Administration For administration by mouth, injection solution may be given orally; it will not have prolonged effect via this route
Note The BP directs that when Vitamin B₁₂ injection is prescribed or demanded hydroxocobalamin injection shall be dispensed or supplied
Powder available from specialist importing companies

FOLIC ACID

Cautions should never be given alone for vitamin B₁₂ deficiency states (may precipitate subacute combined degeneration of the spinal cord); interactions: Appendix 1 (folates)
Side-effects rarely gastro-intestinal disturbances
Licensed use unlicensed for limiting methotrexate toxicity

Indication and dose

Folate supplementation in neonates (see notes above)
• By mouth

Neonate 50 micrograms once daily or 500 micrograms once weekly

Megaloblastic anaemia due to folate deficiency (see notes above)
• By mouth

Neonate initially 500 micrograms/kg once daily for up to 4 months
Child 1 month–1 year initially 500 micrograms/kg once daily (max. 5 mg) for up to 4 months; up to 10 mg daily may be required in malabsorption states
Child 1–18 years 5 mg daily for 4 months; (until term in pregnant women); up to 15 mg daily may be required in malabsorption states

Haemolytic anaemia; metabolic disorders
• By mouth
Child 1 month–12 years 2.5–5 mg once daily
Child 12–18 years 5–10 mg once daily

Prophylaxis of folate deficiency in dialysis
• By mouth
Child 1 month–12 years 250 microgram/kg (max. 10 mg) once daily
Child 12–18 years 5–10 mg once daily

Prevention of methotrexate side-effects in juvenile idiopathic arthritis
• By mouth
Child 2–18 years 1 mg daily or 5 mg once weekly, adjusted according to local guidelines

Prevention of methotrexate side-effects in severe Crohn’s disease or severe psoriasis
• By mouth
See section 1.5.3 and section 13.5.3

Prevention of neural tube defects
• By mouth
See notes above

Folic Acid (Non-proprietary) (HY)
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)
1. Can be sold to the public provided daily doses do not exceed 500 micrograms

9.1.3 Drugs used in hypoplastic, haemolytic, and renal anaemias

Anabolic steroids (see BNF, section 6.4.3), pyridoxine, antilymphocyte immunoglobulin, and various corticosteroids are used in hypoplastic and haemolytic anaemias.

Antilymphocyte globulin given intravenously through a central line over 12–18 hours each day for 5 days produces a response in about 50% of cases of acquired aplastic anaemia; the response rate may be increased when ciclosporin is given as well. Severe reactions are common in the first 2 days and profound immunosuppression can occur; antilymphocyte globulin should be given under specialist supervision with appropriate resuscitation facilities. Alternatively, oxymetholone tablets (available from ‘special-order’ manufacturers or specialist importing companies, see p. 943) may be used in aplastic anaemia at a dose of 1–5 mg/kg daily for 3 to 6 months.

It is unlikely that dietary deficit of pyridoxine (section 9.6.2) produces clinically relevant haematological effects. However, certain forms of sideroblastic anaemia
respond to pharmacological doses, possibly reflecting its role as a co-enzyme during haemoglobin synthesis. Pyridoxine is indicated in both idiopathic acquired and hereditary sideroblastic anaemias. Although complete cures have not been reported, some increase in haemoglobin can occur with high doses. Reversible sideroblastic anaemias respond to treatment of the underlying cause but pyridoxine is indicated in pregnancy, haemolytic anaemias, or during isoniazid treatment.

Corticosteroids (section 6.3) have an important place in the management of haematological disorders including autoimmune haematologic anaemia, idiopathic thrombocytopenias (section 9.1.4) and neutropenias, and major transfusion reactions. They are also used in chemotherapy schedules for many types of lymphoma, lymphoid leukaemias, and paraproteinaemias, including multiple myeloma.

### Erythropoietins

**Epoetins** (recombinant human erythropoietins) are used to treat the anaemia associated with erythropoietin deficiency in chronic renal failure, see below.

**Epoetin beta** is also used for the prevention of anaemia in preterm neonates of low birth-weight; a therapeutic response may take several weeks. Only unpreserved formulations should be used as other preparations may contain benzyl alcohol (see Excipients, p. 3).

There is insufficient information to support the use of erythropoietins in children with leukaemia or in those receiving cancer chemotherapy.

**Darbepoeitin** is a glycosylated derivative of epoetin; it persists longer in the body and can be administered less frequently 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 and in preterm neonates (see section 9.1.1.1). Aluminium toxicity, concurrent infection, or other inflammatory disease can impair the response to erythropoietin.

### Erythropoietins—haemoglobin concentration

In chronic kidney disease, the use of erythropoietins can be considered in a child with anaemia. The aim of treatment is to relieve symptoms of anaemia and to avoid the need for blood transfusion. The optimum haemoglobin concentration is dependent on the child’s age and factors such as symptoms, co-morbidities, and patient preferences. The haemoglobin concentration should not be increased beyond that which provides adequate control of symptoms of anaemia. In adults, overcorrection of haemoglobin concentration with erythropoietins in those with chronic kidney disease may increase the risk of serious cardiovascular events and death; haemoglobin concentrations higher than 12 g/100 mL should be avoided in children.

For MHRA/CHM advice relating to adults, see BNF section 9.1.3.

### 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.

### DARBEPOETIN ALFA

**Cautions** see Epoetin

**Hepatic impairment** manufacturer advises caution

**Pregnancy** no evidence of harm in animal studies—manufacturer advises caution

**Contra-indications** see Epoetin

**Breast-feeding** manufacturer advises avoid—no information available

**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
**Indication and dose**

Symptomatic anaemia associated with chronic renal failure in children on dialysis (see notes above)

- By intravenous or subcutaneous injection

**Child 11–18 years** 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

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 over 4 weeks or if haemoglobin concentration exceeds 2 g/100 mL over 4 weeks.

**Contra-indications**

- Under preparations, below

**Cautions**

- See notes above; also inadequately treated or poorly controlled blood pressure, hypertensive crisis; sickle-cell disease (lower target haemoglobin concentration may be appropriate); status epilepticus requiring immediate medical intervention; dose-dependent increase in blood pressure or aggravation of hypertension; in selected patients with normal or low blood pressure, hypertensive crisis with encephalopathy-like symptoms and generalised tonic-clonic seizures requiring immediate medical attention; 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 subcutaneous 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

**Licensed use**

- Eprex® 20 000–unit, 30 000–unit, and 40 000–unit prefilled syringes not licensed for use in children. NeoRecormon® Multidose Injection and Reco-Pen not licensed for use in children under 3 years

**Indication and dose**

See under preparations, below

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**EPOETIN ALFA, BETA, and ZETA** (Recombinant human erythropoietins)

**Note**

- The prescriber must specify which epoetin is required, see also Biosimilar medicines, p. 2

**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 stabbing migraine-like pain is warning of hypertensive crisis; sickle-cell disease (lower target haemoglobin concentration may be appropriate); ischaemic vascular disease; thrombocytosis (monitor platelet count for first 8 weeks); epilepsy; malignant disease; increase in heparin dose may be needed

**Hepatic impairment**

- Manufacturers advise caution in chronic impairment

**Pregnancy**

- No evidence of harm; benefits probably outweigh risks of anaemia and blood transfusion

**Breast-feeding**

- Unlikely to be present in milk; effect on infant minimal

**Contra-indications**

- Pure red cell aplasia following erythropoietin therapy (see also CSM advice above); uncontrolled hypertension; 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

**Epoetin alfa**

- Binocrit® (Sandoz)

**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
9 Nutrition and Blood

Dose

Symptomatic anaemia associated with chronic renal failure in children on haemodialysis (see also notes above)

- By intravenous injection over 1–5 minutes
  
  **Child 1 month–18 years** 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, 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.

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.

**Eprex** (Janssen-Cilag) \(\uparrow\) (Roche)

**Injection.** prefilled syringe, epoetin alfa, net price 1000 units = £6.29; 2000 units = £12.57; 3000 units = £18.86; 4000 units = £25.14; 5000 units = £31.43; 6000 units = £37.71; 8000 units = £50.28; 10 000 units = £62.85; 20 000 units = £125.70; 30 000 units = £226.26; 40 000 units = £301.68.

An auto-injector device is available for use with prefilled syringes.

Dose

Symptomatic anaemia associated with chronic renal failure in children on haemodialysis (see also notes above)

- By intravenous injection over 1–5 minutes
  
  **Child 1 month–18 years** 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, 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 30–60 kg usually 30–100 units/kg 3 times weekly, body-weight over 60 kg usually 75–300 units/kg weekly (as a single dose or in divided doses).

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.

**Epoetin zeta**

**NeoRecormon** (Roche) \(\uparrow\) (Roche)

**Injection.** prefilled syringe, epoetin zeta, 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 = £233.61.

Excipients include phenylalanine up to 500 micrograms/cartridge (section 9.4.1), benzyl alcohol (avoid in neonates, see Excipients p.3).

**Note** Avoid contact of reconstituted injection with glass; use only plastic materials.
Sickle-cell disease

Sickle-cell disease is caused by a structural abnormality of haemoglobin resulting in deformed, less flexible red blood cells. Acute complications in the more severe forms include sickle-cell crisis, where infarction of the microvasculature and blood supply to organs results in severe pain. Sickle-cell crisis requires hospitalisation, intravenous fluids, analgesia (section 4.7) and treatment of any concurrent infection. Chronic complications include skin ulceration, renal failure and increased susceptibility to infection. Pneumococcal vaccine (section 14.4), haemophilus influenzae type b vaccine (section 14.4), an annual influenza vaccine (section 14.4) and prophylactic penicillin (Table 2, section 5.1) reduce the risk of infection. Hepatitis B vaccine (section 14.4) should be considered if the child is not immune.

In most forms of sickle-cell disease, varying degrees of haemolytic anaemia are present accompanied by increased erythropoiesis; this may increase folate requirements and folate supplementation may be necessary (section 9.1.2).

Hydroxyurea may reduce the rate of crises and the need for blood transfusions. Hydroxyurea should be considered, in consultation with a specialist centre, for children who have recurrent episodes of acute pain (more than 3 admissions in the previous 12 months, or who are very symptomatic in the community) or who have had 2 or more episodes of acute sickle chest syndrome in the last 2 years (or 1 episode requiring ventilatory support). Beneficial effects of hydroxyurea may not become evident for several months. Myelosuppression, nausea, and skin reactions are the most common adverse effects.

**HYDROXYCARBAMIDE**

*(Hydroxyurea)*

**Cautions** see section 8.1 and notes above; also monitor renal and hepatic function before and during treatment; monitor full blood count before treatment, then every 2 weeks for the first 2 months and then every 2 months thereafter (or every 2 weeks if on max. dose); leg ulcers (review treatment if cutaneous vasculitic ulcerations develop); **interactions:** Appendix 1 (hydroxyurea)

**Renal impairment** reduce initial dose by 50% if estimated glomerular filtration rate less than 60 mL/minute/1.73 m$^2$; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m$^2$

**Hepatic impairment** avoid if severe

**Contra-indications**

**Pregnancy** avoid (teratogenic in animal studies); manufacturer advises effective contraception before and during treatment; see also section 8.1

**Breast-feeding** discontinue breast-feeding

**Side-effects** see section 8.1 and notes above; also dizziness, headache; rarely reduced sperm count and activity; fever, amenorrhoea, bleeding, and hypomagnesaemia also reported

**Indication and dose**

**Sickle-cell disease**

- **By mouth**
  - **Child 2–18 years** initially 10–15 mg/kg once daily, increased every 12 weeks in steps of 5 mg/kg daily according to response; usual dose 15–30 mg/kg daily (max. 35 mg/kg daily)

**Siklos** (Nordic) ; Tablets, scored, f/c, hydroxyurea 1 g, net price 30-tab pack = £500.00

- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

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, and in thalassaemia, 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. The initial 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 ascorbic acid (vitamin C, section 9.6.3) 100–200 mg daily by mouth; it should be given separately from food since it also enhances iron absorption. Ascorbic acid should not be given to children with cardiac dysfunction; in children 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 children over 6 years with thalassaemia major who receive frequent blood transfusions (more than 7 mL/kg/month of packed blood cells). It is also licensed for chronic iron overload when desferrioxamine is contra-indicated or inadequate in children with thalassaemia major who receive infrequent blood transfusions (less than 7 mL/kg/month of packed red blood cells), in children with other anaemias, and in children aged 2 to 5 years.

Deferiprone, an oral iron chelator, is licensed for the treatment of iron overload in children over 6 years of age with thalassaemia major in whom desferrioxamine is contra-indicated or is inadequate. Blood dyscrasias, particularly agranulocytosis, have been reported with deferiprone.

**DEFERASIROX**

**Cautions**
- Eye and ear examinations required before treatment and annually during treatment; monitor body-weight, height and sexual development annually; monitor serum ferritin concentration monthly; risk of gastrointestinal ulceration and haemorrhage; history of liver cirrhosis; test liver function before treatment, then every 2 weeks during the first month, and then monthly; measure baseline serum creatinine and monitor renal function weekly during the first month of treatment and monthly thereafter; test for proteinuria monthly; interactions: Appendix 1 (deferasirox)

- **Hepatic impairment**—manufacturer advises caution—no information available; avoid in severe impairment

- **Renal impairment**—reduce dose by 10 mg/kg if serum creatinine increased above age-appropriate limits or estimated glomerular filtration rate less than 90 mL/minute/1.73 m² on 2 consecutive occasions—interrupt treatment if deterioration in renal function persists after dose reduction; avoid if estimated glomerular filtration rate less than 60 mL/minute/1.73 m²

- **Pregnancy**—manufacturer advises avoid unless potential benefit outweighs risk—toxicity in animal studies

- **Breast-feeding**—manufacturer advises avoid—present in milk in animal studies

- **Side-effects**—gastro-intestinal disturbances (including ulceration and haemorrhage); headache; proteinuria; pruritus, rash; less commonly oedema, hepatitis, cholelithiasis, 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

**Indication and dose**

**Chronic iron overload**
- **By mouth**
  - **Child 2–18 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

Note dose should be rounded to nearest whole tablet size

**Exjade®** (Novartis) ▼

**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 and swallow

**DEFERIPRONE**

**Cautions**
- Monitor neutrophil count weekly and discontinue treatment if neutropenia develops

- **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

- **Hepatic impairment**—manufacturer advises monitor liver function—interrupt treatment if persistent elevation in serum alanine aminotransferase

- **Renal impairment**—manufacturer advises caution—no information available
Contra-indications history of agranulocytosis or recurrent neutropenia

Pregnancy manufacturer advises avoid before intended conception and during pregnancy—teratogenic and embryotoxic in animal studies; contraception advised in girls of child-bearing potential

Breast-feeding manufacturer advises avoid—no information available

Side-effects gastro-intestinal disturbances (reducing dose and increasing gradually may improve tolerance), increased appetite; headache; red-brown urine discolouration; neutropenia, agranulocytosis; zinc deficiency; arthropathy

Licensed use see notes above

Indication and dose
Iron overload in thalassaemia major
- By mouth
  Child 6-18 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

Cautions eye and ear examinations before treatment and at 3-month intervals during treatment; monitor body-weight and height in children at 3-month intervals—risk of growth restriction with excessive doses; aluminium-related encephalopathy (may exacerbate neurological dysfunction); interactions: Appendix 1 (desferrioxamine)

Pregnancy teratogenic in animal studies, manufacturer advises use only if potential benefit outweighs risk

Breast-feeding manufacturer advises use only if potential benefit outweighs risk—no information available

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

Indication and dose
Chronic iron overload see notes above

Aluminium overload in dialysis patients
- By intravenous infusion
  Child 1 month-18 years 5 mg/kg once weekly

Iron poisoning see Emergency Treatment of Poisoning, p. 42

Administration For intravenous or subcutaneous infusion, reconstitute powder with Water for Injection to a concentration of 100 mg/mL; dilute with Glucose 5% or Sodium Chloride 0.9%. In haemodialysis or haemofiltration administer over the last hour of dialysis (may be given via the dialysis fistula). Intrapertitoneal: may be added to dialysis fluid. In CAPD give prior to the last exchange of the day.

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

9.1.4 Drugs used in platelet disorders

Idiopathic thrombocytopenic purpura Acute idiopathic thrombocytopenic purpura is usually self-limiting in children. A corticosteroid such as prednisolone (p. 452) is sometimes used if idiopathic thrombocytopenic purpura does not resolve spontaneously or if it is associated with severe cutaneous symptoms or mucous membrane bleeding; corticosteroid treatment should not be continued longer than 14 days regardless of the response.

Immunoglobulin preparations (section 14.5) may be used in idiopathic thromboctopenic purpura or where a temporary rapid rise in platelets is needed, as in pregnancy or pre-operatively; they are often used in preference to a cortico-
steroid. Anti-D immunoglobulin is licensed for the management of idiopathic thrombocytopenic purpura.

Other therapy that has been tried under specialist supervision in refractory idiopathic thrombocytopenic purpura includes azathioprine (section 8.2.1), cyclophosphamide (section 8.1.1), vincristine (section 8.1.4), and ciclosporin (section 8.2.2). Rituximab is also used in specialist centres but experience of its use in children is limited. For patients with chronic severe thrombocytopenia refractory to other therapy, tranexamic acid (section 2.11) may be given to reduce the severity of haemorrhage.

Splenectomy is considered in chronic thrombocytopenic purpura if a satisfactory platelet count is not achieved with regular immunoglobulin infusions, if there is a relapse on withdrawing or reducing the dose of corticosteroid, and if other therapies are considered inappropriate.

Thrombocythaemia  Anagrelide reduces platelets in essential thrombocythaemia in patients at risk of thrombo-haemorrhagic events who have not responded adequately to other drugs or who cannot tolerate other drugs.

## ANAGRELIDE

**Cautions** cardiovascular disease—assess cardiac function before and during treatment; concomitant aspirin in patients at risk of haemorrhage; 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; **interactions:** Appendix 1 (anagrelide)

**Skilled tasks** Dizziness may affect performance of skilled tasks (e.g. driving)

**Hepatic impairment** manufacturer advises caution in mild hepatic impairment; avoid in moderate to severe impairment

**Renal impairment** manufacturer advises avoid if estimated glomerular filtration rate less than 50 mL/minute/1.73 m²

**Contra-indications**

**Pregnancy** manufacturer advises avoid (toxicity in animal studies)

**Breast-feeding** manufacturer advises avoid—no information available

**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, alterations, depression, nervousness, confusion, amnesia, fever, weight changes, impotence, blood disorders, myalgia, arthralgia, epistaxis, dry mouth, alopecia, skin discolouration, and pruritus; rarely gastritis, colitis, postural hypotension, angina, myocardial infarction, vasodilatation, pulmonary infiltrates, migrane, drowsiness, impaired co-ordination, dysarthria, asthenia, tinnitus, renal failure, nocturia, visual disturbances, and gingival bleeding; allergic alveolitis also reported

**Licensed use** not licensed for use in children

**Indication and dose**

**Essential thrombocythaemia in at-risk children who have not responded adequately to other therapy or who are intolerant of it (initiated under specialist supervision)**

- **By mouth**
  - **Child 7–18 years** initially 500 micrograms 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)**

Capsules, anagrelide (as hydrochloride), 500 micrograms, net price 100–cap pack= £337.14. Counseling, skilled tasks, 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 children 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 child 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 children 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]
- Primaquine (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.

### 9.1.6 Drugs used in neutropenia

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, including cytotoxic-induced neutropenia, and neutropenia following bone marrow transplantation, 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. Treatment with recombinant human growth factors should only be prescribed by those experienced in their use.

**Neonatal neutropenia** Filgrastim and lenograstim have been used to abolish sepsis-induced neutropenia in preterm neonates. The majority of studies have used filgrastim. The effects on survival and long-term outcome are unclear.

**Cautions** Recombinant human granulocyte-colony stimulating factors should be used with caution in patients with pre-malignant or malignant myeloid conditions. Full blood counts (including differential white cell count and platelet count) 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.

**Side-effects** Side-effects of granulocyte-colony stimulating factors include gastrointestinal disturbances (including nausea, vomiting, and diarrhoea), mucositis, anorexia, headache, asthenia, fever, musculoskeletal pain, bone pain, rash, alopecia, injection-site reactions, thrombocytopenia, and leucocytosis. Less frequent side-effects include chest pain, hypersensitivity reactions (including anaphylaxis and bronchospasm) and arthralgia. There have been reports of pulmonary side-effects, particularly interstitial pneumonia (see Cautions above), cutaneous vasculitis, and acute febrile neutrophilic dermatosis.

**FILGRASTIM**
(Recombinant human granulocyte-colony stimulating factor, G-CSF)

**Cautions** see notes above; also 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)

**Pregnancy** toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** manufacturer advises avoid—no information available

**Contra-indications** severe congenital neutropenia (Kostman’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, anaemia, transient decrease in blood glucose, and raised uric acid

**Licensed use** not licensed for treatment of glycogen storage disease or neonatal neutropenia

**Indication and dose**

**Cytotoxic-induced neutropenia**
- Preferably by subcutaneous injection or by intravenous infusion (over 30 minutes)

Child 1 month–18 years 5 micrograms/kg daily started not less than 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

Child 1 month–18 years 10 micrograms/kg daily, started not less than 24 hours following cytotoxic chemotherapy (and within 24 hours of bone-marrow infusion), then adjusted according to absolute neutrophil count (consult product literature and local protocol)

Mobilisation of peripheral blood progenitor cells for autologous infusion, used alone
- By subcutaneous injection or by subcutaneous infusion over 24 hours

Child 1 month–18 years 10 micrograms/kg daily for 5–7 days

Mobilisation of peripheral blood progenitor cells for autologous infusion following adjunctive myelosuppressive chemotherapy (to improve yield)
- By subcutaneous injection

Child 1 month–18 years 5 micrograms/kg daily, started the day after completion of 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

Child over 16 years 10 micrograms/kg daily for 4–5 days; for timing of leucopheresis consult product literature
Severe chronic neutropenia
- By subcutaneous injection
  Child 1 month–18 years in severe congenital neutropenia, initially 12 micrograms/kg daily in single or divided doses (initially 5 micrograms/kg daily in idiopathic or cyclic neutropenia), adjusted according to response (consult product literature and local protocol)

Persistent neutropenia in HIV infection
- By subcutaneous injection
  Child 1 month–18 years initially 1 microgram/kg daily, increased as necessary until absolute neutrophil count in normal range (usual max. 4 micrograms/kg daily), then adjusted to maintain absolute neutrophil count in normal range (consult product literature)

Neonatal neutropenia
- By subcutaneous injection
  Neonate 10 micrograms/kg daily, discontinue if white cell count exceeds 50 × 10⁹/litre

Glycogen storage disease type 1b
- By subcutaneous injection
  5 micrograms/kg daily, adjusted as necessary

Administration
For subcutaneous or intravenous injection or infusion, dilute with Glucose 5% to a concentration of not less than 15 micrograms/mL (concentration of 100 micrograms/mL adequate for subcutaneous use in neonates); to dilute to a concentration of 2–15 micrograms/mL, add albumin solution (human serum albumin) to produce a final albumin solution of 2 mg/mL; not compatible with Sodium Chloride solutions

Neupogen® (Amgen) Injection, filgrastim 30 million units (300 micrograms)/mL, net price 1-mL vial = £68.41
Injection (Singleject®), filgrastim 60 million units (600 micrograms)/mL, net price 0.5-mL prefilled syringe = £68.41; 96 million units (960 micrograms)/mL, 0.5-mL prefilled syringe = £109.11

Ratiogranostim® (Ratiopharm UK) 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. 2

LENOGRASTIM
(Recombinant human granulocyte-colony stimulating factor, rHuG-CSF)

Cautions
- see notes above; also sickle-cell disease; monitor spleen size (risk of rupture)
- Pregnancy toxicity in animal studies; manufacturer advises use only if potential benefit outweighs risk
- Breast-feeding manufacturer advises avoid—no information available
- Side-effects see notes above; also splenic rupture and toxic epidermal necrolysis

Licensed use
- not licensed for use in children for cytotoxic-induced neutropenia, mobilisation of peripheral blood progenitor cells (monotherapy or adjunctive therapy), or following peripheral stem cells transplantation

Indication and dose

Following peripheral stem cells or bone-marrow transplantation
- By intravenous infusion over 30 minutes or by subcutaneous injection
  Child 2–18 years 150 micrograms/m² daily started the day after transplantation, continued until neutrophil count stable in acceptable range (max. 28 days)

Cytotoxic-induced neutropenia
- By subcutaneous injection
  Child 2–18 years 150 micrograms/m² 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
  Child 2–18 years 10 micrograms/kg daily for 4–6 days (5–6 days in healthy donors)

Mobilisation of peripheral blood progenitor cells following adjunctive myelosuppressive chemotherapy (to improve yield)
- By subcutaneous injection
  Child 2–18 years 150 micrograms/m² daily, started 1–5 days after completion of chemotherapy and continued until neutrophil count in acceptable range; for timing of leucopheresis consult product literature

Administration
For intravenous infusion, dilute reconstituted solution to a concentration of not less than 2 micrograms/mL (Granocyte-13) or 2.5 micrograms/mL (Granocyte-34) with Sodium Chloride 0.9%

Granocyte® (Chugai) 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)
9.2 Fluids and electrolytes

9.2.1 Oral preparations for fluid and electrolyte imbalance

The following tables give a selection of useful electrolyte values:

### Electrolyte concentrations—intravenous fluids

<table>
<thead>
<tr>
<th>Intravenous infusion</th>
<th>Millimoles per litre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na⁺</td>
</tr>
<tr>
<td>Normal plasma values</td>
<td>142</td>
</tr>
<tr>
<td>Sodium Chloride 0.9%</td>
<td>150</td>
</tr>
<tr>
<td>Compound Sodium Lactate (Hartmann’s)</td>
<td>131</td>
</tr>
<tr>
<td>Sodium Chloride 0.45% and Glucose 5%</td>
<td>75</td>
</tr>
<tr>
<td>Potassium Chloride 0.15% and Glucose 5%</td>
<td>—</td>
</tr>
<tr>
<td>Potassium Chloride 0.15% and Sodium Chloride 0.9%</td>
<td>150</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Glucose 5%</td>
<td>—</td>
</tr>
<tr>
<td>Potassium Chloride 0.3% and Sodium Chloride 0.9%</td>
<td>150</td>
</tr>
</tbody>
</table>

To correct metabolic acidosis

- Sodium Bicarbonate 1.26% | 150 — 150 — —
- Sodium Bicarbonate 8.4% for cardiac arrest | 1000 — 1000 — —
- Sodium Lactate (m/6) | 167 — 167 — —

**Electrolyte content—gastro-intestinal secretions**

<table>
<thead>
<tr>
<th>Type of fluid</th>
<th>Millimoles per litre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>H⁺</td>
</tr>
<tr>
<td>Gastric</td>
<td>40–60</td>
</tr>
<tr>
<td>Biliary</td>
<td>—</td>
</tr>
<tr>
<td>Pancreatic</td>
<td>—</td>
</tr>
<tr>
<td>Small bowel</td>
<td>—</td>
</tr>
</tbody>
</table>

Faeces, vomit, or aspiration should be saved and analysed where possible if abnormal losses are suspected; where this is impracticable the approximations above may be helpful in planning replacement therapy.

9.2.2 Parenteral 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 children in whom secondary hyperaldosteronism occurs, e.g. renal artery stenosis, renal tubule disorder, the nephrotic syndrome, and severe heart failure;
- in children with excessive losses of potassium in the faeces, e.g. chronic diarrhoea associated with intestinal malabsorption or laxative abuse;
- in those taking digoxin or anti-arrhythmic drugs, where potassium depletion may induce arrhythmias.

Measures to compensate for potassium loss may 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 (frusemide) or the thiazides when these are given to eliminate oedema.

**Dosage**

If potassium salts are used for the **prevention of hypokalaemia**, then doses of potassium chloride 1–2 mmol/kg (usual max. 50 mmol potassium) daily by mouth are suitable in patients taking a normal diet. **Smaller doses** must be used if there is **renal insufficiency** otherwise there is **danger of hyperkalaemia**. Potassium salts cause nausea and vomiting therefore poor compliance is a major limitation to their effectiveness (small divided doses may minimise gastric irritation); 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). Potassium chloride solutions suitable for use by mouth in neonates are available from ‘special-order’ manufacturers or specialist importing companies, see p. 943; they should be used with care because they are hypertonic and can damage the gastric mucosa.

**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.

**POTASSIUM CHLORIDE**

**Cautions** intestinal stricture, history of peptic ulcer, hiatus hernia (for modified-release preparations); **important**: special hazard if given with drugs liable to raise plasma-potassium concentration such as potassium-sparing diuretics, ACE inhibitors, or ciclosporin, for other **interactions**: Appendix 1 (potassium salts)

**Renal impairment** close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

**Contra-indications** plasma-potassium concentration above 5 mmol/litre

**Side-effects** nausea and vomiting (severe symptoms may indicate obstruction), oesophageal or small bowel ulceration

**Indication and dose**

**Potassium depletion**

- **Neonate** 0.5–1 mmol/kg K⁺ twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to plasma-potassium concentration

- **Child 1 month–18 years** 0.5–1 mmol/kg K⁺ twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to plasma-potassium concentration

**Management of hyperkalaemia**

Acute severe hyperkalaemia calls for urgent treatment with intravenous infusion of **soluble insulin** (0.3–0.6 units/kg/hour in neonates and 0.05–0.2 units/kg/hour in children over 1 month) with **glucose** 0.5–1 g/kg/hour (5–10 mL/kg of glucose 10%; 2.5–5 mL/kg of glucose 20% via a central venous catheter may also be considered). If insulin cannot be used, **salbutamol** (section 3.1.1.1) can be given in 3 divided doses, adjusted according to plasma-potassium concentration.

Note Do not confuse Effervescent Potassium Tablets BPC 1968 with effervescent potassium chloride tablets. Effervescent Potassium Tablets BPC 1968 do not contain chloride ions and their use should be restricted to hyperchloraemic states (section 9.2.1.3).

**Kay-Cee-L®** (Geistlich)

**Syrup**, sugar-free, red, potassium chloride 7.5% (1 mmol/mL each of K⁺ and Cl⁻), net price 500 mL = £3.74. Label: 21

**Sando-K®** (HK Pharma)

**Tablets**, effervescent, potassium bicarbonate and chloride equivalent to potassium 470 mg (12 mmol of K⁺) and chloride 285 mg (8 mmol of Cl⁻). Net price 20 = £1.53. Label: 13, 21

**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

**BNFC 2009 9.2.1 Oral preparations for fluid and electrolyte imbalance**

9 Nutrition and blood
by intravenous infusion but it has a slower onset of action and may be less effective for reducing plasma-potassium concentration.

Calcium gluconate (section 9.5.1.1) is given by slow intravenous injection to manage cardiac excitability caused by hyperkalaemia.

The correction of causal or compounding acidosis with sodium bicarbonate infusion (section 9.2.2.1) should be considered (important: preparations of sodium bicarbonate and calcium salts should not be administered in the same line—risk of precipitation). Intravenous furosemide can also be given but is less effective in children with renal impairment. Drugs exacerbating hyperkalaemia should be reviewed and stopped as appropriate; dialysis may occasionally be required.

Ion-exchange resins may be used to remove excess potassium in mild hyperkalaemia or in moderate hyperkalaemia when there are no ECG changes. Calcium polystyrene sulphonate is preferred unless plasma-calcium concentrations are high.

**POLYSTYRENE SULPHONATE RESINS**

**Cautions** 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

**Licensed use** licensed for use in children

**Indication and dose**

<table>
<thead>
<tr>
<th>Hyperkalaemia associated with anuria or severe oliguria, and in dialysis patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>• By mouth</td>
</tr>
</tbody>
</table>

**Neonate** not recommended

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**9.2.1.2 Oral sodium and water**

Sodium chloride is indicated in states of sodium depletion. In preterm neonates in the first few weeks of life and 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 (section 9.2.1.3) may be sufficient. Sodium chloride solutions suitable for use by mouth in neonates are available from ‘special-order’ manufacturers or specialist importing companies, see p.943; they should be used with care because they are hypertonic. Supplementation with sodium chloride may be required to replace losses in children with cystic fibrosis particularly in warm weather.
**SODIUM CHLORIDE**

**Indication and dose**

See also section 9.2.2

**Sodium supplementation in neonates**

- **By mouth**
  - Preterm neonate 2 mmol/100 mL of formula feed or 3–4 mmol/100 mL of breast milk, consult dietician

**Sodium replacement**

- **By mouth**
  - Child 1 month–18 years According to requirements, generally 1–2 mmol/kg daily in divided doses, higher doses may be needed in severe depletion

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**Oral rehydration therapy (ORT)**

Diarrhoea in children is usually self-limiting, however, in children under 6 months of age, and more particularly in those under 3 months, symptoms of dehydration may be less obvious and there is a risk of rapid and severe deterioration. 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 prevent the possible induction of osmotic diarrhoea;
- 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.

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**ORAL REHYDRATION SALTS (ORS)**

**Licensed use** Dioralyte® Relief not licensed for use in children under 3 months

**Indication and dose**

- **By mouth**
  - Child 1 month–1 year 1–1½ times usual feed volume

**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

Capsules available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
9.2.1 Oral preparations for fluid and electrolyte imbalance

9.2.1.3 Oral bicarbonate

Sodium bicarbonate is given by mouth for chronic acidotic states such as uremic acidosis or renal tubular acidosis. The dose for correction of metabolic acidosis is not predictable and the response must be assessed. For severe metabolic acidosis, sodium bicarbonate can be given intravenously (section 9.2.2).

Sodium supplements may increase blood pressure or cause fluid retention and pulmonary oedema in those at risk; hypokalaemia may be exacerbated. Sodium bicarbonate may affect the stability or absorption of other drugs if administered at the same time. If possible, allow 1–2 hours before administering other drugs orally.

Where hyperchloremic acidosis is associated with potassium deficiency, as in some renal tubular and gastro-intestinal disorders it may be appropriate to give oral potassium bicarbonate, although acute or severe deficiency should be managed by intravenous therapy.

SODIUM BICARBONATE

Cautions see notes above; avoid in respiratory acidosis; interactions: Appendix 1 (antacids)

Indication and dose

Renal acidosis (see also notes above)
- By mouth

Neonate initially 1–2 mmol/kg daily in divided doses

Child 1 month–18 years initially 1–2 mmol/kg daily in divided doses, adjusted according to response

Metabolic acidosis section 9.2.2.1

Renal hyperkalaemia section 9.2.2.1

Sodium Bicarbonate (Non-proprietary)

Capsules, sodium bicarbonate 500 mg (approx. 6 mmol each of Na+ and HCO3–), net price 56-cap pack = £13.07

Tablets, sodium bicarbonate 600 mg, net price 100 tabs = £2.48

Important Oral solutions of sodium bicarbonate are required occasionally; these need to be obtained from ‘special-order’ manufacturers or specialist importing companies, see p. 943, and the strength of sodium bicarbonate should be stated on the prescription
**POTASSIUM BICARBONATE**

**Cautions** cardiac disease, interactions: Appendix 1 (potassium salts)

Renal impairment close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

Contra-indications hypochloraemia; plasma-potassium concentration above 5 mmol/litre

Side-effects nausea and vomiting

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**Potassium Tablets, Effervescent (Non-proprietary)**
Effervescent tablets, potassium bicarbonate
500 mg, potassium acid tartrate 300 mg, each tablet providing 6.5 mmol of K+. To be dissolved in water before administration. Net price 56 = £28.20.
Label: 13, 21

Note: These tablets do not contain chloride; for effervescent tablets containing potassium and chloride, see under Potassium Chloride, section 9.2.1.1

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**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 it is not possible or desirable to use the oral route. When intravenous administration is not possible, fluid (as sodium chloride 0.9% or glucose 5%) can also be given subcutaneously by hypodermoclysis.

In an individual patient the nature and severity of the electrolyte imbalance must be assessed from the history and clinical and biochemical examination. 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, for example 15% glucose, are best given through an indwelling catheter positioned in a large vein.

**Maintenance fluid requirements** in children are usually derived from the relationship that exists between body-weight and metabolic rate; the figures in the table below may be used as a guide outside the neonatal period. The glucose requirement is that needed to minimise gluconeogenesis from amino acids obtained as substrate from muscle breakdown. Maintenance fluids are intended only to provide hydration for a short period until enteral or parenteral nutrition can be established.

It is usual to meet these requirements by using a standard solution of sodium chloride and glucose. Solutions containing 20 mmol/litre of potassium chloride meet usual potassium requirements when given in the suggested volumes; adjustments may be needed if there is an inability to excrete fluids or electrolytes, excessive renal loss or continuing extra-renal losses. The exact requirements depend upon the nature of the clinical situation and types of losses incurred; see Caution on dilutional hyponatraemia below.

**Fluid requirements for children over 1 month:**

<table>
<thead>
<tr>
<th>Body-weight</th>
<th>24-hour fluid requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 10 kg</td>
<td>100 mL/kg</td>
</tr>
<tr>
<td>10–20 kg</td>
<td>100 mL/kg for the first 10 kg + 50 mL/kg for each 1 kg body-weight over 10 kg</td>
</tr>
<tr>
<td>Over 20 kg</td>
<td>100 mL/kg for the first 10 kg + 50 mL/kg for each 1 kg body-weight between 10–20 kg + 20 mL/kg for each 1 kg body-weight over 20 kg (max. 2 litres in females, 2.5 litres in males)</td>
</tr>
</tbody>
</table>

Important: The baseline fluid requirements shown in the table above should be adjusted to take account of factors that reduce water loss (e.g. increased antidiuretic hormone, renal failure, hypothermia, and high ambient humidity) or increase water loss (e.g. pyrexia or burns).
Caution  During parenteral hydration, fluids and electrolytes should be monitored closely and any disturbance corrected by slow infusion of an appropriate solution. The volume of fluid infused should take into account the possibility of reduced fluid loss owing to increased antidiuretic hormone and factors such as renal failure, hypothermia, and high humidity.

Dilutional hyponatraemia is a rare but potentially fatal risk of parenteral hydration. It may be caused by inappropriate use of hypotonic fluids such as sodium chloride 0.18% and glucose 4% intravenous infusion, especially in the postoperative period when antidiuretic hormone secretion is increased. Dilutional hyponatraemia is characterized by a rapid fall in plasma-sodium concentration leading to cerebral oedema and seizures; any child with severe hyponatraemia or rapidly changing plasma-sodium concentration should be referred urgently to a paediatric high dependency facility.

Safe practice
Sodium chloride 0.18% and glucose 4% intravenous infusion fluid should not generally be used for fluid replacement in children because of the risk of hyponatraemia; availability of this infusion should be restricted to critical care and specialist wards, such as renal, liver, and cardiac units. Local guidelines on intravenous fluids should be consulted.

Replacement therapy: initial intravenous replacement fluid is generally required if the child is over 10% dehydrated, or if 5–10% dehydrated and oral or enteral rehydration is not tolerated or possible. Oral rehydration is adequate, if tolerated, in the majority of those less than 10% dehydrated. Subsequent fluid and electrolyte requirements are determined by clinical assessment of fluid balance.

Neonates  Neonates lose water through the skin and nose, particularly if preterm or if the skin is damaged. The basic fluid requirement for a term baby in average ambient humidity is 40–60 mL/kg/day plus urinary losses. Preterm babies have very high transepidermal losses particularly in the first few days of life; they may need more fluid replacement than full term babies and up to 180 mL/kg/day may be required. Local guidelines for fluid management in the neonatal period should be consulted.

Intravenous sodium
Intravenous sodium chloride in isotonic (0.9%) solution provides the most important extracellular ions in near physiological concentration and is indicated in sodium depletion. It may be given for initial treatment of acute fluid loss and to replace ongoing gastro-intestinal losses from the upper gastro-intestinal tract. Intravenous sodium chloride is commonly given as a component of maintenance and replacement therapy, usually in combination with other electrolytes and glucose, see notes above. Sodium chloride solutions should be used cautiously in renal insufficiency, cardiac failure, cardio-respiratory diseases, hepatic cirrhosis and in children receiving glucocorticoids. Hyponatraemia with serious consequences may occur if maintenance and replacement fluids do not meet sodium requirements (see Caution, dilutional hyponatraemia, above).

Chronic hyponatraemia should ideally be corrected by fluid restriction. However, if sodium chloride is required, the deficit should be corrected slowly to avoid the risk of osmotic demyelination syndrome; the rise in plasma-sodium concentration should be no more than 10 mmol/litre in 24 hours.

Sodium chloride and glucose solutions are indicated when there is combined water and sodium depletion. A 1:1 mixture of isotonic sodium chloride and 5% glucose allows some of the water (free of sodium) to enter body cells which suffer most from dehydration while the sodium salt with a volume of water determined by the normal plasma Na⁺ remains extracellular. Maintenance fluid should accurately reflect daily requirements and close monitoring is required to avoid fluid and electrolyte imbalance. Illness or injury increase the secretion of antidiuretic hormone and therefore the ability to excrete excess water may be impaired. Injudicious use of hypotonic solutions such as sodium chloride 0.18% and glucose 4% may also cause dilutional hyponatraemia especially in children (see Caution on dilutional hyponatraemia, above); if necessary, guidance should be sought from a clinician experienced in the management of fluid and electrolytes.
Combined sodium, potassium, chloride, and water depletion may occur, for example, with severe diarrhoea or persistent vomiting; replacement is carried out with sodium chloride intravenous infusion 0.9% and glucose intravenous infusion 5% with potassium as appropriate.

**Compound sodium lactate** (Hartmann’s solution) can be used instead of isotonic sodium chloride solution during surgery or in the initial management of the injured or wounded.

**Neonates** The sodium requirement for most healthy neonates is 3 mmol/kg daily. Preterm neonates, particularly below 30 weeks gestation, may require up to 6 mmol/kg daily. Hyponatraemia may be caused by excessive renal loss of sodium; it may also be dilutional and restriction of fluid intake may be appropriate. Sodium supplementation is likely to be required if the serum sodium concentration is significantly reduced.

Hypernatraemia may also occur, most often due to dehydration (e.g. breast milk insufficiency). Severe hypernatraemia and hyponaetaemia can cause fits and rarely brain damage. Sodium in drug preparations, delivered via continuous infusions, or in infusions to maintain the patency of intravascular or umbilical lines, can result in significant amounts of sodium being delivered, (e.g. 1 mL/hour of 0.9% sodium chloride infused over 24 hours is equivalent to 3.6 mmol/day of sodium).

### SODIUM CHLORIDE

**Cautions** restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, toxaemia of pregnancy; see also notes above

**Side-effects** administration of large doses may give rise to sodium accumulation and oedema

**Indication and dose**

**Electrolyte imbalance** see notes above, also section 9.2.1.2

#### Sodium Chloride (Non-proprietary)

**Intravenous infusion**, usual strength sodium chloride 0.9% (9 g, 150 mmol each of Na⁺ and Cl⁻/litre), this strength being supplied when normal saline for injection is requested. Net price 2-mL amp = 29p; 5-mL amp = 35p; 10-mL amp = 46p; 20-mL amp = £1.04; 50-mL amp = £2.01

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Note** The term ‘normal saline’ should not be used to describe sodium chloride intravenous infusion 0.9%; the term ‘physiological saline’ is acceptable but it is preferable to give the composition (i.e. sodium chloride intravenous infusion 0.9%).

#### Sodium Chloride and Glucose (Non-proprietary)

**Intravenous infusion**, sodium chloride 0.18% (Na⁺ and Cl⁻ each 30 mmol/litre), glucose 4%

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

#### Ringer’s Solution (Non-proprietary)

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, Compound (Non-proprietary)

(Hartmann’s Solution; Ringer-Lactate Solution)

**Intravenous infusion**, sodium chloride 0.6%, sodium lactate 0.32%, 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

### With other ingredients

**Note** See above for warning on hyponatraemia

### Intravenous glucose

Glucose solutions 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. Water depletion (dehydration) tends to occur when losses are not matched by a comparable intake, as may occur in coma or dysphagia.

Water loss rarely exceeds electrolyte losses but this can occur 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; the rate of infusion should be adjusted to return the plasma-sodium concentration to normal over 48 hours.

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 with insulin for the emergency management of hyperkalaemia (see p. 547). They are also given, after correction of hyperglycaemia, during treatment of diabetic ketoacidosis, when they must be accompanied by continuous insulin infusion (section 6.1.3).

Injections containing more than 10% glucose can be irritant and should be given into a central venous line; however, solutions containing up to 12.5% can be administered for a short period into a peripheral line.

**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

**Side-effects** glucose injections especially if hypertonic may have a low pH and may cause venous irritation and thrombophlebitis

**Indication and dose**

- **Fluid replacement** see notes above
- **Provision of energy** section 9.3
- **Hypoglycaemia** section 6.1.4

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**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 (see under Safe Practice below); for peripheral intravenous infusion, the concentration of potassium should not usually exceed 40 mmol/litre. Potassium infusions should be given slowly over at least 2–3 hours and at a rate not exceeding 0.2 mmol/kg/hour with specialist advice and ECG monitoring in difficult cases. Higher concentrations of potassium chloride or faster infusion rates may be given in very severe depletion, but require specialist advice.

Repeated measurements of plasma-potassium concentration are 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.

**Safe Practice** Potassium overdose can be fatal. Ready-mixed infusion solutions containing potassium should be used. Exceptionally, if potassium chloride concentrate is used for preparing an infusion, the infusion solution should be thoroughly mixed. Local policies on avoiding inadvertent use of potassium chloride concentrate should be followed.

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**POTASSIUM CHLORIDE**

**Cautions** for peripheral intravenous infusion the concentration of solution should not usually exceed 3 g (40 mmol)/litre; specialist advice and ECG monitoring (see notes above); **interactions:** Appendix 1 (potassium salts)

**Renal impairment** close monitoring required—high risk of hyperkalaemia; avoid in severe impairment

**Contra-indications** plasma-potassium concentration above 5 mmol/litre
**Side-effects** rapid infusion toxic to heart

**Indication and dose**

<table>
<thead>
<tr>
<th>Electrolyte imbalance</th>
<th>see also oral potassium supplements, section 9.2.1.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>• By slow intravenous infusion depending on the deficit or the daily maintenance requirements, see also notes above</td>
<td></td>
</tr>
<tr>
<td>Neonate 1–2 mmol/kg daily</td>
<td></td>
</tr>
<tr>
<td>Child 1 month–18 years 1–2 mmol/kg daily</td>
<td></td>
</tr>
</tbody>
</table>

**Administration** see notes above

**Potassium Chloride and Glucose (Non-proprietary)**

**Intravenous infusion**, usual strengths 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 (Non-proprietary)**

**Intravenous infusion**, sodium chloride 0.9% (9 g/litre), containing K⁺ 20 mmol, Na⁺ 150 mmol, and Cl⁻ 170 mmol/litre

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Potassium Chloride, Sodium Chloride, and Glucose (Non-proprietary)**

**Intravenous infusion**, 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 (Non-proprietary)**

**Sterile concentrate**, potassium chloride 15% (150 mg, approximately 2 mmol each of K⁺ and Cl⁻ /mL). Net price 10-mL amp = 48p

Solutions containing 10 and 20% of potassium chloride are also available in both 5- and 10-mL ampoules

**Important** Must be diluted with not less than 50 times its volume of Sodium Chloride 0.9% or other suitable diluent and mixed well; see Safe Practice, above

**Bicarbonate and trometamol**

**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 depletion; in these circumstances sodium bicarbonate is best given intravenously as a small volume of hypertonic solution, such as 8.4%; plasma pH and electrolytes should be monitored. For chronic acidotic states, sodium bicarbonate can be given by mouth (section 9.2.1.3).

**Trometamol** (tris[hydroxymethyl]aminomethane, THAM), an organic buffer, corrects metabolic acidosis by causing an increase in urinary pH and an osmotic diuresis. It is indicated when sodium bicarbonate is unsuitable as in carbon dioxide retention, hypernatraemia, or renal impairment. Respiratory support may be required because trometamol induces respiratory depression. It is also used during cardiac bypass surgery and, very rarely, in cardiac arrest.

**SODIUM BICARBONATE**

**Indication and dose**

<table>
<thead>
<tr>
<th>Metabolic acidosis</th>
<th>see also notes above</th>
</tr>
</thead>
<tbody>
<tr>
<td>• By slow intravenous injection of a strong solution (up to 8.4%), or by continuous intravenous infusion of a weaker solution (usually 1.26%)</td>
<td></td>
</tr>
<tr>
<td>an amount appropriate to the body base deficit</td>
<td></td>
</tr>
<tr>
<td>Renal hyperkalaemia</td>
<td></td>
</tr>
<tr>
<td>• By slow intravenous injection</td>
<td></td>
</tr>
<tr>
<td>Neonate 1 mmol/kg daily</td>
<td></td>
</tr>
<tr>
<td>Child 1 month–18 years 1 mmol/kg daily</td>
<td></td>
</tr>
</tbody>
</table>

**Renal acidosis** section 9.2.1.3

**Sodium Bicarbonate (Non-proprietary)**

**Intravenous infusion**, usual strength sodium bicarbonate 1.26% (12.6 g, 150 mmol each of Na⁺ and HCO₃⁻ /litre); various other strengths available

In hospitals, 500- and 1000-mL packs, and sometimes other sizes, are available

**Administration** For peripheral infusion dilute 8.4% solution at least 1 in 10; for central line infusion dilute 1 in 5 with Glucose 5% or 10% or Sodium Chloride 0.9%. Extravasation can cause severe tissue damage
**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

**TROMETAMOL**

(Tris(hydroxymethyl)aminomethane, THAM)

**Cautions**
- Extravasation can cause severe tissue damage
- Renal impairment: use with caution, may cause hyperkalaemia
- Pregnancy: little information available, hypoglycaemia may harm fetus
- Breast-feeding: no information available

**Contra-indications** anuria; chronic respiratory acidosis

**Side-effects** respiratory depression; hypoglycaemia; hyperkalaemia in renal impairment; liver necrosis reported following administration via umbilical vein in neonates

**Licensed use** unlicensed preparation

**Indication and dose**
- Metabolic acidosis
  - By intravenous infusion
  - An amount appropriate to the body base deficit

**Preparations**
- Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Water**

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

**Plasma and plasma substitutes**

**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 is usually used after the acute phase of illness to correct a plasma-volume deficit; 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 nephrotic syndrome).

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 children whose condition is unstable. Therefore, close monitoring is required and fluid and electrolyte therapy should be adjusted according to the child’s condition at all times.

**ALBUMIN SOLUTION**

(Human Albumin Solution)

A solution containing protein derived from plasma, serum, or normal placenta; at least 95% of the protein is albumin. The solution may be isotonic (containing 3.5–5% protein) or concentrated (containing 15–25% protein).

**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

**Indication and dose**
- See under preparations, below

**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); **Octalin® 5%** (100- and 250-mL bottles—Octapharm); **Zenalb® 4.5%** (50-, 100-, 250-, and 500-mL bottles—BPL)
Concentrated solutions (20%)

**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**

Gelatin and the etherified starches (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.

**Cautions** Plasma substitutes should be used with caution in 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 child should be monitored for hypersensitivity reactions.

**Side-effects** Hypersensitivity reactions may occur including, rarely, severe anaphylactoid reactions. Transient increase in bleeding time may occur.

**GELATIN**

**Note** The gelatin is partially degraded

**Cautions** see notes above

**Pregnancy** manufacturer of Geloplasma® advises avoid at the end of pregnancy

**Side-effects** see notes above

**Indication and dose**

Low blood volume in hypovolaemic shock, burns and cardiopulmonary bypass

- **By intravenous infusion**
  initial 10–20 mL/kg of a 3.5–4% solution (see notes above)

**Gelofusine®** (Braun) Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 154 mmol, Cl⁻ 105 mmol/litre, net price 500-mL Ecobag® = £4.70; 1-litre Ecobag® = £9.45

Contains traces of calcium

**Geloplasma®** (Fresenius Kabi) Intravenous infusion, partially hydrolysed and succinylated gelatin (modified liquid gelatin) (as anhydrous gelatin) 30 g (3%) , Na⁺ 150 mmol, K⁺ 5 mmol, Mg²⁺ 1.5 mmol, Cl⁻ 100 mmol, lactate 30 mmol/litre, net price 500-mL bag = £5.05

**Haemaccel®** (KoRa) Intravenous infusion, polygeline (gelatin derivative, average molecular weight 30 000) 35 g (3.5%), Na⁺ 145 mmol, K⁺ 5.1 mmol, Ca²⁺ 6.25 mmol, Cl⁻ 145 mmol/litre, net price 500-mL bottle = £5.00

**Isoplex®** (IS Pharmaceuticals) Intravenous infusion, succinylated gelatin (modified fluid gelatin, average molecular weight 30 000) 40 g (4%), Na⁺ 145 mmol, K⁺ 4 mmol, Mg²⁺ 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) 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 amylopectin that has been etherified with hydroxyethyl groups; the terms tetrastarch and pentastarch reflect the degree of etherification.

Cautions  see notes above

Side-effects  see notes above; also pruritus, raised serum amylase

Indication and dose

Low blood volume

- By intravenous infusion according to the child's condition (see notes above)

Pentastarch

HAES-steril® (Fresenius Kabi)  Intravenous infusion, pentastarch (weight average molecular weight 200 000) 10% in sodium chloride intravenous infusion 0.9%, net price, 500 mL = £16.50

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

Tetrastarch

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, Mg2+ 1 mmol, Cl− 118 mmol, Ca2+ 2.5 mmol, acetate 24 mmol, malate 5 mmol/litre, net price 500-mL bag = £13.50

Volulyte® (Fresenius Kabi)  Intravenous infusion, hydroxyethyl starch (weight average molecular weight 130 000) 6% in sodium chloride intravenous infusion 0.6%, containing Na+ 137 mmol, K+ 4 mmol, Mg2+ 1.5 mmol, Cl− 110 mmol, acetate 34 mmol/litre, net price 500-mL bag = £13.50

Voluvan® (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

Hypertonic solution

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

9.3 Intravenous nutrition

When adequate feeding through the alimentary tract is not possible, nutrients may be given by intravenous infusion. This may be in addition to oral or enteral tube feeding—supplemental parenteral nutrition, or may be the sole source of nutrition—total parenteral nutrition (TPN). Complete enteral starvation is undesirable and total parenteral nutrition is a last resort.

Indications for parenteral nutrition include prematurity; severe or prolonged disorders of the gastro-intestinal tract; preparation of undernourished patients for surgery, chemotherapy, or radiation therapy; major surgery, trauma, or burns; prolonged coma or inability to eat; and some patients with renal or hepatic failure. The composition of proprietary preparations used in children is given in the table Proprietary Infusion Fluids for Parenteral Feeding, p. 559.

Parenteral nutrition requires the use of a solution containing amino acids, glucose, lipids, electrolytes, trace elements, and vitamins. This is now commonly provided by the pharmacy in the form of an amino-acid, glucose, electrolyte bag, and a separate lipid infusion or, in older children a single ‘all-in-one’ bag. If the patient is 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, 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 nutritional solutions of low osmolality and neutral pH. Nutritional fluids should be given by a dedicated intravenous line; if not possible, compatibility with any drugs or fluids should be checked as precipitation of components may occur. Extravasation of parenteral nutrition solution can cause severe tissue damage and injury; the infusion site should be regularly monitored.
Before starting intravenous nutrition the patient should be clinically stable and renal function and acid-base status should be assessed. Appropriate biochemical tests should have been carried out beforehand and serious deficits corrected. Nutritional and electrolyte status must be monitored throughout treatment. The nutritional components of parenteral nutrition regimens are usually increased gradually over a number of days to prevent metabolic complications and to allow metabolic adaptation to the infused nutrients. The solutions are usually infused over 24 hours but this may be gradually reduced if long-term nutrition is required. Home parenteral nutrition is usually infused over 12 hours overnight.

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.

1. Note. 1000 kcal = 4200 kJ; 1000 kJ = 238.8 kcal. All entries are

2. Excludes protein- or amino acid-derived energy

3. For use in neonates and children only

### 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>ClinOleic 20% (Baxter)</td>
<td></td>
<td>8360</td>
<td></td>
<td>purified olive and soya oil 200 g, glycerol 22.5 g, egg phosphatides 12 g</td>
</tr>
<tr>
<td>Gamin (Fresenius Kabi)</td>
<td></td>
<td>22.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intralipid 10% (Fresenius Kabi)</td>
<td></td>
<td>4600</td>
<td></td>
<td>soya oil 100 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
</tr>
<tr>
<td>Intralipid 20% (Fresenius Kabi)</td>
<td></td>
<td>8400</td>
<td></td>
<td>soya oil 200 g, glycerol 22 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
</tr>
<tr>
<td>Intralipid 30% (Fresenius Kabi)</td>
<td></td>
<td>12600</td>
<td></td>
<td>soya oil 300 g, glycerol 16.7 g, purified egg phospholipids 12 g, phosphate 15 mmol</td>
</tr>
<tr>
<td>Lipofundin MCT/LCT 10% (Braun)</td>
<td></td>
<td>4430</td>
<td></td>
<td>soya oil 50 g, medium chain triglycerides 50 g</td>
</tr>
<tr>
<td>Lipofundin MCT/LCT 20% (Braun)</td>
<td></td>
<td>8000</td>
<td></td>
<td>soya oil 100 g, medium chain triglycerides 100 g</td>
</tr>
<tr>
<td>Primene 10% (Baxter)</td>
<td></td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Synthamin 9 (Baxter)</td>
<td></td>
<td>9.1</td>
<td></td>
<td>acid phosphate 30 mmol</td>
</tr>
<tr>
<td>Synthamin 9 EF (electrolyte-free)</td>
<td></td>
<td>9.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vamin 9 Glucose (Fresenius Kabi)</td>
<td></td>
<td>1700</td>
<td></td>
<td>Ca²⁺ 2.5 mmol, anhydrous glucose 100 g</td>
</tr>
<tr>
<td>Vaminolact (Fresenius Kabi)</td>
<td></td>
<td>9.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Protein (nitrogen) 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. Solutions for use in neonates and children under 1 year of age are based on the amino acid profile of umbilical cord blood (Primene®) or breast milk (Vaminolact®) and contain amino acids that are essential in this age group; these amino acids may not be present in sufficient quantities in preparations designed for older children and adults.

Energy requirements must be met if amino acids are to be utilised for tissue maintenance. An appropriate energy to protein ratio is essential and requirements will vary depending on the child’s age and condition. A mixture of carbohydrate and fat energy sources (usually 30–50% as fat) gives better utilisation of amino acids than glucose alone.

Glucose is the preferred source of carbohydrate, but frequent monitoring of blood glucose is required particularly during initiation and build-up of the regimen; insulin may be necessary. Glucose above a concentration of 12.5% must be infused through a central venous catheter to avoid thrombosis; the maximum concentration of glucose that should normally be infused in fluid restricted children is 20–25%.

In parenteral nutrition regimens, it is necessary to provide adequate phosphate in order to allow phosphorylation of glucose and to prevent hypophosphataemia. Neonates, particularly preterm neonates, and young children also require phosphorus and calcium to ensure adequate bone mineralisation. The compatibility and solubility of calcium and phosphorus salts is complex and unpredictable; precipitation is a risk and specialist pharmacy advice should be sought.

Fat (lipid) 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. Regular monitoring of plasma cholesterol and triglyceride is necessary to ensure clearance from the plasma, particularly in conditions where fat metabolism may be disturbed e.g. infection. Emulsions containing 20% or 30% fat should be used in neonates as they are cleared more efficiently.

Additives may only be mixed with fat emulsions where compatibility is known.

Electrolytes are usually provided as the chloride salts of potassium and sodium. Acetate salts can be used to reduce the amount of chloride infused; hyperchlo-aemic acidosis or hypochloraemic alkalosis can occur in preterm neonates or children with renal impairment.

Administration. Because of the complex requirements relating to parenteral nutrition full details relating to administration have been omitted. In all cases specialist pharmacy advice, product literature and other specialist literature should be consulted.

Supplementary preparations

Compatibility with the infusion solution must be ascertained before adding supplementary preparations.

Addiphos® (Fresenius Kabi) 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) Solution, trace elements for addition to Vamin® solutions and glucose intravenous infusions, traces of Fe³⁺, Zn²⁺, Mn²⁺, Cu²⁺, Cr³⁺, Se⁴⁺, Mo⁶⁺, F⁻, I⁻. For children over 40 kg. Net price 10-mL amp = £2.31
9.4 Oral nutrition

9.4.1 Foods for special diets

Foods for special diets

Preparations that have been modified to eliminate a particular constituent from a food or are nutrient mixtures formulated as food substitutes for children who either cannot tolerate or cannot metabolise certain common constituents of food.

Coeliac disease Intolerance to gluten in coeliac disease is managed by completely eliminating gluten from the diet. A range of gluten-free products is available for prescription—see Appendix 2 (p. 910).

Phenylketonuria Phenylketonuria (hyperphenylalaninaemia, PKU), which results from the inability to metabolise phenylalanine, is managed by restricting dietary intake of phenylalanine to a small amount sufficient for tissue building and repair. Some rare forms of phenylketonuria are caused by a deficiency of tetrahydrobiopterin. Treatment involves oral supplementation of tetrahydrobiopterin; in some severe cases, the addition of the neurotransmitter precursors, levo-dopa (L-dopa, section 4.9.1) and 5-hydroxytryptophan, is also necessary.

Sapropterin, a synthetic form of tetrahydrobiopterin, is licensed as an adjunct to dietary restriction of phenylalanine in the management of patients with phenylketonuria and tetrahydrobiopterin deficiency.

Aspartame (used as a sweetener in some foods and medicines) contributes to the dietary restriction of phenylalanine intake and may affect control of phenylketonuria. If alternatives are
unavailable, children with phenylketonuria should not be denied access to appropriate medication; the amount of aspartame consumed can be taken into account in the management of the condition. Where the presence of aspartame in a preparation is specified in the product literature, aspartame is listed as an excipient in the relevant product entry in BNF for Children; the child or carer should be informed of this.

For further information on special dietary products used in the management of metabolic diseases, see Appendix 2.

### TETRAHYDROBIOPTERIN

**Cautions**

- **Renal impairment** use with caution—accumulation of metabolites
- **Pregnancy** crosses the placenta; use only if benefit outweighs risk
- **Breast-feeding** present in milk, effects unknown

**Side-effects** diarrhoea, urinary frequency, disturbed sleep

**Licensed use** not licensed in the UK

**Indication and dose**

#### Monotherapy in tetrahydrobiopterin-sensitive phenylketonuria (specialist use only)

- **By mouth**
  - **Child 1 month–18 years** 10 mg/kg twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to response

#### In combination with neurotransmitter precursors for tetrahydrobiopterin-sensitive phenylketonuria (specialist use only)

- **By mouth**
  - **Child 1 month–2 years** initially 250–750 micrograms/kg 4 times daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to response; max. 7 mg/kg daily
  - **Child 2–18 years** initially 250–750 micrograms/kg 4 times daily (total daily dose may alternatively be given in 3 divided doses), adjusted according to response; usual max. 10 mg/kg daily

### SAPROPTERIN DIHYDROCHLORIDE

**Note** Sapropterin is a synthetic form of tetrahydrobiopterin

**Cautions** monitor blood-phenylalanine concentration before and after first week of treatment—if unsatisfactory response increase dose at weekly intervals to max. dose and monitor blood-phenylalanine concentration weekly; discontinue treatment if unsatisfactory response after 1 month; monitor blood-phenylalanine and tyrosine concentrations 1–2 weeks after dose adjustment and during treatment; history of convulsions

**Hepatic impairment** manufacturer advises caution—no information available

**Renal impairment** manufacturer advises caution—no information available

**Pregnancy** manufacturer advises caution—consider only if dietary management inadequate

**Contra-indications**

- **Breast-feeding** manufacturer advises avoid—on information available

**Side-effects** diarrhoea, vomiting, abdominal pain; nasal congestion, cough, pharyngolaryngeal pain; headache

### Indication and dose

#### Phenylketonuria (specialist use only)

- **By mouth**
  - **Child 4–18 years** initially 10 mg/kg once daily, preferably in the morning, adjusted according to response; usual dose 5–20 mg/kg daily

#### Tetrahydrobiopterin deficiency (specialist use only)

- **By mouth**
  - **Child 4–18 years** initially 2–5 mg/kg once daily, preferably in the morning, adjusted according to response; max. 20 mg/kg daily; total daily dose may alternatively be given in 2–3 divided doses

**Kuvan® (Merck Serono) ▼**

**Dispersible tablets**, sapropterin dihydrochloride 100 mg, net price 30-tab pack = £597.22, 120-tab pack = £2388.88. Label: 13, 21, counselling. Tablets should be dissolved in water and taken within 20 minutes

### 9.4.2 Enteral nutrition

Children have higher nutrient requirements per kg body-weight, different metabolic rates, and physiological responses compared to adults. They have low nutritional stores and are particularly vulnerable to growth and nutritional problems during critical periods of development. Major illness, operations, or trauma impose increased metabolic demands and can rapidly exhaust nutritional reserves.

Every effort should be made to optimise oral food intake before beginning enteral tube feeding; this may include change of posture, special seating, feeding equip-
ment, oral desensitisation, food texture changes, thickening of liquids, increasing energy density of food, treatment of reflux or oesophagitis, as well as using age-specific nutritional supplements.

Enteral tube feeding has a role in both short-term rehabilitation and long-term nutritional management in paediatrics. It can be used as supportive therapy, in which the enteral feed supplies a proportion of the required nutrients, or as primary therapy, in which the enteral feed delivers all the necessary nutrients. Most children receiving tube feeds should also be encouraged to take oral food and drink. Tube feeding should be considered in the following situations:

- unsafe swallowing and risk of aspiration;
- inability to consume at least 60% of energy needs by mouth;
- total feeding time of more than 4 hours per day;
- weight loss or no weight gain for a period of 3 months (less for younger children and infants);
- weight for height (or length) less than 2nd percentile for age and sex.

Most feeds for enteral use (Appendix 2) contain protein derived from cows’ milk or soya. Elemental feeds containing protein hydrolysates or free amino acids can be used for children who have diminished ability to break down protein, for example in inflammatory bowel disease or pancreatic insufficiency.

Even when nutritionally complete feeds are given, water and electrolyte balance should be monitored. Haematological and biochemical parameters should also be monitored, particularly in the clinically unstable child. 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. Feeds containing vitamin K may affect the INR in children receiving warfarin—see interactions: Appendix 1 (vitamins).

Choosing the best formula for children depends on several factors including: nutritional requirements, gastro-intestinal function, underlying disease, nutrient restrictions, age, and feed characteristics (nutritional composition, viscosity, osmolality, availability and cost). Children have specific dietary requirements and in many situations liquid feeds prepared for adults are totally unsuitable and should not be given. Expert advice from a dietician should be sought before prescribing enteral feeds for a child.

**Infant formula feeds** Child 0–12 months. Term infants with normal gastro-intestinal function are given either breast milk or normal infant formula during the first year of life. The average intake is between 150 mL and 200 mL/kg/day. Infant milk formulas are based on whey- or casein-dominant protein, lactose with or without maltodextrin, amylose, vegetable oil and milk fat. The composition of all normal and soya infant formulas have to meet The Infant Formula and Follow-on Formula Regulations (England and Wales) 2007, which enact the European Community Regulations 2006/141/EC; the composition of other enteral and specialist feeds has to meet the Commission Directive (1999/21/EC) on Dietary Foods for Special Medical Purposes.

A high-energy feed (Appendix 2, p. 885), which contains 9–11% of energy derived from protein can be used for infants who fail to grow adequately. Alternatively, energy supplements (Appendix 2, p. 904) may be added to normal infant formula to achieve a higher energy content (but this will reduce the protein to energy ratio) or the normal infant formula concentration may be increased slightly. Care should be taken not to present an osmotic load of more than 500 milliosmols/kg water to the normal functioning gut, otherwise osmotic diarrhoea will result. Concentrating or supplementing feeds should not be attempted without the advice of a paediatric dietician.

**Enteral feeds** Child 1–6 years (body–weight 8–20 kg). Ready-to-use feeds (Appendix 2, p. 885) based on caseinates, maltodextrin and vegetable oils (with or without added medium chain triglyceride (MCT) oil or fibre) are well tolerated and effective in improving nutritional status in this age group. Although originally designed for children 1–6 years (body–weight 8–20 kg), some products have ACBS approval for use in children weighing up to 30 kg (approx. 10 years of age). Enteral feeds formulated for children 1–6 years are low in sodium and potassium; electrolyte intake and biochemical status should be monitored. Older
children in this age range taking small feed volumes may need to be given additional micronutrients. Fibre-enriched feeds may be helpful for children with chronic constipation or diarrhoea.

**Child 7–12 years (body-weight 21–45 kg).** Depending on age, weight, clinical condition and nutritional requirements, ready-to-use feeds (Appendix 2, p.885) formulated for 7–12 year olds may be given at appropriate rates.

**Child over 12 years (body-weight over 45 kg).** As there are no standard enteral feeds formulated for this age group, adult formulations are used. The intake of protein, electrolytes, vitamins, and trace minerals should be carefully assessed and monitored.

*Note* Adult feeds containing more than 6 g/100 mL protein or 2 g/100 mL fibre should be used with caution and expert advice.

**Specialised formula** It is essential that any infant who is intolerant of breast milk or normal infant formula, or whose condition requires nutrient-specific adaptation, is prescribed an adequate volume of a nutritionally complete replacement formula (see Appendix 2, p. 896). In the first 4 months of life, a volume of 150–200 mL/kg/day is recommended. After 6 months, should the formula still be required, a volume of 600 mL/day should be maintained, in addition to solid food.

**Products for cow’s milk protein intolerance or lactose intolerance.** There are a number of infant formulas formulated for cow’s milk protein intolerance or lactose intolerance; these feeds may contain a residual amount of lactose (less than 1 g/100 mL formula)—sometimes described as clinically lactose-free or ‘lactose-free’ by manufacturers. If the total daily intake of these formulas is low, it may be necessary to supplement with calcium, and a vitamin and mineral supplement.

**Soya-based** infant formulas have a high phytoestrogen content and this may be a long-term reproductive health risk. The Chief Medical Officer has advised that soya-based infant formulas should not be used as the first choice for the management of infants with proven cow’s milk sensitivity, lactose intolerance, galactokinase deficiency and galactosaemia. Most UK paediatricians with expertise in inherited metabolic disease still advocate soya-based formulations for infants with galactosaemia as there are concerns about the residual lactose content of low lactose formulas and protein hydrolysates based on cow’s milk protein.

**Low lactose** infant formulations, based on whole cow’s milk protein, are unsuitable for children with cow’s milk protein intolerance. Liquid soya milks purchased from supermarkets and health food stores are not nutritionally complete and should never be used for infants under 1 year of age.

**Protein hydrolysate formulas.** Non-milk, peptide-based feeds containing hydrolysates of casein, whey, meat and soya protein, are suitable for infants with disaccharide or whole protein intolerance. The total daily intake of electrolytes, vitamins and minerals should be carefully assessed and modified to meet the child’s nutritional requirements; these feeds have a high osmolality when given at recommended dilution and need gradual and careful introduction.

**Elemental (amino acid based formula).** Specially formulated elemental feeds containing essential and non-essential amino acids are available for use in infants and children under 6 years with proven whole protein intolerance. Adult elemental formula may be used for children over 6 years; the intake of electrolytes, vitamins and minerals should be carefully assessed and modified to meet nutritional requirements. These feeds have a high osmolality when given at the recommended concentration and therefore need gradual and careful introduction.

**Modular feeds.** Modular feeds (Appendix 2, p. 901) are based on individual protein, fat, carbohydrate, vitamin and mineral components or modules which can be combined to meet the specific needs of a child. Modular feeds are used when nutritionally complete specialised formula are not tolerated, or if the fluid and nutrient requirements change e.g. in gastro-intestinal, renal or liver disease. The main advantage of modular feeds is their flexibility; disadvantages include their complexity and preparation difficulties. Modular feeds should not be used without the supervision of a paediatric dietician.

**Specialised formula.** Highly specialised formulas are designed to meet the specific requirements in various clinical conditions such as renal and liver diseases. When using these formulas, both the biochemical status of the child and their growth parameters need to be monitored.
Feed thickeners  Carob based thickeners (Appendix 2, p. 909) may be used to thicken feeds for infants under 1 year with significant gastro-oesophageal reflux. Breast-fed infants can be given the thickener mixed to a paste with water or breast-milk prior to feeds.

Pre-thickened formula  Milk-protein- or casein-dominant infant formula, which contains small quantities of pre-gelatinized starch, is recommended primarily for infants with mild gastro-oesophageal reflux. Pre-thickened formula is prepared in the same way as normal infant formula and flows through a standard teat. The feeds do not thicken on standing but thicken in the stomach when exposed to acid pH.

Starched based thickeners can be used to thicken liquids and feeds for children over 1 year of age with dysphagia.

Dietary supplements for oral use  (Appendix 2, p. 890) Three types of prescribable fortified dietary supplements are available: fortified milk and non-milk tasting (juice-style) drinks, and fortified milk-based semi-solid preparations. The recommended daily quantity is age-dependent. The following is a useful guide: 1–2 years, 200 kcal (840 kJ); 3–5 years, 400 kcal (1680 kJ); 6–11 years, 600 kcal (2520 kJ); and over 12 years, 800 kcal (3360 kJ). Supplements containing 1.5 kcal/mL are high in protein and should not be used for children under 3 years of age. Many supplements are high in sugar or maltodextrin; care should be taken to prevent prolonged contact with teeth. Ideally supplements should be administered after meals or at bedtime so as not to affect appetite.

Products for metabolic diseases  There is a large range of disease-specific infant formulas and amino acid-based supplements available for use in children with metabolic diseases (see under specific metabolic diseases, Appendix 2, p. 912). Some of these formulas are nutritionally incomplete and supplementation with vitamins and other nutrients may be necessary. Many of the product names are similar; to prevent metabolic complications in children who cannot tolerate specific amino acids it is important to ensure the correct supplement is supplied.

Preparations (Borderline substances)  See Appendix 2.

### 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**

See section 9.1.1 for iron salts.
persist; in exceptional cases it may be necessary to maintain a continuous calcium infusion over a day or more. Calcium chloride injection is also available, but is more irritant; care should be taken to prevent extravasation.

For the role of calcium gluconate in temporarily reducing the toxic effects of hyperkalaemia; see p. 547.

Persistent hypocalcaemia requires oral calcium supplements and either a vitamin D analogue (alfacalcidol or calcitriol) for hypoparathyroidism and pseudohypoparathyroidism or natural vitamin D (calciferol) if due to vitamin D deficiency (section 9.6.4). It is important to monitor plasma and urinary calcium during long-term maintenance therapy.

**Neonates** Hypocalcaemia is common in the first few days of life, particularly following birth asphyxia or respiratory distress. Late onset at 4–10 days after birth may be secondary to vitamin D deficiency, hypoparathyroidism or hypomagnesaemia and may be associated with seizures.

### CALCIUM SALTS

**Cautions** sarcoidosis; history of nephrolithiasis; avoid calcium chloride in respiratory acidosis or respiratory failure; **interactions**: Appendix 1 (antacids, calcium salts)

**Renal impairment** use with caution, risk of hypercalcaemia and renal calculi

**Contra-indications** conditions associated with hypercalcaemia and hypercalciuria (e.g. some forms of malignant disease)

**Side-effects** gastro-intestinal disturbances, constipation; bradycardia, arrhythmias; with injection, peripheral vasodilatation, fall in blood pressure, injection-site reactions, severe tissue damage with extravasation

#### Indication and dose

**See notes above; calcium deficiency**

- **By mouth**
  - Neonate 0.25 mmol/kg 4 times a day, adjusted to response
  - Child 1 month–4 years 0.25 mmol/kg 4 times a day, adjusted to response
  - Child 5–12 years 0.2 mmol/kg 4 times a day, adjusted to response
  - Child 12–18 years 10 mmol 4 times a day, adjusted to response

**Acute hypocalcaemia, urgent correction; hyperkalaemia (prevention of arrhythmias)**

- **By slow intravenous injection over 5–10 minutes**
  - Neonate 0.11 mmol/kg (0.5 mL/kg of calcium gluconate 10%) as a single dose. [Some units use a dose of 0.46 mmol/kg (2 mL/kg calcium gluconate 10%) for hypocalcaemia in line with US practice]
  - Child 1 month–18 years 0.11 mmol/kg (0.5 mL/kg calcium gluconate 10%), max 4.5 mmol (20 mL calcium gluconate 10%)

**Acute hypocalcaemia, maintenance**

- **By continuous intravenous infusion**
  - Neonate 0.5 mmol/kg daily over 24 hours, adjusted to response, use oral route as soon as possible due to risk of extravasation
  - Child 1 month–2 years 1 mmol/kg daily (usual max 8.8 mmol) over 24 hours, use oral route as soon as possible due to risk of extravasation
  - Child 2–18 years 8.8 mmol over 24 hours, use oral route as soon as possible due to risk of extravasation

#### Oral preparations

**Calcium Gluconate** (Non-proprietary)

- **Tablets**, calcium gluconate 600 mg (calcium 53.4 mg or Ca²⁺ 1.35 mmol), net price 20 = £1.43.
  - Label: 24

- **Effervescent tablets**, calcium gluconate 1 g (calcium 89 mg or Ca²⁺ 2.23 mmol), net price 28-tab pack = £8.83.
  - Label: 13
  - **Note** Each tablet usually contains 4.66 mmol Na⁺

**Calcium Lactate** (Non-proprietary)

- **Tablets**, calcium lactate 300 mg (calcium 39 mg or Ca²⁺ 1 mmol), net price 84 = £3.01

**Adcal®** (Strakan)

- **Chewable tablets**, fruit flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca²⁺ 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 Ca²⁺ 12.5 mmol), net price 76-tab pack = £12.54.
  - Label: 13

**Calcichew®** (Shire)

- **Tablets** (chewable), orange flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca²⁺ 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 Ca²⁺ 25 mmol), net price 60-tab pack = £13.16.

**Excipients** include aspartame (section 9.4.1)
Calcium-500 (Martindale)
Tablets, pink, f/c, calcium carbonate 1.25 g (calcium 500 mg or Ca\(^{2+}\) 12.5 mmol), net price 100-tab pack = £9.46. Label: 25

Calcium-Sandoz® (Alliance)
Syrup, orange flavour, calcium glubionate 1.09 g, calcium lactobionate 727 mg (calcium 108.3 mg or Ca\(^{2+}\) 2.7 mmol)/5 mL, net price 300 mL = £3.39

Sandocal® (Novartis Consumer Health)
Sandocal-400 tablets, effervescent, orange flavour, calcium lactate gluconate 930 mg, calcium carbonate 700 mg, anhydrous citric acid 1.189 g, providing calcium 400 mg (Ca\(^{2+}\) 10 mmol), net price 5 x 20-tab pack = £6.87. Label: 13
Excipients include aspartame (section 9.4.1)
Sandocal-1000 tablets, effervescent, orange flavour, calcium lactate gluconate 2.263 g, calcium carbonate 1.75 g, anhydrous citric acid 2.973 g providing 1 g calcium (Ca\(^{2+}\) 25 mmol), net price 3 x 10-tab pack = £6.17. Label: 13
Excipients include aspartame (section 9.4.1)

Parenteral preparations
Calcium Gluconate (Non-proprietary) (hani)
Injection, calcium gluconate 10% (calcium 8.4 mg or Ca\(^{2+}\) 226 micromol)/mL. Net price 10-mL amp = 60p
Administration For intravenous infusion dilute to at least 45 micromol/mL with Glucose 5% or Sodium Chloride 0.9%. Maximum administration rate 45 micromol/kg/hour (or in neonates max. 22 micromol/kg/hour). May be given more concentrated via a central venous catheter. May be used undiluted (10% calcium gluconate) in emergencies. Avoid extravasation; should not be given by intramuscular injection. Incompatible with sodium bicarbonate and phosphate solutions.

Calcium Chloride (Non-proprietary) (hani)
Injection, calcium chloride dihydrate 10% (calcium 27.3 mg or Ca\(^{2+}\) 680 micromol/mL), net price 10-mL disposable syringe = £4.64
Brands include Minijet® Calcium Chloride 10%
Injection, calcium chloride dihydrate 13.4% (calcium 36 mg or Ca\(^{2+}\) 910 micromol/mL), net price 10–mL amp = £14.94

With vitamin D
Section 9.6.4

9.5.1.2 Hypercalcaemia and hypercalciuria

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 hypercalciuria 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 hypercalcaemia should be avoided; oral administration of a bisphosphonate may be useful. Parathyroidectomy may be indicated for hyperparathyroidism.

Hypercalciuria
Hypercalciuria should be investigated for an underlying cause, which should be treated. Reducing dietary calcium intake may be beneficial but severe restriction of calcium intake has not proved beneficial and may even be harmful.

9.5.1.3 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 gastro-intestinal 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 hypermagnesaemia (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 as a result of treatment with certain drugs. Hypomagnesaemia often causes secondary hypocalcaemia (with which it may be confused), particularly in neonates, and also hypokalaemia and hyponatraemia.

Symptomatic hypomagnesaemia is associated with a deficit of 0.5–1 mmol/kg. 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 divided doses. For maintenance (e.g. in intravenous nutrition), parenteral doses of magnesium are of the order of 0.2–0.4 mmol/kg (usual max. 20 mmol) Mg$^{2+}$ 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 pointes (see also section 2.3.1).

MAGNESIUM SULPHATE

Cautions see notes above; 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); interactions: Appendix 1 (magnesium, parenteral)

Renal impairment avoid or reduce dose; increased risk of toxicity

Pregnancy sufficient may cross the placenta in mothers treated with high doses e.g. in pre-eclampsia, causing hypotonia and respiratory depression in newborns

Breast-feeding present in breast milk; may cause diarrhoea in breast-fed babies

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

Licensed use 20% injection licensed for use in children. Other strengths unlicensed

Indication and dose (See also notes above)

Neonatal hypocalcaemia

- By deep intramuscular injection or intravenous infusion

Neonate 0.4 mmol/kg Mg$^{2+}$ (100 mg/kg magnesium sulphate) 12 hourly for 2–3 doses

Hypomagnesaemia

- By intravenous injection over at least 10 minutes

Neonate 0.4 mmol/kg Mg$^{2+}$ (100 mg/kg magnesium sulphate) 6–12 hourly as necessary

Children

- 0.2 mmol/kg Mg$^{2+}$ (50 mg/kg magnesium sulphate) 12 hourly for 2–3 doses

- 0.4 mmol/kg Mg$^{2+}$ (100 mg/kg magnesium sulphate) 6–12 hourly as necessary

Acute severe asthma section 3.1

Persistent pulmonary hypertension section 2.5.1

Torsade de pointes (consult local guidelines)

- By intravenous injection over 10–15 minutes

Child 1 month–12 years 0.1–0.2 mmol/kg (25–50 mg/kg magnesium sulphate); max. 8 mmol (2 g magnesium sulphate); dose repeated once if necessary

Administration Dilute to 10% (100 mg in 1 mL) with Glucose 5 or 10%, Sodium Chloride 0.45 or 0.9% or Glucose and Sodium Chloride combinations. Up to 20% solution may be given in fluid restriction. Rate of administration should not exceed 10 mg/kg/minute of magnesium sulphate

Note Magnesium sulphate 1 g equivalent to Mg$^{2+}$ approx. 4 mmol

Magnesium Sulphate (Non-proprietary) Injection magnesium sulphate 20% (Mg$^{2+}$ approx. 0.8 mmol/mL), net price 20-mL (4-g) amp = £2.75; 50% (Mg$^{2+}$ 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 Min-I-Jet® Magnesium Sulphate 50%
### MAGNESIUM-L-ASPARTATE

**Cautions**  see under Magnesium Sulphate

**Renal impairment**  avoid or reduce dose; increased risk of toxicity

**Side-effects**  diarrhoea; see also under Magnesium Sulphate

**Licensed use**  classified as a Food for Special Medical Purposes for use in children over 2 years

**Indication and dose**

**Hypomagnesaemia**
- **By mouth**
  - **Child 1 month–2 years**  initially 0.2 mmol/kg of Mg\(^{2+}\) 3 times daily dissolved in water, dose adjusted as required
  - **Child 2–10 years**  half a sachet (5 mmol Mg\(^{2+}\)) daily dissolved in 100 mL of water, dose adjusted as required
  - **Child 10–18 years**  one sachet (10 mmol Mg\(^{2+}\)) daily dissolved in 200 mL of water, dose adjusted as required

**Magnaspartate\(^{\circledast}\) (KoRa)**
- **Oral powder**, magnesium-L-aspartate 6.5 g (10 mmol Mg\(^{2+}\))/sachet, net price 10-sachet pack = £7.50
- **Excipients**  include sucrose

![Child 2–10 years](half a sachet (5 mmol Mg\(^{2+}\)) daily dissolved in 100 mL of water, dose adjusted as required)

![Child 10–18 years](one sachet (10 mmol Mg\(^{2+}\)) daily dissolved in 200 mL of water, dose adjusted as required)

### MAGNESIUM GLYCEROPHOSPHATE

**Cautions**  see under Magnesium Sulphate

**Renal impairment**  avoid or reduce dose; increased risk of toxicity

**Side-effects**  diarrhoea; see also under Magnesium Sulphate

**Licensed use**  not licensed for use

**Indication and dose**

**Hypomagnesaemia**
- **By mouth**
  - **Child 1 month–12 years**  initially 0.2 mmol/kg Mg\(^{2+}\) 3 times daily, dose adjusted as required
  - **Child 12–18 years**  initially 4–8 mmol Mg\(^{2+}\) 3 times daily, dose adjusted as required

**Administration**  tablets may be dispersed in water

**Magnesium Glycerophosphate** (Non-proprietary)
- **Tablets**, magnesium glycerophosphate 1 g (approximately magnesium 97 mg or Mg\(^{2+}\) 4 mmol)
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
- **Liquid**, magnesium glycerophosphate 250 mg/mL (approximately magnesium 24.25 mg or Mg\(^{2+}\) 1 mmol/mL)
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

### 9.5.2 Phosphorus

#### 9.5.2.1 Phosphate supplements

**Oral phosphate supplements** may be required in addition to vitamin D in children with hypophosphataemic vitamin D-resistant rickets (section 9.6.4). Diarrhoea is a common side-effect and should prompt a reduction in dosage. Phosphate infusion is occasionally needed in phosphate deficiency arising from use of parenteral nutrition deficient in phosphate supplements; phosphate depletion also occurs in severe diabetic ketoacidosis. It is difficult to provide detailed guidelines for the treatment of severe hypophosphataemia because of the extent of total body deficits and response to therapy are difficult to predict. High doses of phosphate may result in a transient serum elevation followed by redistribution into intracellular compartments or bone tissue; excessive doses may cause hypocalcaemia and metastatic calcification. It is essential to monitor plasma concentrations of calcium, phosphate, potassium and other electrolytes. It is recommended that severe hypophosphataemia be treated intravenously as large doses of oral phosphate may cause diarrhoea; intestinal absorption may be unreliable and dose adjustment may be necessary. Phosphate is not the first choice for the treatment of hypercalcaemia because of the risk of precipitation of calcium phosphate in the kidney and other tissues. If used, the child should be well hydrated and electrolytes monitored.

**Neonates**  Phosphate deficiency may occur in very low-birthweight infants and may compromise bone growth if not corrected. Parenterally fed infants may be at risk of phosphate deficiency due to the limited solubility of phosphate. Some units routinely supplement expressed breast milk with phosphate, although the effect on the osmolality of the milk should be considered.
PHOSPHATE

Cautions see notes above, also cardiac disease, diabetes mellitus, dehydration; avoid extravasation with parenteral forms, severe tissue necrosis; sodium and potassium concentrations of preparations
Renal impairment reduce dose in renal impairment, monitor closely
Contra-indications hyperphosphataemia

Side-effects nausea, diarrhoea; hypotension, oedema; hypocalcaemia; acute renal failure; phlebitis; tissue necrosis on extravasation

Renal impairment reduce dose in renal impairment, monitor closely

Contra-indications hyperphosphataemia

Side-effects nausea, diarrhoea; hypotension, oedema; hypocalcaemia; acute renal failure; phlebitis; tissue necrosis on extravasation

Indication and dose
Hypophosphataemia, including hypophosphataemic rickets and osteomalacia (see notes above)

By mouth
Neonate 1 mmol/kg daily in 1–2 divided doses, or as a supplement in breast milk
Child 1 month–5 years 2–3 mmol/kg (max. 48 mmol) phosphate daily in 2–4 divided doses, adjusted as necessary
Child 5–18 years 2–3 mmol/kg (max. 97 mmol) phosphate daily in 2–4 divided doses, adjusted as necessary
Administration Caution, solubility in breast milk is limited to 1.2 mmol in 100 mL if calcium also added, contact pharmacy department for details

By intravenous infusion (see administration below)
Neonate 1 mmol/kg phosphate daily, adjusted as necessary
Child 1 month–2 years 0.7 mmol/kg phosphate daily, adjusted as necessary
Child 2–18 years 0.4 mmol/kg phosphate daily, adjusted as necessary
Administration (see also Important, below) Dilute injection with Sodium Chloride 0.9% or 0.45% or Glucose 5% or 10%. Administration rate of phosphate should not exceed 0.05 mmol/kg/hour. In emergencies in intensive care faster rates may be used—seek specialist advice

Oral
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⁺ 20.4 mmol), potassium 123 mg (K⁺ 3.1 mmol). Net price 20 = £3.29. Label: 13

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
Various strengths and salts available, caution electrolyte load

Injection
Phosphates (Fresenius Kabi) Intravenous infusion, phosphates (providing phosphate 100 mmol/litre, potassium 19 mmol/litre, sodium 162 mmol/litre), net price 500 mL (Polyfusor®) = £3.75.

Potassium acid phosphate (Non-proprietary)
Injection, 13.6% (1 mmol/mL phosphate, 1 mmol/mL potassium) 10 mL ampoule
Note See also Important, above

Dipotassium hydrogen phosphate (Non-proprietary)
Injection, 17.42% (1 mmol/mL phosphate and 2 mmol/mL potassium) 10 mL ampoule
Note See also Important, above

Disodium hydrogen phosphate (Non-proprietary)
Injection, 17.42% (0.6 mmol/mL phosphate and 1.2 mmol/mL sodium) 10 mL ampoule

9.5.2 Phosphorus BNFC 2009

Phosphate-binding agents
Calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Aluminium-containing preparations are rarely used and have a high risk of aluminium accumulation.

Sevelamer is licensed for the treatment of hyperphosphataemia in adults on haemodialysis or peritoneal dialysis. Although experience is limited in children sevelamer may be useful when hypercalcaemia prevents the use of calcium carbonate.

ALUMINIUM HYDROXIDE

Cautions hyperaluminaemia; see also notes above; 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

Important Some phosphate injection preparations also contain potassium. For peripheral intravenous administration the concentration of potassium should not usually exceed 40 mmol/litre. The infusion solution should be thoroughly mixed. Local policies on avoiding inadvertent use of potassium concentrate should be followed. The potassium content of some phosphate preparations may also limit the rate at which they may be administered, see section 9.2.2.1.

Oral
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⁺ 20.4 mmol), potassium 123 mg (K⁺ 3.1 mmol). Net price 20 = £3.29. Label: 13

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
Various strengths and salts available, caution electrolyte load

Injection
Phosphates (Fresenius Kabi) Intravenous infusion, phosphates (providing phosphate 100 mmol/litre, potassium 19 mmol/litre, sodium 162 mmol/litre), net price 500 mL (Polyfusor®) = £3.75.

Potassium acid phosphate (Non-proprietary)
Injection, 13.6% (1 mmol/mL phosphate, 1 mmol/mL potassium) 10 mL ampoule
Note See also Important, above

Dipotassium hydrogen phosphate (Non-proprietary)
Injection, 17.42% (1 mmol/mL phosphate and 2 mmol/mL potassium) 10 mL ampoule
Note See also Important, above

Disodium hydrogen phosphate (Non-proprietary)
Injection, 17.42% (0.6 mmol/mL phosphate and 1.2 mmol/mL sodium) 10 mL ampoule

9.5.2 Phosphorus BNFC 2009

Phosphate-binding agents
Calcium-containing preparations are used as phosphate-binding agents in the management of hyperphosphataemia complicating renal failure. Aluminium-containing preparations are rarely used and have a high risk of aluminium accumulation.

Sevelamer is licensed for the treatment of hyperphosphataemia in adults on haemodialysis or peritoneal dialysis. Although experience is limited in children sevelamer may be useful when hypercalcaemia prevents the use of calcium carbonate.

ALUMINIUM HYDROXIDE

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

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Oral
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⁺ 20.4 mmol), potassium 123 mg (K⁺ 3.1 mmol). Net price 20 = £3.29. Label: 13

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
Various strengths and salts available, caution electrolyte load

Injection
Phosphates (Fresenius Kabi) Intravenous infusion, phosphates (providing phosphate 100 mmol/litre, potassium 19 mmol/litre, sodium 162 mmol/litre), net price 500 mL (Polyfusor®) = £3.75.

Potassium acid phosphate (Non-proprietary)
Injection, 13.6% (1 mmol/mL phosphate, 1 mmol/mL potassium) 10 mL ampoule
Note See also Important, above

Dipotassium hydrogen phosphate (Non-proprietary)
Injection, 17.42% (1 mmol/mL phosphate and 2 mmol/mL potassium) 10 mL ampoule
Note See also Important, above

Disodium hydrogen phosphate (Non-proprietary)
Injection, 17.42% (0.6 mmol/mL phosphate and 1.2 mmol/mL sodium) 10 mL ampoule
### Calcium Salts

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

**Contra-indications** hypercalcaemia, hypercalciuria

**Side-effects** hypercalcaemia

**Indication and dose**

**Phosphate binding in renal failure and hyperphosphataemia**

- **By mouth**
  - **Child 1 month–1 year** 120 mg calcium carbonate 3–4 times daily with feeds, adjusted as necessary
  - **Child 1–6 years** 300 mg calcium carbonate 3–4 times daily prior to or with meals, adjusted as necessary
  - **Child 6–12 years** 600 mg calcium carbonate 3–4 times daily prior to or with meals, adjusted as necessary
  - **Child 12–18 years** 1.25 g calcium carbonate 3–4 times daily prior to or with meals, adjusted as necessary

**Adcal®**

Section 9.5.1.1

**Calcichew®**

Section 9.5.1.1

**Calcium-500**

Section 9.5.1.1

**Phosex** (Vitaline)

Tablets, yellow, calcium acetate 1 g (calcium $250 \text{ mg or } \text{Ca}^{2+} 6.2 \text{ mmol}$), 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

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

### Sevelamer

**Cautions** gastro-intestinal disorders; **interactions:** Appendix 1 (sevelamer)

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding** manufacturer advises use only if potential benefit outweighs risk

**Contra-indications** bowel obstruction

**Side-effects** gastro-intestinal disturbances; *very rarely* intestinal obstruction

**Licensed use** not licensed for use in children under 18 years

**Indication and dose**

**Hyperphosphataemia in patients on haemodialysis or peritoneal dialysis**

- **By mouth**
  - **Child 12–18 years** initially 0.8–1.6 g 3 times daily with meals, then adjusted according to plasma-phosphate concentration

**Renagel®** (Genzyme)

Tablets, $1/3$, sevelamer 800 mg, net price 180-tab pack = £122.76. Label: 25, counselling, with meals

### 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 protection by use of fluoride rinses or by application of 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 the child 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

**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

**Indication and dose**

Prophylaxis of dental caries—see notes above

- **By mouth**
  - Child 6 months–3 years: F⁻°C⁰ 250 micrograms daily
  - Child 3–6 years: F⁻°C⁰ 500 micrograms daily
  - Child 6 years and over: F⁻°C⁰ 1 mg daily

Water content between F⁻°C⁰ 300 and 700 micrograms/litre (0.3–0.7 parts per million)

- Child 3–6 years: F⁻°C⁰ 250 micrograms daily
  - Child 6 years and over: F⁻°C⁰ 500 micrograms daily

Water content above F⁻°C⁰ 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

There are 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.

**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

**FluorGard®** (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

**Oral drops**

**Note** Fluoride supplements not considered necessary below 6 months of age (see notes above)

**En-De-Kay®** (Manx)

- **Fluodrops (= 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**

**Counselling** Avoid eating, drinking, or rinsing mouth for 15 minutes after use

**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%

**Fluorinse®** (Colgate-Palmolive)

- **Daily fluoride mouthrinse (= 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%
FluoriGard® (Colgate-Palmolive)
Daily dental rinse (= mouthwash), blue, sodium fluoride 0.05%. Net price 500 mL = £3.14. Counseling, 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%

Gels
FluoriGard® (Colgate-Palmolive)
Gel-Kam (= gel), stannous fluoride 0.4% in glycerol basis. Net price 100 mL = £2.97. Counseling, see below

Dose
Child over 3 years for daily use, using a toothbrush, apply on to all tooth surfaces
Counseling Swish between teeth for 1 minute before spitting out. Avoid eating, drinking, or rinsing mouth for at least 30 minutes after use

Dental prescribing on NHS May be prescribed as Sodium Fluoride Mouthwash 0.05%

Toothpastes
Duraphat® (Colgate-Palmolive)
Duraphat® ‘2800 ppm’ toothpaste, sodium fluoride 0.619%. Net price 75 mL = £3.26. Counseling, see below

Dose
Child over 10 years apply 1 cm twice daily using a toothbrush
Counseling Brush teeth for 1 minute before spitting out. Avoid drinking or rinsing mouth for 30 minutes after use

Dental prescribing on NHS May be prescribed as Sodium Fluoride Toothpaste 0.619%

Duraphat® ‘5000 ppm’ toothpaste, sodium fluoride 1.1%. Net price 51 g = £4.45. Counseling, see below

Dose
Child over 16 years apply 2 cm 3 times daily after meals using a toothbrush
Counseling Brush teeth for 3 minutes before spitting out
Dental prescribing on NHS May be prescribed as Sodium Fluoride Toothpaste 1.1%

 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, or in zinc-losing states. Zinc is used in the treatment of Wilson’s disease (section 9.8.1) and acrodermatitis enteropathica, a rare inherited abnormality of zinc absorption.

Parenteral nutrition regimens usually include trace amounts of zinc (section 9.3). If necessary, further zinc can be added to some intravenous feeding regimens.

ZINC SULPHATE

Cautions interactions: Appendix 1 (zinc)
Renal impairment accumulation may occur in acute renal failure
Pregnancy crosses placenta, risk theoretically minimal but no information available
Breast-feeding present in breast milk, risk theoretically minimal but no information available
Side-effects abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, gastritis; irritability, headache, lethargy
Licensed use Solvazinc® not licensed in Wilson’s disease or acrodermatitis enteropathica

Solvazinc® (KoGEN)
Effervescent tablets, yellow-white, zinc sulphate monohydrate 125 mg (45 mg zinc), net price 30 = £4.32. Label: 13, 21

Dose
Zinc deficiency (see notes above)
• By mouth
Neonate 1 mg/kg elemental zinc daily

Child under 10 kg half a tablet daily in water after food, adjusted as necessary
Child 10–30 kg half a tablet 1–3 times daily in water after food, adjusted as necessary
Child over 30 kg 1 tablet 1–3 times daily in water after food, adjusted as necessary

Acrodermatitis enteropathica
• By mouth
Neonate 0.5–1 mg/kg elemental zinc twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted as necessary
Child 1 month–18 years 0.5–1 mg/kg elemental zinc twice daily (total daily dose may alternatively be given in 3 divided doses), adjusted as necessary
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. Except for iron-deficiency anaemia, a primary vitamin or mineral deficiency due to simple dietary inadequacy is rare in the developed world. Some children may be at risk of developing deficiencies because of an inadequate intake, impaired vitamin synthesis or malabsorption in disease states such as cystic fibrosis and Crohn's disease.

The use of vitamins as general 'pick-me-ups' is of unproven value and the 'fad' for mega-vitamin therapy with water-soluble vitamins, such as ascorbic acid and pyridoxine, is unscientific and can be harmful. Many vitamin supplements are described as 'multivitamin' but few contain the whole range of essential vitamins and many contain relatively high amounts of vitamins A and D. Care should be taken to ensure the correct dose is not exceeded.

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).

Vitamin A supplementation may be required in children with liver disease, particularly cholestatic liver disease, due to the malabsorption of fat soluble vitamins. In those with complete biliary obstruction an intramuscular dose once a month may be appropriate.

Treatment is sometimes initiated with very high doses of vitamin A and the child should be monitored closely; very high doses are associated with acute toxicity.

Preterm neonates have low plasma concentrations of vitamin A and are usually given vitamin A supplements, often as part of an oral multivitamin preparation (section 9.6.7) once enteral feeding has been established.

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.

Pregnancy 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 paté or liver sausage.

VITAMIN A

(Retinol)

Cautions see notes above; interactions: Appendix 1 (vitamins)

Pregnancy teratogenic; see notes above

Breast-feeding toxicity likely if mother taking high doses

Side-effects see notes above
9.6.2 Vitamin B group

Deficiency of the B vitamins, other than deficiency of vitamin B₁₂ (section 9.1.2), is rare in the UK and is usually treated by preparations containing thiamine (B₁), riboflavin (B₂), and nicotinamide, which is used in preference to nicotinic acid, as it does not cause vasodilatation. Other members (or substances traditionally classified as members) of the vitamin B complex such as aminobenzoic acid, biotin, choline, inositol, and pantothenic acid or panthenol may be included in vitamin B preparations but there is no evidence of their value as supplements; however they can be used in the management of certain metabolic disorders.
Anaphylaxis has been reported with parenteral B vitamins (see MHRA/CHM advice, below). As with other vitamins of the B group, pyridoxine (B6) deficiency is rare, but it may occur during isoniazid therapy (section 5.1.9) or penicillamine treatment in Wilson’s disease (section 9.8.1) and is characterised by peripheral neuritis. High doses of pyridoxine are given in some metabolic disorders, such as hyperoxaluria, cystathioninuria and homocystinuria; folic acid supplementation may also be beneficial in these disorders (section 9.1.2). Pyridoxine is also used in sideroblastic anaemia (section 9.1.3). Rarely, seizures in the neonatal period or during infancy respond to pyridoxine treatment; pyridoxine should be tried in all cases of early-onset intractable seizures and status epilepticus. Pyridoxine has been tried for a wide variety of other disorders, but there is little sound evidence to support the claims of efficacy, and overdosage induces toxic effects.

A number of mitochondrial disorders may respond to treatment with certain B vitamins but these disorders require specialist management. Thiamine is used in the treatment of maple syrup urine disease, mitochondrial respiratory chain defects and, together with riboflavin, in the treatment of congenital lactic acidosis; riboflavin is also used in glutaric acidemias and cytochrome oxidase deficiencies; biotin (section 9.8.1) is used in carboxylase defects.

Nicotinic acid inhibits the synthesis of cholesterol and triglyceride (section 2.12). Folic acid and vitamin B12 are used in the treatment of megaloblastic anaemia (section 9.1.2). Folinic acid (available as calcium folinate) is used in association with cytotoxic therapy (section 8.1).

RIBOFLAVIN
(Riboflavine, vitamin B2)

Cautions see notes above

Pregnancy crosses the placenta but no adverse effects reported, information at high doses limited

Breast-feeding present in breast milk but no adverse effects reported, information at high doses limited

Side-effects bright yellow urine

Licensed use not licensed in children

Indication and dose
See also notes above

Metabolic diseases

• By mouth

Neonate 50 mg 1–2 times daily, adjusted according to response

Child 1 month–18 years 50–100 mg 1–2 times daily, adjusted according to response, up to 400 mg daily has been used

Rifoflavin (Non-proprietary)
Tablets, 10 mg, 50 mg and 100 mg
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Oral vitamin B complex preparations
See below

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

THIAMINE
(Vitamin B1)

MHRA/CHM advice (September 2007) Although potentially serious allergic adverse reactions may rarely occur during, or shortly after, parenteral administration, the CHM has recommended that:

1. This should not preclude the use of parenteral thiamine in patients where this route of administration is required, particularly in patients at risk of Wernicke-Korsakoff syndrome where treatment with thiamine is essential;
2. Intravenous administration should be by infusion over 30 minutes;
3. Facilities for treating anaphylaxis (including resuscitation facilities) should be available when parenteral thiamine is administered.

Cautions anaphylactic shock may occasionally follow injection (see MHRA/CHM advice above)

Contra-indications
Breast-feeding severely thiamine-deficient mothers should avoid breast-feeding as toxic methyl-glyoxal present in milk

Side-effects hypersensitivity reactions to injection

Licensed use not licensed in children

Indication and dose
See also notes above

Maple syrup urine disease

• By mouth

Neonate 5 mg/kg daily, adjusted as necessary

Child 1 month–18 years 5 mg/kg daily, adjusted as necessary
Metabolic disorders including congenital lactic acidosis

- By mouth or by intravenous infusion over 30 minutes

Neonate 50–200 mg once daily (total dose may alternatively be given in 2–3 divided doses), adjusted as necessary

Child 1 month–18 years 100–300 mg once daily (total dose may alternatively be given in 2–3 divided doses), adjusted as necessary; up to 2 g daily may be necessary

Thiamine (Non-proprietary)
Tablets, thiamine hydrochloride 50 mg, net price 20 = £1.31; 100 mg, 20 = £1.50
Brands include Benerv®
Injection, 50 mg/mL, 2-mL vial; 100 mg/mL, 2-mL vial
Injection (intramuscular), 100 mg/mL, 5-mL vial
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
Note Some preparations may contain phenol as a preservative

Oral vitamin B complex preparations
See below

PYRIDOXINE HYDROCHLORIDE (Vitamin B6)

Cautions see notes above; risk of cardiovascular collapse with intravenous injection; interactions: Appendix 1 (vitamins)

Side-effects sensory neuropathy reported with high doses given for extended periods

Licensed use not licensed for use in children

Indication and dose
See also notes above

Metabolic diseases including cystathioninuria and homocystinuria
- By mouth

Neonate 50–100 mg 1–2 times daily

Child 1 month–18 years 50–250 mg 1–2 times daily

Treatment of isoniazid-induced neuropathy
- By mouth

Neonate 5–10 mg daily

Child 1 month–12 years 10–20 mg 2–3 times daily

Child 12–18 years 30–50 mg 2–3 times daily

Prevention of isoniazid-induced neuropathy
- By mouth

Neonate 5 mg daily

Child 1 month–12 years 5–10 mg daily

Child 12–18 years 10 mg daily

Pyridoxine-dependent seizures
- By intravenous injection or by mouth

Neonate initial test dose 50–100 mg by intravenous injection, may be repeated; if responsive followed by an oral maintenance dose of 50–100 mg once daily, adjusted as necessary

Child 1 month–12 years initial test dose 50–100 mg daily; if responsive followed by an oral dose of 20–50 mg 1–2 times daily, adjusted as necessary; doses up to 30 mg/kg or 1 g daily have been used

Pyridoxine (Non-proprietary)
Tablets, pyridoxine hydrochloride 10 mg, net price 20 = 34p; 20 mg, 20 = 34p; 50 mg, 28 = 76p
Injection, 25 mg/mL, 2 mL vial
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

NICOTINAMIDE

Indication and dose
See notes above, Acne vulgaris see section 13.6.1

Nicotinamide (Non-proprietary)
Tablets, nicotinamide 50 mg. Net price 20 = £1.37

Vitamin B Tablets, Compound
Tablets, nicotinamide 15 mg, riboflavin 1 mg. thiamine hydrochloride 1 mg. Net price 20 = 7p

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

Note Other multivitamin preparations are in section 9.6.7.
Vigranon B® (Wallace Mfg)  1  1  1
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

### Dose
- **Treatment of deficiency**
  - **By mouth**
    - Child 1 month–1 year: 5 mL 3 times daily
    - Child 12–18 years: 10 mL 3 times daily

### Prophylaxis of deficiency
- **By mouth**
  - Child 1 month–1 year: 5 mL once daily
  - Child 1–12 years: 5 mL twice daily
  - Child 12–18 years: 5 mL 3 times daily

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### 9.6.3 Vitamin C

**Ascorbic acid**

Vitamin C therapy is essential in scurvy, but less florid manifestations of vitamin C deficiency have been reported. Vitamin C is used to enhance the excretion of iron one month after starting desferrioxamine therapy (section 9.1.3); it is given separately from food as it also enhances iron absorption. Vitamin C is also used in the treatment of some inherited metabolic disorders, particularly mitochondrial disorders; specialist management of these conditions is required.

Severe scurvy causes gingival swelling and bleeding margins as well as petechiae on the skin. This is, however, exceedingly rare and a child 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

**Vitamin C**

**Cautions**
- Interactions: Appendix 1 (vitamins)

**Contra-indications**
- Hyperoxaluria

**Side-effects**
- Nausea, diarrhoea; headache, fatigue; hyperoxaluria

**Licensed use**
- Not licensed for metabolic disorders

### Indication and dose
- **Treatment of scurvy**
  - **By mouth**
    - Child 1 month–4 years: 125–250 mg daily in 1–2 divided doses
    - Child 4–12 years: 250–500 mg daily in 1–2 divided doses
    - Child 12–18 years: 500 mg–1 g daily in 1–2 divided doses

- **Adjunct to desferrioxamine (see notes above)**
  - **By mouth**
    - Child 1 month–18 years: 100–200 mg daily 1 hour before food

### Metabolic disorders (tyrosinaemia type III; transient tyrosinaemia of the newborn; glutathione synthase deficiency; Hawkinsinuria)
- **By mouth**
  - Neonate: 50–200 mg daily, adjusted as necessary
  - Child 1 month–18 years: 200–400 mg daily in 1–2 divided doses, adjusted as necessary; up to 1 g daily may be required

### 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
- **Excipients** may include aspartame
- **Brands include** Redoxon®

- **Injection**, ascorbic acid 100 mg/mL. Net price 5-mL amp = £2.51
- **Excipients** include metabisulphite
- Available from UCB Pharma

### 9.6.4 Vitamin D

**Note** The term Vitamin D is used for a range of compounds including ergocalciferol (calciferol, vitamin D2), colecalciferol (vitamin D3), dihydrotachysterol, alfalcaldiol (1α-hydroxycholecalciferol), and calcitriol (1,25-dihydroxycholecalciferol).

Symptomatic deficiency of vitamin D is uncommon in the United Kingdom, but may occur in certain ethnic groups, and rarely in association with malabsorption. The amount of vitamin D required in infancy is related to the stores built up in-utero and subsequent exposure to sunlight. The amount of vitamin D in breast milk varies and some breast-fed babies, particularly if preterm or born to vitamin D deficient mothers, may become deficient. Most formula milk and supplement feeds contain adequate vitamin D to prevent deficiency.
Simple, nutritional vitamin D deficiency can be prevented by oral supplementation of 400 units of ergocalciferol (calciferol, vitamin D$_2$) or colecalciferol (vitamin D$_3$) daily, using multi-vitamin drops (section 9.6.7), manufactured 'special' solutions, or as calcium and ergocalciferol tablets (although the calcium is unnecessary); excessive supplementation may cause hypercalcaemia.

Inadequate bone mineralisation can be caused by a deficiency, or a lack of action of vitamin D or its active metabolite. In childhood this causes bowing and distortion of bones (rickets); initial high doses of vitamin D should be reduced after a few weeks, as there is a significant risk of hypercalcaemia (see caution below).

Poor bone mineralisation in neonates and young children may also be due to inadequate intake of phosphate or calcium particularly during long-term parenteral nutrition—supplementation with phosphate (section 9.5.2.1) or calcium (section 9.5.1.1) may be required.

Hypophosphataemic rickets occurs due to abnormal phosphate excretion; treatment with high doses of oral phosphate (section 9.5.2.1), and hydroxylated (activated) forms of vitamin D allow bone mineralisation and optimise growth.

Nutritional deficiency of vitamin D is best treated with colecalciferol or ergocalciferol. Preparations containing calcium and colecalciferol are also occasionally used in children where there is evidence of combined calcium and vitamin D deficiency. Vitamin D deficiency caused by intestinal malabsorption or chronic liver disease usually requires vitamin D in pharmacological doses, such as ergocalciferol in doses of up to 40 000 units daily; the hypocalcaemia of hypoparathyroidism often requires higher doses in order to achieve normocalcaemia and alfalcacitol is generally preferred.

Vitamin D supplementation is often given in combination with calcium supplements for persistent hypocalcaemia in neonates, and in chronic renal disease.

Vitamin D requires hydroxylation, by the kidney and liver, to its active form therefore the hydroxylated derivatives alfalcacitol or calcitriol should be prescribed if patients with severe liver or renal impairment require vitamin D therapy. Alfalcacitrol is generally preferred in children as there is more experience of its use and appropriate formulations are available. Calcitriol is unlicensed for use in children and is generally reserved for those with severe liver disease.

Important. All patients receiving pharmacological doses of vitamin D or 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.
### Nutritional or physiological supplement; prevention of rickets

- **By mouth**
  - **Neonate** 400 units daily
  - **Child 1 month–18 years** 400–600 units daily

### Vitamin D deficiency in intestinal malabsorption or in chronic liver disease

- **By mouth or by intramuscular injection**
  - **Child 1–12 years** 10 000–25 000 units daily, adjusted as necessary
  - **Child 12–18 years** 10 000–40 000 units daily, adjusted as necessary

### Pharmacological strengths

(see notes above)

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 100 = £21.99; 1.25 mg (50 000 units), 100 = £30.34

**Note** May be difficult to obtain

**Important** When the strength of the tablets ordered or prescribed is not clear, the intention of the prescriber or purchaser with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

#### Solution

- **ergocalciferol 3000 units/mL**
- **Excipients** may include peanut oil
- Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Injection**, colecalciferol or ergocalciferol, 7.5 mg (300 000 units)/mL in oil. Net price 1-mL amp = £7.44, 2-mL amp = £8.93

### Daily supplements

**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

#### Calcium and Ergocalciferol (Non-proprietary)

**Calcium and Vitamin D**

- **Tablets**, calcium lactate 300 mg, calcium phosphate 150 mg (calcium 97 mg or Ca$^{2+}$ 2.4 mmol), ergocalciferol 10 micrograms (400 units). Net price 28-tab pack = £2.38. Counselling, crush before administration or may be chewed

### Hypophosphataemic rickets; persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism

- **By mouth or by intravenous injection**
  - **Child 1 month–12 years** 25–50 nanograms/kg (max. 1 microgram) once daily, adjusted as necessary
  - **Child 12–18 years** 250–500 nanograms once daily, adjusted as necessary

### Persistent neonatal hypocalcaemia

- **By mouth or by intravenous injection**
  - **Neonate** 50–100 nanograms/kg once daily, adjusted as necessary (up to 2 micrograms/kg daily may be needed in resistant cases)

### Prevention of vitamin D deficiency in renal or cholestatic liver disease

- **By mouth or by intravenous injection**
  - **Neonate** 20 nanograms/kg once daily, adjusted as necessary

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**ERGOCALCIFEROL (continued)**

**Nutritional or physiological supplement; prevention of rickets**

- **By mouth**
  - **Neonate** 400 units daily
  - **Child 1 month–18 years** 400–600 units daily

**Vitamin D deficiency in intestinal malabsorption or in chronic liver disease**

- **By mouth or by intramuscular injection**
  - **Child 1–12 years** 10 000–25 000 units daily, adjusted as necessary
  - **Child 12–18 years** 10 000–40 000 units daily, adjusted as necessary

**Pharmacological strengths**

(see notes above)

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 100 = £21.99; 1.25 mg (50 000 units), 100 = £30.34

**Note** May be difficult to obtain

**Important** When the strength of the tablets ordered or prescribed is not clear, the intention of the prescriber or purchaser with respect to the strength (expressed in micrograms or milligrams per tablet) should be ascertained.

#### Solution

- **ergocalciferol 3000 units/mL**
- **Excipients** may include peanut oil
- Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Injection**, colecalciferol or ergocalciferol, 7.5 mg (300 000 units)/mL in oil. Net price 1-mL amp = £7.44, 2-mL amp = £8.93

### Daily supplements

**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

#### Calcium and Ergocalciferol (Non-proprietary)

**Calcium and Vitamin D**

- **Tablets**, calcium lactate 300 mg, calcium phosphate 150 mg (calcium 97 mg or Ca$^{2+}$ 2.4 mmol), ergocalciferol 10 micrograms (400 units). Net price 28-tab pack = £2.38. Counselling, crush before administration or may be chewed

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**ALFACALCIDOL**

(1α-hydroxycholecalciferol)

**Cautions** see under Ergocalciferol; also nephrolithiasis

**Contra-indications** see under Ergocalciferol

**Side-effects** see under Ergocalciferol; also rarely nephrocalcinosis, pruritus, rash, urticaria

**Indication and dose**

- **See also notes above**

**Hypophosphataemic rickets; persistent hypocalcaemia due to hypoparathyroidism or pseudohypoparathyroidism**

- **By mouth or by intravenous injection**
  - **Child 1 month–12 years** 25–50 nanograms/kg (max. 1 microgram) once daily, adjusted as necessary
  - **Child 12–18 years** 1 microgram once daily, adjusted as necessary

**Persistent neonatal hypocalcaemia**

- **By mouth or by intravenous injection**
  - **Neonate** 50–100 nanograms/kg once daily, adjusted as necessary (up to 2 micrograms/kg daily may be needed in resistant cases)

**Prevention of vitamin D deficiency in renal or cholestatic liver disease**

- **By mouth or by intravenous injection**
  - **Neonate** 20 nanograms/kg once daily, adjusted as necessary

**Calcium and Ergocalciferol**

- **Tablets**, calcium lactate 300 mg, calcium phosphate 150 mg (calcium 97 mg or Ca$^{2+}$ 2.4 mmol), ergocalciferol 10 micrograms (400 units). Net price 28-tab pack = £9.99; 1 microgram 30-cap pack = £13.89

**One-Alpha® (LEO)**

- **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

**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

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**Nutrition and blood**
**Calcitriol**

(1,25-Dihydroxycholecalciferol)

**Cautions** see under Ergocalciferol

**Contra-indications** see under Ergocalciferol

**Side-effects** see under Ergocalciferol

**Licensed use** not licensed for use in children

**Indication and dose**

See also notes above

**Vitamin D dependent rickets; hypophosphataemic rickets; persistent hypocalcaemia due to hypoparathyroidism (limited experience)**

- **By mouth**
  - **Child 1 month–12 years** initially 15 nanograms/kg (max. 250 nanograms) once daily, increased if necessary in steps of 5 nanograms/kg daily (max. 250 nanograms) every 2–4 weeks
  - **Child 12–18 years** initially 250 nanograms once daily increased if necessary in steps of 5 nanograms/kg daily (max. 250 nanograms step) every 2–4 weeks; usual dose 0.5–3 micrograms daily

**Hypocalcaemia in dialysis patients** (limited experience)

- **By intravenous injection**
  - **Child 12–18 years** initially 250–500 nanograms approx. 10 nanograms/kg) 3 times a week, increased if necessary in steps of 2–5 nanograms/kg every 2–4 weeks; usual dose 0.5–3 micrograms 3 times a week

**Administration**

For administration by mouth, injection solution may be given orally or contents of capsule administered by oral syringe; capsules contain approx. 0.188 mL of fluid

For administration by intravenous injection, injection may be given via catheter after dialysis

**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

**Cacit D3** (Procter & Gamble Pharm.)

- **Granules**, effervescent, lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca$^{2+}$ 12.5 mmol), colecalciferol 11 micrograms (440 units)/sachet, net price 30-sachet pack = £4.31. Label: 13

**Calceos** (Galen)

- **Tablets** (chewable), lemon flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca$^{2+}$ 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £3.90. Label: 24

**Calcichew D3** (Shire)

- **Tablets** (chewable), orange flavour, calcium carbonate 1.25 g (calcium 500 mg or Ca$^{2+}$ 12.5 mmol), colecalciferol 10 micrograms (400 units), net price 500 nanograms, 30-cap pack = £10.50, 100-cap pack = £19.15; 500 nanograms, 30-cap pack = £15.02. Label: 24

**Excipients** include aspartame (section 9.4.1)

**Calceos D3** (Menarini)

- **Powder**, lemon flavour, calcium phosphate 3.1 g (calcium 1.2 g or Ca$^{2+}$ 30 mmol), colecalciferol 20 micrograms (800 units), net price 30-sachet pack = £4.32. Label: 13, 21

**Natecal D3** (Chiesi)

- **Tablets**, aniseed, peppermint, and molasses flavour, calcium carbonate 1.5 g (calcium 600 mg or Ca$^{2+}$ 15 mmol)
COLECALCIFEROL (continued)

Ca\(^{++}\) 15 mmol), colecalciferol 10 micrograms (400 units), net price 60-tab pack = £3.85. Label: 24

Excipients include aspartame (section 9.4.1)

Sandocal\(^{c+D\ 600\) (Novartis Consumer Health)

Tablets, effervescent, orange flavour, calcium lactate gluconate 1.36 g, calcium carbonate 1.05 g, providing calcium 600 mg (Ca\(^{++}\) 15 mmol), colecalciferol concentrate 4 mg, providing colecalciferol 10 micrograms (400 units), net price 60-tab pack = £5.35, 100-tab pack = £8.75. Label: 13

Excipients include aspartame (section 9.4.1)

9.6.5 Vitamin E

(Tocopherols)

The daily requirement of vitamin E has not been well defined. Vitamin E supplements are given to children with fat malabsorption such as in cystic fibrosis and cholestatic liver disease. In children with abetalipoproteinaemia abnormally low vitamin E concentrations may occur in association with neuromuscular problems; this usually responds to high doses of vitamin E. Some neonatal units still administer a single intramuscular dose of vitamin E at birth to preterm neonates to reduce the risk of complications; no trials of long-term outcome have been carried out. The intramuscular route should also be considered in children with severe liver disease when response to oral therapy is inadequate.

Vitamin E has been tried for various other conditions but there is little scientific evidence of its value.

ALPHA TOCOPHERYL ACETATE

(Vitamin E)

Cautions predisposition to thrombosis; increased risk of necrotising enterocolitis in preterm neonates (see administration); Interactions: Appendix 1 (vitamins)

Pregnancy avoid high doses in first trimester

Breast-feeding excreted in breast milk, minimal risk although caution with large doses

Side-effects diarrhea and abdominal pain, particularly with high doses

Indication and dose

Vitamin E deficiency

• By mouth

Neonate 10 mg/kg once daily

Child 1 month–18 years 2–10 mg/kg daily, up to 20 mg/kg has been used

Malabsorption in cystic fibrosis

• By mouth (with food and pancreatic enzymes)

Child 1 month–1 year 50 mg once daily, adjusted as necessary

Child 1–12 years 100 mg once daily, adjusted as necessary

Child 12–18 years 100–200 mg once daily, adjusted as necessary

Vitamin E deficiency in cholestasis and severe liver disease

• By mouth

Neonate 10 mg/kg daily

Child 1 month–12 years initially 100 mg daily, adjusted according to response; up to 200 mg/kg daily may be required

Child 12–18 years initially 200 mg daily, adjusted according to response; up to 200 mg/kg daily may be required

• By intramuscular injection

Neonate 10 mg/kg once a month

Child 1 month–18 years 10 mg/kg (max. 100 mg) once a month

Malabsorption in abetalipoproteinaemia

• By mouth

Neonate 100 mg/kg once daily

Child 1 month–18 years 50–100 mg/kg once daily

Vitamin E Suspension (Cambridge)

Suspension, alpha tocopheryl acetate 100 mg/mL.

Net price 100 mL = £25.08

Excipients include sucrose

Administration consider dilution in neonates due to high osmolality (see Cautions)

Note Tablets containing tocopheryl acetate are available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Vitamin E Injection (Roche)

Injection tocopheryl acetate 50 mg/mL, 2-mL ampoule

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
Vitamin K is necessary for the production of blood clotting factors and proteins necessary for the normal calcification of bone.

Because vitamin K is fat soluble, children with fat malabsorption, especially in biliary obstruction or hepatic disease, may become deficient. For oral administration to prevent vitamin K deficiency in malabsorption syndromes, a water-soluble preparation, menadiol sodium phosphate (see Contra-indications below) must be used.

Oral coumarin anticoagulants act by interfering with vitamin K metabolism in the hepatic cells and their effects can be antagonised by giving vitamin K (see also section 2.8.2).

**Vitamin K deficiency bleeding** Neonates are relatively deficient in vitamin K and those who do not receive supplements are at risk of serious bleeds (haemorrhagic disease), including intracranial bleeding. The Chief Medical Officer and the Chief Nursing Officer have recommended that all newborn babies should receive vitamin K to prevent vitamin K deficiency bleeding (haemorrhagic disease of the newborn). Local protocols may vary and an appropriate regimen should be selected after discussion with parents in the antenatal period.

Vitamin K (as phytomenadione) 1 mg may be given by a single intramuscular injection at birth; this prevents vitamin K deficiency bleeding in virtually all babies; preterm neonates may be given 400 micrograms/kg (max. 1 mg). The intravenous route is preferred by some in preterm neonates of very low birth-weight but it does not provide the prolonged protection of the intramuscular injection, and any babies receiving intravenous vitamin K should be given subsequent oral doses, as described below.

Babies considered at particular risk of vitamin K deficiency bleeding should receive intramuscular vitamin K at birth; this includes those experiencing birth asphyxia or bleeding problems, those born to mothers with liver disease or taking enzyme inducing anticonvulsant drugs (carbamazepine, phenobarbital, phenytoin), rifampicin or warfarin. In infants with cholestatic disease, vitamin K must be given either intramuscularly or intravenously because oral absorption is likely to be impaired.

Alternatively, in healthy babies who are not at particular risk of bleeding disorders, vitamin K may be given by mouth, and arrangements must be in place to ensure the appropriate regimen is followed. Two doses of a colloidal (mixed micelle) preparation of phytomenadione 2 mg should be given in the first week, the first dose being given at birth. For exclusively breast-fed babies, a third dose of phytomenadione 2 mg is given at 1 month of age; the third dose is omitted in formula-fed babies because formula feeds contain vitamin K.

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**MENADIOL SODIUM PHOSPHATE**

**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

**Indication and dose**

See notes above

**Supplementation in vitamin K malabsorption**

- Child 1–12 years 5–10 mg daily, adjusted as necessary

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**PHYTOMENADIONE** (Vitamin K$_1$)

**Cautions** intravenous injections should be given very slowly—risk of vascular collapse (see also below); interactions: Appendix 1 (vitamins)

**Indication and dose**

Neonatal prophylaxis of vitamin-K deficiency bleeding see notes above
**Acute bleeding**

- **Neonatal hypoprothrombinemia or vitamin-K deficiency bleeding**
  - **By intravenous injection**
  - **Neonate:** 1 mg repeated 8 hourly if necessary

- **Neonatal biliary atresia and liver disease**
  - **By mouth**
  - **Neonate:** 1 mg daily

Reversal of coumarin anticoagulation when continued anticoagulation required or if no significant bleeding (see also section 2.8.2)—seek specialist advice

- **By intravenous injection**
  - **Child 1 month–18 years:** 15–30 micrograms/kg (max. 1 mg) as a single dose, repeated as necessary

Reversal of coumarin anticoagulation when anticoagulation not required or if significant bleeding; treatment of haemorrhage associated with vitamin-K deficiency (see also section 2.8.2)—seek specialist advice

- **By intravenous injection**
  - **Child 1 month–18 years:** 250–300 micrograms/kg (max. 10 mg) as a single dose

**Konakion (Roche)**

- **Tablets, s/c:** phytomenadione 10 mg, net price 10-tab pack = £1.65. To be chewed or allowed to dissolve slowly in the mouth. Label: 24

**Konakion MM (Roche)**

- **Injection:** phytomenadione 10 mg/mL in a mixed micelles vehicle. Net price 1-mL amp = 40p

**Konakion MM Paediatric (Roche)**

- **Injection:** phytomenadione 10 mg/mL in a mixed micelles vehicle, net price 0.2-mL amp = £1.00

**Konakion MM Paediatric (Roche)**

- **Injection:** phytomenadione 10 mg/mL in a mixed micelles vehicle, net price 0.2-mL amp = £1.00

**Cautions**

- see individual vitamins; concentration of preparations varies

**Contra-indications**

- see individual vitamins

**Side-effects**

- see individual vitamins

**Licensed use**

- **Dalivit®** not licensed for use in children under 6 weeks

**Indication and dose**

- See under preparations below

**Vitamins**

- **Capsules:** ascorbic acid 15 mg, nicotinamide 7.5 mg, riboflavin 50 micrograms, thiamine hydrochloride 1 mg, vitamin A 2500 units, vitamin D 300 units. Net price 20 = 22p

**Dose**

- **Prevention of deficiency**
  - **By mouth**
  - **Child 1–12 years:** 1 capsule daily
  - **Child 12–18 years:** 2 capsules daily

**Abidec (Chefaro UK)**

- **Drops:** vitamins A, B group, C, and D. Net price 25 mL (with dropper) = £2.08

**Note**

- Contains 1333 units of vitamin A (as palmitate) per 0.6 mL dose

**Excipients**

- include arachis (peanut) oil and sucrose

**Dose**

- **Prevention of deficiency**
  - **By mouth**
  - **Preterm neonate:** 0.6 mL daily
  - **Neonate:** 0.3 mL daily
  - **Child 1 month–1 year:** 0.3 mL daily
  - **Child 1–18 years:** 0.6 mL daily

**9.6.7 Multivitamin preparations**

Multivitamin supplements are used in children with vitamin deficiencies and also in malabsorption conditions such as cystic fibrosis or liver disease. To avoid potential toxicity, the content of all vitamin preparations, particularly vitamin A, should be considered when used together with other supplements. Supplementation is not required if nutrient enriched feeds are used; consult a dietician for further advice.

**MULTIVITAMIN PREPARATIONS**

- **Cystic fibrosis: prevention of deficiency**
  - **By mouth**
  - **Child 1–18 years:** 2–3 capsules daily

**Abidec**

- **Drops:** vitamins A, B group, C, and D. Net price 25 mL (with dropper) = £2.08

**Note**

- Contains 1333 units of vitamin A (as palmitate) per 0.6 mL dose

**Excipients**

- include arachis (peanut) oil and sucrose

**Dose**

- **Prevention of deficiency**
  - **By mouth**
  - **Preterm neonate:** 0.6 mL daily
  - **Neonate:** 0.3 mL daily
  - **Child 1 month–1 year:** 0.3 mL daily
  - **Child 1–18 years:** 0.6 mL daily
### Cystic fibrosis: prevention of deficiency

**By mouth**

- **Child 1 month–1 year**: 0.6 mL daily
- **Child 1–18 years**: 1.2 mL daily

### 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

**Excipients** include sucrose

### Vitamin and mineral supplements and adjuncts to synthetic diets

#### Forceval® (Alliance)
**Capsules**, brown/red, vitamins (ascorbic acid 60 mg, biotin 100 micrograms, cyanocobalamin 3 micrograms, folic acid 400 micrograms, nicotinamide 18 mg, pantothenic acid 4 mg, pyridoxine 2 mg, riboflavin 1.6 mg, thiamine 1.2 mg, vitamin A 2500 units, vitamin D 400 units, vitamin E 10 mg, minerals and trace elements (calcium 100 mg, chromium 200 micrograms, copper 2 mg, iodine 140 micrograms, iron 12 mg, magnesium 30 mg, manganese 3 mg, molybdenum 250 micrograms, phosphorus 77 mg, potassium 4 mg, selenium 50 micrograms, zinc 15 mg), net price 15-cap pack = £2.83, 30-cap pack = £4.94, 90-cap pack = £11.93. **Label**: 25

#### Dose

**Vitamin and mineral deficiency and as adjunct in synthetic diets**

- **Child 12–18 years**: 1 capsule daily one hour after a meal

#### 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 microgram, 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 5–12 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 tocopherol acetate 5 mg, inositol 50 mg, biotin 170 micrograms, folic acid 250 micrograms, acetomenaphthone 500 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**

- **Child 1 month–18 years**: 1 tablet 3 times daily; dose adjusted according to condition, diet, or age; use with Ketovite® Liquid for complete vitamin supplementation

#### Administration

May be crushed immediately before use

#### 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**

- **Child 1 month–18 years**: 5 mL daily; dose adjusted according to condition, diet, or age; use with Ketovite® Tablets for complete vitamin supplementation

#### Administration

May be mixed with milk, cereal, or fruit juice

### 9.7 Bitters and tonics

Classification not included in *BNF for Children.*
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

Metabolic disorders should be managed under the guidance of a specialist. As many preparations are unlicensed and may be difficult to obtain, arrangements for continued prescribing and supply should be made in primary care.

General advice on the use of medicines in metabolic disorders can be obtained from:

- Alder Hey Children’s Hospital Medicines Information Centre
  Tel: (0151) 252 5381
- Great Ormond Street Hospital for Children Pharmacy
  Tel: (020) 7405 9200

Wilson’s disease

Penicillamine is used in Wilson’s disease (hepatolenticular degeneration) to aid the elimination of copper ions; it is also used for cystinuria. Children who are hypersensitive to penicillin may react rarely to penicillamine.

Trientine is used for the treatment of Wilson’s disease only, in patients intolerant of penicillamine; it is not an alternative to penicillamine in other diseases such as 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

Cautions concomitant nephrotoxic drugs (increased risk of toxicity); monitor urine for proteinuria; monitor blood and platelet count regularly (see below); neurological involvement; interactions: Appendix 1 (penicillamine)

Renal impairment reduce dose and monitor renal function or avoid—consult product literature

Pregnancy fetal abnormalities reported rarely; avoid if possible

Breast-feeding manufacturer advises avoid unless potential benefit outweighs risk—no information available

Blood counts and urine tests Consider withdrawal if platelet count falls below 120 000/mm$^3$ or white blood cells below 2500/mm$^3$ 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 child and carer to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers, or rashes develop

Contra-indications lupus erythematosus

Side-effects 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, pancreatitis, cholestatic jaundice, nephrotic syndrome, lupus erythematosus-like syndrome, myasthenia gravis-like syndrome, neuropathy (especially if neurological involvement in Wilson’s disease—prophylactic pyridoxine recommended, see section 9.6.2, p. 577), polymyositis (rarely with cardiac involvement), dermatomyositis, mouth ulcers, stomatitis, alopecia, bronchiolitis and pneumonitis, pemphigus, 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)

Indication and dose

Wilson’s disease

- By mouth

  Child 1 month–12 years 2.5 mg/kg twice daily before food, increased at 1–2 week intervals to 10 mg/kg twice daily

  Child 12–18 years 0.75–1 g twice daily before food, max. 2 g daily for 1 year; usual maintenance dose 0.75–1 g daily
Cystinuria

- **By mouth**
  - **Child 1 month–12 years**  5–10 mg/kg twice daily before food, adjusted to maintain urinary cystine below 200 mg/litre; maintain adequate fluid intake
  - **Child 12–18 years**  0.5–1.5 g twice daily before food, adjusted to maintain urinary cystine below 200 mg/litre; maintain adequate fluid intake

Penicillamine

- **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)

- **Tablets**, all l/c, penicillamine 125 mg, net price 100 = £8.62; 250 mg, 100 = £14.82. **Label**: 6, 22, counselling, blood disorder symptoms (see above)

TRIENTINE DIHYDROCHLORIDE

- **Cautions**  see notes above; **interactions**: Appendix 1 (trientine)
  - **Pregnancy**  teratogenic in animal studies—use only if benefit outweighs risk; monitor maternal and neonatal serum-copper concentrations
- **Side-effects**  nausea, rash; rarely anaemia

**Indication and dose**

- **Wilson’s disease in patients intolerant of penicillamine**
  - **By mouth**
  - **Child 2–12 years**  0.6–1.5 g daily in 2–4 divided doses before food, adjusted according to response; reduce dose and increase frequency if nausea is a problem
  - **Child 12–18 years**  1.2–2.4 g daily in 2–4 divided doses before food, adjusted according to response; reduce dose and increase frequency if nausea is a problem

Trientine Dihydrochloride (Univar)

- **Capsules**, trientine dihydrochloride 300 mg. **Label**: 6, 22

ZINC ACETATE

- **Cautions**  portal hypertension (risk of hepatic decompensation when switching from chelating agent); monitor full blood count and serum cholesterol; **interactions**: Appendix 1 (zinc)
  - **Pregnancy**  usual dose 25 mg 3 times daily adjusted according to plasma-copper concentration and urinary copper excretion
- **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

**Indication and dose**

- **Wilson’s disease**
  - **Note**: dose expressed as elemental zinc
  - **By mouth**
  - **Child 1–6 years**  25 mg twice daily
  - **Child 6–16 years**  body-weight under 57 kg, 25 mg 3 times daily; body-weight 57 kg or over, 50 mg 3 times daily
  - **Child 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
- **Administration**  capsules may be opened and the contents mixed with water

CARNITINE

- **Cautions**  diabetes mellitus; monitoring of free and acyl carnitine in blood and urine recommended
- **Renal impairment**  accumulation of metabolites may occur with chronic oral administration in severe renal impairment
  - **Pregnancy**  appropriate to use; no evidence of teratogenicity in animal studies
- **Side-effects**  nausea, vomiting, abdominal pain, diarrhoea, fishy body odour; side-effects may be dose-related—monitor tolerance during first week and after any dose increase
- **Licensed use**  not licensed for use by intravenous infusion; oral liquid (10%) not licensed in children under 12 years; Paediatric solution (30%) not licensed in children over 12 years; not licensed for use in organic acidaemias

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 is also used in the treatment of some organic acidaemias; however, use in fatty acid oxidation is controversial.
**CARNITINE (continued)**

### Indication and dose

<table>
<thead>
<tr>
<th>Indication and organic acidaemias</th>
<th>By mouth</th>
<th>Child 1 month–18 years</th>
<th>By intravenous infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary deficiency and organic acidaemias</td>
<td>Neonate 50 mg/kg twice daily, higher doses up to 200 mg/kg daily occasionally required</td>
<td>Child 1 month–18 years 50 mg/kg twice daily, higher doses up to 200 mg/kg daily or 3 g daily occasionally required</td>
<td>Neonate initially 100 mg/kg over 30 minutes followed by a continuous infusion of 4 mg/kg/hour</td>
</tr>
<tr>
<td>Secondary deficiency in dialysis patients</td>
<td>By slow intravenous injection over 2–3 minutes</td>
<td>Child 1 month–18 years initially 100 mg/kg over 30 minutes followed by a continuous infusion of 4mg/kg/hour</td>
<td>Child 1 month–18 years 100 mg/kg/daily in 2–4 divided doses</td>
</tr>
<tr>
<td>By slow intravenous injection over 2–3 minutes</td>
<td>Neonate 100 mg/kg daily in 2–4 divided doses</td>
<td>Child 1 month–18 years 100 mg/kg/daily in 2–4 divided doses</td>
<td></td>
</tr>
</tbody>
</table>

### 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

**Cautions** interactions: Appendix 1 (agalsidase alfa and beta)

**Pregnancy** use with caution

**Breast-feeding** use with caution—no information available

**Infusion-related reactions** Infusion-related reactions very common; manage by slowing the infusion rate or interrupting the infusion, or minimise by pre-treatment with an antihistamine, antipyretic, or corticosteroid—consult product literature

**Side-effects** gastro-intestinal disturbances, taste disturbances; tachycardia, bradycardia, palpitation, hypertension, hypotension, chest pain, oedema, flushing; dyspnoea, cough, wheezing, hoarseness, rhinorrhoea; headache, fatigue, dizziness, asthenia, paraesthesia, syncope, neuro-pathic 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

**Indication and dose**

**Fabry’s disease** (specialist use only) see under preparations

**Fabrazyme®** (Genzyme) ** Intravenous infusion** powder for reconstitution, agalsidase beta, net price 5-mg vial = £325.50; 35-mg vial = £2269.20

**Dose**

**Fabry’s disease** (specialist use only)

- **By intravenous infusion**
  - Child 8–18 years 1 mg/kg every 2 weeks

**Administration** for intravenous infusion, reconstitute initially with Water for Injections (5 mg in 1.1 mL, 35 mg in 7.2 mL) to produce a solution containing 5 mg/mL; dilute with Sodium Chloride 0.9% (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

**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**

**Fabry’s disease** (specialist use only)

- **By intravenous infusion**
  - Child 7–18 years 200 micrograms/kg every 2 weeks

**Administration** for intravenous infusion, dilute requisite dose with 100 mL Sodium Chloride 0.9% and give over 40 minutes using an in-line filter; use within 3 hours of dilution
Gaucher’s disease

Imiglucerase, an enzyme produced by recombinant DNA technology, is administered as enzyme replacement therapy in Gaucher’s disease, a familial disorder affecting principally the liver, spleen, bone marrow, and lymph nodes.

Miglustat, an inhibitor of glucosylceramide synthase, is licensed in adults for the treatment of mild to moderate type I Gaucher’s disease in patients for whom imiglucerase is unsuitable; it is given by mouth.

**Cautions**
- Monitor for imiglucerase antibodies; when stabilised, monitor all parameters and response to treatment at intervals of 6–12 months
- Pregnancy: Manufacturer advises use only if potential benefit outweighs risk—no information available
- Breast-feeding: No information available

**Side-effects**
- Hypersensitivity reactions (including urticaria, angioedema, hypotension, flushing, tachycardia); less commonly nausea, vomiting, diarrhoea, abdominal cramps, fatigue, headache, dizziness, paraesthesia, fever, arthralgia, injection-site reactions

**Indication and dose**
- **Gaucher’s disease type I** (specialist use only)
  - By intravenous infusion
    - Neonate: 60 units/kg once every 2 weeks, adjusted according to response
    - Child 1 month–18 years: 60 units/kg once every 2 weeks, adjusted according to response

**Administration**
- For intravenous infusion, initially reconstitute with Water for Injections (200 units in 5.1 mL, 400 units in 10.2 mL) to a concentration of 40 units/mL; dilute requisite dose with Sodium Chloride 0.9% to a final volume of 100–200 mL; give over 1–2 hours or at a rate not exceeding 1 unit/kg/minute; administer within 3 hours of reconstitution

**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

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.

**Cautions**
- Respiratory disease; acute febrile or respiratory illness (consider delaying treatment)
- Pregnancy: Manufacturer advises avoid unless essential
- Infusion-related reactions: See notes above
- Contra-indications: Manufacturer advises avoid—no information available

**Side-effects**
- Abdominal pain, umbilical hernia, gastroenteritis; chest pain, hypertension; dyspnoea, apnoea, nasal congestion; rigors, malaise, areflexia; pharyngitis; conjunctivitis, corneal opacity; ear pain; facial oedema
Indication and dose

Mucopolysaccharidosis VI (specialist use only)

- **By intravenous infusion**
  - **Child 5–18 years** 1 mg/kg once weekly

Administration for intravenous infusion, dilute requisite dose with Sodium Chloride 0.9% to a 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 Sodium Chloride 0.9% and give over at least 4 hours

Naglazyme® (BioMarin) ▼
Concentrate for intravenous infusion, galsulfase 1 mg/mL, net price 5-mL vial = £982.00

IDURSULFASE

Cautions  severe respiratory disease; acute febrile respiratory illness (consider delaying treatment)

Breast-feeding  no information available

Infusion-related reactions  See notes above

Contra-indications  women of child-bearing potential

Pregnancy  manufacturer advises avoid—no information available

Side-effects  gastro-intestinal disturbances, swollen tongue; arrhythmia, chest pain, cyanosis, peripheral oedema, hypertension, hypotension, flushing, pulmonary embolism; bronchospasm, cough, wheezing, tachypnoea, dyspnoea; headache, dizziness, tremor; pyrexia; arthralgia; increased lacrimation; facial oedema, urticaria, pruritus, rash, infusion-site swelling, erythema, and eczema; anaphylaxis also reported

Indication and dose

Mucopolysaccharidosis II (specialist use only)

- **By intravenous infusion**
  - **Child 5–18 years** 500 micrograms/kg once weekly

Administration for intravenous infusion, dilute requisite dose in 100 mL Sodium Chloride 0.9% and mix gently (do not shake); give over 3 hours (gradually reduced to 1 hour if no infusion-related reactions)

Elaprase® (Shire) ▼
Concentrate for intravenous infusion, idursulfase 2 mg/mL, net price 3-mL vial = £1985.00

LARONIDASE

Cautions  monitor immunoglobulin G (IgG) antibody concentration; interactions: Appendix 1 (laronidase)

Pregnancy  manufacturer advises avoid unless essential—no information available

Breast-feeding  manufacturer advises avoid—no information available

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; musculoskeletal pain, pain in extremities; rash, pruritus, urticaria, alopecia, infusion-site reactions; bronchospasm and respiratory arrest also reported

Indication and dose

Non-neurological manifestations of mucopolysaccharidosis I (specialist use only)

- **By intravenous infusion**
  - **Child 1 month–18 years** 100 units/kg once weekly

Administration for intravenous infusion, dilute with Sodium Chloride 0.9%; body-weight under 20 kg, dilute to 100 mL; body-weight over 20 kg dilute to 250 mL; give through in-line filter (0.22 micron) initially at a rate of 2 units/kg/hour then increase gradually every 15 minutes to max. 43 units/kg/hour

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

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. 4) has advised (February 2007) that alglucosidase alfa (Myozyme®) is not recommended for use within NHS Scotland for the treatment of Pompe disease.
ALGLUCOSIDASE ALFA

**Cautions**  cardiac and respiratory dysfunction—monitor closely; monitor immunoglobulin G (IgG) antibody concentration

**Pregnancy**  manufacturer advises avoid unless essential—no information available

**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**  manufacturer advises avoid—no information available

**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; antibody formation; sweating, rash, pruritus, and urticaria; anaphylaxis

**Indication and dose**

- **Pompe disease**  (specialist use only)
  - By intravenous infusion
    - Child 1 month –18 years  20 mg/kg every 2 weeks

**Administration**  for intravenous infusion, 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 sodium chloride 0.9% 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 2 mg/kg/hour every 30 minutes to max. 7 mg/kg/hour

**Myozyme®**  (Genzyme)

- **Intravenous infusion**, powder for reconstitution, alglucosidase alfa, net price 50-mg vial = £368.59

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**Urea cycle disorders**

**Sodium benzoate** and **sodium phenylbutyrate** are used in the management of urea cycle disorders. Both, either singly or in combination, are 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. Sodium benzoate is also used in non-ketotic hyperglycinemia. In anuric states dialysis is necessary to treat hyperammonemia.

Gastro-intestinal side-effects of sodium benzoate or sodium phenylbutyrate may be reduced by giving smaller doses more frequently. The preparations contain significant amounts of sodium; therefore, they should be used with caution in children with congestive heart failure, renal insufficiency and clinical conditions involving sodium retention with oedema.

The long-term management of urea cycle disorders includes oral maintenance treatment with sodium benzoate and sodium phenylbutyrate combined with a low protein diet and other drugs such as arginine or citrulline, depending on the specific disorder.

**Carglumic acid** is licensed for the treatment of hyperammonaemia due to N-acetylglutamate synthase deficiency.

**ARGinine**

**Cautions**  monitor plasma pH and chloride

**Contra-indications**  not to be used in the treatment of arginase deficiency

**Pregnancy**  no information available

**Breast-feeding**  no information available

**Side-effects**  intravenous injection only: nausea, vomiting; flushing, hypotension; headache, numbness; hyperchloraemic metabolic acidosis; irritation at injection-site

**Licensed use**  injection and tablets not licensed in children; powder licensed for urea cycle disorders in children

**Indication and dose**

- **Acute hyperammonaemia in carbamylphosphatase synthetase deficiency, ornithine carbamyl transferase deficiency** (specialist use only)
  - By intravenous infusion
    - Neonate  200 mg/kg over 90 minutes followed by 8 mg/kg/hour

**Maintenance treatment of hyperammonaemia in carbamylphosphatase synthetase deficiency, ornithine carbamyl transferase deficiency** (specialist use only)

- By mouth
  - Neonate  100 mg/kg daily in 3–4 divided doses
  - Child 1 month–18 years  100 mg/kg daily in 3–4 divided doses

**Acute hyperammonaemia in citrullinaemia, arginosuccinic aciduria** (specialist use only)

- By intravenous infusion
  - Neonate  initially 600 mg/kg over 90 minutes followed by 25 mg/kg/hour
  - Child 1 month–18 years  initially 600 mg/kg over 90 minutes followed by 25 mg/kg/hour
ARGinine (continued)

Maintenance treatment of hyperammonaemia in citrullinaemia, arginosuccinic aciduria (specialist use only)
- By mouth
- **Neonate**: 100–175 mg/kg 3–4 times daily, with food, adjusted according to response
- **Child 1 month–18 years**: 100–175 mg/kg 3–4 times daily, with food, adjusted according to response

L-Arginine (Non-proprietary)
- **Tablets**, L-arginine (as hydrochloride) 500 mg,
- **Oral solution**, L-arginine 100 mg/mL

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Note**: Other strengths may be available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Administration**: dilute to a concentration of 20 mg/mL with Sodium Chloride 0.9% or 0.45%, or Glucose 5% or 10%; max. concentration 100 mg/mL; may be given orally

CARGLUMIC ACID

**Cautions**
- Pregnancy: manufacturer advises avoid unless essential—no information available
- Contra-indications
- Breast-feeding: manufacturer advises avoid—present in milk in animal studies
- **Side-effects**: sweating

**Indication and dose**
- Hyperammonaemia due to N-acetyl glutamate synthase deficiency (initiated under specialist supervision)
  - **By mouth**
  - **Neonate**: initially 50–125 mg/kg twice daily immediately before feeds, adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily; total daily dose may alternatively be given in 3–4 divided doses
  - **Child 1 month–18 years**: initially 50–125 mg/kg twice daily immediately before food, adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily; total daily dose may alternatively be given in 3–4 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

CITRULLINE

**Cautions**
- Pregnancy: no information available
- Breast-feeding: no information available

**Indication and dose**
- Carbamyl phosphate synthase deficiency, ornithine carbamyl transferase deficiency
  - **By mouth**
  - **Neonate**: 150 mg/kg daily in 3–4 divided doses, adjusted according to response
  - **Child 1 month–18 years**: 150 mg/kg daily in 3–4 divided doses, adjusted according to response

Citrulline Powder (Non-proprietary)
- **Powder**, L-citrulline 100 g
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
  - **Administration**: May be mixed with drinks or taken as a paste

SODIUM BENZOATE

**Cautions**
- see notes above; neonates (risk of kernicterus and increased side-effects); interactions: Appendix 1 (sodium benzoate)
- Pregnancy: no information available
- Breast-feeding: no information available
- **Side-effects**: nausea, vomiting, anorexia; irritability, lethargy, coma
- **Licensed use**: not licensed for use in children

**Indication and dose**
- Acute hyperammonaemia due to urea cycle disorders (specialist use only)
  - **By intravenous infusion**
  - **Neonate**: initially 250 mg/kg over 90 minutes followed by 20 mg/kg/hour, adjusted according to response
  - **Child 1 month–18 years**: initially 250 mg/kg over 90 minutes followed by 20 mg/kg/hour, adjusted according to response

**Note**: Plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily; total daily dose may be increased in 3–4 divided doses

**Child 1 month–18 years**: initially 50–125 mg/kg twice daily immediately before food, adjusted according to plasma-ammonia concentration; maintenance 5–50 mg/kg twice daily; total daily dose may alternatively be given in 3–4 divided doses

**Child 1 month–18 years**: 150 mg/kg daily in 3–4 divided doses, adjusted according to response

**Citrulline Powder (Non-proprietary)**
- **Powder**, L-citrulline 100 g
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
  - **Administration**: May be mixed with drinks or taken as a paste

**SODIUM BENZOATE**

**Cautions**
- see notes above; neonates (risk of kernicterus and increased side-effects); interactions: Appendix 1 (sodium benzoate)
- Pregnancy: no information available
- Breast-feeding: no information available
- **Side-effects**: nausea, vomiting, anorexia; irritability, lethargy, coma
- **Licensed use**: not licensed for use in children

**Indication and dose**
- Acute hyperammonaemia due to urea cycle disorders (specialist use only)
  - **By intravenous infusion**
  - **Neonate**: initially 250 mg/kg over 90 minutes followed by 20 mg/kg/hour, adjusted according to response
  - **Child 1 month–18 years**: initially 250 mg/kg over 90 minutes followed by 20 mg/kg/hour, adjusted according to response
Maintenance treatment of hyperammonaemia due to urea cycle disorders; non-ketotic hyperglycinæmia (specialist use only)

- **By mouth**
  - Neonate: 50–150 mg/kg 3–4 times daily, with food, adjusted according to response
  - Child 1 month–18 years: 50–150 mg/kg 3–4 times daily, with food, adjusted according to response

**Administration** for administration by mouth, oral solution or powder may be administered in fruit drinks; less soluble in acidic drinks

**Sodium Benzoate** (Non-proprietary)

- Tablets, sodium benzoate 500 mg
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p 943

- Capsules, sodium benzoate 50 mg; 250 mg; 400 mg; 500 mg
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p 943

- Oral solution, sodium benzoate 100 mg/mL; 200 mg/mL; 300 mg/mL
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p 943

- Powder
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p 943

- Injection, sodium benzoate 200 mg/mL, 5-mL amp
  - Contains Na⁺ 1.4 mmol/mL
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p 943

**SODIUM PHENYL BUTYRATE**

- **Cautions** congestive heart failure, hepatic and renal impairment; **interactions**: Appendix 1 (sodium phenylbutyrate)

- **Contra-indications**
  - Pregnancy: avoid
  - Breast-feeding: avoid

- **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

- **Licensed use** injection not licensed for use in children

**Indication and dose**

**Acute hyperammonaemia due to urea cycle disorders** (specialist use only)

- **By continuous intravenous infusion**
  - Neonate: initially 250 mg/kg over 90 minutes followed by 20 mg/kg/hour adjusted according to response
  - Child 1 month–18 years: initially 250 mg/kg over 90 minutes followed by 20 mg/kg/hour adjusted according to response

**Maintenance treatment of hyperammonaemia due to urea cycle disorders** (specialist use only)

- **By mouth**
  - Neonate: 75–150 mg/kg 3–4 times daily, with food
  - Child 1 month–18 years: 75–150 mg/kg 3–4 times daily, with food (max. 20 g daily)

**Ammonaps®** (Swedish Orphan)

- 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

**Nephropathic cystinosis**

**Mercaptamine** (cysteamine) is available for the treatment of nephropathic cystinosis. The oral dose is increased over several weeks to avoid intolerance. Mercaptamine eye drops are used in the management of ocular symptoms arising from the deposition of cystine crystals in the eye.

**Phosphocysteamine** is a pro-drug of mercaptamine; it is available from specialist centres only, as a powder or specially manufactured capsule. Mercaptamine does not contain phosphate, therefore, if transferring from phosphocysteamine to mercaptamine phosphate supplements may need to be initiated or adjusted. Mercaptamine 1 mg is approximately equivalent to 3 mg of phosphocysteamine.

Both mercaptamine and phosphocysteamine have a very unpleasant taste and smell, which can affect compliance.
MERCAPTAMINE
(Cysteamine)

Cautions leucocyte-cystine concentration and haematological monitoring required—consult product literature; dose of phosphate supplement may need to be adjusted

Contra-indications hypersensitivity to mercaptamine or penicillamine

Pregnancy avoid

Breast-feeding avoid

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, leucopenia, rarely gastrointestinal ulceration and bleeding, seizures, hallucinations, urticaria, interstitial nephritis

Licensed use eye drops not licensed

Indication and dose

Nephropathic cystinosis (specialist use only)

• By mouth

Neonate initially 2–3 mg/kg 4 times daily, increased over 4–6 weeks to 12.5 mg/kg 4 times daily

Child 1 month–12 years or under 50 kg initially 2–3 mg/kg 4 times daily, increased over 4–6 weeks to 12.5 mg/kg 4 times daily

Child 12–18 years or over 50 kg initially 100 mg 4 times daily, increased over 4–6 weeks to 500 mg 4 times daily

Cystagon® (Orphan Europe) Capsules, mercaptamine (as bitartrate) 50 mg, net price 100-cap pack = £59.00; 150 mg, 100-cap pack = £162.00

Note For 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)

Eye drops

Mercaptamine (Non-proprietary) Eye drops, mercaptamine 0.11%, 10 mL Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Other metabolic disorders

Other metabolic disorders and the drugs used in their management include:

Amino acid disorders: maple syrup urine disease (thiamine section 9.6.2); tyrosinaemia type III, hawkinsinuria (Vitamin C, section 9.6.3); tyrosinaemia type I (nitisinone).

Mitochondrial disorders: isolated carboxylase defects, defects of biotin metabolism (biotin, see below); mitochondrial myopathies (ubidecarenone); congenital lactic acidosis (riboflavin and thiamine, section 9.6.2); respiratory chain defects (thiamine, section 9.6.2); pyruvate dehydrogenase defects (sodium dichloracetate)

Neimann-Pick type C disease: miglustat is available for the treatment of progressive neurological manifestations of Neimann-Pick type C disease, a neurodegenerative disorder characterised by impaired intracellular lipid trafficking.

Homocystinuria and defects in cobalamin metabolism: betaine, pyridoxine (section 9.6.2), hydroxocobalamin (section 9.1.2)

Tetrahydrofolate reductase deficiency: betaine, folic acid (section 9.1.2)

The Scottish Medicines Consortium (p. 4) has advised (February 2009) that betaine anhydrous powder (Cystadane®) is not recommended for use as adjunctive treatment of homocystinuria.

BETAINE

Cautions monitor plasma-methionine concentration before and during treatment—interrupt treatment if symptoms of cerebral oedema occur

Pregnancy manufacturer advises avoid unless essential—limited information available

Breast-feeding manufacturer advises caution—no information available

Side-effects less commonly gastro-intestinal disorders, anorexia, reversible cerebral oedema (see Cautions), agitation, depression, personality disorder, sleep disturbances, urinary incontinence, alopecia, and urticaria
BETAIN (continued)

Indication and dose

Adjunctive treatment of homocystinuria (specialist use only)

- **By mouth**
  - Neonate: 50 mg/kg twice daily, dose and frequency adjusted according to response; max. 75 mg/kg twice daily
  - Child 1 month–10 years: 50 mg/kg twice daily, dose and frequency adjusted according to response; max. 75 mg/kg twice daily
  - Child 10–18 years: 3 g twice daily, adjusted according to response; max. 10 g twice daily

Administration

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 Cystadane® powder.

BETAIN (Non-proprietary) (BN)

Powder (for oral solution), betaine anhydrous 500 mg/mL when reconstituted

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Tablets, betaine anhydrous 500 mg

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Biotin

(Vitamin H)

Cautions

- Pregnancy: no information available
- Breast-feeding: no information available

Indication and dose

Isolated carboxylase defects

- **By mouth or by slow intravenous injection**
  - Neonate: 5 mg once daily, adjusted according to response; usual maintenance 10–50 mg daily, higher doses may be required
  - Child 1 month–18 years: 10 mg once daily, adjusted according to response; usual maintenance 10–50 mg daily but up to 100 mg daily may be required

Defects of biotin metabolism

- **By mouth or by slow intravenous injection**
  - Neonate: 10 mg once daily adjusted according to response; usual maintenance 5–20 mg daily but higher doses may be required
  - Child 1 month–18 years: 10 mg once daily adjusted according to response; usual maintenance 5–20 mg daily but higher doses may be required

Biotin (Non-proprietary) (BN)

Tablets, biotin 5 mg, 20-tab pack

Injection, biotin 5 mg/mL

Available from ‘special order’ manufacturers or specialist importing companies, see p. 943

Administration

For administration by mouth, tablets may be crushed and mixed with food or drink

MIGLUSTAT

Cautions

- monitor cognitive and neurological function, growth, and platelet count
- Hepatic impairment: manufacturer advises caution—no information available
- Renal impairment: child 12–18 years, initially 200 mg twice daily if estimated glomerular filtration rate 50–70 mL/minute/1.73 m²; child 12–18 years, initially 100 mg twice daily if estimated glomerular filtration rate 30–50 mL/minute/1.73 m²; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²; child under 12 years—consult product literature

Contra-indications

- Pregnancy: 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
- Breast-feeding: manufacturer advises avoid—no information available
- Side-effects: diarrhoea, flatulence, abdominal pain, dyspepsia, constipation, nausea, vomiting, anorexia, weight changes; tremor, dizziness, headache, peripheral neuropathy, ataxia, hypoesthesia, paraesthesia, insomnia, fatigue, asthenia; decreased libido; thrombocytopenia; muscle spasm

Indication and dose

Niemann-Pick type C disease (specialist supervision only)

- **By mouth**
  - Child 4–12 years
  - Body surface area less than 0.47 m²: 100 mg once daily
  - Body surface area 0.47–0.73 m²: 100 mg twice daily
  - Body surface area 0.73–0.88 m²: 200 mg twice daily
  - Body surface area greater than 0.88 m²: 200 mg three times daily
  - Child 12–18 years: 200 mg three times daily

Miglustat

(Capsules, miglustat 100 mg, net price 84-cap pack = £4015.00 (hospital only)
**NITISINONE** (NTBC)

**Cautions** slit-lamp examination of eyes recommended before treatment; monitor liver function regularly; monitor platelet and white blood cell count every 6 months

**Pregnancy** manufacturer advises avoid unless potential benefit outweighs risk (toxicity in animal studies)

**Contra-indications**

**Breast-feeding** manufacturer advises avoid—adverse effect in animal studies

**Side-effects** thrombocytopenia, leucopenia, granulocytopenia; conjunctivitis, photophobia, corneal opacity, keratitis, eye pain; less commonly leucocytosis, blepharitis, pruritus, exfoliative dermatitis, and erythematous rash

**Indication and dose**

*Hereditary tyrosinaemia type I* (in combination with dietary restriction of tyrosine and phenylalanine)

- **By mouth**
  - **Neonate** initially 500 micrograms/kg twice daily, adjusted according to response; max. 2 mg/kg daily
  - **Child 1 month–18 years** initially 500 micrograms/kg twice daily, adjusted according to response; max. 2 mg/kg daily

**Administration** capsules can be opened and the contents suspended in a small amount of water or formula diet and taken immediately

**Orfadin®** (Swedish Orphan)

Capsules, nitisinone 2 mg, net price 60-cap pack = £564.00; 5mg, 60-cap pack = £1127.00; 10mg, 60-cap pack = £2062.00

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**SODIUM DICHLOROACETATE**

**Cautions**

- **Pregnancy** no information available
- **Breast-feeding** no information available

**Side-effects** polyneuropathy on prolonged use; abnormal oxalate metabolism; metabolic acidosis

**Indication and dose**

*Pyruvate dehydrogenase defects*

- **By mouth**
  - **Neonate** initially 12.5 mg/kg 4 times daily, adjusted according to response; up to 200 mg/kg daily may be required
  - **Child 1 month–18 years** initially 12.5 mg/kg 4 times daily, adjusted according to response; up to 200 mg/kg daily may be required

**Sodium dichloroacetate** (Non-proprietary) Powder (for oral solution), sodium dichloroacetate 50 mg/mL when reconstituted with water

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

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**UBIDECARENONE** (Ubiquinone, Co-enzyme Q10)

**Cautions** may reduce insulin requirement in diabetes mellitus; *interactions*: Appendix 1 (ubidecarenone)

**Hepatic impairment** reduce dose in moderate and severe liver disease

**Side-effects** nausea, diarrhoea, heartburn; rarely headache, irritability, agitation, dizziness

**Licensed use** not licensed for the treatment of mitochondrial disorders

**Indication and dose**

*Mitochondrial disorders*

- **By mouth**
  - **Neonate** initially 5 mg once or twice daily with food, adjusted according to response, up to 200 mg daily may be required
  - **Child 1 month–18 years** initially 5 mg once or twice daily with food, adjusted according to response, up to 300 mg daily may be required

**Ubidecarenone** (Non-proprietary) Oral solution ubidecarenone 50 mg/10mL

Tablets, ubidecarenone 10 mg

Capsules, ubidecarenone 10 mg, 30 mg

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
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. Acute attacks of porphyria are exceptionally rare before puberty. When acute porphyria is suspected in a child, support from an expert porphyria service should be sought.

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 porphyria crises.

Supplies of haem arginate may be obtained outside office hours from the on-call pharmacist at:
St Thomas’ Hospital, London
Tel: (020) 7188 7188

Normosang® (Orphan Europe)
Concentrate for intravenous infusion, haem arginate 25 mg/mL, net price 10-mL amp = £338.50
Administration administer over at least 30 minutes; dilute requisite dose in 100 mL Sodium Chloride 0.9% in glass bottle; administer within 1 hour after dilution; max. concentration 2.5 mg/mL

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 porphyrias is available at www.wmic.wales.nhs.uk/porphyria_info.php.

Further information may be obtained from www.porphyria-europe.com 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)

| Amphetamines | Anabolic steroids | Antidepressants | Barbiturates | Calcium channel blockers | Contraceptives, hormonal | Erythromycin | Ethosuximide | Oxycodone | Pentazocine | Pentoxifylline (oxpentifylline) | Phenoxybenzamine | Phenyltoin | Pimelodocline | Pivmethione | Probenecid | Pyrazinamide | Rifabutin | Rifampicin | Spirinolactone | Sulfinpyrazine | Sulpiride | Tamoxifen | Temoporfin | Theophylline | Thalidomide | Valproate | Xipamide | Zidovudine | Zuclopenthixol |  |
|--------------|-------------------|-----------------|--------------|-------------------------|--------------------------|-------------|--------------|-----------|--------------|-------------------------------|------------------------|-------------|----------------|----------------|-------------|----------------|-----------|-------------|----------------|----------------|-------------|--------------|-----------|-------------|--------------------|----------------|---------------|-------------|-----------|----------------|--------|-----------|-------|--------|---|
| Amiodarone   | Benzodiazepines   | Beta-blockers   | Benzodiazepines | Betamethasone | Bisphosphonates | Buprenorphine | Butorphanol | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Codeine | Code | |
10 Musculoskeletal and joint diseases

10.1 Drugs used in rheumatic diseases
10.1.1 Non-steroidal anti-inflammatory drugs
10.1.2 Corticosteroids
10.1.3 Drugs that suppress the rheumatic disease process
10.1.4 Cytotoxic-induced hyperuricaemia
10.1.5 Other drugs for rheumatic diseases

10.2 Drugs used in neuromuscular disorders
10.2.1 Drugs that enhance neuromuscular transmission
10.2.2 Skeletal muscle relaxants

10.3 Drugs for the relief of soft-tissue inflammation
10.3.1 Enzymes
10.3.2 Rubefacients and other topical antirheumatics

This chapter also includes advice on the drug management of the following:
- dental and orofacial pain, p. 600
- extravasation, p. 618
- myasthenia gravis, p. 614
- soft-tissue and other musculoskeletal disorders, below
- juvenile idiopathic arthritis and other inflammatory disorders, below

For treatment of septic arthritis see Table 1, section 5.1.

10.1 Drugs used in rheumatic diseases

Juvenile idiopathic arthritis and other inflammatory disorders
Rheumatic diseases require symptomatic treatment to relieve pain, swelling, and stiffness, together with treatment to control and suppress disease activity. Treatment of juvenile idiopathic arthritis may involve non-steroidal anti-inflammatory drugs (NSAIDs) (section 10.1.1), a disease modifying antirheumatic drug (DMARD) (section 10.1.3) usually methotrexate or etanercept, and intra-articular, intravenous, or oral corticosteroids (section 10.1.2).

Soft-tissue and musculoskeletal disorders
The management of children with soft-tissue injuries and strains, and musculoskeletal disorders, may include temporary rest together with the local application of heat or cold, local massage and physiotherapy. For pain relief, paracetamol (section 4.7.1) is often adequate and should be used first. Alternatively, the lowest effective dose of a NSAID (e.g. ibuprofen) can be used. If pain relief with either drug is inadequate, both paracetamol (in a full dose appropriate for the child) and a low dose of a NSAID may be required.
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.

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.

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. A large proportion of children 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. However, in juvenile idiopathic arthritis NSAIDs may take 4–12 weeks to be effective. If appropriate responses are not obtained within these times, another NSAID should be tried. The availability of appropriate formulations needs to be considered when prescribing NSAIDs for children.

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. However, in children gastro-intestinal symptoms are rare in those taking NSAIDs for short periods. The role of selective inhibitors of cyclo-oxygenase-2 is undetermined in children.

Ibuprofen and naproxen are propionic acid derivatives used in children:

Ibuprofen combines anti-inflammatory, analgesic, and antipyretic properties. It has fewer side-effects than other NSAIDs but its anti-inflammatory properties are weaker.

Naproxen combines good efficacy with a low incidence of side-effects.

Diclofenac, indometacin, mefenamic acid, and piroxicam have properties similar to those of propionic acid derivatives:

Diclofenac has actions and side-effects similar to those of naproxen.

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 gastro-intestinal disturbances. It is rarely used in children and should be reserved for when other NSAIDs have been unsuccessful.

Mefenamic acid has minor anti-inflammatory properties. It has occasionally been associated with diarrhoea and haemolytic anaemia which require discontinue of treatment.

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. 606).

Meloxicam is a selective inhibitor of cyclo-oxygenase-2. Its use may be considered in adolescents intolerant to other NSAIDs.

Ketorolac can be used for the short-term management of postoperative pain (section 15.1.4.2).

Etoricoxib, a selective inhibitor of cyclo-oxygenase-2, is licensed for the relief of pain in osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and acute gout in children aged 16 years and over. For concerns about the cardiovascular safety of cyclo-oxygenase-2 selective inhibitors (see below).

For the role of aspirin in children, see section 2.9.

Dental and orofacial pain  Most mild to moderate dental pain and inflammation is effectively relieved by ibuprofen or diclofenac. In an appraisal of the relative safety in adults of 7 non-selective NSAIDs, the CSM assessed ibuprofen to have the lowest risk of serious gastro-intestinal side-effects (see below).

For further information on the management of dental and orofacial pain, see p. 246.
Cautions and contra-indications

NSAIDs should be used with caution in children with a history of hypersensitivity to any NSAID—which includes those in whom attacks of asthma, angioedema, urticaria or rhinitis have been precipitated by any NSAID. NSAIDs should also be used with caution during pregnancy (see below) and breast-feeding (see individual drug monographs), and in coagulation defects. Caution may also be required in children with allergic disorders.

In patients with renal, cardiac, or hepatic impairment, caution is required since the use of NSAIDs may result in deterioration of renal function (see also under Side-effects below); the dose should be kept as low as possible and renal function should be monitored. In mild renal impairment the lowest effective dose should be used for the shortest possible duration and renal function monitored; sodium and water retention may occur, as may deterioration in renal function possibly leading to renal failure. In moderate to severe renal impairment NSAIDs should be avoided if possible.

All NSAIDs are contra-indicated in severe heart failure. The selective inhibitor of cyclo-oxygenase-2, etoricoxib, is contra-indicated in ischaemic heart disease, cerebrovascular disease, peripheral arterial disease, and moderate or severe heart failure. Etoricoxib should be used with caution in children with a history of cardiac failure, left ventricular dysfunction, hypertension, in children with oedema for any other reason, and in children with risk factors for heart disease.

NSAIDs and cardiovascular events

The role of cyclo-oxygenase-2 selective inhibitors is undetermined in children. 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 children at a particularly high risk of developing gastrointestinal ulcers 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. In adults, 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 etoricoxib. Naproxen (in adults, 1 g daily) is associated with a lower thrombotic risk, and lower doses of ibuprofen (in adults, 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, or in children.

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 of time to control symptoms, and that the need for long-term treatment should be reviewed periodically.

Most manufacturers advise avoiding NSAIDs during pregnancy or avoiding them unless the potential benefit outweighs risk. Ibuprofen and diclofenac are generally considered safe during the first and second trimesters. In the third trimester, NSAIDs are associated with a risk of closure of fetal ductus arteriosus and possibly persistent pulmonary hypertension of the newborn; also, labour may be delayed and its duration may be increased.

NSAIDs are generally contra-indicated if there is active or previous gastro-intestinal ulceration or bleeding; however, some children may require NSAIDs for effective relief of pain and stiffness, and prophylaxis or treatment of NSAID-associated peptic ulcers may be necessary (see section 1.3).

For interactions of NSAIDs, see Appendix 1 (NSAIDs).

Side-effects

The side-effects of NSAIDs vary in severity and frequency. Gastro-intestinal discomfort, nausea, diarrhoea, and occasionally bleeding and ulceration may occur. Other side-effects include hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), headache, dizziness, nervousness, depression, drowsiness, insomnia, vertigo, hearing disturbances such as tinnitus, photosensitivity, 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 pre-existing 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; children with connective tissue disorders such as systemic lupus erythematosus may be especially susceptible.

**Overdosage:** see Emergency Treatment of Poisoning, p. 36.

### Gastro-intestinal side-effects

All NSAIDs are associated with gastro-intestinal toxicity. In adults, evidence on the relative safety of NSAIDs indicates differences in the risks of serious upper gastro-intestinal side-effects. **Ibuprofen** is associated with the **lowest risk**; **piroxicam, indometacin, naproxen**, and **diclofenac** are associated with **intermediate risks** (possibly higher in the case of piroxicam, see also CHMP advice, p. 606). **Selective inhibitors of cyclo-oxygenase-2** are associated with a **lower risk** of serious upper gastro-intestinal side-effects than non-selective NSAIDs.

Children appear to tolerate NSAIDs better than adults and gastro-intestinal side-effects are less common; use of drugs such as **ranitidine** or **omeprazole** may not be necessary.

### Asthma

All NSAIDs have the potential to worsen asthma, either acutely or as a gradual worsening of symptoms; consider both prescribed NSAIDs and those that are purchased over the counter.

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**DICLOFENAC SODIUM**

### Cautions

see notes above; **interactions:** Appendix 1 (NSAIDs)

### Hepatic impairment

increased risk of gastro-intestinal bleeding and fluid retention; avoid in severe liver disease

### Breast-feeding

amount too small to be harmful

### 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

### Rectal route

Additional contra-indications include ulcerative or acute inflammatory conditions of the anus, rectum, or sigmoid colon

### Side-effects

see notes above; suppositories may cause rectal irritation; injection site reactions

### Licensed use

not licensed for use in children under 1 year; **suppositories** not licensed for use in children under 6 years except for use in children over 1 year for juvenile idiopathic arthritis; solid dose forms containing more than 25 mg not licensed for use in children; **diclofenac potassium tablets** not licensed for use in children under 14 years; **injection** not licensed for use in children under 1 year

### Indication and dose

**Inflammation and mild to moderate pain**

- **By mouth or by rectum**
  - **Child 6 months–18 years** 0.3–1 mg/kg (max. 50 mg) 3 times daily

**Postoperative pain**

- **By rectum**
  - **Child 6–18 years** 0.5–1 mg/kg (max. 75 mg) twice daily for max. 4 days; total daily dose may alternatively be given in 3 divided doses

- **By intravenous infusion or deep intramuscular injection into gluteal muscle**
  - **Child 2–18 years** 0.3–1 mg/kg once or twice daily for max. 2 days (max. 150 mg daily)

**Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis**

- **By mouth**
  - **Child 6 months–18 years** 1.5–2.5 mg/kg (max. 75 mg) twice daily; total daily dose may alternatively be given in 3 divided doses

**Administration** for intravenous infusion, dilute 75 mg with 100–500 mL Glucose 5% or Sodium Chloride 0.9% (previously buffered with 0.5 mL Sodium Bicarbonate 8.4% solution or with 1 mL Sodium Bicarbonate 4.2% solution); give over 30–120 minutes

**Diclofenac Sodium** (Non-proprietary) (*Hall*)

**Tablets**, both 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 **Defenac**, **Dicloflex**, **Diclozip**, **Fenactol**, **Flamrase**

**Dispersible tablets**, sugar-free, diclofenac sodium 10 mg

Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

**Suppositories**, diclofenac sodium 100 mg, net price 10 = £3.06

Brands include **Econac**
DICLOFENAC SODIUM (continued)

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

Injection, diclofenac sodium 25 mg/mL, net price 3-mL amp = £8.3

Excipients include benzyl alcohol (avoid in neonates unless there is no safer alternative, see Excipients, p. 3), propylene glycol

Suppositories, diclofenac sodium 12.5 mg, net price 10 = £7.10; 25 mg, 10 = £1.26; 50 mg, 10 = £2.07; 100 mg, 10 = £3.70

Diclofenac potassium

Voltarol® Rapid (Novartis)

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, postoperative pain

Child 14–18 years 75–100 mg daily in 2–3 divided doses

Modified release

Diclomax SR® (Provalis)

Capsules, m/r, yellow, diclofenac sodium 75 mg, net price 56-cap pack = £12.10. Label: 21, 25

Diclomax Retard® (Provalis)

Capsules, m/r, diclofenac sodium 100 mg, net price 28-tab pack = £8.70. Label: 21, 25

Motifene® 75 mg (Daiichi Sankyo)

Capsules, e/c, m/r, diclofenac sodium 75 mg (enclosing e/c pellets containing diclofenac sodium 25 mg and m/r pellets containing diclofenac sodium 50 mg), net price 56-cap pack = £8.00. Label: 25

Voltarol® 75 mg SR (Novartis)

Tablets, m/r, pink, diclofenac sodium 75 mg, net price 28-tab pack = £8.08; 56-tab pack = £16.15. Label: 21, 25

Note Other brands of modified-release tablets containing diclofenac sodium 75 mg include Defenac® SR, Dexomon® 75 SR, Dicloflex SR, Diclofox SR, Fenactol® SR, Flexotard® MR 75, Rheumatic® Retard 75, Rhumalgan® CR, Slofenac® SR, Volsaid® Retard 75

Voltarol® Retard (Novartis)

Tablets, m/r, red, diclofenac sodium 100 mg, net price 28-tab pack = £11.84. Label: 21, 25

Note Other brands of modified-release tablets containing diclofenac sodium 100 mg include Defenac® Retard, Dexomon® Retard 100, Diclofox® Retard, Fenactol® Retard 100 mg, Flamatox® 100 MR, Flamraxe® SR, Rhumalgan® CR, Slofenac® SR, Volsaid® Retard 100

ETORICOXIB

Cautions see notes above; also dehydration; monitor blood pressure before treatment, 2 weeks after initiation and periodically during treatment; interactions: Appendix 1 (NSAIDs)

Hepatic impairment increased risk of gastrointestinal bleeding and fluid retention; max. 60 mg daily in mild impairment; max. 60 mg on alternate days or 30 mg once daily in moderate impairment; avoid in severe impairment

Renal impairment see notes above; avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

Contra-indications see notes above; inflammatory bowel disease; uncontrolled hypertension (persistently above 140/90 mmHg)

Breast-feeding manufacturer advises avoid—present in milk in animal studies

Side-effects see notes above; also flatulence, palpitation, fatigue, influenza-like symptoms, ecchymosis; 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

Indication and dose

Osteoarthritis

• By mouth

Child 16–18 years 30 mg once daily, increased if necessary to 60 mg once daily

Rheumatoid arthritis and ankylosing spondylitis

• By mouth

Child 16–18 years 90 mg once daily

Acute gout

• By mouth

Child 16–18 years 120 mg once daily for max. 8 days

Arcoxia® (MSD)

Tablets, f/c, etoricoxib 30 mg (blue-green), net price 28-tab pack = £13.99; 60 mg (dark green), 28-tab pack = £20.11; 90 mg (white), 28-tab pack = £22.96; 120 mg (pale green), 7-tab pack = £5.74
IBUPROFEN

Cautions see notes above; interactions: Appendix 1 (NSAIDs)

Hepatic impairment increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease

Breast-feeding amount too small to be harmful, but some manufacturers advise avoid

Contra-indications see notes above

Side-effects see notes above; overdosage: see Emergency Treatment of Poisoning, p. 36

Licensed use not licensed for use in children under 3 months or body-weight under 5 kg

Indication and dose Mild to moderate pain, pain and inflammation of soft-tissue injuries, pyrexia with discomfort

• By mouth
  Child 1–3 months 5 mg/kg 3–4 times daily
  Child 3–6 months 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 in 3–4 divided doses
  Child 7–10 years 200 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses
  Child 10–12 years 300 mg 3 times daily; max. 30 mg/kg (max. 2.4 g) daily in 3–4 divided doses
  Child 12–18 years initially 300–400 mg 3–4 times daily; increased if necessary to max. 600 mg 4 times daily; maintenance dose of 200–400 mg 3 times daily may be adequate

Pain and inflammation in rheumatic disease including juvenile idiopathic arthritis

• By mouth
  Child 3 months–18 years 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

Post-immunisation pyrexia in infants (see also p. 727)

• By mouth
  Child 2–3 months 50 mg as a single dose repeated once after 6 hours if necessary

Closure of patent ductus arteriosus in neonates see section 2.14

1 Ibuprofen (Non-proprietary) 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. Label: 21

Brands include Arthrob fen®, Eubuc®, Rimafem®

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 Calprofen®, Fenpaed®, Feverfen®, Nurofen® for Children, Orbifen® for Children

Dental prescribing on NHS Ibuprofen Tablets and Ibuprofen Oral Suspension Sugar-free may be prescribed

Brufen® (Abbott) Tablets, I/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

Contains sodium approx. 9 mmol/sachet

Modified release Brufen Retard® (Abbott) Tablets, m/r, ibuprofen 800 mg, net price 56-tab pack = £6.74. Label: 25, 27

Dose Pain and inflammation

• By mouth
  Child 12–18 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) Spansule® (= capsule m/r), maroon/pink, enclosing off-white pellets, ibuprofen 300 mg, net price 120-cap pack = £9.64. Label: 25

Dose Pain and inflammation

• By mouth
  Child 12–18 years initially 2 capsules twice daily, increased in severe cases to 3 capsules twice daily; then 1–2 capsules twice daily

INDOMETACIN
(Indomethacin)

Cautions see notes above; also epilepsy, psychiatric disturbances; during prolonged therapy ophthalmic and blood examinations particularly advisable; avoid rectal administration in proctitis and haemorrhoids; interactions: Appendix 1 (NSAIDs)

Skilled tasks Dizziness may affect performance of skilled tasks (e.g. driving)

Hepatic impairment increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease

Breast-feeding amount probably too small to be harmful—manufacturer advises avoid

Contra-indications see notes above

1. Can be sold to the public under certain circumstances; for exemptions see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available)
**INDOMETACIN** (continued)

### Side-effects
see notes above; frequently gastrointestinal 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 thrombocytopeinia), hypertension, hyperglycaemia, blurred vision, corneal deposits, peripheral neuropathy, and intestinal strictures; suppositories may cause rectal irritation and occasional bleeding.

### Licensed use
not licensed for use in children.

### Indication and dose
**Relief of pain and inflammation in rheumatic diseases including juvenile idiopathic arthritis**
- By mouth
  - Child 1 month –18 years: 0.5–1 mg/kg twice daily; higher doses may be used under specialist supervision.

### Closure of patent ductus arteriosus in premature babies section 2.14

**Indometacin** (Non-proprietary)
- Capsules, indometacin 25 mg, net price 28-cap pack = £1.59; 50 mg, 28-cap pack = £1.93.
  - Label: 21, counselling, driving, see above.
  - Brands include Rimacid®

**Suppositories**, indometacin 100 mg, net price 10 = £14.46.
  - Counselling, driving, see above.

**Suspension**, indometacin 5 mg/mL.
  - Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943.

### Modified release
**Indometacin m/r preparations**
- Capsules, m/r, indometacin 75 mg. Label: 21, 25, counselling, driving, see above.
  - Brands include Indolar SR®, Pardelprin®, Slo-Indo®

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### MEFENAMIC ACID

#### Cautions
see notes above; epilepsy; acute porphyria (section 9.8.2); **interactions**: Appendix 1 (NSAIDs).

#### Hepatic impairment
increased risk of gastro-intestinal bleeding and can cause fluid retention; avoid in severe liver disease.

#### Breast-feeding
amount too small to be harmful but manufacturer advises avoid.

#### Contra-indications
see notes above; inflammatory bowel disease.

#### Side-effects
see notes above; also diarrhoea or rashes (withdraw treatment), vomiting, flatulence, constipation, ulcerative stomatitis; fatigue; *less commonly* paraesthesia; *rarely* hypotension, palpitation, and glucose intolerance, thrombocytopeinia, haemolytic anaemia (positive Coombs’ test), and aplastic anaemia reported.

#### Indication and dose
**Acute pain including dysmenorrhoea, menorrhagia**
- By mouth
  - Child 6 months–12 years: not recommended
  - Child 12–18 years: 500 mg 3 times daily.

### Mefenamic Acid** (Non-proprietary)
- Tablets, mefenamic acid 500 mg, net price 28-tab pack = £1.97.
- Suspension, mefenamic acid 50 mg/5 mL, net price 125 mL = £79.99.
  - Excipients include ethanol.

#### Ponstan® (Chemidex)
- Capsules, blue/ivory, mefenamic acid 250 mg, net price 100-cap pack = £8.17.
- Forte tablets, yellow, mefenamic acid 500 mg, net price 100-tab pack = £15.72.

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### MELOXICAM

#### Cautions
see notes above; **interactions**: Appendix 1 (NSAIDs).

#### Hepatic impairment
increased risk of gastro-intestinal bleeding and can cause fluid retention; avoid in severe liver disease.

#### Breast-feeding
no information available—manufacturer advises avoid.

#### Contra-indications
see notes above; renal failure (unless receiving dialysis); severe heart failure.

#### Side-effects
see notes above.

#### Licensed use
not licensed for use in children under 15 years.

#### Indication and dose
**Relief of pain and inflammation in juvenile idiopathic arthritis and other musculoskeletal disorders in children intolerant to other NSAIDs**
- By mouth
  - Child 12–18 years and body-weight under 50 kg: 7.5 mg once daily.
  - Child 12–18 years and body-weight over 50 kg: 15 mg once daily.

**Administration**
- Mobic® tablets may be dispersed in water.
Meloxicam (Non-proprietary) Tablets, meloxicam 7.5 mg, net price 30-tab pack = £2.85; 15 mg, 30-tab pack = £3.52

Mobic (Boehringer Ingelheim) Tablets, yellow, scored, meloxicam 7.5 mg, net price 30-tab pack = £9.30; 15 mg, 30-tab pack = £12.93. Label: 21

Naproxen (Non-proprietary) Tablets, naproxen 250 mg, net price 28-tab pack = £1.29; 500 mg, 28-tab pack = £1.71. Label: 21

Brands include Arthroxen 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

Suspension, naproxen 25 mg/mL Available from ‘special-order’ manufacturers or specialist importing companies, see p.943

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 x 250 mg tablets; for exemptions see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available)

Naprosyn (Roche) Tablets, yellow, scored, naproxen 250 mg, net price 56-tab pack = £4.55; 500 mg, 56-tab pack = £9.09. Label: 21

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

Synflex (Roche) Tablets, blue, naproxen sodium 275 mg, net price 60-tab pack = £7.54. Label: 21

Note 275 mg naproxen sodium: 250 mg naproxen

PIROXICAM

Cautions see notes above and CHMP advice below; interactions: Appendix 1 (NSAIDs)

Hepatic impairment increased risk of gastro-intestinal bleeding and can cause fluid retention; avoid in severe liver disease

Breast-feeding amount too small to be harmful

Contra-indications see notes above

Side-effects see notes above

Licensed use capsules and non-dispersible tablets not licensed for use in children

Indication and dose Relief of pain and inflammation in juvenile idiopathic arthritis

• By mouth

Child 6–18 years and body-weight under 15 kg 5 mg daily

Child 6–18 years and body-weight 16–25 kg 10 mg daily

Child 6–18 years and body-weight 26–45 kg 15 mg daily

Child 6–18 years and body-weight over 46 kg 20 mg daily

CHMP advice

Piroxicam (June 2007) The CHMP has recommended restrictions on the use of piroxicam because of the increased risk of gastro-intestinal 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 acute painful and inflammatory conditions

• treatment should be reviewed 2 weeks after initiating piroxicam, and periodically thereafter

• concomitant administration of a gastro-protective agent (section 1.3) should be considered

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

Feldene® (Pfizer) 
Capsules, piroxicam 10 mg (maroon/blue), net price 56-cap pack = £7.20; 20 mg (maroon), 28-cap pack = £7.20. Label: 21

Tablets, (Feldene Melt®), piroxicam 20 mg, net price 28-tab pack = £9.83. Label: 10, patient information leaflet, 21

Excipients include aspartame equivalent to phenylalanine 140 micrograms/tablet (section 9.4.1)

Note: Tablets may be halved [unlicensed] to give 10-mg dose; tablet placed on tongue and allowed to dissolve or may be swallowed.

Brexidol® (Chiesi) 
Tablets, yellow, scored, piroxicam (as betadex), 20 mg, net price 30-tab pack = £14.66. Label: 21

10.1.2 Corticosteroids

10.1.2.1 Systemic corticosteroids

The general actions, uses, and cautions of corticosteroids are described in section 6.3. In children with rheumatic diseases corticosteroids should be reserved for specific indications (e.g. when other anti-inflammatory drugs are unsuccessful) and should be used only under the supervision of a specialist.

Systemic corticosteroids may be considered for the management of juvenile idiopathic arthritis in systemic disease or when several joints are affected. Systemic corticosteroids may also be considered in severe, possibly life-threatening conditions such as systemic lupus erythematosus, systemic vasculitis, juvenile dermatomyositis, Behçet’s disease, and polyarticular joint disease.

In severe conditions, short courses (‘pulses’) of high-dose intravenous methylprednisolone or a pulsed oral corticosteroid may be particularly effective for providing rapid relief, and has fewer long-term adverse effects than continuous treatment.

Corticosteroid doses should be reduced with care because of the possibility of relapse if the reduction is too rapid. If complete discontinuation of corticosteroids is not possible, consideration should be given to alternate-day (or alternate high-dose, low-dose) administration; on days when no corticosteroid is given, or a lower dose is given, an additional dose of a NSAID may be helpful. In some conditions, alternative treatment using an antimalarial or concomitant use of an immunosuppressant drug, such as azathioprine, methotrexate or cyclophosphamide may prove useful; in less severe conditions treatment with a NSAID alone may be adequate.

Administration of corticosteroids may result in suppression of growth and may affect the development of puberty. The risk of corticosteroid-induced osteoporosis should be considered for those on long-term corticosteroid treatment (section 6.6); corticosteroids may also increase the risk of osteopenia in those unable to exercise. For the disadvantages of corticosteroid treatment see section 6.3.2.

10.1.2.2 Local corticosteroid injections

Corticosteroids are injected locally for an anti-inflammatory effect. In inflammatory conditions of the joints, including juvenile idiopathic arthritis, they are given by intra-articular injection as an adjunct to long-term therapy to reduce swelling and deformity in one or a few joints. Aseptic precautions (e.g. a no-touch technique) are essential, as is a clinician skilled in the technique; infected areas should be avoided and general anaesthesia, or local anaesthesia, or conscious sedation should be used. 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.

Triamcinolone hexacetonide is preferred for intra-articular injection because it is almost insoluble and has a long-acting (depot) effect. Triamcinolone acetonide and methylprednisolone may also be considered for intra-articular injection into larger joints, whilst hydrocortisone acetate should be reserved for smaller joints or for soft-tissue injections. Intra-articular corticosteroid injections can cause
flushing and may affect the hyaline cartilage. Each joint should usually be treated no more than 3–4 times in one year.

A smaller amount of corticosteroid 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 and a high risk of rupture, the Achilles tendon should not be injected).

Corticosteroid injections are also injected into soft tissues for the treatment of skin lesions (see section 13.4).
Unlike NSAIDs, disease-modifying antirheumatic drugs can affect the progression of disease but they may require 3–6 months of treatment for a full therapeutic response. Response to a disease-modifying antirheumatic 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 and C-reactive protein.

**Antimalarials**

The antimalarial hydroxychloroquine is rarely used to treat juvenile idiopathic arthritis. Hydroxychloroquine can also be useful for systemic or discoid lupus erythematosus, particularly involving the skin and joints, and in sarcoidosis.

Retinopathy (see below) rarely occurs provided that the recommended doses are not exceeded.

**Mepacrine** is used on rare occasions to treat discoid lupus erythematosus [unlicensed].

**Cautions** Hydroxychloroquine should be used with caution in hepatic impairment and in renal impairment (see hydroxychloroquine sulphate, below). Hydroxychloroquine 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 9.1.5), and in acute porphyria. Hydroxychloroquine may exacerbate psoriasis and aggravate myasthenia gravis. Concurrent use of hepatotoxic drugs should be avoided; other interactions: Appendix 1 (chloroquine and hydroxychloroquine).

**Pregnancy and breast-feeding** It is not necessary to withdraw an antimalarial drug during pregnancy if the rheumatic disease is well controlled. Hydroxychloroquine is present in breast milk and breast-feeding should be avoided when it is used to treat rheumatic disease.

**Screening for ocular toxicity**

Hydroxychloroquine is rarely associated with ocular toxicity. The British Society for Paediatric and Adolescent Rheumatology recommends that children should have their vision tested before long-term treatment with hydroxychloroquine and have an annual review of visual acuity. Children should be referred to an ophthalmologist if there is visual impairment, changes in visual acuity, or blurred vision. The Royal College of Ophthalmologists has recommended that a locally agreed protocol between the prescribing doctor and ophthalmologist be established to monitor the vision of these children.

**Note** To avoid excessive dosage in obese children, the dose of hydroxychloroquine should be calculated on the basis of lean body weight; ocular toxicity is unlikely with doses under 5–6.5 mg/kg or max. 400 mg daily.

**Side-effects** The side-effects of 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; angioedema and bronchospasm have also been reported. Important: very toxic in overdosage—immediate advice from poisons centres essential (see also p. 41).

**HYDROXYCHLOROQUINE SULPHATE**

**Cautions** see notes above

**Renal impairment** Manufacturer advises caution and monitoring of plasma-hydroxychloroquine concentration in severe renal impairment

**Pregnancy** manufacturer advises avoid but see also notes above

**Breast-feeding** avoid—risk of toxicity in infant

**Side-effects** see notes above
**Licensed use**  Juvenile idiopathic arthritis, systemic and discoid lupus erythematosus, dermatological conditions caused or aggravated by sunlight

**Indication and dose**

- **By mouth**
  - **Child 1 month–18 years**  5–6.5 mg/kg (max. 400 mg) once daily

**Plaquenil** (Sanofi-Synthelabo) Tablets, f/c, hydroxychloroquine sulphate 200 mg, net price 60-tab pack = £5.46. Label: 5, 21

- Extemporaneous formulations available see Extemporaneous Preparations, p. 8

**Drugs affecting the immune response**

**Methotrexate**

Given as a once weekly dose, is the disease-modifying antirheumatic drug of choice in the treatment of juvenile idiopathic arthritis and also has a role in juvenile dermatomyositis, vasculitis, uveitis, systemic lupus erythematosus, localised scleroderma, and sarcoidosis. For these indications it is given by the intramuscular, subcutaneous, or oral routes. Absorption from intramuscular or subcutaneous routes may be more predictable than from the oral route; if the oral route is ineffective subcutaneous administration is generally preferred. Regular full blood counts (including differential white cell count and platelet count), renal and liver function tests are required. Folic acid may reduce mucosal or gastrointestinal side-effects of methotrexate. The dosage regimen for folic acid has not been established—in children over 2 years a dose of 5 mg weekly may be given, usually at least 24 hours after the dose of methotrexate.

**Azathioprine** may be used in children for vasculitis which has failed to respond to other treatments, for the management of severe cases of systemic lupus erythematosus and other connective tissue disorders, in conjunction with corticosteroids for patients with severe or progressive renal disease, and in cases of polymyositis which are resistant to corticosteroids. Azathioprine has a corticosteroid-sparing effect in patients whose corticosteroid requirements are excessive.

**Ciclosporin** (cyclosporin) is rarely used in juvenile idiopathic arthritis, connective tissue diseases, vasculitis, and uveitis; it may be considered if the condition has failed to respond to other treatments.

**AZATHIOPRINE**

**Cautions**  see section 8.2.1

**Contra-indications**  see section 8.2.1

**Side-effects**  see section 8.2.1

**Indication and dose**

- **Juvenile idiopathic arthritis, vasculitis, autoimmune conditions usually when corticosteroid therapy alone has proved inadequate**
  - **By mouth**
    - **Child 1 month–18 years** initially 1 mg/kg daily, adjusted according to response to max. 3 mg/kg daily (consider withdrawal if no improvement within 3 months)

**METHOTREXATE**

**Cautions**  section 8.1.3; see advice below (blood count, gastro-intestinal, liver, and pulmonary toxicity); extreme caution in blood disorders (avoid if severe); risk of accumulation in pleural effusion or ascites—drain before treatment; full blood count and liver function tests before starting treatment repeated fortnightly for at least the first 4 weeks and at this frequency after any change in dose until therapy stabilised, thereafter monthly; regular renal function tests are also necessary; children or their carers should 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; check immunity to varicella-zoster and consider vaccination (section 14.4) before initiating therapy; acute porphyria (section 9.8.2); **interactions**: see below and Appendix 1 (methotrexate)

**Blood count** Bone marrow suppression can occur abruptly; factors likely to increase toxicity include renal impairment and concomitant use with another anti-folate drug. A clinically significant drop in white cell count or
platelet count calls for immediate withdrawal of methotrexate and introduction of supportive therapy

Gastro-intestinal toxicity Withdraw treatment if stomatitis develops—may be first sign of gastro-intestinal toxicity

Liver toxicity Persistent 2–fold rise in liver transaminases may necessitate dose reduction or rarely discontinuation; abrupt withdrawal should be avoided as this can lead to disease flare

Pulmonary toxicity Acute pulmonary toxicity is rare in children treated for juvenile idiopathic arthritis, but children and carers should seek medical attention if dyspnoea, cough or fever develops; discontinue if pneumonia suspected

NSAIDs Children and carers should be advised to avoid self-medication with over-the-counter ibuprofen

Hepatic impairment dose-related toxicity—avoid in non-malignant conditions

Contra-indications see section 8.1.3 and cautions above

Side-effects section 8.1.3; chronic pulmonary fibrosis; blood dyscrasias (including fatalities); liver cirrhosis

Licensed use not licensed for use in children for non-malignant conditions

Indication and dose

Juvenile idiopathic arthritis, juvenile dermatomyositis, vasculitis, uveitis, systemic lupus erythematosus, localised scleroderma, sarcoidosis

- By mouth, subcutaneous injection, or intramuscular injection

Child 1 month–18 years 10–15 mg/m² once weekly initially, increased if necessary to max. 25 mg/m² once weekly

Safe Practice Note that the above dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:
- the child or their carer 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 child or their carer 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).

Severe Crohn’s disease section 1.5.3

Malignant disease section 8.1.3

Psoriasis section 13.5.3

Methotrexate (Non-proprietary) Tablets, yellow, methotrexate 2.5 mg, net price 28-tab pack = £3.27. Counselling, dose, NSAIDs

Brands include Maxtrex Tablets, yellow, methotrexate 10 mg, net price 20-tab pack (Hospira) = £11.44; (Pharmacia, Maxtrex*) = £9.03. Counselling, dose, NSAIDs

Suspension Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

Parenteral preparations See also section 8.1.3

Metject® (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

Etanercept for the treatment of juvenile idiopathic arthritis (March 2002) Etanercept is recommended in children aged 4–17 years with active poly-articular-course juvenile idiopathic arthritis who have not responded adequately to methotrexate or who are intolerant of it. Etanercept should be used under specialist supervision according to the guidelines of the British Society for Paediatric and Adolescent Rheumatology [previously the British Paediatric Rheumatology Group].

Etanercept should be withdrawn if severe side-effects develop or if there is no response after 6 months or if the initial response is not maintained. A decision to continue therapy beyond 2 years should be based on disease activity and clinical effectiveness in individual cases.

Prescribers of etanercept should register consenting patients with the Biologics Registry of the British Society for Paediatric and Adolescent Rheumatology.
Side-effects Adalimumab, etanercept, and infliximab 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 (including angioedema, bronchospasm, urticaria, and anaphylaxis), fever, headache, depression, antibody formation (including lupus erythematosus-like syndrome), pruritus, injection-site reactions, and blood disorders (including anaemia, leucopenia, thrombocytopenia, pancypopenia, aplastic anaemia).

**ADALIMUMAB**

**Contra-indications** severe infection (see also Cautions)

**Pregnancy** avoid; manufacturer advises adequate contraception during and for at least 5 months after last dose

**Breast-feeding** manufacturer advises avoid for at least 5 months after last dose

**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; discontinue if new serious infection develops; 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 children with history of PUVA treatment for psoriasis or extensive immunosuppressant therapy;

**interactions:** Appendix 1 (adalimumab)

**Tuberculosis** Children 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. Children who have previously received adequate treatment for tuberculosis can start adalimumab but should be monitored every 3 months for possible recurrence. In those without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting adalimumab. Children and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop

**Side-effects**

See under Cytokine Modulators, above and Cautions above; also mouth ulceration, stomatitis, diarrhoea, cough, dizziness, fatigue, paraesthesia, musculoskeletal pain, rash, and pruritus; less commonly vomiting, dyspepsia, constipation, rectal bleeding, arrhythmias, syncpope, chest pain, hyperlipidaemia, hypertension, flushing, dyspnoea, dysphonia, appetite disorders, anxiety, tremor, sleep disturbances, influenza-like symptoms, menstrual disorders, electrolyte disturbances, haematuria, renal impairment, hyperuricaemia, eye disorders, and skin papilloma, alopecia; rarely pancreatitis, colitis, oesophagitis, gastritis, hepatitis, cholelithiasis, palpitation, myocardial infarction, vascular occlusion, pleural effusion, demyelinating disorders, facial palsy, thyroid disorders, malignancy, rhabdomyolysis, hearing loss, tinnitus, and erythema multiforme; also reported intestinal perforation, vasculitis, and interstitial lung disease

**Indication and dose**

Active polyarticular juvenile idiopathic arthritis (in combination with methotrexate or alone if methotrexate inappropriate) in children who have not responded adequately to one or more disease-modifying antirheumatic drug

- **By subcutaneous injection**
  - **Child 13–17 years** 40 mg on alternate weeks; review treatment if no response within 12 weeks

**Humira** (Abbott) £75.00

**Injection,** adalimumab, net price 40-mg prefilled pen or prefilled syringe = £357.50. Counselling, tuberculosis

**ETANERCEPT**

**Cautions** predisposition to infection (avoid if predisposition to septicemia); significant exposure to herpes zoster virus—interrupt treatment and consider varicella–zoster immunoglobulin; hepatitis B virus—monitor for active infection; monitor for worsening hepatitis C infection; heart failure (risk of exacerbation); demyelinating CNS disorders (risk of exacerbation); history of blood disorders;

**interactions:** Appendix 1 (etanercept)

**Tuberculosis** Children 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. Children who have previously received adequate treatment for tuberculosis can start etanercept but should be monitored every 3 months for possible recurrence. In those without active tuberculosis but who were previously not treated adequately, chemoprophylaxis should ideally be completed before starting etanercept. In children at high risk of tuberculosis who cannot be assessed by tuberculin skin test, chemoprophylaxis can be given concurrently with etanercept. Children and their carers should be advised to seek medical attention if symptoms suggestive of tuberculosis (e.g. persistent cough, weight loss, and fever) develop

**Blood disorders** Children and their carers should be advised to seek medical attention if symptoms suggestive of blood disorders (such as fever, sore throat, bruising, or bleeding) develop

**Contra-indications** active infection; avoid injections containing benzyl alcohol in neonates (see preparations below)

**Pregnancy** manufacturer advises avoid—no information available

**Breast-feeding** manufacturer advises avoid—present in milk in animal studies
Side-effects  see under Cytokine Modulators, p. 612; also less commonly interstitial lung disease, rash; rarely demyelinating disorders, seizures, Stevens-Johnson syndrome, and cutaneous vasculitis; very rarely toxic epidermal necrolysis; also reported appendicitis, cholecystitis, gastritis, gastrointestinal haemorrhage, intestinal obstruction, liver damage, oesophagitis, pancreatitis, ulcerative colitis, vomiting, cerebral ischaemia, hypertension, hypotenension, myocardial infarction, thrombophlebitis, thromboembolism, asthma, dyspnoea, aseptic meningitis, confusion, paresis, paraesthesia, vertigo, lymphadenopathy, diabetes mellitus, haematuria, malignancy, renal calculi, renal impairment, bone fracture, bursitis, polymyositis, scleritis, and cutaneous ulcer.

Indication and dose

Polyarticular-course juvenile idiopathic arthritis in children who have had an inadequate response to methotrexate or who cannot tolerate it.

- By subcutaneous injection
  Child 4–18 years 400 micrograms/kg (max. 25 mg) twice weekly, with an interval of 3–4 days between doses.

Severe plaque psoriasis section 13.5.3

Enbrel® (Wyeth) ▼ See section 8.1.1.1

Injection, powder for reconstitution, etanercept, net price 25-mg vial (with solvent) = £89.38. Label: 10, alert card, counselling, tuberculosis and blood disorders.

Paediatric injection, powder for reconstitution, etanercept, net price 25-mg vial (with solvent) = £89.38. Label: 10, alert card, counselling, tuberculosis and blood disorders.

Excipients include benzyl alcohol (avoid in neonates, see Excipients, p. 3).

Injection, etanercept, net price 25-mg prefilled syringe = £89.38. Label: 10, alert card, counselling, tuberculosis and blood disorders.

Sulfasalazine

Sulfasalazine (sulphasalazine) has a beneficial effect in suppressing the inflammatory activity associated with some forms of juvenile idiopathic arthritis; it is generally not used in systemic-onset disease. Sulfasalazine may cause haematological abnormalities including leucopenia, neutropenia, and thrombocytopenia and 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. For use of sulfasalazine also see section 1.5.1, aminosalicylates.

Indication and dose

Juvenile idiopathic arthritis (see also notes above).

- By mouth
  Child 2–18 years initially 5 mg/kg twice daily for 1 week, then 10 mg/kg twice daily for 1 week, then 20 mg/kg twice daily for 1 week, maintenance dose 20–25 mg/kg twice daily;
  Child 2–12 years max. 2 g daily, Child 12–18 years max. 3 g daily.

Preparations

Section 1.5.1

10.1.4 Cytotoxic-induced hyperuricaemia

This section is not included in BNF for Children. For the role of allopurinol and rasburicase in the prophylaxis of hyperuricaemia associated with cancer chemotherapy and in enzyme disorders causing increased serum urate, see section 8.1. The management of gout in adolescents requires specialist supervision.
10.1.5 Other drugs for rheumatic diseases

Classification not used in BNF for Children.

10.2 Drugs used in neuromuscular disorders

10.2.1 Drugs that enhance neuromuscular transmission

10.2.2 Skeletal muscle relaxants

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 thymectomy.

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 secretions, 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, give 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 antimuscarinic 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. In infants, neostigmine by either subcutaneous or intramuscular injection is preferred for the short-term management of myasthenia.

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 required. It is inadvisable to use excessive doses because acetylcholine receptor down regulation may occur. Immunosuppressant therapy may be considered if high doses of pyridostigmine are needed. Neostigmine and pyridostigmine should be given to neonates 30 minutes before feeds to improve suckling.

Neostigmine and edrophonium are also used to reverse the actions of the non-depolarising neuromuscular blocking drugs (section 15.1.6).
NEOSTIGMINE

Cautions  
- Asthma (extreme caution), bradycardia, arrhythmias, recent myocardial infarction, epilepsy, hypotension, parkinsonism, vagotonia, peptic ulceration, hyperthyroidism; atropine or other antidote to muscarinic effects may be necessary (particularly when neostigmine is given by injection), but not given routinely because it may mask signs of overdosage; interactions: Appendix 1 (parasympathomimetics)
- Renal impairment may need dose reduction
- Pregnancy: manufacturer advises use only if potential benefit outweighs risk
- Breast-feeding: amount probably too small to be harmful; monitor infant

Contra-indications  
- Intestinal or urinary obstruction

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

Indication and dose  

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>Initially 1–2 mg, then 1–5 mg every 4 hours, give 30 minutes before feeds</td>
</tr>
<tr>
<td>Child 1–6 years</td>
<td>Initially 7.5 mg repeated at suitable intervals throughout the day, total daily dose 15–90 mg</td>
</tr>
<tr>
<td>Child 6–12 years</td>
<td>Initially 15 mg repeated at suitable intervals throughout the day, total daily dose 15–90 mg</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>Initially 15–30 mg repeated at suitable intervals throughout the day, total daily dose 75–300 mg (but max. most can tolerate is 180 mg daily)</td>
</tr>
</tbody>
</table>

By subcutaneous or intramuscular injection (as neostigmine metilsulfate)

- Neonate: 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 repeated at suitable intervals throughout the day
- Child 12–18 years: 1–2.5 mg repeated at suitable intervals throughout the day

Pyridostigmine bromide

Cautions  
- See under Neostigmine; weaker muscarinic action

Contra-indications  
- See under Neostigmine

Side-effects  
- See under Neostigmine

Indication and dose  

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>Initially 1–1.5 mg/kg, increased gradually to max. 10 mg, repeated throughout the day, give 30–60 minutes before feeds</td>
</tr>
</tbody>
</table>

EDROPHONIUM CHLORIDE

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

Licensed use  
- Not licensed for use in children under 1 year as a diagnostic test for myasthenia gravis

Indication and dose  

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1–12 years</td>
<td>20 micrograms/kg followed after 30 seconds (if no adverse reaction has occurred) by 80 micrograms/kg</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>2 mg followed after 30 seconds (if no adverse reaction has occurred) by 8 mg</td>
</tr>
</tbody>
</table>

Detection of overdosage or underdosage of cholinergic drugs

- By intravenous injection

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–12 years</td>
<td>20 micrograms/kg (preferably just before next dose of anticholinesterase, see notes above)</td>
</tr>
<tr>
<td>Child 12–18 years</td>
<td>2 mg (preferably just before next dose of anticholinesterase, see notes above)</td>
</tr>
</tbody>
</table>

PYRIDOSTIGMINE BROMIDE

Cautions  
- See under Neostigmine; weaker muscarinic action

Contra-indications  
- See under Neostigmine

Side-effects  
- See under Neostigmine

Indication and dose  

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>Initially 1–1.5 mg/kg, increased gradually to max. 10 mg, repeated throughout the day, give 30–60 minutes before feeds</td>
</tr>
</tbody>
</table>

Neostigmine (Non-proprietary)  
- Tablets, scored, neostigmine bromide 15 mg, net price 20 = £7.29
- Injection, neostigmine metilsulfate 2.5 mg/mL, net price 1-mL amp = 57p

Edrophonium (Cambridge)  
- Injection, edrophonium chloride 10 mg/mL, net price 1-mL amp = £7.89
Child 1 month – 12 years
initially 1–1.5 mg/kg/day, increased gradually to 7 mg/kg/day in 6 divided doses; usual total daily dose 30–360 mg
Child 12 – 18 years
30–120 mg, repeated throughout the day; usual total daily dose 0.3–1.2 g (but consider immunosuppressant therapy if total daily dose exceeds 360 mg, down-regulation of acetylcholine receptors possible if total daily dose exceeds 450 mg; see notes above)

**Immunosuppressant therapy**

A course of corticosteroids (section 6.3) is an established treatment in severe cases of myasthenia gravis and may be particularly useful when antibodies to the acetylcholine receptor are present in high titre. Short courses of high-dose (‘pulsed’) methylprednisolone followed by maintenance therapy with oral corticosteroids may also be useful.

Corticosteroid treatment is usually initiated under specialist supervision. For disadvantages of corticosteroid treatment, see section 6.3.2. Transient but very serious worsening of symptoms can occur in the first 2–3 weeks, especially if the corticosteroid is started at a high dose. Once remission has occurred (usually after 2–6 months), the dose of prednisolone should be reduced slowly to the minimum effective dose.

**Skeletal muscle relaxants**

The drugs described below are used for the relief of chronic muscle spasm or spasticity associated with 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 splinting 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. It is generally used in resistant cases. 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** has undoubted efficacy in some children. Sedation and occasionally extensor hypotonus are disadvantages. Other benzodiazepines also have muscle-relaxant properties.

**BACLOFEN**

- **Cautions** psychiatric illness, respiratory impairment, epilepsy; history of peptic ulcer (avoid oral route in active peptic ulceration); diabetes; hypertonic bladder sphincter; 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 occur)
- **Skilled tasks** Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced
- **Renal impairment** use smaller doses; excreted by kidney
- **Pregnancy** manufacturer advises use only if potential benefit outweighs risk (toxicity in animal studies)
- **Breast-feeding** amount too small to be harmful

**Mestinon® (Valeant)**

Tablets, scored, pyridostigmine bromide 60 mg, net price 20 = £4.81

Extemporaneous formulations available see Extemporaneous Preparations, p. 8
BACLOFEN (continued)

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; nystagmus; visual disorders; rash, hyperhidrosis; rarely taste disturbances, abdominal pain, paraesthesia, erectile dysfunction, dysarthria; very rarely hypothermia

Indication and dose

Chronic severe spasticity of voluntary muscle
- By mouth
  - Child 1–10 years: 0.75–2 mg/kg daily or 2.5 mg 4 times daily increased gradually according to age to maintenance: Child 1–2 years: 10–20 mg daily in divided doses, Child 2–6 years: 20–30 mg daily in divided doses, Child 6–10 years: 30–60 mg daily in divided doses
  - Child 10–18 years: 5 mg 3 times daily increased gradually, max. 2.5 mg/kg or 100 mg daily

Severe chronic spasticity of cerebral origin unresponsive to oral antispastic drugs (or oral therapy not tolerated), as alternative to ablative neurosurgical procedures—specialist use only
- By intrathecal injection
  - Child 4–18 years: initial test dose 25 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-titration phase, most often using infusion pump (implanted into chest wall or abdominal wall tissues) to establish maintenance dose (ranging from 24 micrograms to 1.2 mg daily in children under 12 years or 1.4 mg daily for those over 12 years) retaining some spasticity to avoid sensation of paralysis

Safe Practice Consult product literature for details on dose testing 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

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 Lyfex® (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

DANTROLENE SODIUM

Cautions
- 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, 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
- Children and their carers 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

Skilled tasks
- Drowsiness may affect performance of skilled tasks (eg. driving); effects of alcohol enhanced

Breast-feeding
- present in milk—manufacturer advises avoid

Contra-indications
- hepatic impairment (may cause severe liver damage); acute muscle spasm; avoid when spasticity is useful, for example, locomotion

Pregnancy
- avoid use in chronic spasticity—embryotoxic in animal studies

Side-effects
- diarrhoea (withdraw if severe, discontinue treatment if it 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, dyspnoea, depression, confusion, nervousness, insomnia, increased urinary frequency, urinary incontinence or retention, haematuria, crystalluria, and increased sweating

Licensed use
- not licensed for use in children

Indication and dose

Chronic severe spasticity of voluntary muscle
- By mouth
  - Child 5–12 years: initially 500 micrograms/kg once daily; after 7 days increase to 500 micrograms/kg/dose 3 times daily; every 7 days increase by further 500 micrograms/kg/dose until satisfactory response; max. 2 mg/kg 3–4 times daily (max. total daily dose 400 mg)
  - Child 12–18 years: initially 25 mg once daily; increase to 3 times daily after 7 days; every 7 days increase by further 500 micrograms/kg/dose until satisfactory response; max. 2 mg/kg 3–4 times daily (max. total daily dose 400 mg)

10.2.2 Skeletal muscle relaxants 617
10 Musculoskeletal and joint diseases
### DANTROLENE SODIUM (continued)

<table>
<thead>
<tr>
<th>Malignant hyperthermia section 15.1.8</th>
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</table>

**Capsules**, orange/brown, dantrolene sodium
25 mg, net price 20 = £2.46; 100 mg, 20 = £8.61.
Label: 2, counselling, driving, hepatotoxicity

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### DIAZEPAM

<table>
<thead>
<tr>
<th>Cautions</th>
<th>see section 4.8.2</th>
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<tbody>
<tr>
<td>Contra-indications</td>
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<tr>
<td>Side-effects</td>
<td>see section 4.8.2; also hypotonia</td>
</tr>
</tbody>
</table>

**Indication and dose**
- **Muscle spasm in cerebral spasticity or in postoperative skeletal muscle spasm**
  - **Child 1–12 months** initially 250 microgram/kg twice daily
  - **Child 1–5 years** initially 2.5 mg twice daily
  - **Child 5–12 years** initially 5 mg twice daily
  - **Child 12–18 years** initially 10 mg twice daily; max. total daily dose 40 mg

**Tetanus**
- **By intravenous injection**
  - **Child 1 month–18 years** 100–300 micrograms/kg repeated every 1–4 hours
- **By intravenous infusion (or by nasoduodenal tube)**
  - **Child 1 month–18 years** 3–10 mg/kg over 24 hours, adjusted according to response

**Status epilepticus** section 4.8.2

**Febrile convulsions** section 4.8.3

**Peri-operative use** section 15.1.4.1

**Administration** for **continuous intravenous infusion** of diazepam emulsion, dilute to a concentration of max. 400 micrograms/mL with Glucose 5% or 10%; max. 6 hours between addition and completion of infusion; diazepam adsorbed by plastics of infusion bags and giving sets

For **continuous intravenous infusion** of diazepam solution, dilute to a concentration of max. 50 micrograms/mL with Glucose 5% or Sodium Chloride 0.9%; diazepam adsorbed by plastics of infusion bags and giving sets

**Oral preparations**
Section 15.1.4.1

**Parenteral preparations**
Section 4.8.2

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### 10.3 Drugs for the relief of soft-tissue inflammation

#### 10.3.1 Enzymes

#### 10.3.2 Rubefacients and other topical antirheumatics

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### Extravasation

**Local guidelines for the management of extravasation should be followed where they exist or specialist advice sought.**

Extravasation injury follows leakage of drugs or intravenous fluids from the veins or inadvertent administration into the subcutaneous or subdermal tissue. It must be dealt with **promptly** to prevent tissue necrosis.

Acidic or alkaline preparations and those with an osmolarity 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. Very young children are at increased risk. Those receiving anticoagulants 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 children 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 or using glyceryl trinitrate ointment distal to the cannula may improve the patency of the vessel in children with small veins or in those whose veins are prone to collapse.
Children or their carers 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. The first method may be appropriate following extravasation of vesicant drugs and involves administration of an antidote (if available) and the application of cold compresses 3–4 times a day (consult specialist literature for details of specific antidotes). Spreading and diluting the offending substance involves infiltrating the area with physiological saline, applying warm compresses, elevating the affected limb, and administering hyaluronidase (section 10.3.1). A saline flush-out technique (involving flushing the subcutaneous tissue with physiological saline) may be effective but requires specialist advice. Hyaluronidase should not be administered following extravasation of vesicant drugs (unless it is either specifically indicated or used in the saline flush-out technique).

### 10.3.1 Enzymes

Hyaluronidase is used for the management of extravasation. For preparations, see **BNF section 10.3.1**.

### 10.3.2 Rubefacients and other topical antirheumatics

Classification not used in **BNF for Children**.
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 especially by the visually impaired or otherwise physically limited patients; they may be useful in children in whom normal application is difficult.

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; in neonates and infants it may be more appropriate to administer the drop in the inner angle of the open eye. 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 carer or child should therefore leave an interval of at least 5 minutes between the two. Eye ointment should be applied after drops. Both drops and ointment may cause transient blurred vision.

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, this route is suitable only for drugs which are readily soluble. Drugs such as antimicrobials and corticosteroids may be administered systemically to treat an eye condition.

Preservatives and sensitisers
Information on preservatives and on substances identified as skin sensitisers (section 13.1.3) is provided under preparation entries.

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 home 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 (24 hours if preservative-free). Individual containers should be provided for each child, and for each eye 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 (section 11.8.2) 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; large volume 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
11.3.2 Antifungals
11.3.3 Antivirals

Eye infections
Most acute superficial eye infections can be treated topically. Blepharitis and conjunctivitis are often caused by staphylococci; keratitis and endophthalmitis may be bacterial, viral, or fungal.

Bacterial blepharitis is treated by lid hygiene and application of antibacterial eye drops to the conjunctival sac or to the lid margins. Systemic treatment may be required and may be necessary for 3 months or longer.

Most cases of acute bacterial conjunctivitis are self-limiting; where treatment is appropriate, antibacterial eye drops or an eye ointment are used. A poor response might indicate viral or allergic conjunctivitis or antibiotic resistance.
Corneal ulcer and keratitis require specialist treatment, usually under inpatient care, and may call for intensive topical, subconjunctival, or systemic administration of antimicrobials.

Endophthalmitis is a medical emergency which also calls for specialist management and often requires parenteral, subconjunctival, or intra-ocular administration of antimicrobials.

For reference to the treatment of crab lice of the eyelashes, see section 13.10.4

11.3.1 Antibacterials

Bacterial infections are generally treated topically with eye drops and eye ointments; systemic treatment 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 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).

Other antibacterial eye drops may be prepared aseptically in a specialist manufacturing unit from material supplied for injection, see section 11.8.

Neonates Antibacterial eye drops are used to treat acute bacterial conjunctivitis in neonates (ophthalmia neonatorum); where possible the causative micro-organism should be identified. Chloramphenicol or neomycin eye drops are used to treat mild conjunctivitis; more serious infections also require a systemic antibacterial. Failure to respond to initial treatment requires further investigation; chlamydial infection is one of the most frequent causes of neonatal conjunctivitis and should be considered.

Gonococcal eye infections are treated with a single-dose of ceftriaxone. Chlamydial eye infections should be managed with oral erythromycin. Gentamicin eye drops together with appropriate systemic antibacterials are used in the treatment of pseudomonal eye infections; high-strength gentamicin eye drops (1.5%) [unlicensed] are available for severe infections.

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 irreversible ocular damage; antibacterial eye preparations are usually administered as follows.

Eye drops. Apply 1 drop at least every 2 hours in severe infection then reduce frequency as infection is controlled and continue for 48 hours after healing. For less severe infection 3–4 times daily is generally sufficient.

Eye ointment. Apply either at night (if eye drops used during the day) or 3–4 times daily (if eye ointment used alone).
CHLORAMPHENICOL

**Side-effects** transient stinging; see also notes above

**Indication and dose** See notes above

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

Chloramphenicol 0.5% eye drops can be sold to the public (in max. pack size 10 mL) for treatment of acute bacterial conjunctivitis in adults and children over 2 years; max. duration of treatment 5 days

**Ciprofloxacin**

**Cautions** not recommended for children under 1 year

**Pregnancy** Manufacturer advises caution

**Breast-feeding** Manufacturer advises caution but unlikely to appear in milk

**Side-effects** local burning and itching; lid margin crusting; hyperaemia; taste disturbances; corneal staining, keratitis, lid oedema, lacrimation, photophobia, corneal infiltrates; nausea and visual disturbances reported

**Licensed use** not licensed for use in children under 1 year

**Indication and dose**

**Superficial bacterial infections** See notes above

Ciloxan® (Alcon) 

**Ophthalmic solution** (= eye drops), ciprofloxacin (as hydrochloride) 0.3%. Net price 5 mL = £4.94

**Excipients** include benzalkonium chloride

**Eye ointment**, ciprofloxacin (as hydrochloride) 0.3%. Net price 3.5 g = £5.49

**Fusidic Acid**

**Indication and 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**

**Indication and dose** See notes above

Gentamicin (Non-proprietary) 

**Drops** (for ear or eye), gentamicin 0.3% (as sulphate). Net price 10 mL = £1.78

**Excipients** include benzalkonium chloride

**Licensed use** not licensed for use in children under 1 year

**Indication and dose** See notes above

**Levofloxacin**

**Contra-indications**

**Pregnancy** manufacturer advises avoid—systemic quinolones have caused arthropathy in animal studies

**Breast-feeding** manufacturer advises avoid

**Side-effects** transient ocular irritation, visual disturbances, lid margin crusting, lid or conjunctival oedema, hyperaemia, conjunctival follicles, photophobia, headache, rhinitis

**Licensed use** not licensed for use in children under 1 year

**Indication and dose** See notes above

Oftaquix® (Kestrel Ophthalmics) 

**Eye drops**, levofloxacin 0.5%, net price 5 mL = £6.95
11.3.2 Antifungals

Fungal infections of the cornea are rare. Orbital mycosis is rarer, and when it occurs it is usually because of a direct spread of infection from the paranasal sinuses. 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 is normally 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 in Scotland or Northern Ireland), or to the nearest hospital ophthalmology unit, see also ‘special-order’ manufacturers or specialist importing companies, p. 943.

### 11.3.3 Antivirals

Herpes simplex infections producing, for example, dendritic corneal ulcer can be treated with aciclovir.

For systemic treatment of CMV retinitis, see section 5.3.

**ACICLOVIR**

**(Acyclovir)**

**Side-effects**

- local irritation and inflammation,
- superficial punctate keratopathy; rarely blepharitis; very rarely hypersensitivity reactions including angioedema

**Indication and dose**

Local treatment of herpes simplex infections

Apply 5 times daily (continue for at least 3 days after complete healing)

- **Zovirax**
  - **Eye ointment**, aciclovir 3%. Net price 4.5 g = £9.92
  - **Tablets**, see section 5.3.2.1
  - **Injection**, see section 5.3.2.1
  - **Cream**, see section 13.10.3

### 11.4 Corticosteroids and other anti-inflammatory preparations

#### 11.4.1 Corticosteroids

Corticosteroids administered locally to the eye or given by mouth are effective for treating anterior segment inflammation in uveitis (section 11.5) and following surgery.

**Topical corticosteroids** should normally only be used under expert supervision; three main dangers are associated with their use:

- a ‘red eye’, where the diagnosis is unconfirmed, may be due to herpes simplex virus, and a corticosteroid may aggravate the condition, leading to corneal ulceration, with possible damage to vision and even loss of the eye. Bacterial, fungal and amoebic infections pose a similar hazard;
- ‘steroid glaucoma’ may follow the use of corticosteroid eye preparations in susceptible individuals;
- a ‘steroid cataract’ may follow prolonged use.

Other side-effects of ocular corticosteroids include thinning of the cornea and sclera. Prolonged use in neonates and infants can cause adrenal suppression.

Products combining a corticosteroid with an antimicrobial are used after ocular 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.
BETAMETHASONE

Cautions see notes above
Side-effects see notes above

Indication and dose

Local treatment of inflammation (short-term)
Apply eye drops every 1–2 hours until controlled then reduce frequency; eye ointment 2–4 times daily or at night when used with eye drops

Betnesol® (UCB Pharma) 
Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%. Net price 10 mL = £2.32
Excipients include benzalkonium chloride, disodium edetate
Eye ointment, betamethasone sodium phosphate 0.1%. Net price 3 g = £1.41

Vistamethasone® (Martindale) 
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

With neomycin

Betnesol-N® (UCB Pharma) 
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
Note May be difficult to obtain

Vistamethasone N® (Martindale)
Drops (for ear, eye, or nose), see section 12.1.1

DEXAMETHASONE

Cautions see notes above
Side-effects see notes above

Indication and dose

Local treatment of inflammation (short-term)
Apply eye drops 4–6 times daily; severe conditions every 30–60 minutes until controlled then reduce frequency

Maxidex® (Alcon) 
Eye drops, dexamethasone 0.1%, hypromellose 0.5%. Net price 5 mL = £1.49; 10 mL = £2.95
Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

Maxitrol® (Alcon) 
Eye drops, dexamethasone 0.1%, hypromellose 0.5%, neomycin 0.35% (as sulphate), polymyxin B sulphate 6000 units/mL. Net price 5 mL = £1.77
Excipients 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
Excipients include hydroxybenzoates (parabens), wool fat

Sofradex® (Sanofi-Aventis) 
Drops (for ear or eye), see section 12.1.1

FLUOROMETHOLONE

Cautions see notes above
Side-effects see notes above
Licensed use not licensed for use in children under 2 years

Indication and dose

Local treatment of inflammation (short-term)
Apply 2–4 times daily (initially every hour for 24–48 hours then reduce frequency)

FML® (Allergan) 
Ophthalmic suspension (= eye drops), fluorometholone 0.1%, polyvinyl alcohol (Liquifilm®) 1.4%. Net price 5 mL = £1.71; 10 mL = £2.95
Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

HYDROCORTISONE ACETATE

Cautions see notes above
Side-effects see notes above

Indication and dose

Local treatment of inflammation (short-term)
Apply eye drops 4 times daily; apply eye ointment twice daily or at night

Hydrocortisone (Non-proprietary) 
Eye drops, hydrocortisone acetate 1%. Net price 10 mL = £3.21
Eye ointment, hydrocortisone acetate 0.5%, net price 3 g = £2.40; 1%, 3 g = £2.42; 2.5%, 3 g = £6.55

PREDNISOLONE

Cautions see notes above
Side-effects see notes above

Indication and dose

Local treatment of inflammation (short-term)
Apply every 1–2 hours until controlled then reduce frequency
Pred Forte® (Allergan) (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® (UCB Pharma) (UCB Pharma)
Drops (for ear or eye), prednisolone sodium phosphate 0.5%. Net price 10 mL = £2.00
Excipients include benzalkonium chloride, disodium edetate

Minims® Prednisolone Sodium Phosphate (Chauvin) (Chauvin)
Eye drops, prednisolone sodium phosphate 0.5%, Net price 20 × 0.5 mL = £5.75
Excipients include disodium edetate

Predsol-N® (UCB Pharma) (UCB Pharma)
Drops (for ear or eye), see section 12.1.1

11.4.2 Other anti-inflammatory preparations

Topical preparations of antihistamines such as eye drops containing antazoline (with xylometazoline as Otrivine-Antistin®), azelastine, epinastine, ketotifen, and olopatadine may be used for allergic conjunctivitis.

Sodium cromoglicate and nedocromil sodium eye drops may be useful for vernal keratoconjunctivitis and other allergic forms of conjunctivitis.

Lodoxamide eye drops are used for allergic conjunctival conditions including seasonal allergic conjunctivitis.

Emedastine eye drops are licensed for seasonal allergic conjunctivitis.

ANTAZOLINE SULPHATE

Indication and dose

Allergic conjunctivitis
See preparation below

Otrivine-Antistin® (Novartis Consumer Health)
Eye drops, antazoline sulphate 0.5%, xylometazoline hydrochloride 0.05%. Net price 10 mL = £2.35
Excipients include benzalkonium chloride, disodium edetate

Dose
Child 5–18 years apply 2–3 times daily

Note Xylometazoline is a sympathomimetic; it should be avoided in angle-closure glaucoma; absorption of antazoline and xylometazoline may result in systemic side-effects and the possibility of interaction with other drugs, see Appendix 1 (antihistamines and sympathomimetics)

AZELASTINE HYDROCHLORIDE

Side-effects mild transient irritation; bitter taste reported

Indication and dose

Allergic conjunctivitis, seasonal allergic conjunctivitis
Child 4–18 years apply twice daily, increased if necessary to 4 times daily

Perennial conjunctivitis
Child 12–18 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 children over 12 years

EMEDASTINE

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

Indication and dose

Seasonal allergic conjunctivitis
Child 3–18 years apply twice daily

Emadine® (Alcon)
Eye drops, emedastine 0.05% (as difumarate), net price 5 mL = £7.69
Excipients include benzalkonium chloride

Note
**EPINASTINE HYDROCHLORIDE**

**Side-effects**
burning; less commonly dry mouth, taste disturbance; nasal irritation, rhinitis, headache, blepharoptosis, conjunctival oedema and hyperaemia, dry eye, local irritation, photophobia, visual disturbance; pruritus

**Indication and dose**
Seasonal allergic conjunctivitis
Child 12–18 years apply twice daily; max. duration of treatment 8 weeks

**Relestat** (Allergan)
Eye drops, epinastine hydrochloride 500 micrograms/mL, net price 5 mL = £9.90
*Excipients* include benzalkonium chloride, disodium edetate

**KETOTIFEN**

**Side-effects**
transient burning or stinging, punctate corneal epithelial erosion; less commonly dry eye, subconjunctival haemorrhage, photophobia; headache, drowsiness, skin reactions, and dry mouth also reported

**Indication and dose**
Seasonal allergic conjunctivitis
Child 3–18 years apply twice daily

**Zaditen** (Novartis)
Eye drops, ketotifen (as fumarate) 250 micrograms/mL, net price 5 mL = £9.75
*Excipients* include benzalkonium chloride

**LODOXAMIDE**

**Side-effects**
mild transient burning, stinging, itching, and lacrimation; flushing and dizziness reported

**Indication and dose**
Allergic conjunctivitis
Child 4–18 years apply 4 times daily

**Alomide** (Alcon)
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 treatment of allergic conjunctivitis in children over 4 years

**NEDOCROMIL SODIUM**

**Side-effects**
transient burning and stinging; distinctive taste reported

**Indication and dose**
Seasonal and perennial allergic conjunctivitis
Child 6–18 years apply twice daily increased if necessary to 4 times daily; max. 12 weeks treatment for seasonal allergic conjunctivitis

**Rapitil** (Aventis Pharma)
Eye drops, nedocromil sodium 2%. Net price 5 mL = £5.12
*Excipients* include benzalkonium chloride, disodium edetate

**OLOPATADINE**

**Side-effects**
local irritation; less commonly keratitis, dry eye, local oedema, photophobia; headache, asthenia, dizziness; dry nose also reported

**Indication and dose**
Seasonal allergic conjunctivitis
Child 3–18 years apply twice daily; max. duration of treatment 4 months

**Opatanol** (Alcon)
Eye drops, olopatadine (as hydrochloride) 1 mg/mL, net price 5 mL = £4.11
*Excipients* include benzalkonium chloride

**SODIUM CROMOGlicate**
(Sodium cromoglicate)

**Side-effects**
transient burning and stinging

**Indication and dose**
Allergic conjunctivitis, vernal keratoconjunctivitis
apply eye drops 4 times daily

*1 Sodium Cromoglicate* (Non-proprietary)
Eye drops, sodium cromoglicate 2%. Net price 13.5 mL = £2.01
Brands include Hay-Crom® Aqueous, Opticrom® Aqueous, Vividrin®

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% (action lasts for 4–6 hours), facilitate the examination of the fundus of the eye. Cyclopentolate 1% (action up to 24 hours) or atropine (action up to 7 days) are preferable for producing cycloplegia for refraction in young children; tropicamide may be preferred in neonates. Atropine ointment 1% is sometimes preferred for children under 5 years because systemic absorption from the ointment is reduced. Phenylephrine 2.5% is used for mydriasis in diagnostic or therapeutic procedures; mydriasis occurs within 60–90 minutes and lasts up to 5–7 hours. Phenylephrine 10% drops are contra-indicated in children owing to the risk of systemic effects.

Mydriatics and cycloplegics are used in the treatment of anterior uveitis, usually as an adjunct to corticosteroids (section 11.4.1). Atropine is used in anterior uveitis mainly to prevent posterior synechiae and to relieve ciliary spasm, often in combination with phenylephrine eye drops; cyclopentolate or homatropine (action up to 3 days) can also be used and may be preferred because they have a shorter duration of action.

Cautions and contra-indications Darkly pigmented irides are more resistant to pupillary dilatation and caution should be exercised to avoid overdosage. Mydriasis can precipitate acute angle-closure glaucoma in the very few children who are predisposed to the condition because of a shallow anterior chamber. Atropine, cyclopentolate, and homatropine should be used with caution in children under 3 months owing to the possible association between cycloplegia and the development of amblyopia; also, neonates are at increased risk of systemic toxicity.

Skilled tasks Children may not be able to undertake skilled tasks 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.

Toxic systemic reactions to atropine and cyclopentolate can occur in neonates and children; see section 1.2 for systemic side-effects of antimuscarinic drugs.

### Antimuscarinics

#### ATROPINE SULPHATE

**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

**Licensed use** not licensed for use in children for uveitis

**Indication and dose**

- **Cycloplegia**
  - Child 3 months–18 years apply drops or ointment twice daily for 3 days before procedure
  - Anterior uveitis
    - Child 2–18 years 1 drop up to 4 times daily

**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

**Isopto Atropine** (Alcon)

- Eye drops, atropine sulphate 1%, hypromellose 0.5%. Net price 5 mL = 99p
- Excipients include benzalkonium chloride

**Minims® Atropine Sulphate** (Chauvin)

- Eye drops, atropine sulphate 1%. Net price 20 × 0.5 mL = £4.92

- Single use

#### CYCLOPENTOLATE HYDROCHLORIDE

**Cautions** see notes above

**Side-effects** see notes above

**Indication and dose**

- See notes above

**Cycloplegia**

- Child 3 months–12 years 1 drop of 1% eye drops 30–60 minutes before examination
- Child 12–18 years 1 drop of 0.5% eye drops 30–60 minutes before examination
Uveitis

Child 3 months–18 years 1 drop of 0.5% eye drops (1% for deeply pigmented eyes) 2–4 times daily

Mydrilate® (Intrapharm) (\textsuperscript{\textregistered})
Eye drops, cyclopentolate hydrochloride 0.5%, net price 5 mL = 97\textpence; 1%, 5 mL = £1.19
Excipients include benzalkonium chloride

\begin{table}
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\begin{tabular}{|l|l|}
\hline
\textbf{Cautions} & see notes above \\
\textbf{Side-effects} & see notes above \\
\textbf{Licensed use} & not licensed for use in children under 3 months \\
\textbf{Indication and dose} & \begin{tabular}{l}
See notes above \\
Child 3 months–2 years (0.5% only) 1 drop daily or on alternate days adjusted according to response \\
Child 2–18 years 1 drop twice daily adjusted according to response
\end{tabular} \\
\hline
\end{tabular}
\end{table}

HOMATROPINE HYDROBROMIDE

Homatropine (Non-proprietary) (\textsuperscript{\textregistered})
Eye drops, homatropine hydrobromide 1%, net price 10 mL = £2.14; 2%, 10 mL = £2.26
Available without preservatives as manufactured specials from Moorfields Eye Hospital
Eye drops, homatropine 0.125% and 0.5%, 10 mL, available as a manufactured special from Moorfields Eye Hospital, see also ‘special-order’ manufacturers or specialist importing companies, p. 943
Excipients include chlorhexidine

TROPICAMIDE

Mydriacyl® (Alcon) (\textsuperscript{\textregistered})
Eye drops, tropicamide 0.5%, net price 5 mL = £1.36; 1%, 5 mL = £1.68
Excipients include benzalkonium chloride, disodium edetate

PHENYLEPHRINE HYDROCHLORIDE

Indication and dose
Mydriasis
See notes above

\begin{table}
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\begin{tabular}{|l|l|}
\hline
\textbf{Cautions} & cardiovascular disease (avoid or use 2.5% strength only); tachycardia; hyperthyroidism; diabetes; susceptibility to angle-closure glaucoma; see also notes above \\
\textbf{Contra-indications} & 10% drops in neonates and children \\
\textbf{Side-effects} & eye pain and stinging; blurred vision, photophobia; systemic effects include palpitations, arrhythmias, hypertension, coronary artery spasm \\
\textbf{Indication and dose} & \begin{tabular}{l}
Mydriasis
\end{tabular} \\
\hline
\end{tabular}
\end{table}

Sympathomimetics

\begin{table}
\centering
\begin{tabular}{|l|l|}
\hline
\textbf{Cautions} & \begin{tabular}{l}
cardiovascular disease (avoid or use 2.5% strength only); tachycardia; hyperthyroidism; diabetes; susceptibility to angle-closure glaucoma; see also notes above
\end{tabular} \\
\textbf{Contra-indications} & 10% drops in neonates and children \\
\textbf{Side-effects} & eye pain and stinging; blurred vision, photophobia; systemic effects include palpitations, arrhythmias, hypertension, coronary artery spasm \\
\textbf{Indication and dose} & \begin{tabular}{l}
Mydriasis
\end{tabular} \\
\hline
\end{tabular}
\end{table}

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 and is generally associated with raised intra-ocular pressure.

Glaucoma is rare in children and should always be managed by a specialist. 

Primary congenital glaucoma is the most common form of glaucoma in children, followed by secondary glucomas, such as following hereditary anterior segment
malformations; juvenile open-angle glaucoma is less common and usually occurs in older children. Primary angle closure glaucoma (acute closed-angle glaucoma, narrow angle glaucoma) is very rare in children; it results from blockage of aqueous humour flow into the anterior chamber and is a medical emergency that requires urgent reduction of intra-ocular pressure, see below.

Treatment of glaucoma is determined by the pathophysiology and usually involves controlling raised intra-ocular pressure with surgery and drug therapy. Drugs that reduce intra-ocular pressure by different mechanisms are available for managing glaucoma. A topical beta-blocker or a prostaglandin analogue can be used. 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 (see section 2.2.5). 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.

**Cautions, contra-indications and side-effects** Systemic absorption may follow topical application to the eye; therefore, eye drops containing a beta-blocker are contra-indicated in bradycardia, heart block, or uncontrolled heart failure. **Important**: avoid in asthma, see CSM advice below. Consider also other cautions, contra-indications and side-effects of beta-blockers (p. 113). 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).
**LEVOBUNOLOL HYDROCHLORIDE**

**Cautions** see notes above  
**Contra-indications** see notes above  
**Side-effects** see notes above; anterior uveitis occasionally reported  
**Licensed use** not licensed for use in children  
**Indication and dose**  
See notes above  
Apply once or twice daily  

Levodobunol (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

**TIMOLOL MALEATE**

**Cautions** see notes above  
**Contra-indications** see notes above  
**Side-effects** see notes above  
**Licensed use** not licensed for use in children  
**Indication and dose**  
See notes above  
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

Nyogel® (Novartis)  
Eye gel (= eye drops), timolol (as maleate) 0.1%, net price 5 g = £2.85  
**Excipients** include benzalkonium chloride  
**Dose**  
Child 12–18 years apply once daily

Timoptol®-LA (MSD)  
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 eye drops once daily

With dorzolamide  
See under Dorzolamide

**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. They are not licensed for use in children. Children receiving prostaglandin analogues should be managed by a specialist and monitored for any changes to eye coloration since an increase in the brown pigment in the iris can occur; particular care is required in those with mixed coloured irides and those receiving treatment to one eye only.

**Sympathomimetics**

Dipivefrine is a pro-drug of adrenaline. It is claimed to pass more rapidly than adrenaline through the cornea and is then converted to the active form. Adrenaline (epinephrine) probably acts both by reducing the rate of production of aqueous humour and by increasing the outflow through the trabecular meshwork. It is contra-indicated in angle-closure glaucoma because it is a mydriatic, unless an iridectomy has been carried out. Side-effects include severe smarting and redness of the eye; adrenaline should be used with caution in children with hypertension and heart disease.

Apraclonidine (section 11.8.2) is an alpha, adrenoceptor agonist. Eye drops containing apraclonidine 0.5% are used for a short period 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 is an alpha, adrenoceptor agonist that reduces intra-ocular pressure; it should be used with caution in children because it has been associated with severe systemic side-effects.
**Dipivefrine Hydrochloride**

**Contra-indications** see notes above

**Side-effects** see notes above

**Licensed use** not licensed for use in children

**Indication and dose**

See notes above

Apply twice daily

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**Propine® (Allergan)**

Eye drops, dipivefrine hydrochloride 0.1%, net price 5 mL = £3.81, 10 mL = £4.77

Excipients include benzalkonium chloride, disodium edetate

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**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 of acetazolamide also produces weak diuresis.

**Acetazolamide** is given by mouth or, rarely in children, 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 unlicensed in children but are used in those 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.

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**Acetazolamide**

**Cautions** not generally recommended for prolonged use but if given monitor blood count and plasma electrolyte concentration; pulmonary obstruction (risk of acidosis); avoid extravasation at injection site (risk of necrosis); **interactions**: Appendix 1 (diuretics)

**Pregnancy** manufacturer advises avoid, especially in first trimester (toxicity in animal studies)

**Breast-feeding** amount too small to be harmful

**Contra-indications** hypokalaemia, hyponatraemia, hyperchloraemic acidosis; sulphonamide hypersensitivity

**Hepatic impairment** avoid in severe impairment

**Renal impairment** avoid; metabolic acidosis

**Side-effects** nausea, vomiting, diarrhoea, taste disturbance; loss of appetite, paraesthesia, flushing, headache, dizziness, fatigue, irritability, depression; thirst, polyuria; metabolic acidosis and electrolyte disturbances on long-term therapy; occasionally, drowsiness, confusion, hearing disturbances, uticaria, 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

**Licensed use** not licensed for use in children for treatment of glaucoma

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**Indication and dose**

**Reduction of intra-ocular pressure in open-angle glaucoma, secondary glaucoma, peri-operatively in angle-closure glaucoma.**

- **By mouth** or **by intravenous injection**
  - **Child 1 month–12 years** 5 mg/kg 2–4 times daily, adjusted according to response, max. 750 mg daily
  - **Child 12–18 years** 250 mg 2–4 times daily

**Epilepsy**

- **By mouth** or **slow intravenous injection**
  - **Neonate** initially 2.5 mg/kg 2–3 times daily, followed by 5–7 mg/kg 2–3 times daily (maintenance dose)
  - **Child 1 month–12 years** initially 2.5 mg/kg 2–3 times daily, followed by 5–7 mg/kg 2–3 times daily, max. 750 mg daily (maintenance dose)
  - **Child 12–18 years** 250 mg 2–4 times daily

**Raised intracranial pressure**

- **By mouth** or **slow intravenous injection**
  - **Child 1 month–12 years** initially 2.5 mg/kg 3 times daily, increased as necessary to max. 100 mg/kg daily
**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

**Modified release**

**Diamox SR** (Goldshield)

Capsules, m/r, orange, enclosing orange f/c pellets, acetazolamide 250 mg. Net price 30-cap pack = £13.88. Label: 3, 25

**Dose**

Child 12–18 years glaucoma, 1–2 capsules daily

**Extemporaneous formulations available see Extemporaneous Preparations, p. 8**

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**BRINZOLAMIDE**

**Cautions** systemic absorption follows topical application; neonates and infants with immature renal tubules—risk of metabolic acidosis; **interactions**: Appendix 1 (brinzolamide)

**Hepatic impairment** manufacturer advises caution—no information available

**Pregnancy** manufacturer advises avoid unless essential—embryotoxic in animal studies

**Contra-indications** hyperchloroemic acidosis

**Renal impairment** avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

**Breast-feeding** manufacturer advises avoid—no information available

**Side-effects** local irritation, taste disturbance; less commonly nausea, dyspepsia, dry mouth, chest pain, epistaxis, haemoptysis, dyspnoea, rhinitis, pharyngitis, bronchitis, paraesthesia, depression, dizziness, headache, dermatitis, alopecia, corneal erosion

**Licensed use** not licensed for use in children

**Indication and dose**

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

Apply twice daily increased to 3 times daily if necessary

**Azopt** (Alcon)

**Eye drops**, brinzolamide 10 mg/mL, net price 5 mL = £6.90

**Excipients** include benzalkonium chloride, disodium edetate

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**DORZOLAMIDE**

**Cautions** systemic absorption follows topical application; history of renal calculi; neonates and infants with immature renal tubules—risk of metabolic acidosis; chronic corneal defects, history of intra-ocular surgery; **interactions**: Appendix 1 (dorzolamide)

**Hepatic impairment** manufacturer advises caution—no information available

**Contra-indications** hyperchloroemic acidosis

**Renal impairment** avoid if estimated glomerular filtration rate less than 30 mL/minute/1.73 m²

**Pregnancy** manufacturer advises avoid—embryotoxic in animal studies

**Breast-feeding** manufacturer advises avoid—no information available

**Side-effects** nausea, bitter taste; headache, asthenia; ocular irritation, blurred vision, lacrimation, conjunctivitis, superficial punctuate keratitis, eyelid inflammation; less commonly iridocyclitis; rarely hypersensitivity reactions (including urticaria, angioedema, bronchospasm), dizziness, paraesthesia, urolithiasis, eyelid crusting, transient myopia, corneal oedema, epistaxis, dry mouth, throat irritation; also reported metabolic acidosis

**Licensed use** not licensed for use in children

**Indication and dose**

Raised intra-ocular pressure in ocular hypertension, open-angle glaucoma, pseudo-exfoliative glaucoma either as adjunct to beta-blocker or used alone in patients unresponsive to beta-blockers or if beta-blockers contra-indicated

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

**Dose**

Raised intra-ocular pressure in open-angle glaucoma, or pseudoexfoliative glaucoma when beta-blockers alone not adequate

Apply twice daily
Miotics

Pilocarpine is a miotic used in the management of raised intra-ocular pressure. The small pupil is an unfortunate side-effect of these drugs (except when pilocarpine is used temporarily before an operation for angle-closure glaucoma). Miotics act by opening up the inefficient drainage channels in the trabecular meshwork which may be occluded by contraction or spasm of the ciliary muscle.

Cautions A darkly pigmented iris may require higher concentration of the miotic or more frequent administration and care should be taken to avoid over-dosage. 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 and urinary-tract obstruction.

Counselling Blurred vision may affect performance of skilled tasks (e.g. driving) particularly at night or in reduced lighting.

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. 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 are rare following application to the eye.

PILOCARPINE

Cautions see notes above
Contra-indications see notes above
Side-effects see notes above
Licensed use not licensed for use in children
Indication and dose
See also notes above

Pre-operatively in goniotomy and trabeculotomy
Child 1 month–18 years apply 1% or 2% solution once daily

Dry mouth (section 12.3.5)

Pilocarpine Hydrochloride (Non-proprietary) [32]
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) [32]
Eye drops, pilocarpine nitrate 2%, net price 20 × 0.5 mL = £4.92

Local anaesthetics

Oxybuprocaine and tetracaine (amethocaine) are widely used topical local anaesthetics. Proxymetacaine causes less initial stinging and is particularly useful for children. Oxybuprocaine or a combined preparation of lidocaine ( lignocaine) and fluorescein is used for tonometry. Tetracaine produces 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.

Caution Local anaesthetic eye drops should be avoided in preterm neonates because of the immaturity of the metabolising enzyme system.
LIDOCAINE HYDROCHLORIDE
(Lignocaine hydrochloride)
Contra-indications  avoid in preterm neonates
Indication and dose
Local anaesthetic
Use as required
Minims® Lignocaine and Fluorescein (Chauvin)
Eye drops, lidocaine hydrochloride 4%, fluorescein sodium 0.25%. Net price $20 × 0.5 mL = £6.93

OXYBUPROCAINE HYDROCHLORIDE
Contra-indications  avoid in preterm neonates
Indication and dose
Local anaesthetic
Use as required
Minims® Benoxinate (Oxybuprocaine) Hydrochloride (Chauvin)
Eye drops, oxybuprocaine hydrochloride 0.4%. Net price $20 × 0.5 mL = £4.92

PROXYMETACAINE HYDROCHLORIDE
Contra-indications  avoid in preterm neonates
Indication and dose
Local anaesthetic
Use as required
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)
Contra-indications  avoid in preterm neonates
Indication and dose
Local anaesthetic
Use as required
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

Certain eye drops, e.g. amphotericin, ceftazidime, cefuroxime, colistin, desferri-oxamine, dexamethasone, gentamicin and vancomycin, may be prepared aseptically in a specialist manufacturing unit from material supplied for injection.
Preparations may also be available from Moorfields Eye Hospital as manufactured specials, see also ‘special-order’ manufacturers or specialist importing companies, p. 943.

11.8.1 Tear deficiency, ocular lubricants, and astringents

Chronic soreness of the eyes associated with reduced or abnormal tear secretion often responds to tear replacement therapy. The severity of the condition and the child’s preference will often guide the choice of preparation.

Hyromellose 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 hyromellose 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.

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 intra-ocular surgery and in first-aid for removal of harmful substances.

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.

### ACETYLICYSTEINE

**Indication and dose**

Tear deficiency, impaired or abnormal mucus production

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)

Synthetic high molecular weight polymers of acrylic acid cross-linked with either allyl ethers of sucrose or allyl ethers of pentaeritritol!

**Licensed use** Some preparations not licensed for use in children

**Indication and dose**

Dry eyes including keratoconjunctivitis sicca, unstable tear film

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

Viscoat®s (Novartis)

Liquid gel (= eye drops), carbomer 980 (polyacrylic acid) 0.2%, net price 30 × 0.6-mL single-dose units = £5.75

### CARMELLOSE SODIUM

**Indication and dose**

Dry eye conditions

Apply as required

Optive® (Allergan)

Eye drops, carmellose sodium 0.5%, glycerol, net price 10 mL = £7.49

### HYDROXYETHYLCELLULOSE

**Indication and dose**

Tear deficiency

Apply as required

Minims® Artificial Tears (Chauvin)

Eye drops, hydroxyethylcellulose 0.44%, sodium chloride 0.35%. Net price 20 × 0.5 mL = £5.75
**HYPROMELLOSE**

**Indication and dose**

<table>
<thead>
<tr>
<th>Tear deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply as required</td>
</tr>
</tbody>
</table>

*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

**LIQUID PARAFFIN**

**Indication and dose**

<table>
<thead>
<tr>
<th>Dry eye conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply as required</td>
</tr>
</tbody>
</table>

**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**

**Indication and dose**

<table>
<thead>
<tr>
<th>See notes above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply 2 hourly as required</td>
</tr>
</tbody>
</table>

**Simple Eye Ointment**
Ointment, liquid paraffin 10%, wool fat 10%, in yellow soft paraffin. Net price 4 g = £3.03

**POLYVINYL ALCOHOL**

**Indication and dose**

<table>
<thead>
<tr>
<th>Tear deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apply as required</td>
</tr>
</tbody>
</table>

Liquifilm Tears® (Allergan)
Ophthalmic solution (= eye drops), polyvinyl alcohol 1.4%. Net price 15 mL = £1.93
Excipients include benzalkonium chloride, disodium edetate

Sno Tears® (Chauvin)
Eye drops, polyvinyl alcohol 1.4%. Net price 10 mL = £1.06
Excipients include benzalkonium chloride, disodium edetate

**SODIUM CHLORIDE**

**Indication and dose**

<table>
<thead>
<tr>
<th>Irrigation, including first-aid removal of harmful substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use as required</td>
</tr>
</tbody>
</table>

Sodium Chloride 0.9% Solutions
See section 13.11.1

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®*

Minims® Saline (Chauvin)
Eye drops, sodium chloride 0.9%. Net price 20 × 0.5 mL = £4.92
**SODIUM HYALURONATE**

**Indication and dose**
- **Dry eye conditions**
  - Apply as required

**Oxyl (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

**SODIUM HYALURONATE**

**Single use**
- **Clinitas** (Altacor)
  - **Eye drops**, sodium hyaluronate 0.4%, net price 30 × 0.5 mL = £5.70

- **Ocusan** (Agepha)
  - **Eye drops**, sodium hyaluronate 0.2%, net price 20 × 0.5 mL = £5.25

- **Vismed** (TRB Chemedica)
  - **Eye drops**, sodium hyaluronate 0.18%, net price 20 × 0.3 mL = £5.10

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**11.8.2 Ocular diagnostic and peri-operative preparations**

**Ocular diagnostic preparations**

**Fluorescein sodium** is used in diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

**FLUORESCEIN SODIUM**

**Indication and dose**
- Detection of lesions and foreign bodies sufficient to stain damaged areas

**Minims Fluorescein Sodium** (Chauvin)
- **Eye drops**, fluorescein sodium 1% or 2%. Net price 20 × 0.5 mL (both) = £4.92

**With local anaesthetic**
- **Section 11.7**

**Ocular peri-operative drugs**

Drugs used to prepare the eye for surgery and drugs that are injected into the anterior chamber at the time of surgery are included here.

Sodium hyaluronate is used during surgical procedures on the eye.

**Apraclonidine**, an alpha₂-adrenoceptor agonist, reduces intra-ocular pressure possibly by reducing the production of aqueous humour. It is used for short-term treatment only.

**Balanced Salt Solution** is used routinely in intra-ocular surgery (section 11.8.1).

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**ACETYLCHOLINE CHLORIDE**

**Licensed use** not licensed for use in children

**Indication and dose**
- Cataract surgery, penetrating keratoplasty, iridectomy, other anterior segment surgery requiring rapid complete miosis
  - consult product literature

**Miochol-E** (Novartis)
- **Solution for intra-ocular irrigation**, acetylcholine chloride 1%, mannitol 3% when reconstituted. Net price 2 mL-vial = £9.10

---

**APRACLONIDINE**

**Note** Apraclonidine is a derivative of clonidine

**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 (alpha₂-adrenoceptor stimulants)

**Skilled tasks** 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.

Licensed use  0.5% drops not licensed for use in children under 12 years; 1% drops not licensed for use in children.

Indication and dose  See preparations below.

diclofenac sodium

Licensed use  not licensed for use in children.

Indication and dose  Inhibition of intra-operative miosis during cataract surgery (but does not possess intrinsic mydriatic properties), postoperative inflammation in cataract surgery, strabismus surgery, argon laser trabeculoplasty. Consult product literature.

Voltarol ophtha multidose

Eye drops, diclofenac sodium 0.1%, net price 5 mL = £6.68.
Excipients include benzalkonium chloride, disodium edetate, propylene glycol.

Single use

Voltarol ophtha

Eye drops, diclofenac sodium 0.1%. Net price pack of 5 single-dose units = £4.00, 40 single-dose units = £32.00.

flurbiprofen sodium

Licensed use  not licensed for use in children.

Indication and dose  Inhibition of intra-operative miosis (but does not possess intrinsic mydriatic properties), control of postoperative and post-laser trabeculoplasty inflammation (if corticosteroids contra-indicated). Consult product literature.

Ocufen

Ophthalamic solution (= eye drops), flurbiprofen sodium 0.03%, polyvinyl alcohol (Liquifilm) 1.4%. Net price 40 × 0.4 mL = £37.15.

Ketorolac trometamol

Licensed use  not licensed for use in children.

Indication and dose  Prophylaxis and reduction of inflammation and associated symptoms following ocular surgery. Consult product literature.

Acular

Eye drops, ketorolac trometamol 0.5%. Net price 5 mL = £5.00.
Excipients include benzalkonium chloride, disodium edetate.

Contact lenses

Note  Some recommendations in this section involve non-licensed indications.

Some children and adolescents prefer to wear contact lenses rather than spectacles for both cosmetic and medical reasons. Visual defects are corrected by either rigid (‘hard’ or gas permeable) lenses or soft (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 can cause adverse 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 ephedrine and hydralazine). Other drugs that can 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

12.1.1 Otitis externa

12.1.2 Otitis media

12.1.3 Removal of ear wax

12.2 Drugs acting on the nose

12.2.1 Drugs used in nasal allergy

12.2.2 Topical nasal decongestants

12.2.3 Nasal preparations for infection

12.3 Drugs acting on the oropharynx

12.3.1 Drugs for oral ulceration and inflammation

12.3.2 Oropharyngeal anti-infective drugs

12.3.3 Lozenges and sprays

12.3.4 Mouthwashes and gargles

12.3.5 Treatment of dry mouth

This chapter also includes advice on the drug management of the following:
- allergic rhinitis, p. 648
- nasal polyps, p. 648
- oropharyngeal infections, p. 657
- periodontitis, p. 655

12.1 Drugs acting on the ear

12.1.1 Otitis externa

Otitis externa is an inflammatory reaction of the lining of the ear canal usually associated with an underlying seborrhoeic dermatitis or eczema; 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.

Secondary infection in otitis externa may be of bacterial, fungal, or viral origin. 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 because excessive use may result in fungal infections that are difficult to treat. 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 children when infection is present with inflammation and eczema. Clotrimazole 1% solution is used topically to treat fungal infection in otitis externa.

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 children 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 and may be used to treat mild otitis externa. More severe cases require treatment with an anti-inflammatory preparation with or without an anti-infective drug. A proprietary preparation containing acetic acid 2% (EarCalm® spray) is on sale to the public for children over 12 years.

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 child is systemically unwell. When a resistant staphylococcal infection (a boil) is present in the external auditory canal, oral flucloxacillin (section 5.1.1.2) is the drug of choice; oral ciprofloxacin (section 5.1.12) or a systemic aminoglycoside may be needed for pseudomonal infections, particularly in children with diabetes or compromised immunity.

The skin of the pinna adjacent to the ear canal is often affected by eczema. A topical corticosteroid (section 13.4) cream or ointment is then required, but prolonged use should be avoided.

**Administration**  To administer ear drops, lay the child down with the head turned to one side; for an infant pull the earlobe back and down, for an older child pull the earlobe back and up.

### Astringent preparations

**ALUMINIUM ACETATE**

**Licensed use**  not licensed

**Indication and dose**

**Inflammation in otitis externa** (see notes above)

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 as manufactured special

**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

Cautions  see notes above  
Contra-indications  see notes above  
Side-effects  see notes above  
Licensed use  licensed for use in children (age range not specified by manufacturers)

Indication and dose  
Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

Eye  section 11.4.1

Nose  section 12.2.1 and section 12.2.3

Betnesol® (UCB Pharma)  (TM)  
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, instil 2–3 drops every 2–3 hours; reduce frequency when relief obtained

With antibacterial
Betnesol-N® (UCB Pharma)  (TM)  
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  Ear, instil 2–3 drops every 3–4 hours; reduce frequency when relief obtained

Vistamethasone® (Martindale)  (TM)  
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, instil 2–3 drops every 3–4 hours; reduce frequency when relief obtained

With antibacterial
Vistamethasone N® (Martindale)  (TM)  
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  Ear, instil 2–3 drops every 3–4 hours; reduce frequency when relief obtained

DEXAMETHASONE

Cautions  see notes above  
Contra-indications  see notes above  
Side-effects  see notes above  
Licensed use  licensed for use in children (age range not specified by manufacturers)

Indication and dose  
Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

With antibacterial
Otomize® (GSK Consumer Healthcare)  (TM)  
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 hydroxybenzoates (parabens)

Dose  Ear, apply 1 metered spray 3 times daily

Sofradex® (Sanofi-Aventis)  (TM)  
Drops (for ear or eye), dexamethasone (as sodium metasulphobenzoate) 0.05%, framycetin sulphate 0.5%, gramicidin 0.005%. Net price 10 mL = £5.21  
Excipients include polysorbate 80

Dose  Ear, instil 2–3 drops 3–4 times daily; eye, section 11.4.1

HYDROCORTISONE

Cautions  see notes above  
Contra-indications  see notes above  
Side-effects  see notes above  
Licensed use  Otosporin® not licensed for use in children under 3 years; other preparations licensed for use in children (age range not specified by manufacturers)

Indication and dose  
Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

Licenced use  licensed for use in children (age range not specified by manufacturers)

With antibacterial
Locorten-Vioform® (Amidpharm)  (TM)  
Ear drops, flumetasone pivalate 0.02%, clioquinol 1%. Net price 7.5 mL = £1.47  
Contra-indications  iodine sensitivity

Dose  Child 2–18 years instil 2–3 drops into the ear twice daily for 7–10 days

Note  Clioquinol stains skin and clothing

FLUMETASONE PIVALATE
(Flatmethasone Pivalate)

Cautions  see notes above  
Contra-indications  see notes above  
Side-effects  see notes above  
Licensed use  licensed for use in children (age range not specified by manufacturers)

Indication and dose  
Eczematous inflammation in otitis externa (see notes above); for dose, see under preparations

With antibacterial
Locorten-Vioform® (Amidpharm)  (TM)  
Ear drops, flumetasone pivalate 0.02%, clioquinol 1%. Net price 7.5 mL = £1.47  
Contra-indications  iodine sensitivity

Dose  Child 2–18 years instil 2–3 drops into the ear twice daily for 7–10 days

Note  Clioquinol stains skin and clothing

HYDROCORTISONE

Cautions  see notes above  
Contra-indications  see notes above  
Side-effects  see notes above  
Licensed use  Otosporin® not licensed for use in children under 3 years; other preparations licensed for use in children (age range not specified by manufacturers)
### PREDNISOLONE SODIUM PHOSPHATE

**Cautions** see notes above  
**Contra-indications** see notes above  
**Side-effects** see notes above  
**Licensed use** licensed for use in children (age range not specified by manufacturers)  

**Indication and dose**  
**Eczematous inflammation in otitis externa** (see notes above); for dose, see under preparations

<table>
<thead>
<tr>
<th>Ear drop preparation</th>
<th>Description</th>
<th>Price 5 mL</th>
<th>Price 10 mL</th>
<th>Excipients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predsol® (UCB Pharma)</td>
<td>Prednisolone sodium phosphate 0.5%</td>
<td>£1.83</td>
<td>£3.66</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–3 drops every 2–3 hours; reduce frequency when relief obtained</td>
</tr>
<tr>
<td>Predsol-N® (UCB Pharma)</td>
<td>Prednisolone sodium phosphate 0.5%, neomycin sulphate 0.5%</td>
<td>£1.99</td>
<td>£3.98</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–3 drops 3–4 times daily</td>
</tr>
</tbody>
</table>

### Anti-infective preparations

### CHLORAMPHENICOL

**Cautions** avoid prolonged use (see notes above)  
**Side-effects** high incidence of sensitivity reactions to vehicle  
**Licensed use** licensed for use in children (age range not specified by manufacturers)  

**Indication and dose**  
**Bacterial infection in otitis externa** (but see notes above); for dose, see under preparations

<table>
<thead>
<tr>
<th>Ear drop preparation</th>
<th>Description</th>
<th>Price 5 mL</th>
<th>Price 10 mL</th>
<th>Excipients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol (Non-proprietary)</td>
<td>Chloramphenicol in propylene glycol</td>
<td>£1.83</td>
<td>£5.64</td>
<td>Propylene glycol</td>
<td>Ear, instil 2–3 drops 2–3 times daily</td>
</tr>
</tbody>
</table>

### CLOTRIMAZOLE

**Side-effects** occasional local irritation or sensitivity  
**Licensed use** licensed for use in children (age range not specified by manufacturer)  

**Indication and dose**  
**Fungal infection in otitis externa** (see notes above); for dose, see under preparation

<table>
<thead>
<tr>
<th>Solution preparation</th>
<th>Description</th>
<th>Price 20 mL</th>
<th>Excipients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Canesten® (Bayer Consumer Care)</td>
<td>Clotrimazole 1% in polyethylene glycol 400 (macrogol 400)</td>
<td>£2.43</td>
<td>Propylene glycol</td>
<td>Ear, apply 2–3 times daily continuing for at least 14 days after disappearance of infection</td>
</tr>
</tbody>
</table>

### FRAMYCETIN SULPHATE

**Side-effects** local sensitivity  
**Contra-indications** perforated tympanic membrane (see p. 643)  

<table>
<thead>
<tr>
<th>Solution preparation</th>
<th>Description</th>
<th>Price 20 mL</th>
<th>Excipients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otosporin® (GSK)</td>
<td>Gentisone HC (Amdipharm) Ear drops, hydrocortisone acetate 1%, gentamicin 0.3% (as sulphate)</td>
<td>£3.69</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Child 3–18 years instil 3 drops into the ear 3–4 times daily</td>
</tr>
</tbody>
</table>

**With antibacterial**

<table>
<thead>
<tr>
<th>Ear drop preparation</th>
<th>Description</th>
<th>Price 5 mL</th>
<th>Price 10 mL</th>
<th>Excipients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentisone® HC (Amdipharm)</td>
<td>Gentisone HC Ear drops, hydrocortisone acetate 1%, gentamicin 0.3% (as sulphate)</td>
<td>£3.69</td>
<td>£7.38</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–4 drops 3–4 times daily and at night</td>
</tr>
<tr>
<td>Predsol-N® (UCB Pharma)</td>
<td>Prednisolone sodium phosphate 0.5%, neomycin sulphate 0.5%</td>
<td>£2.00</td>
<td>£4.00</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–3 drops 3–4 times daily</td>
</tr>
</tbody>
</table>

**With antibacterial**

<table>
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<tr>
<th>Ear drop preparation</th>
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<td>Prednisolone sodium phosphate 0.5%, neomycin sulphate 0.5%</td>
<td>£2.00</td>
<td>£4.00</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–3 drops 3–4 times daily</td>
</tr>
</tbody>
</table>

### Hydrocortisone

**Cautions** see notes above  
**Contra-indications** see notes above  
**Side-effects** see notes above  

**Licensed use** licensed for use in children (age range not specified by manufacturers)  

**Indication and dose**  
**Eczematous inflammation in otitis externa** (see notes above); for dose, see under preparations

<table>
<thead>
<tr>
<th>Ear drop preparation</th>
<th>Description</th>
<th>Price 5 mL</th>
<th>Price 10 mL</th>
<th>Excipients</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentisone® HC (Amdipharm)</td>
<td>Gentisone HC Ear drops, hydrocortisone acetate 1%, gentamicin 0.3% (as sulphate)</td>
<td>£3.69</td>
<td>£7.38</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–4 drops 3–4 times daily and at night</td>
</tr>
<tr>
<td>Predsol-N® (UCB Pharma)</td>
<td>Prednisolone sodium phosphate 0.5%, neomycin sulphate 0.5%</td>
<td>£2.00</td>
<td>£4.00</td>
<td>Benzalkonium chloride, disodium edetate</td>
<td>Ear, instil 2–3 drops 3–4 times daily</td>
</tr>
</tbody>
</table>
12.1.2 Otitis media

Acute otitis media

Acute otitis media is the commonest cause of severe aural pain in young children and may occur with even minor upper respiratory tract infections. Children diagnosed with acute otitis media should not be prescribed antibacterials routinely as 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 (Table 1, section 5.1) may be started after 72 hours if there is no improvement, or earlier if there is deterioration, if the child is systemically unwell, if the child is at high risk of serious complications (e.g. in immunosuppression, cystic fibrosis), if mastoiditis is present, or in children under 2 years of age with bilateral otitis media. Perforation of the tympanic membrane in children 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. Topical antibacterial treatment of acute otitis media is ineffective and there is no place for ear drops containing a local anaesthetic.

Otitis media with effusion

Otitis media with effusion (‘glue ear’) occurs in about 10% of children and in 90% of children with cleft palates. Antimicrobials, corticosteroids, decongestants, and antihistamines have little place in the routine management of otitis media with effusion. 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 children with chronic otitis media. The mainstay of treatment is thorough cleansing with aural microsuction, which may completely resolve long-standing infection. Cleansing may be followed by topical treatment as for otitis externa (section 12.1.1); this is particularly beneficial for discharging ears or infections of the mastoid cavity. Acute exacerbations of chronic infection may require treatment with an oral antibacterial (Table 1, section 5.1); a swab should be taken to identify infecting organisms and antibacterial sensitivity. Parenteral antibacterial treatment is required if *Pseudomonas aeruginosa* or *Proteus* spp. are present.

The CSM has stated that topical treatment with ototoxic antibacterials is contraindicated 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 (available from specialist importing companies) 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.

**Removal of ear wax**

Ear wax (cerumen) is a normal bodily secretion which provides a protective film on the meatal skin and need only be removed if it causes hearing loss or interferes with a proper view of the ear drum. Irrigation of the ear canal is generally best avoided in young children and in children with a history of recurrent otitis externa, a history of ear-drum perforation, previous ear surgery, or unilateral deafness.

Ear wax causing discomfort or impaired hearing may be softened with 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 or cleansing with aural microsuction. The child 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. 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.

For administration of ear drops, see p. 643.

**12.1.3 Removal of 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® (Thornton & Ross)

**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

### Molcer® (Wallace Mfg)

**Ear drops**, docusate sodium 5%. Net price 15 mL = £1.90  
Excipients include propylene glycol

### Otex® (DDD)

**Ear drops**, urea–hydrogen peroxide 5%. Net price 8 mL = £2.64

### Waxsol® (Norgine)

**Ear drops**, docusate sodium 0.5%. Net price 10 mL = £1.26

### 12.2 Drugs acting on the nose

#### 12.2.1 Drugs used in nasal allergy

#### 12.2.2 Topical nasal decongestants

#### 12.2.3 Nasal preparations for infection

Rhinitis is often self-limiting but bacterial sinusitis may require treatment with antibacterials (Table 1, section 5.1). Many nasal preparations contain sympatho-
mimetic drugs (section 12.2.2) which can give rise to rebound congestion (*rhinitis medicamentosa*) and may damage the nasal cilia. **Sodium chloride 0.9% solution may be used as a douche or ‘sniff’ following endonasal surgery.**

**Administration** To administer nasal drops, lay the child face-upward with the neck extended, instil the drops, then sit the child up and tilt the head forward.

**Nasal polyps** Short-term use of corticosteroid nasal drops helps to shrink nasal polyps; to be effective, the drops must be administered with the child in the ‘head down’ position. A short course of a systemic corticosteroid (section 6.3.2) may be required initially to shrink large polyps. A corticosteroid nasal spray can be used to maintain the reduction in swelling and also for the initial treatment of small polyps.

### 12.2.1 Drugs used in nasal allergy

Mild allergic rhinitis is controlled by **antihistamines** (see also section 3.4.1) or topical **nasal corticosteroids**; systemic nasal decongestants (section 3.10) are not recommended for use in children. Topical nasal decongestants can be used for a short period to relieve congestion and allow penetration of a topical nasal corticosteroid.

More persistent symptoms can be relieved by topical nasal **corticosteroids** or **cromoglicate**; the topical antihistamine, **azelastine**, is useful for controlling breakthrough symptoms in allergic rhinitis. Azelastine is less effective than nasal corticosteroids, but probably more effective than sodium cromoglicate. In seasonal allergic rhinitis (e.g. hay fever), treatment should begin 2 to 3 weeks before the season commences and may have to be continued for several months; continuous long-term treatment may be required in perennial rhinitis.

**Monteleukast** (section 3.3.2) can be used in children with seasonal allergic rhinitis (unresponsive to other treatments) and concomitant asthma; monteleukast is less effective than topical nasal corticosteroids.

Children with disabling symptoms of seasonal rhinitis (e.g. students taking important examinations), may be treated with oral **corticosteroids** (section 6.3.2) for short periods. Oral corticosteroids 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 mucosa.

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 rhinorrhoea.

**Pregnancy** If a pregnant woman cannot tolerate the symptoms of allergic rhinitis, treatment with nasal beclometasone, budesonide, fluticasone propionate, or sodium cromoglicate may be considered.

### Antihistamines

#### AZELASTINE HYDROCHLORIDE

**Side-effects** irritation of nasal mucosa; bitter taste (if applied incorrectly)

**Indication and dose**

**Treatment of allergic rhinitis** for dose, see under preparation

**Rhinolast®** (Viatris)  
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**

**Child 5–18 years** apply 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) for the treatment of seasonal allergic rhinitis or perennial allergic rhinitis in 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 have a useful role in the prophylaxis and treatment of allergic rhinitis (see notes above). Preparations containing budesonide, fluticasone propionate, mometasone, or triamcinolone are preferred in children.

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. 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, and epistaxis. Nasal ulceration has been reported, and occurs commonly with nasal preparations containing fluticasone furoate or mometasone furoate. Nasal septal perforation (usually following nasal surgery) occurs very rarely. Raised intra-ocular pressure or glaucoma may occur rarely. Headache, smell and taste disturbances may also occur. Hypersensitivity reactions, including bronchospasm, have been reported.

BECLOMETASONE DIPROPIONATE

(Beclomethasone Dipropionate)

Cautions  see notes above

Side-effects  see notes above

Indication and dose

Prophylaxis and treatment of allergic and vasomotor rhinitis

Child 6–18 years  apply 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 NasoBec Aqueous®

Beconase®  (A&H)  
Nasal spray (aqueous suspension), beclometasone dipropionate 50 micrograms/metered spray. Net price 200-spray unit with applicator = £2.19
Excipients include benzalkonium chloride, polysorbate 80

BETAMETHASONE SODIUM PHOSPHATE

Cautions  see notes above

Side-effects  see notes above

Licensed use  licensed for use in children (age range not specified by manufacturer)

Indication and dose

Non-infected inflammatory conditions of nose for dose, see under preparations

Eye  section 11.4.1

Ear  section 12.1.1

Betnesol®  (UCB Pharma)  
Drops (for ear, eye, or nose), betamethasone sodium phosphate 0.1%, net price 10 mL = £2.32
Excipients include benzalkonium chloride, disodium edetate

Dose

Nose, instil 2–3 drops into each nostril 2–3 times daily

Vistamethasone®  (Martindale)  
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

Nose, instil 2–3 drops into each nostril twice daily

BUDESONIDE

Cautions  see notes above; interactions: Appendix 1 (corticosteroids)

Side-effects  see notes above

Indication and dose

See under preparations
**Budesonide (continued)**

**Budesonide** (Non-proprietary)  
Nasal spray, budesonide 100 micrograms/metered spray, net price 100-spray unit = £5.66

**Dose**

- **Prophylaxis and treatment of allergic and vasomotor rhinitis**
  - **Child 12–18 years** apply 200 micrograms (2 sprays) into each nostril once daily in the morning or 100 micrograms (1 spray) into each nostril twice daily; when control achieved reduce to 100 micrograms (1 spray) into each nostril once daily

**Nasal polyps**

- **Child 12–18 years** apply 100 micrograms (1 spray) into each nostril twice daily for up to 3 months

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**FLUNISOLIDE**

**Cautions** see notes above

**Side-effects** see notes above

**Indication and dose**

- **Prophylaxis and treatment of allergic rhinitis**
  - **Child 5–14 years** initially 25 micrograms (1 spray) into each nostril up to 3 times daily then reduced for maintenance
  - **Child 14–18 years** 50 micrograms (2 sprays) into each nostril twice daily, increased if necessary to max. 3 times daily then reduced for maintenance

**Nasal polyps** see **Flixonase Nasule** below

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**FLUTICASONE PROPIONATE**

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

**Side-effects** see notes above

**Indication and dose**

- **Prophylaxis and treatment of allergic rhinitis**
  - **Child 4–12 years** 50 micrograms (1 spray) into each nostril once daily, preferably in the morning, increased to max. twice daily if required
  - **Child 12–18 years** 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

- **Nasal polyps** see **Flixonase Nasule** below

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**Flixonase** (A&H)  
Aqueous nasal spray, fluticasone propionate 50 micrograms/metered spray. Net price 150-spray unit = £10.52

**Excipients** include benzalkonium chloride, polysorbate 80

**Dose**

- **Nasal polyps**
  - **Child 16–18 years** instil 200 micrograms (approx. 6 drops) into each nostril once or twice daily; consider alternative treatment if no improvement after 4–6 weeks

---

**Flixonase Nasule** (A&H)  
Aqueous nasal spray, fluticasone propionate 400 micrograms/unit dose, net price 28 × 0.4-mL units = £13.76

**Excipients** include polysorbate 20

**Dose**

- **Nasal polyps**
  - **Child 16–18 years** instil 200 micrograms (approx. 6 drops) into each nostril once or twice daily; consider alternative treatment if no improvement after 4–6 weeks

**Avamys** (GSK)  
Nasal spray, fluticasone furoate 27.5 micrograms/metered spray. Net price 120-spray unit = £6.44

**Excipients** include benzalkonium chloride, disodium edetate, polysorbate 80

**Dose**

- **Prophylaxis and treatment of allergic rhinitis**
  - **Child 6–12 years** 27.5 micrograms (1 spray) into each nostril once daily, increased if necessary to 55 micrograms (2 sprays) into each nostril once daily; when control achieved reduce to 27.5 micrograms (1 spray) into each nostril once daily
  - **Child 12–18 years** 55 micrograms (2 sprays) into each nostril once daily; when control achieved reduce to 27.5 micrograms (1 spray) into each nostril once daily
MOMETASONE FUROATE

Cautions  see notes above
Side-effects  see notes above

Indication and dose
See under preparation

Nasonex® (Schering-Plough)  
Nasal spray, mometasone furoate 50 micrograms/ metered spray. Net price 140-spray unit = £7.83  
Excipients include benzalkonium chloride, polysorbate 80

Dose
Prophylaxis and treatment of allergic rhinitis
Child 6–12 years  50 micrograms (1 spray) into each nostril once daily
Child 12–18 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

TRIAMCINOLONE ACetonIDE

Cautions  see notes above
Side-effects  see notes above

Indication and dose
Treatment of allergic rhinitis
Child 6–12 years  55 micrograms (1 spray) into each nostril once daily, increased if necessary to 110 micrograms (2 sprays) into each nostril once daily; when control achieved reduce to 55 micrograms (1 spray) into each nostril once daily; max. duration of treatment 3 months
Child 12–18 years  110 micrograms (2 sprays) into each nostril once daily; when control achieved, reduce to 55 micrograms (1 spray) into each nostril once daily

Nasacort® (Aventis Pharma)  
Aqueous nasal spray, triamcinolone acetonide 55 micrograms/metered spray. Net price 120-spray unit = £7.39  
Excipients include benzalkonium chloride, disodium edetate, polysorbate 80

Cromoglicate

(Sodium Cromoglycate)

Side-effects  local irritation; rarely transient bronchospasm
Licensed use  licensed for use in children (age range not specified by manufacturers)

Indication and dose
Prophylaxis of allergic rhinitis for dose, see under preparations

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
Nose, 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
Nose, 1 spray into each nostril 4–6 times daily

12.2.2 Topical nasal decongestants

Sodium chloride  0.9% given as nasal drops may relieve nasal congestion by helping to liquefy mucous secretions in children with rhinitis. In infants, 1–2 drops of sodium chloride 0.9% solution in each nostril before feeds will help relieve congestion and allow more effective suckling.

Inhalation of warm moist air is useful in the treatment of symptoms of acute nasal congestion in infants and children, but the use of boiling water for steam inhalation is dangerous for children and should not be recommended. Volatile substances (section 3.8) such as menthol and eucalyptus may encourage inhalation of warm moist air.

Topical nasal decongestants containing sympathomimetics can cause rebound congestion (rhinitis medicamentosa) following prolonged use (more than 7 days), and are therefore of limited value in the treatment of nasal congestion.

Ephedrine nasal drops is the least likely of the sympathomimetic nasal decongestants to cause rebound congestion and can provide relief for several hours. The more potent sympathomimetic drugs oxymetazoline and xylometazoline are more likely to cause a rebound effect.
The CHM/MHRA has stated that non-prescription cough and cold medicines containing ephedrine, oxymetazoline, or xylometazoline can be considered in children aged 6–12 years after basic principles of best care have been tried; these medicines should not be used in children under 6 years of age (section 3.9.1).

However, in special circumstances, some specialists prescribe nasal drops containing ephedrine or xylometazoline to children under 6 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 watery rhinorhoea often responds well to treatment with the antimuscarinic ipratropium bromide.

Recurrent, persistent bleeding may respond to the use of a sympathomimetic nasal spray; if infection is present, chlorhexidine and neomycin (Naseptin®) cream (section 12.2.3) may be effective.

Systemic nasal decongestants—see section 3.10.

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 ephedrine nasal drops (see above). For antibacterial treatment of sinusitis, see Table 1, section 5.1.

**EPHEDRINE HYDROCHLORIDE**

**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 (sympathomimetics)

**Side-effects** local irritation, nausea, headache; after excessive use tolerance with diminished effect, rebound congestion; cardiovascular effects also reported

**Licensed use** not licensed for use in children under 3 months

**Indication and dose**

**Nasal congestion** (see notes above)

Child 1–3 months (on a specialist’s advice only) instil 1–2 drops (0.25% strength) into each nostril 3–4 times daily, 15 minutes before feeds; max. duration 5 days

Child 3 months–18 years (on a specialist’s advice only for children under 6 years) instil 1–2 drops (0.5% strength) into each nostril 3–4 times daily; max. duration 5 days (7 days in child over 12 years of age)

1 Ephedrine (Non-proprietary)

Nasal drops, ephedrine hydrochloride 0.5%, net price 10 mL = £1.25; 1%, 10 mL = £1.31

**Note** Ephedrine 0.25% nasal solution is prepared by diluting ephedrine 0.5% solution with sodium chloride 0.9% solution. Discard diluted solution after 1 week. The BP directs that if no strength is specified 0.5% drops should be supplied

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 details see Medicines, Ethics and Practice, No. 32, London, Pharmaceutical Press, 2008 (and subsequent editions as available)

**XYLOMETAZOLINE HYDROCHLORIDE**

**Cautions** see under Ephedrine Hydrochloride and notes above

**Side-effects** see under Ephedrine Hydrochloride and notes above

**Indication and dose**

**Nasal congestion** for dose, see under preparations

Xylometazoline (Non-proprietary)

**Nasal drops,** xylometazoline hydrochloride 0.1%, net price 10 mL = £1.91

**Dose**

Child 12–18 years instil 2–3 drops into each nostril 2–3 times daily when required; max. duration 7 days

Brands include Otracold®.

**Nasal spray,** xylometazoline hydrochloride 0.1%, net price 10 mL = £1.91

**Dose**

Child 12–18 years apply 1 spray into each nostril 2–3 times daily when required; max. duration 7 days

Brands include Otraspray®.
**Antimuscarinic**

**IPRATROPIUM BROMIDE**

**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

**Indication and dose**

| Child 12–18 years | apply 42 micrograms (2 sprays) into each nostril 2–3 times daily
| Asthma and reversible airways obstruction | section 3.1.2
| 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

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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. Acute complications such as periorbital cellulitis require hospital treatment. For 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, instil 2–3 drops into each nostril 2–3 times daily

**Note** Betnesol-N® licensed for use in children (age range not specified by manufacturer)

**Vistamethasone N®** (Martindale)

**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, instil 2–3 drops into each nostril twice daily

**Note** Vistamethasone N® licensed for use in children (age range not specified by manufacturer)

**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 infections. In hospitals or in care establishments, mupirocin nasal ointment should be reserved for the eradication (in both patients and staff) of nasal carriage of meticillin-resistant Staphylococcus aureus (MRSA). The ointment should be applied 3 times daily for 5 days and a sample taken 2 days after treatment to confirm eradication. The course may be repeated if the sample is positive (and the throat is not colonised). To avoid the development of resistance, the treatment course should not exceed 7 days and the course should not be repeated on more than one occasion. If the MRSA strain is mupirocin-resistant or does not respond after 2 courses, consider alternative products such as chlorhexidine and neomycin cream. For eradication of MRSA also consult local infection control policy. See section 13.10.1 for treatment of MRSA-infected open wounds. See section 5.1.1.2 for treatment of children with MRSA-positive throat swabs or systemic MRSA infection.

**Bactroban Nasal®** (GSK)

**Nasal ointment**, mupirocin 2% (as calcium salt) in white soft paraffin basis. Net price 3 g = £5.80

**Dose**

For eradication of nasal carriage of staphylococci, including meticillin-resistant *Staphylococcus aureus* (MRSA)

Apply 2–3 times daily to the inner surface of each nostril (see notes above)

**Naseptin®** (Alliance)

**Cream**, chlorhexidine hydrochloride 0.1%, neomycin sulphate 0.5%, net price 15 g = £1.58

**Excipients** include arachis (peanut) oil, cetostearyl alcohol

**Dose**

For eradication of nasal carriage of staphylococci

Apply to nostrils 4 times daily for 10 days

For preventing nasal carriage of staphylococci

Apply to nostrils twice daily
Drugs acting on the oropharynx

12.3 Drugs for oral ulceration and inflammation
12.3.1 Drugs for oral ulceration and inflammation
12.3.2 Oropharyngeal anti-infective drugs
12.3.3 Lozenges and sprays
12.3.4 Mouthwashes and gargles
12.3.5 Treatment of dry mouth

Ulceration of the oral mucosa may be caused by trauma (physical or chemical), recurrent aphthous ulcers, infections, carcinoma, dermatological disorders, nutritional deficiencies, gastro-intestinal disease, haematopoietic disorders, and drug therapy. 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. Children with an unexplained mouth ulcer of more than 3 weeks’ duration require urgent referral to hospital to exclude secondary causes such as leukaemia.

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 aphthous ulcers.

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 effectively to the tongue and oropharynx.

Corticosteroids  Topical corticosteroid therapy may be used for some forms of oral ulceration; for 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 useful in recurrent aphthous ulcers and erosive lichenoid lesions.

Triamcinolone dental paste is formulated 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 effectively to the tongue and oropharynx.

Beclometasone dipropionate inhaler (p. 185) 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.

Systemic corticosteroid therapy (section 6.3.2) is reserved for severe conditions such as pemphigus vulgaris.

Local analgesics  Local analgesics have a limited role in the management of oral ulceration. When applied topically their action is of a relatively short duration and analgesia cannot be maintained continuously throughout the day. 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 tonsillectomy and post-irradiation mucositis. Some children 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 in adolescents.

Choline salicylate dental gel has some analgesic action and may provide relief for recurrent aphthous ulcers in children over 16 years of age.
**Periodontitis**  Low-dose doxycycline (*Periostat®*) is licensed as an adjunct to scaling and root planing for the treatment of periodontitis in children over 12 years; 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.

**BENZYDAMINE HYDROCHLORIDE**

**Side-effects**  occasional numbness or stinging; rarely hypersensitivity reactions

**Licensed use** *Difflam® Spray* licensed for use in children (age range not specified by manufacturer)

**Indication and dose**  Painful inflammatory conditions of oropharynx for dose, see under preparations

*Difflam®* (3M)

**Oral rinse**, green, benzydamine hydrochloride 0.15%, net price 200 mL (*Difflam® Sore Throat Rinse*) = £2.63; 300 mL = £4.01

**Dose**

- **Child 12–18 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%

**CARMELLOSE SODIUM**

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**  Mechanical protection of oral and perioral lesions for dose, see under preparation

*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 = £4.48

**Dose**

- **Apply a thin layer when necessary after meals**

**Dental prescribing on NHS** May be prescribed as Carmellose Gelatin Paste

**CORTICOSTEROIDS**

**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

**Licensed use** *Adcortyl in Orabase®* licensed for use in children (age range not specified by manufacturer); *Corlan® Pellets* licensed for use in children (under 12 years—on medical advice only)

**Indication and dose**  Oral and perioral lesions for dose, see under preparations

*Adcortyl in Orabase®* (Squibb)

**Oral paste**, triamcinolone acetonide 0.1% in adhesive basis. Net price 10 g = £1.18

**Dose**

- **Apply a thin layer 2–4 times daily for max. 5 days; do not rub in**

**Dental prescribing on NHS** May be prescribed as Triamcinolone Dental Paste

*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

**Dose**

- **Oral ulceration**
  - **Child 12–18 years** 500 micrograms dissolved in 20 mL water and rinsed around the mouth 4 times daily; not to be swallowed

**Dental prescribing on NHS** May be prescribed as Betamethasone Soluble Tablets 500 micrograms
**CORTICOSTEROIDS (continued)**

**Corlan** (UCB Pharma)

Pellets (= oromucosal tablets), hydrocortisone 2.5 mg (as sodium succinate). Net price 20 = £2.54

**Dose**

1 lozenge 4 times daily, allowed to dissolve slowly in the mouth in contact with the ulcer

**Dental prescribing on NHS** May be prescribed as Hydrocortisone Oromucosal Tablets

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**DOXYCYCLINE**

**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

**Indication and dose**

See under preparations

**Oral herpes** section 12.3.2

**Other indications** section 5.1.3

**Periostat** (Alliance)

Tablets, 1/2, 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)

Child 12–18 years 20 mg twice daily for 3 months

**Counselling**

Tablets should be swallowed whole with plenty of fluid, while sitting or standing

**Dental prescribing on NHS** May be prescribed as Doxycycline Tablets 20 mg

**Local application**

For severe 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].

**Note**

Doxycycline stains teeth; avoid in children under 12 years of age

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**FLURBIPROFEN**

**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

**Indication and dose**

Relief of sore throat for dose, see under preparation

**Strefen** (Crookes)

Lozenges, flurbiprofen 8.75 mg, net price 16 = £2.24

**Dose**

Child 12–18 years allow 1 lozenge to dissolve slowly in the mouth every 3–6 hours, max. 5 lozenges in 24 hours, for max. 3 days

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**SALICYLATES**

**Cautions** frequent application, especially in children, may give rise to salicylate poisoning

**Contra-indications** children under 16 years

**Reyes syndrome** The CHM has advised (April 2009) that topical oral pain relief products containing salicylate salts should not be used in children under 16 years, as a cautionary measure due to the theoretical risk of Reyes syndrome

**Indication and dose**

Mild oral and perioral lesions for dose, see under preparations

**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 *Bonjela* (sugar-free)

**Dose**

Child 16–18 years apply ½-inch of gel with gentle massage not more often than every 3 hours

**Dental prescribing on NHS** Choline Salicylate Dental Gel may be prescribed

**Salicylic acid**

**Pyraval** (Norgine)

**Oral paint** brown, rhubarb extract (anthraquinone glycosides 0.5%), salicylic acid 1%. Net price 10 mL with brush = £3.38

**Dose**

Child 16–18 years apply 3–4 times daily

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12.3.1 Drugs for oral ulceration and inflammation BNFC 2009
### 12.3.2 Oropharyngeal anti-infective drugs

Sore throat is usually a self-limiting condition often caused by viral infection which does not benefit from anti-infective treatment. Adequate analgesia may be all that is required. Systemic antibacterials (Table 1, section 5.1) should only be used in severe cases where there is concern for the child’s overall clinical condition. Acute ulcerative gingivitis (Vincent’s infection) requires treatment with oral metronidazole (section 5.1.11).

*Benzydamine* (section 12.3.1) may be beneficial in relieving pain and dysphagia in children, especially after tonsillectomy or the use of a nasogastric tube.

### Oropharyngeal viral infections

Children with varicella–zoster infection often develop painful lesions in the mouth and throat. *Benzydamine* (section 12.3.1) may be used to provide local analgesia. *Chlorhexidine* mouthwash or gel (section 12.3.4) will control plaque accumulation if toothbrushing is painful and will also help to control secondary infection in general.

In severe herpetic stomatitis systemic *aciclovir* or *valaciclovir* (section 5.3.2.1) may be used for oral lesions associated with herpes zoster. Aciclovir and valaciclovir are also used to prevent frequently recurring herpes simplex lesions of the mouth particularly when associated with the initiation of erythema multiforme. For the treatment of labial herpes simplex infections, see section 13.10.3.

Herpes infections of the mouth in children aged over 12 years may also respond to rinsing the mouth with *doxycycline* (section 12.3.1).

### 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 (thrush), is usually an acute infection but it may persist for months in patients receiving inhaled corticosteroids, cytotoxics, or broad-spectrum antibacterials. Thrusl also occurs in patients with serious systemic disease associated with reduced immunity such as leukaeamia, 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. Topical therapy may not be adequate in immunocompromised children 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).

**Angular cheilitis**

Angular cheilitis (angular stomatitis) is characterised by soreness, erythema and fissuring at the angles of the mouth. It may represent a nutritional deficiency or it may be related to oro-facial granulomatosis or HIV infection. Both yeasts (*Candida* spp.) and bacteria (*Staphylococcus aureus* and beta-haemolytic streptococci) are commonly involved as interacting, infective factors. While the underlying cause is being identified and treated, it is often helpful to apply *miconazole* and *hydrocortisone* cream or ointment (see p. 674), *miconazole* cream (see p. 711), or *sodium fusidate* ointment (p. 709).

**Immunocompromised patients**

For advice on prevention of fungal infections in immunocompromised children see p. 362.

For the role of antiseptic mouthwashes in the prevention of oral candidiasis in immunocompromised children, see section 12.3.4.

**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 used by local application (as an oral gel) in the mouth but it is also absorbed to the extent that potential interactions need to be considered. Miconazole also has
some activity against Gram-positive bacteria including streptococci and staphylococci. In neonates, nystatin oral suspension or miconazole oral gel is used for the treatment of oropharyngeal candidiasis; to prevent re-infection it is important to ensure that the mother’s breast nipples and the teats of feeding bottles are cleaned adequately.

**Fluconazole** (section 5.2) given by mouth is reliably absorbed; it is used for infections that do not respond to topical therapy or when topical therapy cannot be used. **Itraconazole** (section 5.2) can be used for fluconazole-resistant infections.

If candidal infection fails to respond after 1 to 2 weeks of treatment with antifungal drugs the child should be sent for investigation to eliminate the possibility of underlying disease. Persistent infection may also be caused by re-infection from the genito-urinary or gastro-intestinal tract.

### AMPHOTERICIN

**Side-effects** mild gastro-intestinal disturbances reported

**Licensed use** lozenges not licensed for use in children

**Indication and dose**

- Oral and perioral fungal infections for doses, see under preparations

- **Fungilin®** (Squibb) [www]
  - Lozenges, yellow, amphotericin 10 mg. Net price 60-lozenge pack = £3.67. Label: 9, 24, counselling, after food

  **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

**Cautions** avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (antifungals, imidazole)

**Pregnancy** manufacturer advises avoid if possible—毒性 at high doses in animal studies

**Breast-feeding** manufacturer advises caution—no information available

**Contra-indications** impaired swallowing reflex

**Hepatic impairment** avoid

**Side-effects** nausea and vomiting, very rarely diarrhoea (usually on long-term treatment), hepatitis, rash, toxic epidermal necrolysis, and Stevens-Johnson syndrome

**Licensed use** not licensed for use in children under 4 months of age or during first 5–6 months of life of an infant born pre-term

**Indication and dose**

- Prevention and treatment of oral and intestinal fungal infections
  - **By mouth**
  - **Neonate** (oral fungal infections only) 1 mL 2–4 times daily smeared around the mouth after feeds
  - **Child 1 month–2 years** 2.5 mL twice daily smeared around the mouth after food
  - **Child 2–6 years** 5 mL twice daily after food; retain near lesions before swallowing
  - **Child 6–12 years** 5 mL 4 times daily after food; retain near lesions before swallowing
  - **Child 12–18 years** 5–10 mL 4 times daily after food; retain near lesions before swallowing

  **Note** Treatment should be continued for 48 hours after lesions have healed

**Localised lesions**

- **Child 6–18 years** smear small amount on affected area with clean finger 4 times daily for 5–7 days (orthodontic appliances should be removed at night and brushed with gel); continue treatment for 48 hours after lesions have healed

- **Daktarin®** (Janssen-Cilag) [www]
  - Oral gel, sugar-free, orange-flavoured, miconazole 24 mg/mL (20 mg/g). Net price 15-g tube = £2.45, 80-g tube = £4.65. Label: 9, counselling, hold in mouth, after food

  **Dental prescribing on NHS** May be prescribed as Miconazole Oromucosal Gel

  1 15-g tube can be sold to the public

### NYSTATIN

**Side-effects** oral irritation and sensitisation, nausea reported; see also section 5.2

**Licensed use** suspension not licensed for use in neonates for the treatment of candidiasis
**Indication and dose**

**Oral and perioral fungal infections**

- **Neonate**: 100,000 units 4 times daily after feeds
- **Child 1 month–18 years**: 100,000 units 4 times daily after food

**Note** Treatment is usually given for 7 days, and continued for 48 hours after lesions have healed.

**Intestinal fungal infections** section 5.2

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**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 preparations also contain local anaesthetics which relieve pain but may cause sensitisation.

**12.3.4 Mouthwashes and gargles**

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. Mouthwashes may not be suitable for children under 7 years (risk of the solution being swallowed); the mouthwash or dental gel may be applied using a cotton bud.

A warm saline mouthwash is ideal for its cleansing effect 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** containing thymol 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). Hydrogen peroxide solution has also a mechanical cleansing effect arising from frothing when in contact with oral debris, but in concentrations greater than 1.5% may cause ulceration and tissue damage.

**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 preparations are of little value in the control of acute necrotising ulcerative gingivitis. With prolonged use, chlorhexidine causes reversible brown staining of teeth and tongue. Chlorhexidine may be incompatible with some ingredients in toothpaste, causing an unpleasant taste in the mouth; allow at least 30 minutes between using the mouthwash and toothpaste.

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 child has a haemorrhagic disorder, or is disabled. Chlorhexidine mouthwash is 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 children undergoing dental procedures.

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**CHLORHEXIDINE GLUCONATE**

**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 GLUCONATE (continued)

Licensed use licensed for use in children (age range not specified by manufacturer)

Indication and dose
See under preparations below

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 apthous ulcers
Rinse mouth with 10 mL for about 1 minute twice daily
Dental prescribing on NHS Chlorhexidine Mouthwash may be prescribed

Chlorohex® (Colgate-Palmolive)
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

Corsodyl® (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
Oral candidiasis and management of apthous ulcers
Apply to affected areas once or twice daily
Dental prescribing on NHS May be prescribed as Chlorhexidine Gluconate Gel 1%

HEXETIDINE

Side-effects local irritation; very rarely taste disturbance and transient anaesthesia

Indication and dose
Oral hygiene for dose, see preparation below

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
Child 6–18 years use 15 mL (undiluted) 2–3 times daily

HYDROGEN PEROXIDE

Side-effects hypertrophy of papillae of tongue on prolonged use

Indication and dose
Oral hygiene (see notes above); for dose, see under preparations

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 (see notes above)
Dental prescribing on NHS Hydrogen Peroxide Mouthwash may be prescribed

Oral hygiene and plaque inhibition, oral candidiasis, gingivitis, and management of apthous ulcers
Rinse mouth with 10 mL for about 1 minute 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 apthous 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

Peroxyl® (Colgate-Palmolive)
Mouthwash, hydrogen peroxide 1.5%, net price 300 mL = £2.95

Dose
Child 6–18 years, rinse the mouth with 10 mL for about 1 minute 3 times daily (after meals and at bedtime) for max. 7 days
SODIUM CHLORIDE

Indication and dose

Oral hygiene (see notes above); for dose, see under preparation

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

Indication and dose

Oral hygiene (see notes above); for dose, see under preparation

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. Net price 100-tab pack = £14.12

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 and sedating antihistamines), by irradiation of the head and neck region or by damage to or disease of the salivary glands. Children with a persistently dry mouth may develop a burning or scalded sensation and have poor oral hygiene; they may develop dental caries, periodontal disease, 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 salivation 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.

Local treatment

Artificial saliva products with ACBS approval may be prescribed for children with dry mouth as a result of having (or having undergone) radiotherapy, or sicca syndrome. SST tablets and Salinum® liquid may also be prescribed on the NHS.

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) 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 45-lozenge pack = £3.50

Note

AS Saliva Orthana® lozenges do not contain fluoride

Dental prescribing on NHS AS Saliva Orthana® Oral Spray and Lozenges may be prescribed

Biote`ne 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) apply to gums and tongue as required

Note

Avoid use with toothpastes containing detergents (including foaming agents)

Dental prescribing on NHS Biote`ne Oralbalance® Saliva Replacement Gel may be prescribed
BioXtra® (RIS Products)
Gel, lactoperoxidase, lactoferrin, lysozyme, whey colostrum, xylitol and other ingredients, net price 40-mL tube = £3.94, 50-mL spray = £3.94

Dose
(ACBS) 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) spray onto oral and pharyngeal mucosa as required
Dental prescribing on NHS Glandosane® Aerosol Spray may be prescribed

Luborant® (Goldshield)
Oral spray, pink, 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 micromg/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

Salivix® (KoGEN)
Pastilles, sugar-free, reddish-amber, acacia, malic acid and other ingredients. Net price 50-pastille pack = £3.50

Dose
(ACBS) suck 1 pastille when required
Dental prescribing on NHS Salivix® Pastilles may be prescribed

SSS (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
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 Barrier preparations

13.3 Topical 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 camouflagers

13.8.1 Sunscreen preparations

13.8.2 Camouflagers

13.9 Shampoos and other preparations for scalp conditions

13.10 Anti-infective skin preparations

13.10.1 Antibacterial preparations

13.10.2 Antifungal preparations

13.10.3 Antiviral preparations

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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 management of the following:
- candidiasis, p. 711
- dermatophytoses, p. 710
- head lice, p. 716
- nappy rash, p. 670
- pityriasis versicolor, p. 711
- scabies, p. 715

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

When prescribing topical preparations for the treatment of skin conditions in children, the site of application, the condition being treated, and the child’s (and carer’s) preference for a particular vehicle all need to be taken into consideration.

**Neonates**  Caution is required when prescribing topical preparations for neonates—their large body surface area in relation to body mass increases susceptibility to toxicity from systemic absorption of substances applied to the skin. Topical preparations containing potentially sensitising substances such as corticosteroids, aminoglycosides, iodine, and parasiticidal drugs should be avoided. Preparations containing alcohol should be avoided because they can dehydrate the skin, cause pain if applied to raw areas, and the alcohol can cause necrosis. In *preterm neonates*, the skin is more fragile and offers a poor barrier, especially in the first fortnight after birth. Preterm infants, especially if below 32 weeks postmenstrual age, may also require special measures to maintain skin hydration.

13.1.1 Vehicles

The vehicle in topical preparations for the skin affects the degree of hydration, has a mild anti-inflammatory effect, and aids the penetration of the active drug. Therefore, the vehicle, as well as the active drug, should be chosen on the basis of their suitability for the child’s skin condition.

**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 macro-gols which are freely soluble in water and are therefore readily washed off; they have a limited but useful role where ready removal is desirable.

**Paste**s are stiff preparations containing a high proportion of finely powdered solids such as zinc oxide and starch suspended in an ointment. They are used for
circumscribed lesions such as those which occur in lichen simplex, chronic eczema, or psoriasis. They are less occlusive than ointments and can be used to protect inflamed, lichenified, or excoriated skin.

**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 their preparation.

### 13.1.2 Suitable quantities for prescribing

#### Suitable quantities of dermatological preparations to be prescribed for specific areas of the body

<table>
<thead>
<tr>
<th>Area 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>

The amounts shown above are usually suitable for children 12–18 years for twice daily application for 1 week; smaller quantities will be required for children under 12 years. These recommendations **do not apply** to corticosteroid preparations.

### 13.1.3 Excipients and sensitisation

Excipients in topical products rarely cause problems. If a patch test indicates allergy to an excipient, then products containing the substance should be avoided (see also Anaphylaxis, p. 198). The following excipients in topical preparations may rarely be associated with sensitisation; the presence of these excipients is indicated in the entries for topical products. See also Excipients, under General Guidance, p. 3.

<table>
<thead>
<tr>
<th>Beeswax</th>
<th>Imidurea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzyl alcohol</td>
<td>Isopropyl palmitate</td>
</tr>
<tr>
<td>Butylated hydroxyanisole</td>
<td>N-(3-Chlorally)(hexaminium chloride (quaternium 15)</td>
</tr>
<tr>
<td>Butylated hydroxytoluene</td>
<td>Polysorbates</td>
</tr>
<tr>
<td>Cetostearyl alcohol (including cetyl and stearyl alcohol)</td>
<td>Propylene glycol</td>
</tr>
<tr>
<td>Chlorocresol</td>
<td>Sodium metabisulphite</td>
</tr>
<tr>
<td>Edetic acid (EDTA)</td>
<td>Sorbic acid</td>
</tr>
<tr>
<td>Ethylenediamine</td>
<td>Wool fat and related substances including lanolin¹</td>
</tr>
<tr>
<td>Fragrances</td>
<td></td>
</tr>
<tr>
<td>Hydroxybenzoates (parabens)</td>
<td></td>
</tr>
</tbody>
</table>

¹: Purified versions of wool fat have reduced the problem

### 13.2 Emollient and barrier preparations

#### 13.2.1 Emollients

#### 13.2.2 Barrier preparations

**Borderline substances** The preparations marked ‘ACBS’ are regarded as drugs when prescribed in accordance with the advice of the Advisory Committee on Borderline Substances for the clinical conditions listed. Prescriptions issued in accordance with this advice and endorsed ‘ACBS’ will normally not be investigated. See Appendix 2 for listing by clinical condition.
Emollients hydrate the skin, soften the skin, act as barrier to water and external irritants, 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); they should be applied immediately after washing or bathing to maximise the effect of skin hydration. Light emollients such as aqueous cream are suitable for many dry skin conditions but more greasy preparations, such as white soft paraffin, emulsifying ointment, and liquid and white soft paraffin ointment, are often more effective. The severity of the condition, the child’s (or carer’s) preference, and the site of application will often guide the choice of emollient. Some ingredients rarely cause sensitisation (section 13.1.3) and this should be suspected if an eczematous reaction occurs. Ointments may exacerbate acne and folliculitis.

Fire hazard with paraffin-based emollients
Emulsifying ointment or 50% Liquid Paraffin and 50% White Soft Paraffin Ointment in contact with dressings and clothing is easily ignited by a naked flame. The risk is greater when these preparations are applied to large areas of the body, and clothing or dressings become soaked with the ointment. Patients should be told to keep away from fire or flames, and not to smoke when using these preparations. The risk of fire should be considered when using large quantities of any paraffin-based emollient.

Preparations such as aqueous cream and emulsifying ointment can be used as soap substitutes; the preparation is rubbed on the skin before rinsing off completely. The addition of a bath oil (section 13.2.1.1) may also be helpful.

In the neonate, a preservative-free paraffin-based emollient hydrates the skin without affecting the normal skin flora; substances such as olive oil are also used. The development of blisters (epidermolysis bullosa) or ichthyosis may be alleviated by applying liquid and white soft paraffin ointment while awaiting dermatological investigation.

Preparations containing an antibacterial (section 13.10.1) should be avoided unless infection is present or is a frequent complication of the dry skin condition.

Urea is a keratin softener used in the treatment of dry, scaling conditions (including ichthyosis). 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 100 g = 47p
Excipients include cetostearyl alcohol

Emulsifying Ointment, BP
Ointment, emulsifying wax 30%, white soft paraffin 50%, liquid paraffin 20%, net price 100 g = 57p
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 100 g = 40p

Liquid and White Soft Paraffin Ointment, NPF
Ointment, liquid paraffin 50%, white soft paraffin 50%, net price 250 g = £3.94

Paraffin, Yellow Soft, BP
Yellow petroleum jelly, net price 100 g = 34p

Proprietary emollient preparations
Aveeno® (J&J)
Cream, colloidal oatmeal in emollient basis, net price 100 mL = £3.78, 300-mL pump pack = £6.80
Excipients include benzyl alcohol, cetyl alcohol, isopropyl palmitate
ACBS: For endogenous and exogenous eczema, xeroderma, and ichthyosis
Lotion, colloidal oatmeal in emollient basis, net price 400 mL = £6.42
Excipients include benzyl alcohol, cetyl alcohol, isopropyl palmitate
ACBS: as for Aveeno® Cream

Cetraben® (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 cetostearyl alcohol, hydroxybenzoates (parabens)
Epaderm® (Medlock)
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
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 Diprobase® cream, net price 50 g = £1.34; 500-g pump pack = £6.76
Excipients include cetostearyl alcohol, chlorocresol
Ointment, liquid paraffin 5%, white soft paraffin 95%, basis used for Diprobase® ointment, net price 50 g = £1.34
Excipients none as listed in section 13.1.3

Doublebase® (Dermal)
Emollient shower gel, isopropyl myristate 15%, liquid paraffin 15%, net price 200 g = £5.45
Excipients none as listed in section 13.1.3
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

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, hydroxybenzoates (parabens)
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, and ichthyosis
Lotion, light liquid paraffin 4%, cetomacrogol, white soft paraffin 10%, hypoallergenic anhydrous wool fat (hypoallergenic lanolin) 1% in glycerol monostearate, net price 200 mL = £2.40; 500-mL pump pack = £4.50
Excipients include isopropyl palmitate, hydroxybenzoates (parabens), benzyl alcohol
ACBS: for symptomatic relief of dry skin conditions, such as those associated with atopic eczema and contact dermatitis

Emolllin® (C D Medical)
Spray, liquid paraffin 50%, white soft paraffin 50% in aerosol basis, net price 240 mL = £5.98
Excipients none as listed in section 13.1.3

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
Excipients include cetostearyl alcohol

Hewlett® 10% (Kestrel)
Cream, hydrox wax fat 4%, zinc oxide 8%, arachis (peanut) oil, oleic acid, white soft paraffin, net price 35 g = £1.43, 400 g = £6.69
Excipients include fragrance

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
Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)
Ointment, yellow soft paraffin 30%, emulsifying wax 30%, liquid paraffin 40%, net price 125 g = £2.79, 500 g = £4.74
Excipients include cetostearyl alcohol

Linol® (Linol®)
Cream, evening primrose oil 20%, net price 50 g = £2.83, 250 g = £8.20
Excipients include beeswax, hydroxybenzoates (parabens), propylene glycol
Cautions epilepsy (but hazard unlikely with topical preparations)

Lipobase® (Astellas)
Cream, fatty cream basis used for Locoid Lipocream®
Net price 50 g = £2.08
Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)
For dry skin conditions, also for use during treatment with topical corticosteroid and as diluent for Locoid Lipocream®

Oilatum® (Stiefel)
Cream, light 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; Oilatum® Junior 150 g = £3.38, 500-mL pump pack = £4.65, 500-mL pump pack = £6.35, 1.05-litre pump pack = £14.67
Excipients include benzyl alcohol, cetostearyl alcohol
Shower emollient (gel), light liquid paraffin 70%, net price 150 g = £5.15
Excipients include fragrance

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)
Lotion, white soft paraffin 5%, net price 250 mL = £3.00
Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)
Wash, glycerol 10%, net price 200 mL = £2.50
Excipients include hydroxybenzoates (parabens)

Ultrabase® (Valeant)
Cream, water-miscible, containing liquid paraffin and white soft paraffin, net price 50 g = 89p, 500-g pump pack = £6.44
Excipients include fragrance, hydroxybenzoates (parabens), disodium edetate, stearyl alcohol

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 = £8.48
Excipients include cetostearyl alcohol, polyglycerol 40, propylene glycol, sorbic acid

Zerobase® (Zeroderma)
Cream, liquid paraffin 11%, net price 500 g pump pack = £5.99
Excipients include cetostearyl alcohol, chlorocresol
### 13.2.1 Emollients

#### Emollient bath additives

Emollient bath additives should be added to bath water; some can be applied to wet skin undiluted and rinsed off. Hydration can be improved by soaking in the bath for 10–20 minutes. In dry skin conditions soap should be avoided (see section 13.2.1 for soap substitutes).

The quantities of bath additives recommended for older children are suitable for an adult-size bath. Proportionately less should be used for a child-size bath or a washbasin; recommended bath additive quantities for younger children reflect this.

These preparations make skin and surfaces slippery—particular care is needed when bathing a child.

### 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**
- Apply thinly and rub into area when required

**Balneum® Plus (Crookes)**
- **Cream**, urea 5%, lauromacrogols 3%, net price 100 g = £3.29, 175-g pump pack = £8.33, 500-g pump pack = £17.09
- **Excipients** include benzyl alcohol, polysorbates

**Dose**
- Apply twice daily

**Calmurid® (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**
- 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

**E45® Itch Relief Cream (Crookes)**
- **Cream**, urea 5%, macrogol lauryl ether 3%, net price 50 g = £2.55, 100 g = £3.47, 500 g = £17.09
- **Excipients** include benzyl alcohol, polysorbates

**Dose**
- Apply twice daily

**Eucerin® Intensive (Beiersdorf)**
- **Cream**, urea 10%, net price 100 mL = £7.59
- **Excipients** include benzyl alcohol, isopropyl palmitate, wool fat

**Dose**
- Apply thinly and rub into area twice daily

**Nutraplus® (Galderma)**
- **Cream**, urea 10%, net price 100 g = £4.37
- **Excipients** include hydroxybenzoates (parabens), propylene glycol

**Dose**
- 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
- **Excipients** include cetostearyl alcohol

**Dose**
- 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
- **Excipients** include cetostearyl alcohol

**Dose**
- 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
- **Excipients** include cetostearyl alcohol

**Dose**
- Apply to skin or use as soap substitute

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**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
- **Excipients** include fragrance

**Dose**
- **Neonate** add 5 mL to bath water or apply to wet skin and rinse
- **Child 1 month–2 years** add 5 mL to bath water or apply to wet skin and rinse
- **Child 2–18 years** add 10–20 mL to bath water or apply to wet skin and rinse
**Aveeno® (J&J)**

- **Bath oil,** colloidal oatmeal, white oat fraction in emollient basis, net price 250 mL = £4.28
- **Excipients** include beeswax, fragrance
- **ACBS:** for endogenous and exogenous eczema, xeroderma, and ichthyosis

**Dose**
- **Child 2–18 years** add 20–30 mL to bath water or apply to wet skin and rinse

**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
- **ACBS:** as for Aveeno® Bath oil

**Dose**
- **Child 1 month–12 years** add 15 g to bath water
- **Child 12–18 years** add 50 g to bath water

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**Balneum® (Crookes)**

- **Balneum® bath oil,** soya oil 84.75%, net price 200 mL = £2.48, 500 mL = £5.38, 1 litre = £10.39
- **Excipients** include butylated hydroxytoluene, propylene glycol, fragrance

**Dose**
- **Neonate** add 5–15 mL to bath water; do not use undiluted
- **Child 1 month–2 years** add 5–15 mL to bath water; do not use undiluted
- **Child 2–18 years** add 20–60 mL to bath water; do not use undiluted

**Balneum Plus® bath oil,** soya oil 82.95%, mixed lauromacrogols 15%, net price 500 mL = £6.66
- **Excipients** include butylated hydroxytoluene, propylene glycol, fragrance

**Dose**
- **Neonate** add 5 mL to bath water or apply to wet skin and rinse
- **Child 1 month–2 years** add 5 mL to bath water or apply to wet skin and rinse
- **Child 2–18 years** add 10–20 mL to bath water or apply to wet skin and rinse

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**Cetraben® (Genus)**

- **Emollient bath additive,** light liquid paraffin 82.8%, net price 500 mL = £5.25

**Dose**
- **Neonate** add ½ capful to bath water or apply to wet skin and rinse
- **Child 1 month–12 years** add ½–2 capfuls to bath water or apply to wet skin and rinse
- **Child 12–18 years** add 1–3 capfuls to bath water or apply to wet skin and rinse

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**Dermalo® (Dermal)**

- **Bath emollient,** acetylated wool alcohols 5%, liquid paraffin 65%, net price 500 mL = £3.60

**Dose**
- **Neonate** add 5 mL to bath water or apply to wet skin and rinse
- **Child 1 month–12 years** add 5–10 mL to bath water or apply to wet skin and rinse
- **Child 12–18 years** add 15–20 mL to bath water or apply to wet skin and rinse

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**Diprobath® (Schering-Plough)**

- **Bath additive,** isopropyl myristate 39%, light liquid paraffin 46%, net price 500 mL = £6.97
- **Excipients** none as listed in section 13.1.3

**Dose**
- **Neonate** add 5 mL to bath water; do not use undiluted
- **Child 1 month–12 years** add 10 mL to bath water; do not use undiluted
- **Child 12–18 years** add 25–50 mL to bath water; do not use undiluted

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**Doublebase® (Dermal)**

- **Emollient bath additive,** liquid paraffin 65%, net price 500 mL = £5.70
- **Excipients** include cetostearyl alcohol

**Dose**
- **Neonate** add 5–10 mL to bath water
- **Child 1 month–12 years** add 5–10 mL to bath water
- **Child 12–18 years** add 15–20 mL to bath water

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**E45® (Crookes)**

- **Emollient bath oil,** cetyl dimeticone 5%, liquid paraffin 91%, net price 250 mL = £3.19, 500 mL = £5.11
- **Excipients** none as listed in section 13.1.3
- **ACBS:** for endogenous and exogenous eczema, xeroderma, and ichthyosis

**Dose**
- **Neonate** add 5 mL to bath water or apply to wet skin and rinse
- **Child 1 month–12 years** add 5–10 mL to bath water or apply to wet skin and rinse
- **Child 12–18 years** add 15 mL to bath water or apply to wet skin and rinse

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**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
- **Excipients** none as listed in section 13.1.3
- **ACBS:** for endogenous and exogenous eczema, xeroderma, and ichthyosis

**Dose**
- **Neonate** add ½ capful to bath water or apply to wet skin and rinse
- **Child 1 month–12 years** add ½–2 capfuls to bath water or apply to wet skin and rinse
- **Child 12–18 years** add 1–3 capfuls to bath water or apply to wet skin and rinse

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**Imuderm® (Goldshield)**

- **Bath oil,** almond oil 30%, light liquid paraffin 69.6%, net price 250 mL = £3.75
- **Excipients** include butylated hydroxyanisole

**Dose**
- **Neonate** add 7.5 mL to bath water or rub into dry skin until absorbed
- **Child 1 month–12 years** add 7.5–15 mL to bath water or rub into dry skin until absorbed
- **Child 12–18 years** add 15–30 mL to bath water or rub into dry skin until absorbed

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13 Skin
**Oilatum**® (Stiefel)
*Emollient bath additive* (emulsion), acetylated wool alcohols 5%, liquid paraffin 63.4%, net price
250 mL = £2.75, 500 mL = £4.57
**Excipients** include isopropyl palmitate, fragrance

**Dose**
- **Neonate**: add ¼ capful to bath water or apply to wet skin and rinse
- **Child 1 month–12 years**: add ½–2 capfuls to bath water or apply to wet skin and rinse
- **Child 12–18 years**: add 1–3 capfuls to bath water 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
**Excipients** include wool fat, isopropyl palmitate

**Dose**
- **Neonate**: add ¼ capful to bath water or apply to wet skin and rinse
- **Child 1 month–12 years**: add ½–2 capfuls to bath water or apply to wet skin and rinse
- **Child 12–18 years**: add 1–3 capfuls to bath water 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
**Excipients** include hydroxybenzoates (parabens)

**Dose**
- **Child 1 month–1 year**: add 4 mL to bath water or apply to wet skin and rinse
- **Child 1–12 years**: add 7 mL to bath water or apply to wet skin and rinse
- **Child 12–18 years**: add 10 mL to bath water or apply to wet skin and rinse

**With antimicrobials**

**Dermol**® 600 (Dermal)
*Bath emollient*, benzalkonium chloride 0.5%, liquid paraffin 25%, isopropyl myristate 25%, net price
600 mL = £7.90
**Excipients** include polysorbate 60

**Dose**
- **Child 1 month–2 years**: add 5–15 mL to bath water; do not use undiluted
- **Child 2–18 years**: add 15–30 mL to bath water; do not use undiluted

**Emulsiderm**® (Dermal)
*Liquid emulsion*, liquid paraffin 25%, isopropyl myristate 25%, benzalkonium chloride 0.5%, net price
300 mL (with 15-mL measure) = £4.03, 1 litre (with 30-mL measure) = £12.55
**Excipients** include polysorbate 60

**Dose**
- **Child 1 month–2 years**: add 5–10 mL to bath water or rub into dry skin until absorbed
- **Child 2–18 years**: add 10–30 mL to bath water or rub into dry skin until absorbed

**Oilatum** Plus (Stiefel)
*Bath additive*, benzalkonium chloride 6%, triclosan 2%, light liquid paraffin 52.5%, net price
500 mL = £6.98
**Excipients** include wool fat, isopropyl palmitate

**Dose**
- **Child 6 months–1 year**: add 1 mL to bath water; do not use undiluted
- **Child 1–18 years**: add 1–2 capfuls to bath water; do not use undiluted

**With tar**

Section 13.5.2

### Barrier preparations

Barrier preparations often contain water-repellent substances such as *dimethicone* (dimethicone), natural oils, and paraffins, to help protect the skin from abrasion and irritation; they are used to protect intact skin around stomas and pressure sores, and as a barrier against nappy rash. In neonates, barrier preparations which do not contain potentially sensitising excipients (section 13.1.3) are preferred. Where the skin has broken down, barrier preparations have a limited role in protecting adjacent skin. *Zinc ointments* or barrier creams with zinc oxide or titanium salts, are used to aid healing of uninfected, excoriated skin.

**Nappy rash (dermatitis)** The first line of treatment is to ensure that nappies are changed frequently and that tightly fitting water-proof pants are avoided. The rash may clear when left exposed to the air and a barrier preparation can be helpful. If the rash is associated with a yeast or fungal infection, an antifungal cream such as clotrimazole cream (section 13.10.2) is useful. A mild corticosteroid such as hydrocortisone 1% is useful in moderate to severe inflammation, but it should be avoided in neonates. The barrier preparation is applied after the corticosteroid preparation to prevent further damage. Hydrocortisone may be used in combination with antifungal and antibacterial drugs (section 13.4) if there is considerable inflammation, erosion, and infection. Preparations containing hydrocortisone should be applied for no more than a week; the hydrocortisone should be discontinued as soon as the inflammation subsides. The occlusive effect of nappies and water-proof pants may increase absorption of corticosteroid (for cautions, see section 13.4).
### 13.3 Topical antipruritics

*Pruritus* may be caused by systemic disease (such as drug hypersensitivity, obstructive jaundice, endocrine disease, and certain malignant diseases), skin disease (e.g. eczema, psoriasis, urticaria, and scabies) or as a side-effect of opioid analgesics. Where possible the underlying cause should be treated. For the treatment of pruritus in palliative care, see Prescribing in Palliative Care, p. 27.

Pruritus caused by cholestasis generally requires a bile acid sequestrant (section 1.9.2).

An *emollient* (section 13.2.1) may be of value where the pruritus is associated with dry skin. Preparations containing *calamine* or *crotamiton* are sometimes used but are of uncertain value.

A topical preparation containing *doxepin* 5% is licensed for the relief of pruritus in eczema in children over 12 years; it can cause drowsiness and there may be a risk of sensitisation.

Topical antihistamines and local anaesthetics (section 15.2) 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.

In *pruritus ani*, the underlying cause such as faecal soiling, eczema, psoriasis, or helminth infection should be treated; for preparations used to relieve pruritus ani, see section 1.7.
### Calamine

**Indication and dose**

**Pruritus** but see notes above

**Calamine** (Non-proprietary)

*Aqueous cream*, calamine 4%, zinc oxide 3%, liquid paraffin 20%, self-emulsifying glyceryl monoesterate 5%, cetomacrogol emulsifying wax 5%, phe-noxyethanol 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 phenol 0.5%, in freshly boiled and cooled purified water, net price 200 mL = 63p

### Crotamiton

**Cautions**

- Avoid use near eyes and broken skin; use on doctor’s advice for children under 3 years

**Contra-indications**

- Acute exudative dermatoses

**Indication and dose**

**Pruritus (including pruritus after scabies—section 13.10.4)** see notes above

- Apply 2–3 times daily (for pruritus after scabies in children under 3 years apply once daily only)

**Eurax®** (Novartis Consumer Health)

*Cream*, crotamiton 10%, net price 30 g = £2.27, 100 g = £3.95

**Excipients** include beeswax, fragrance, hydroxybenzoates (parabens), stearyl alcohol

*Lotion*, crotamiton 10%, net price 100 mL = £2.99

**Excipients** include cetyl alcohol, fragrance, propylene glycol, sorbic acid, stearyl alcohol

### Doxepin Hydrochloride

**Cautions**

- Glaucoma, urinary retention, severe liver impairment, mania; avoid application to large areas; interactions: Appendix 1 (antidepressants, tricyclic)

**Driving**

- Drowsiness may affect performance of skilled tasks (e.g. driving); effects of alcohol enhanced

**Pregnancy**

- Manufacturer advises use only if potential benefit outweighs risk

**Breast-feeding**

- Manufacturer advises use only if potential benefit outweighs risk

**Side-effects**

- Drowsiness; local burning, stinging, irritation, tingling and rash; systemic side-effects such as antimuscarinic affects, headache, fever, dizziness, gastro-intestinal disturbances also reported

**Indication and dose**

**Pruritus in eczema**

- **Child 12–18 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

**Depressive illness** section 4.3.1

**Xepin®** (CHS)

*Cream*, doxepin hydrochloride 5%, net price 30 g = £11.70. Label: 2, 10, patient information leaflet

**Excipients** include benzyl alcohol

### Topical corticosteroids

Topical corticosteroids are used for the treatment of inflammatory conditions of the skin (other than those arising from an infection), particularly eczema (section 13.5.1), contact dermatitis, insect stings (p. 48), 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.

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. 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 child’s condition.

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. Continuous daily application of a mild corticosteroid such as hydrocortisone 1% is equivalent to a potent corticosteroid such as betamethasone 0.1% applied intermittently.
Topical corticosteroids are of no value in the treatment of urticaria. 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 fluocinonide 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 on 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.

**Choice**  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 polythene 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). Disposable nappies and tight fitting pants increase the risk of side-effects by increasing absorption of the corticosteroid. The inclusion of urea or salicylic acid also increases the penetration of the corticosteroid.

‘Wet-wrap bandaging’ (section 13.5.1) increases absorption into the skin, but should be initiated only by a dermatologist and application supervised by a healthcare professional trained in the technique.

In the *BNF for Children*, topical corticosteroids for the skin are categorised as ‘mild’, ‘moderately potent’, ‘potent’ or ‘very potent’ (see p. 675); the least potent preparation which is effective should be chosen but dilution should be avoided whenever possible.

Topical hydrocortisone is usually used in children under 1 year of age. Moderately potent and potent topical corticosteroids should be used with great care in children and for short periods (1–2 weeks) only. A very potent corticosteroid should be initiated under the supervision of a specialist.

Appropriate topical corticosteroids for specific conditions are:

- **insect bites and stings**—mild corticosteroid such as hydrocortisone 1% cream;
- **severely inflamed nappy rash** in infant over 1 month (section 13.2.2)—mild corticosteroid such as hydrocortisone 0.5 or 1% for 5–7 days (combined with antimicrobial if infected);
- **mild to moderate eczema, flexural and facial eczema or psoriasis**—mild corticosteroid such as hydrocortisone 1%;
- **severe eczema of the face and neck**—moderately potent corticosteroid for 3–5 days only;
- **severe eczema on the trunk and limbs** in children over 1 year—moderately potent or potent corticosteroid for 1–2 weeks only, switching to a less potent preparation as the condition improves;
- **eczema affecting area with thickened skin** (e.g. soles of feet)—potent topical corticosteroid in combination with urea or salicylic acid (to increase penetration of corticosteroid).
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. 657). Organisms susceptible to miconazole include Candida spp. and many Gram-positive bacteria including streptococci and staphylococci.

Cautions  Avoid prolonged use of a topical corticosteroid particularly on the face (and keep away from eyes). 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, see notes above.

Contra-indications  Topical corticosteroids are contra-indicated in untreated bacterial, fungal, or viral skin lesions, in acne, 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 particular care is required when treating neonates and infants, and 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 of corticosteroid is greatest from severely inflamed skin, thin skin (especially on the face or genital area), from flexural sites (e.g. axillae groins), and in infants where skin surface area is higher in relation to body-weight; absorption 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; perioral dermatitis; acne, or worsening of acne or rosacea; mild depigmentation which may be reversible; hypertrichosis also reported.

Children and their carers should be reassured that side effects such as skin thinning and systemic effects rarely occur when topical corticosteroids are used appropriately.

Safe Practice  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.

If a child is using topical corticosteroids of different potencies, the child and their carers should be told when to use each corticosteroid. The potency of each topical corticosteroid (see Topical Corticosteroid Preparation Potencies, p. 675) 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.

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.

### Topical corticosteroid potencies

Potency of a topical corticosteroid preparation depends upon 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, Fucidin H, Nystaform-HC, Timodine*
- **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, Calmurd HC*

**Potent**
- *Betamethasone valerate 0.1%, Betacap, Bettamousse, Betnovate, Cutivate, Diprosone, Elocon, Hydrocortisone butyrate, Locoid, Locoid Crelo, Metosyn, Nerisode, Synalar*
- **Potent with antimicrobials** *Aureocort, Betnovate-C, Betnovate-N, Fucibet, Lotriderm, Synalar C, Synalar N*
- **Potent with salicylic acid** *Diprosalic*

**Very potent**
- *Dermovate, Nerisode Forte*

### HYDROCORTISONE

**Cautions** see notes above

**Contra-indications** see notes above

**Side-effects** see notes above

**Indication and dose**

**Mild inflammatory skin disorders such as eczemas (but for over-the-counter preparations), see below**

Apply thinly 1–2 times daily

**Nappy rash** see notes above and section 13.2.2

**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 in children over 10 years, 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).

**Hydrocortisone** (Non-proprietary)

- **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 p. 674. 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 p. 674. Potency: mild

When hydrocortisone cream or ointment is prescribed and no strength is stated, the 1% strength should be supplied

**Proprietary hydrocortisone preparations**

**Dioderm®** (Dermal)®

- **Cream**, hydrocortisone 0.1%, net price 30 g = £2.50. Label: 28, counselling, application, see p. 674. Potency: mild

**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

**Mildison®** (Astellas)®

- **Lipocream**, hydrocortisone 1%, net price 30 g = £2.45. Label: 28, counselling, application, see p. 674. Potency: mild

**Excipients** include cetostearyl alcohol, propylene glycol

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13 Skin
HYDROCORTISONE (continued)

1 Compounds preparations

Compounds 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. 674. 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. 674. 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)

1. A 15-g tube is on sale to the public for the treatment of contact dermatitis and insect bites in children 10–18 years.

With antimicrobials

See notes above for comment on compound preparations

1. Eurax-Hydrocortisone® (Novartis Consumer Health) Cream, hydrocortisone 0.25%, crotamiton 10%, net price 30 g = 87p. Label: 28, counselling, application, see p. 674. Potency: mild

Excipients include fragrance, hydroxybenzoates (parabens), propylene glycol, stearyl alcohol

1. A 15-g tube is on sale to the public for treatment of athlete’s foot and candidal intertrigo in children 10–18 years.

1. Canesten HC® (Bayer Consumer Care) Cream, hydrocortisone 1%, clotrimazole 1%, net price 30 g = £2.42. Label: 28, counselling, application, see p. 674. Potency: mild

Excipients include benzyl alcohol, cetostearyl alcohol

1. A 15-g tube is on sale to the public for treatment of athlete’s foot and fungal infection of skin folds with associated inflammation in children 10–18 years.

Daktacort® (Janssen-Cilag) Cream, hydrocortisone 1%, miconazole nitrate 2%, net price 30 g = £2.09. Label: 28, counselling, application, see p. 674. Potency: mild

Excipients include butylated hydroxyanisole, disodium edetate

Ointment, hydrocortisone 1%, miconazole nitrate 2%, net price 30 g = £2.09. Label: 28, counselling, application, see p. 674. Potency: mild

Excipients none as listed in section 13.1.3

Dental prescribing on NHS May be prescribed as Miconazole Hydrocortisone Cream or Ointment for max. 7 days

1. A 15-g tube is on sale to the public for the treatment of athlete’s foot and candidal intertrigo in children 10–18 years

Econacort® (Squibb) Cream, hydrocortisone 1%, econazole nitrate 1%, net price 30 g = £2.25. Label: 28, counselling, application, see p. 674. 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. 674. Potency: mild

Excipients include butylated hydroxyanisole, 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. 674. 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. 674. Potency: mild

Excipients include benzyl alcohol, cetostearyl alcohol, polysorbate ‘60’

Ointment, hydrocortisone 1%, nystatin 100 000 units/g, chlorhexidine acetate 1%, net price 30 g = £2.66. Label: 28, counselling, application, see p. 674. Potency: mild

Excipients none as listed in section 13.1.3

Timodine® (R&G) Cream, hydrocortisone 0.5%, nystatin 100 000 units/g, benzalkonium chloride solution 0.2%, dimethicone ‘350’ 10%, net price 30 g = £2.38. Label: 28, counselling, application, see p. 674. Potency: mild

Excipients include butylated hydroxyanisole, cetostearyl alcohol, hydroxybenzoates (parabens), sodium metabisulphite, sorbic acid

HYDROCORTISONE BUTYRATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Indication and dose

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Child 1–18 years apply thinly 1–2 times daily

Locoid® (Astellas) Cream, hydrocortisone butyrate 0.1%, net price 30 g = £2.29, 100 g = £7.05. Label: 28, counselling, application, see p. 674. 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. 674. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, hydroxybenzoates (parabens)

Note For bland cream basis see Lipobase®, 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. 674. Potency: potent

Excipients none as listed in section 13.1.3
\textbf{HYDROCORTISONE BUTYRATE (continued)}

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. 674. Potency: potent

\textbf{Excipients} none as listed in section 13.1.3

\textbf{ALCLOMETASONE DIPROPIONATE}

\textbf{Cautions} see notes above

\textbf{Contra-indications} see notes above

\textbf{Side-effects} see notes above

\textbf{Licensed use} licensed for use in children (age range not specified by manufacturer)

\textbf{Indication and dose}

\textbf{Inflammatory skin disorders such as eczemas}

Apply thinly 1–2 times daily

\textbf{BETAMETHASONE ESTERS}

\textbf{Cautions} see notes above; use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression

\textbf{Contra-indications} see notes above

\textbf{Side-effects} see notes above

\textbf{Licensed use} Betacap\textsuperscript{®}, Betnovate\textsuperscript{®}, Betnovate-C\textsuperscript{®}, and Betnovate-RO\textsuperscript{®} not licensed for use in children under 1 year; Bettamousse\textsuperscript{®} and Fucibet\textsuperscript{®}

\textbf{Lipid Cream} not licensed for use in children under 6 years; Betnovate-N\textsuperscript{®} not licensed for use in children under 2 years; Lotriderm\textsuperscript{®} not licensed for use in children under 12 years; all other preparations licensed for use in children (age range not specified by manufacturer)

\textbf{Indication and dose}

\textbf{Severe inflammatory skin disorders such as eczemas}

Apply thinly 1–2 times daily

\textbf{Betamethasone Valerate (Non-proprietary)}

\textbf{Cream}, betamethasone (as valerate) 0.1%, net price 30 g = £1.63, 100 g = £4.36. Label: 28, counselling, application, see p. 674. Potency: potent

\textbf{Ointment}, betamethasone (as valerate) 0.1%, net price 30 g = £1.70, 100 g = £4.15. Label: 28, counselling, application, see p. 674. Potency: potent

\textbf{Betacap\textsuperscript{®} (Dermal)}

\textbf{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. 674. Potency: potent

\textbf{Betnovate\textsuperscript{®} (GSK)}

\textbf{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. 674. Potency: potent

\textbf{Excipients} include betamethasone alcohol, chlororesol

\textbf{Locoid Crelo\textsuperscript{®} (Astellas)}

\textbf{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. 674. Potency: potent

\textbf{Excipients} include butylated hydroxytoluene, cetostearyl alcohol, hydroxybenzoates (parabens), propylene glycol

\textbf{Modrasone\textsuperscript{®} (PLIVA)}

\textbf{Cream}, alclometasone dipropionate 0.05%, net price 50 g = £2.68. Label: 28, counselling, application, see p. 674. Potency: moderate

\textbf{Excipients} include cetostearyl alcohol, chlororesol, propylene glycol

\textbf{Ointment}, alclometasone dipropionate 0.05%, net price 50 g = £2.68. Label: 28, counselling, application, see p. 674. Potency: moderate

\textbf{Excipients} include beeswax, propylene glycol

\textbf{Betnovate-RD\textsuperscript{®} (GSK)}

\textbf{Cream}, 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. 674. Potency: potent

\textbf{Excipients} none as listed in section 13.1.3

\textbf{Lotion}, betamethasone (as valerate) 0.1%, net price 100 mL = £4.86. Label: 28, counselling, application, see p. 674. Potency: potent

\textbf{Excipients} include cetostearyl alcohol, hydroxybenzoates (parabens)

\textbf{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. 674. Potency: potent

\textbf{Excipients} none as listed in section 13.1.3

\textbf{Betnovate-RD\textsuperscript{®} (GSK)}

\textbf{Cream}, betamethasone (as valerate) 0.025% in a water-miscible basis (1 in 4 dilution of Betnovate\textsuperscript{®} cream), net price 100 g = £3.34. Label: 28, counselling, application, see p. 674. Potency: moderate

\textbf{Excipients} include cetostearyl alcohol, chlororesol

\textbf{Ointment}, betamethasone (as valerate) 0.025% in an anhydrous paraffin basis (1 in 4 dilution of Betnovate\textsuperscript{®} ointment), net price 100 g = £3.34. Label: 28, counselling, application, see p. 674. Potency: moderate

\textbf{Excipients} none as listed in section 13.1.3

\textbf{Bettamousse\textsuperscript{®} (UCB Pharma)}

\textbf{Foam} (= scalp application), betamethasone valerate 0.12% (= betamethasone 0.1%), net price 100 g = £9.75. Label: 28, counselling, application, see p. 674. Potency: potent

\textbf{Excipients} include cetyl alcohol, polysorbate 60, propylene glycol, stearyl alcohol

\textbf{Note} Flammable

\textbf{Diprosone\textsuperscript{®} (Schering-Plough)}

\textbf{Cream}, betamethasone (as dipropionate) 0.05%, net price 30 g = £2.24, 100 g = £6.36. Label: 28, counselling, application, see p. 674. Potency: potent

\textbf{Excipients} include cetostearyl alcohol, chlororesol
13.4 Topical corticosteroids

**BETAMETHASONE ESTERS (continued)**

**Ointment**, betamethasone (as dipropionate) 0.05%, net price 30 g = £2.24, 100 g = £6.36. Label: 28, counselling, application, see p. 674. 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. 674. Potency: potent

Excipients none as listed in section 13.1.3

**With salicylic acid** See notes above for comment on compound preparations

**Diprosalic** (Schering-Plough)

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. 674. 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 30 g = £1.76. Label: 28, counselling, application, see p. 674. 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)

Cream, betamethasone (as valerate) 0.1%, clobetasol 0.5%, fusidic acid 2%, net price 30 g = £5.62, 60 g = £11.23. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients include benzy alcohol, cetostearyl alcohol, chlorocresol

Note Stains clothing

**Betnovate-N** (Chemidex)

Cream, betamethasone (as valerate) 0.1%, neomycin sulphate 0.5%, net price 30 g = £3.50. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, chlorocresol

Ointment, betamethasone (as valerate) 0.1%, neomycin sulphate 0.5%, net price 30 g = £6.34. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients none as listed in section 13.1.3

**Fucibet** (LEO)

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. 674. Potency: potent

Excipients include benzyl alcohol, cetostearyl alcohol, chlorocresol

Note Stains clothing

**Lipid cream**, betamethasone (as valerate) 0.1%, fusidic acid 2%, net price 30 g = £5.62. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

**Lotriderm** (PLIVA)

Cream, betamethasone dipropionate 0.064% (≡ betamethasone 0.05%), clotrimazole 1%, net price 30 g = £6.34. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients include benzy alcohol, cetostearyl alcohol, propylene glycol

CLOBETASOL PROPIONATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 1 year

Indication and dose Short-term treatment only of severe resistant inflammatory skin disorders such as recalcitrant eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily for up to 4 weeks; max. 50 g of 0.05% preparation per week

**Dermovate** (GSK)

Cream, clobetasol propionate 0.05%, net price 30 g = £2.86, 100 g = £8.39. Label: 28, counselling, application, see p. 674. Potency: very potent

Excipients include beeswax (or beeswax substitute), cetostearyl alcohol, chlorocresol, propylene glycol

Ointment, clobetasol propionate 0.05%, net price 30 g = £2.86, 100 g = £8.39. Label: 28, counselling, application, see p. 674. 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. 674. Potency: very potent

Excipients none as listed in section 13.1.3

CLOBETASONE BUTYRATE

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indication and dose Eczemas and dermatitis of all types; maintenance between courses of more potent corticosteroids

Apply thinly 1–2 times daily
1. **Eumovate** (GSK) Cream, clobetasone butyrate 0.05%, net price 30 g = £1.97, 100 g = £5.77. Label: 28, counselling, application, see p. 674. Potency: moderate

Excipients include beeswax substitute, cetostearyl alcohol, chlorocresol

Ointment, clobetasone butyrate 0.05%, net price 30 g = £1.97, 100 g = £5.77. Label: 28, counselling, application, see p. 674. 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 children over 12 years provided pack does not contain more than 15 g

**Trimovate** (GSK) 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. 674. Potency: moderate

Excipients include cetostearyl alcohol, chlorocresol, sodium metabisulphite

Note Stains clothing

**DIFLUCORTOLONE VALERATE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use Nerisone® licensed for use in children (age range not specified by manufacturer); Nerisone Forte® not licensed for use in children under 4 years

Indication and dose

**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

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) Cream, diflucortolone valerate 0.1%, net price 30 g = £1.59. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients include disodium edetate, hydroxybenzoates (parabens), stearyl alcohol

Oily cream, diflucortolone valerate 0.1%, net price 30 g = £2.56. Label: 28, counselling, application, see p. 674. Potency: potent

Excipients include beeswax

Ointment, diflucortolone valerate 0.1%, net price 15 g = £2.09. Label: 28, counselling, application, see p. 674. Potency: very potent

Excipients none as listed in section 13.1.3

Nerisone Forte® (Meadow) Oily cream, diflucortolone valerate 0.3%, net price 15 g = £2.09. Label: 28, counselling, application, see p. 674. Potency: very potent

Excipients none as listed in section 13.1.3

**FLUDROXYCORTIDE** (Flurandrenolone)

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

Indication and dose

**Inflammatory skin disorders such as eczemas** Apply thinly 1–2 times daily

Haelan® (Typharm) Cream, fludroxycortide 0.0125%, net price 60 g = £3.26. Label: 28, counselling, application, see p. 674. Potency: moderate

Excipients include cetyl alcohol, propylene glycol

Ointment, fludroxycortide 0.0125%, net price 60 g = £3.26. Label: 28, counselling, application, see p. 674. Potency: moderate

Excipients include beeswax, cetyl alcohol, polysorbate

Tape, polythene adhesive film impregnated with fludroxycortide 4 micrograms/cm², net price 7.5 cm × 50 cm = £9.27, 7.5 cm × 200 cm = £24.95

Dose

**Chronic localised recalcitrant dermatoses (but not acute or weeping)**

Cut tape to fit lesion, apply to clean, dry skin shorn of hair, usually for 12 hours daily

**FLUOCINOLONE ACETONIDE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 1 year
**Indication and dose**

Severe inflammatory skin disorders such as eczemas, psoriasis see notes above

Apply thinly 1–2 times daily, reducing strength as condition responds

**Synalar® (GP Pharma)**

*Cream*, fluocinolone acetonide 0.025%, net price 50 g = £4.16. Label: 28, counselling, application, see p. 674. Potency: mild

*Exipients* include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol

**Synalar 1 in 10 Dilution® (GP Pharma)**

*Cream*, fluocinolone acetonide 0.0025%, net price 50 g = £16. Label: 28, counselling, application, see p. 674. Potency: weak

*Exipients* include benzyl alcohol, cetostearyl alcohol, polysorbates, propylene glycol

**Synalar 1 in 10 Dilution® With antibacterials**

See notes above for comment on compound preparations

**Synalar C® (GP Pharma)**

*Cream*, fluocinolone acetonide 0.025%, clioquinol 3%, net price 50 g = £2.42. Label: 28, counselling, application, see p. 674. Potency: potent

*Exipients* include cetostearyl alcohol, disodium edetate, hydroxybenzoates (parabens), polysorbates, propylene glycol

**Synalar N® (GP Pharma)**

*Cream*, fluocinolone acetonide 0.025%, neomycin sulphate 0.5%, net price 50 g = £3.96. Label: 28, counselling, application, see p. 674. Potency: potent

*Exipients* include propylene glycol, wool fat

**Metosyn® (GP Pharma)**

*FAPG cream*, fluocinolone acetonide 0.05%, net price 25 g = £3.00, 50 g = £6.00. Label: 28, counselling, application, see p. 674. Potency: moderate

*Exipients* include propylene glycol

**Ultralanum Plain® (Meadow)**

*Cream*, fluocortolone caproate 0.25%, fluocortolone pivalate 0.25%, net price 50 g = £2.95. Label: 28, counselling, application, see p. 674. Potency: moderate

*Exipients* include disodium edetate, fragrance, hydroxybenzoates (parabens), stearyl alcohol

**FLUCINOLONE ACETONIDE (continued)**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

**FLUCORTOLONE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

**FLUTICASONE PROPIONATE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 3 months

**FLUCINOLONE ACETONIDE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 1 year

**Indication and dose**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

**FLUCORTOLONE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

Severe inflammatory skin disorders such as eczemas unresponsive to less potent corticosteroids, psoriasis see notes above

Apply thinly 1–2 times daily

**FLUTICASONE PROPIONATE**

Cautions see notes above

Contra-indications see notes above

Side-effects see notes above

Licensed use not licensed for use in children under 3 months
**13.5 Preparations for eczema and psoriasis**

### 13.5.1 Preparations for eczema

The main types of eczema (dermatitis) in children are atopic, irritant and allergic contact; different types may co-exist. *Atopic eczema* is the most common type and it usually involves dry skin as well as infection and lichenification caused by scratching and rubbing. *Seborrhoeic dermatitis* (see below) is also common in infants.

Management of eczema involves the removal or treatment of contributory factors; known or suspected irritants and contact allergens should be avoided. Rarely, ingredients in topical medicinal products may sensitise the skin (section 13.1.3); *BNF for Children* lists active ingredients together with excipients that have been associated with skin sensitisation.

### 13.5.2 Preparations for psoriasis

### 13.5.3 Drugs affecting the immune response
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, and the age of the child. Mild corticosteroids are generally used on the face and on flexures; the more potent corticosteroids are generally required for use on lichenified areas of eczema or for severe 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. Wet elasticated viscose stockinette is used for ‘wet-wrap’ bandaging over topical corticosteroids or emollients to cool the skin and relieve itching, but there is an increased risk of infection and excessive absorption of the corticosteroid; ‘wet-wrap’ bandaging should be used under specialist supervision.

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. A topical antibacterial such as fusidic acid (section 13.10.1) may be used for small areas of mild infection; treatment should be limited to a short course (typically 1 week) to reduce the risk of drug resistance or skin sensitisation. Associated eczema is treated simultaneously with a moderately potent or potent topical corticosteroid which can be combined with an antimicrobial such as clioquinol.

Eczema involving moderate to severe, widespread, or recurrent infection requires the use of a systemic antibacterial (section 5.1, table 1) that is active against the infecting organism. Preparations that combine an antiseptic with an emollient (section 13.2.1) and with a bath emollient (section 13.2.1.1) can also be used; antiseptic shampoos (section 13.9) can be used on the scalp.

**Intertriginous eczema** commonly involves candida and bacteria; it is best treated with a mild or moderately potent topical corticosteroid combined with a suitable antimicrobial drug. For the treatment of nappy rash, see section 13.2.2.

Widespread **herpes simplex infection** may complicate atopic eczema (eczema herpeticum) and treatment under specialist supervision with a systemic antiviral drug (section 5.3.2.1) is indicated. Secondary bacterial infection often exacerbates eczema herpeticum.

The management of **seborrhoeic dermatitis** is described below.

**Management of other features of eczema**  
**Lichenification**, which results from repeated scratching, is treated initially with a potent corticosteroid. Bandages containing **ichthammol** (to reduce pruritus) and other substances such as **zinc oxide** can be applied over the corticosteroid or emollient. **Coal tar** (section 13.5.2) and ichthammol can be useful in some cases of **chronic eczema**. **Discoid eczema**, with thickened plaques in chronic atopic eczema, is usually treated with a topical antiseptic preparation, a potent topical corticosteroid, and paste bandages containing zinc oxide and ichthammol.

A **non-sedating** antihistamine (section 3.4.1) may be of some value in relieving severe itching or urticaria associated with eczema. A **sedating** antihistamine (section 3.4.1) may be used at night if itching causes sleep disturbance, but a large dose may be needed and drowsiness may persist on the following day.

**Exudative** (‘weeping’) **eczema** requires a potent corticosteroid initially; infection may also be present and require specific treatment (see above). **Potassium permanganate** solution (1 in 10 000) can be used as a soak in exudating eczema for its antiseptic and astringent effects; treatment should be stopped when exudation stops.

**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).
Seborrhoeic dermatitis  

Seborrhoeic dermatitis (seborrhoeic eczema) is associated with species of the yeast Malassezia. Infantile seborrhoeic dermatitis affects particularly the body folds, nappy area and scalp; it is treated with emollients and mild topical corticosteroids with suitable antimicrobials. Infantile seborrhoeic dermatitis affecting the scalp (cradle cap) is treated by hydrating the scalp using natural oils and the use of mild shampoo (section 13.9).

In older children, seborrhoeic dermatitis 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 topical corticosteroids with suitable antimicrobials (section 13.4) are used to treat older children.

**ICHTHAMMOL**

**Side-effects**  skin irritation

**Licensed use**  no information available

**Indication and dose**

<table>
<thead>
<tr>
<th>Chronic lichenified eczema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1–18 years apply 1–3 times daily</td>
</tr>
</tbody>
</table>

**Ichthammol Ointment, BP 1980**

Ointment, ichthammol 10%, yellow soft paraffin 45%, wool fat 45%

**Zinc and Ichthammol Cream, BP**

Cream, ichthammol 5%, cetostearyl alcohol 3%, wool fat 10%, in zinc cream

**Medicated bandages**

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 (but the inclusion of clioquinol may lead to irritation in susceptible children).

**Zinc Paste Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide; requires additional bandaging. Net price 6 m × 7.5 cm = £3.24 (Mölnlycke—Steripaste® (15%), excipients: include polysorbate 80); £3.23 (Mölnlycke—Zincaband® (15%), excipients: include hydroxybenzoates); £3.35 (S&N Hlth—Vicopaste FB® (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. Net price 6 m × 7.5 cm = £3.33 (Mölnlycke—Calaband®)

**Zinc Paste, Calamine, and Clioquinol Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing calamine, clioquinol, and zinc oxide; requires additional bandaging. Net price 6 m × 7.5 cm = £3.33 (Mölnlycke—Quinaband® excipients: include hydroxybenzoates)

**Zinc Paste and Ichthammol Bandage, BP 1993**

Cotton fabric, plain weave, impregnated with suitable paste containing zinc oxide and ichthammol; requires additional bandaging. Net price 6 m × 7.5 cm = £3.38 (S&N Hlth—Ichthopaste® (6/2%), excipients: include cetostearyl alcohol)

**Medicated stocking**

Zipzoc® (S&N Hlth.)

Sterile rayon stocking impregnated with ointment containing zinc oxide 20%. 4-pouch carton = £12.52; 10-pouch carton = £31.30

**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. Guttate psoriasis is a distinctive form of psoriasis that characteristically occurs in children and young adults, often following a streptococcal throat infection or tonsillitis.

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 occur 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 antiproliferative effect in psoriasis. They are particularly useful in inflammatory psoriasis and in chronic stable plaque psoriasis.

For chronic stable plaque psoriasis on extensor surfaces of trunk and limbs preparations containing coal tar are moderately effective, but the smell is unacceptable to some children. Vitamin D and its analogues are effective and cosmetically acceptable alternatives to preparations containing coal tar or dithranol.
Dithranol is the most effective topical antipsoriatic agent but it irritates and stains the skin and it should be used only under specialist supervision. Adverse effects of dithranol are minimised by using a ‘short-contact technique’ (see below) and by starting with low concentration preparations. Tazarotene, a topical retinoid for the treatment of mild to moderate plaque psoriasis, is not recommended for use in children under 18 years. These medications can irritate the skin particularly in the flexures and they 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 erythrodermic or generalised pustular type requires urgent specialist assessment. Initial topical treatment should be limited to using emollients frequently and generously. 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. 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 for psoriasis affecting the scalp combine salicylic acid with coal tar or sulphur. The preparation should be applied generously and 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. 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. Contact of coal tar products with normal skin is not normally harmful and preparations containing coal tar can be used for widespread small lesions; however, irritation, contact allergy, and sterile folliculitis can occur. Preparations containing up to 6% coal tar may be used on children 1 month to 2 years; preparations containing coal tar 10% may be used on children over 2 years with more severe psoriasis. For shampoo preparations containing coal tar, see section 13.9.

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 20–30 minutes (‘short contact’ technique). 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.

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.
Systemic or potent topical corticosteroids should be avoided or used only under specialist supervision; although corticosteroids may suppress psoriasis in the short term, relapse or vigorous rebound occurs on withdrawal.

**Phototherapy** Phototherapy is available in specialist centres under the supervision of a dermatologist. Narrow band ultraviolet B (UVB) radiation is usually effective for *chronic stable psoriasis* and for *guttate psoriasis*. It can be considered for children with moderately severe psoriasis in whom topical treatment has failed, but it may irritate inflammatory psoriasis. The use of phototherapy and photopheresis in children is limited by concerns over carcinogenicity and premature ageing.

**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 the *localised palmoplantar pustular psoriasis*. Early adverse effects include phototoxicity 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 cataracts. Phototherapy combined with coal tar, dithranol, 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 and drugs that affect the immune response (section 13.5.3).

**Acitretin**, a metabolite of etretinate, is a retinoid (vitamin A derivative); it is prescribed by specialists. The main indication of acitretin is severe psoriasis resistant to other forms of therapy. 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; adverse effects are a limiting factor. A therapeutic effect occurs after 2 to 4 weeks and the maximum benefit after 4 to 6 weeks or longer. Continuous treatment for longer than 6 months is not usually necessary in psoriasis. However, some patients, particularly those with severe ichthyosis, 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. Topical preparations containing keratolytics should normally be stopped before administration of acitretin. Liberal use of emollients should be encouraged and topical corticosteroids can be continued if necessary. Acitretin is teratogenic; in females of child-bearing age, 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 before starting treatment, after 1 month, and then 3-monthly during treatment. Musculoskeletal development should also be monitored closely.

**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**

**Cautions** see notes above; avoid use on face; avoid excessive exposure to sunlight and sunlamps

**Pregnancy** manufacturer advises avoid if possible

**Breast-feeding** no information available

**Contra-indications** see notes above

**Side-effects** see notes above; also photosensitivity; rarely facial or perioral dermatitis, skin atrophy

**Licensed use** Calcipotriol ointment, *Dovonex*® *Scalp Solution* and *Dovobet*® not licensed for use in children

**Indication and dose**

**Plaque psoriasis**

**Child 6–18 years** apply cream or ointment twice daily; 6–12 years max. 50 g weekly, over 12 years max. 75 g weekly (less with scalp solution, see below)

**Note** Patient information leaflet for *Dovonex*® cream advises liberal application (but note max. recommended weekly dose, above)

**Scalp solution**, calcipotriol 50 micrograms/mL, net price 60 mL = £13.04, 120 mL = £26.07

**Excipients** include propylene glycol

**Dose**

**Scalp psoriasis (specialist use only)**

**Child 6–12 years** apply to scalp twice daily; max. 30 mL weekly (less when used with cream or ointment, see below)

**Child 12–18 years** apply to scalp twice daily; max. 45 mL weekly (less when used with cream or ointment, see below)

**Note** When preparations used together max. total calcipotriol 2.5 mg in any one week for child 6–12 years (e.g. scalp solution 20 mL with cream or ointment 30 g); max. 3.75 mg in any one week for child 12–18 years (e.g. scalp solution 30 mL with cream or ointment 45 g)

**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**

**Stable plaque psoriasis (specialist use only)**

**Child 12–18 years** apply once daily to max. 30% of body surface for up to 4 weeks; max. 75 g weekly; subsequent courses repeated after an interval of at least 4 weeks

**Note** When different preparations containing calcipotriol used together, max. total calcipotriol 3.75 mg in any one week for child 12–18 years

**Silkis® (Galderma)**

Ointment, calcitriol 3 micrograms/g, net price 100 g = £16.34

**Excipients** none as listed in section 13.1.3

**Indication and dose**

**Mild to moderate plaque psoriasis**

**Child 12–18 years** apply twice daily; not more than 35% of body surface to be treated daily, max. 30 g daily

**Silkis® (Galderma)**

Ointment, calcitriol 3 micrograms/g, net price 100 g = £16.34

**Excipients** none as listed in section 13.1.3

**TACALCITOL**

**Cautions** see notes above; avoid eyes; monitor plasma-calcium concentration if risk of hypercalcaemia or in renal impairment; if used in conjunction with UV treatment, UV radiation should be given in the morning and tacalcitol applied at bedtime

**Pregnancy** avoid if possible

**Breast-feeding** no information available

**Contra-indications** see notes above

**Side-effects** see notes above

**Indication and dose**

**Plaque psoriasis**

**Child 12–18 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 tacalcitol 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 disodium 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
Cautions  avoid eyes, mucosa, genital or rectal areas, and broken or inflamed skin; use suitable chemical protection gloves for extemporaneous preparation
Pregnancy  no adverse effects reported
Breast-feeding  no adverse effects reported
Contra-indications  not for use in sore, acute, or pustular psoriasis or in presence of infection
Side-effects  skin irritation and acne-like eruptions, photosensitivity; stains skin, hair, and fabric

Indication and dose
Psoriasis and occasionally chronic atopic eczema
Apply 1–3 times daily starting with low-strength preparations; proprietary preparations, see individual entries below
Note  For shampoo preparations see section 13.9

Non-proprietary preparations
May be difficult to obtain. Patients may find newer proprietary preparations more acceptable

Coal Tar Paste, BP
Paste, strong coal tar solution 7.5%, in compound zinc paste

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

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

Cocois® (UCB Pharma)
Scalp ointment, coal tar solution 12%, salicylic acid 2%, precipitated sulphur 4%, in a coconut oil emollient basis, net price 40 g = £6.22, 100 g = £11.69
Excipients include cetostearyl alcohol

Dose
Scaly scalp disorders including psoriasis, eczema, seborrhoecic dermatitis and dandruff
Child 6–12 years medical supervision required
Child 12–18 years apply to scalp as necessary (if severe use daily for first 3–7 days), shampoo off after 1 hour

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 an adult-size bath, and proportionally less for a child’s 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
Ecema and psoriasis
Use 15–30 mL in adult-size bath or apply directly to wet skin and rinse after a few minutes; can be used as a soap substitute

GeL, tar 1.6%, net price 100 g = £4.95

Dose
Ecema and psoriasis
Apply directly to wet skin and rinse after a few minutes; can be used as a soap substitute
688 13.5.2 Preparations for psoriasis  BNFC 2009

\( \text{TARS (continued)} \)

Solution, tar 2.3%, net price 200 mL = £4.45, 500 mL = £7.45
Dose

Ecema and psoriasis
Use 15–30 mL in adult-size 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 a soap substitute

Polytar Emollient® (Stiefel)
Bath additive, coal tar solution 2.5%, arachis (peanut) oil extract of coal tar 7.5%, tar 7.5%, cade oil 7.5%, liquid paraffin 35%, net price 500 mL = £5.78
Excipients include isopropyl palmitate
Dose

Psoriasis, eczema, atopic and pruritic dermatoses
Use 2–4 capfuls (15–30 mL) in adult-size bath and proportionally less for a child’s bath; soak for 20 minutes

\( \text{With corticosteroids} \)

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), isopropyl palmitate, wool fat
Dose

Psoriasis
Child 5–18 years apply thinly twice daily

\( \text{Dithranol} \)

\( \text{Anthralin} \)

Cautions avoid use near eyes and sensitive areas of skin; see also notes above
Pregnancy no adverse effects reported
Breast-feeding no adverse effects reported
Contra-indications hypersensitivity; acute and pustular psoriasis
Side-effects local burning sensation and irritation; stains skin, hair, and fabrics
Licensed use Dithrocream® and Psorin® licensed for use in children (age range not specified by manufacturer); Micanol® licensed for use in children, but not recommended for infants or young children (age range not specified by manufacturer)
Indication and dose

Subacute and chronic psoriasis
See notes above and under preparations
Note Some of these dithranol preparations also contain coal tar or salicylic acid—for cautions, contraindications, and side-effects see under Tars or under Salicylic Acid

\( \text{Non-proprietary preparations} \)

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
1. (BP) if dithranol content more than 1%, otherwise may be sold to the public

Dithranol Paste, BP
Paste, dithranol in zinc and salicylic acid (Lassar’s) paste. Usual strengths 0.1–1% of dithranol. Label: 28

Psoriderm® (Dermal)
Bath emulsion, coal tar 40%, net price 200 mL = £2.87
Excipients include polysorbate 20
Dose

Psoriasis
Use 30 mL in adult-size bath, and proportionally less for a child’s bath; soak for 5 minutes

Psorin® (LPC)
Ointment, dithranol 0.11%, coal tar 1%, salicylic acid 1.6%, net price 50 g = £9.22, 100 g = £18.44. Label: 28
Excipients include 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
Excipients 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

Micanol® (GP Pharma)
Cream, dithranol 1% in a lipid-stabilised basis, net price 50 g = £13.48; (BP) 3%, 50 g = £16.79. Label: 28
Excipients none as listed in section 13.1.3
Dose

For application to skin or scalp; 0.1–0.5% cream suitable for overnight treatment, 1–2% cream for max. 1 hour

Proprietary preparations

Dithrocream® (Dermal)
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; (BP) 2%, 50 g = £7.10. Label: 28
Excipients include 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 the 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. Label: 28
Excipients include 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
Excipients 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

With corticosteroids

Alphosyl HC® (GSK Consumer Healthcare) (BP) 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), isopropyl palmitate, wool fat
Dose

Psoriasis
Child 5–18 years apply thinly twice daily
Salicylic acid

**SALICYLIC ACID**

For coal tar preparations containing salicylic acid, see under Tars p. 687; for dithranol preparations containing salicylic acid see under Dithranol, above.

**Cautions** see notes above; avoid broken or inflamed skin.

**Salicylate toxicity** Salicylate toxicity may occur particularly if applied on large areas of skin or on neonatal skin.

**Side-effects** sensitivity, excessive drying, irritation, systemic effects after widespread use (see under Cautions).

**Indication and dose**

Hyperkeratotic skin disorders see under preparation.

**Acne** section 13.6.1

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**ORAL RETINOIDS FOR PSORIASIS**

**ACITRETIN**

**Note** Acitretin is a metabolite of etretinate.

**Cautions** in children use only in exceptional circumstances (premature epiphyseal closure reported); in females of childbearing age 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)—females of childbearing age (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, after 1 month, 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; avoid excessive exposure to sunlight and unsupervised use of sunlamps; interactions: Appendix 1 (retinoids).

**Contra-indications** hyperlipidaemia

Hepatic impairment avoid—further impairment may occur.

Renal impairment avoid; increased risk of toxicity.

Pregnancy teratogenic; effective contraception must be used (see Cautions above).

Breast-feeding avoid.

**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, paraonychia, granulomatous lesions, bullous eruptions, reversible hair thinning and alopecia, myalgia and arthralgia, occasional nausea, headache, malaise, drowsiness, rhinitis, sweating, taste disturbance, and gingivitis; benign intracranial hypertension (discontinue if severe headache, vomiting, diarrhoea, abdominal pain, and visual disturbance occur; avoid concomitant tetracyclines); photosensitivity; corneal ulceration, raised liver enzymes, rarely jaundice and hepatitis (avoid concomitant methotrexate); raised serum triglycerides or cholesterol; decreased night vision reported; skeletal hyperostosis and extrasosseous calcification reported following long-term administration of etretinate (and premature epiphyseal closure in children, see Cautions).

**Indication and dose**

Harlequin ichthyosis (under expert supervision only)

- By mouth

Neonate 500 micrograms/kg once daily with food or milk (occasionally up to 1 mg/kg daily) with careful monitoring of musculoskeletal development.

Severe extensive psoriasis resistant to other forms of therapy, palmoplantar pustular psoriasis, severe congenital ichthyosis, severe Darier’s disease (keratosis follicularis) (all under expert supervision only)

- By mouth

Child 1 month–12 years 500 micrograms/kg once daily with food or milk (occasionally up to 1 mg/kg daily) to max. 35 mg daily with careful monitoring of musculoskeletal development (see also p. 685).

Child 12–18 years 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 (see also p. 685).
13.5.3 Drugs affecting the immune response

Drugs affecting the immune response are used for eczema or psoriasis.

**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 treatment 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 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 systemic corticosteroid (section 6.3.2) such as prednisolone may be used in *severe* refractory eczema.

Systemic drugs acting on the immune system are generally used by specialists in a hospital setting.

**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 also used for severe refractory eczema in children.

**Methotrexate** can be used for *severe resistant psoriasis*; the dose is given *once weekly* and adjusted according to severity of the condition and haematological and biochemical measurements. Folic acid (section 9.1.2) should be given to reduce the possibility of methotrexate toxicity. Folic acid can be given at a dose of 5 mg once weekly; alternative regimens may be used in some settings.

**Etanercept** (a cytokine modulator) is licensed in children over 8 years of age for the treatment of severe plaque psoriasis that is inadequately controlled by other systemic treatments and photochemotherapy, or when these other treatments cannot be used because of intolerance or contra-indications.

**CICLOSPORIN** (Cyclosporin)

**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 for first 3 months then every month; reduce dose by 25–50% if serum creatinine increases more than 30% above baseline (even if within normal range) and discontinue if reduction not successful within one month. Discontinue if hypertension develops that cannot be controlled by dose reduction or antihyper-tensive therapy. Avoid excessive exposure to sunlight and avoid use of UVB or PUVA. In *atopic dermatitis*, also allow herpes simplex infections to clear before starting (if they occur during treatment withdraw if severe); *Staphylococcus aureus* skin infections not absolute contra-indication providing controlled (but avoid erythromycin unless no other alternative—see also interactions: Appendix 1 (ciclosporin)); investigate lymphadenopathy that persists despite improvement in atopic dermatitis. In *psoriasis*, also exclude malignancies (including those of skin and cervix) before starting (biopsy any lesions not typical of psoriasis) and treat patients with malignant or pre-malignant conditions of skin only after appropriate treatment (and if no other option); discontinue if lymphoproliferative disorder develops
Side-effects see section 8.2.2
Licensed use not licensed for use in children under 16 years for atopic eczema (dermatitis)

Indication and dose
Short-term treatment (usually max. 8 weeks but may be used for longer by specialists) of severe atopic dermatitis where conventional therapy ineffective or inappropriate
- By mouth, administered in accordance with expert advice
  Child 1 month–18 years initially 1.25 mg/kg twice daily; if good initial response not achieved within 2 weeks, increase rapidly to max. 2.5 mg/kg twice daily; initial dose of 2.5 mg/kg twice daily if very severe

METHOTREXATE

Cautions see section 8.1.3, also photosensitivity—psoriasis lesions aggravated by UV radiation (skin ulceration reported)
Contra-indications see section 8.1.3
Side-effects see section 8.1.3
Licensed use not licensed for use in children with psoriasis

Indication and dose
Severe uncontrolled psoriasis unresponsive to conventional therapy (specialist use only)
- By mouth
  Child 2–18 years initially 200 micrograms/kg (max. 10 mg) once weekly increased according to response to 400 micrograms/kg (max. 25 mg) once weekly

SAFE PRACTICE
Note that the above dose is a weekly dose. To avoid error with low-dose methotrexate, it is recommended that:
- the child or their carer 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 child or their carer 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).

Malignant disease section 8.1.3
Rheumatoid arthritis section 10.1.3
Severe Crohn’s disease section 1.5.3

Preparations
Section 8.2.2

PIMECROLIMUS

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, infection 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 ulcers

Preparations
Section 10.1.3

CICLOSPORIN (continued)
A 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

**Indication and dose**

Short-term treatment of moderate to severe atopic eczema (including flares) either unresponsive to, or in children intolerant of conventional therapy; see also notes above.

- **Child 2–16 years** initially apply 0.03% ointment thinly 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.
- **Child 16–18 years** initially apply 0.1% ointment thinly twice daily until lesion clears (consider other treatment if eczema worsens or if no improvement after 2 weeks); reduce to once daily or switch to 0.03% ointment if clinical condition allows.

**Other indications** section 8.2.2

**Protopic** (Astellas)®

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

**ETANERCEPT**

**Indication and dose**

Severe plaque psoriasis

- By subcutaneous injection

  - **Child 8–18 years** 800 micrograms/kg (max. 50 mg) once weekly; max. treatment duration 24 weeks; discontinue if no response after 12 weeks

**Preparations**

Section 10.1.3

### Polyarticular-course juvenile idiopathic arthritis

Section 10.1.3

## Acne and rosacea

### 13.6.1 Topical preparations for acne

**Acne vulgaris** Acne vulgaris commonly affects children around puberty and occasionally affects infants. Treatment of acne should be commenced early to
prevent scarring; lesions may worsen before improving. The choice of treatment depends on age, severity, and whether the acne is predominantly inflammatory or comedonal.

**Mild to moderate acne** is generally treated with topical preparations, such as benzoyl peroxide, azelaic acid, and retinoids, (section 13.6.1).

For **moderate to severe inflammatory acne** or where topical preparations are not tolerated or are ineffective or where application to the site is difficult, systemic treatment (section 13.6.2) with oral antibacterials may be effective. **Co-cyprindiol** (cyproterone acetate with ethinylestradiol) has anti-androgenic properties and may be useful in young women with acne refractory to other treatments.

**Severe acne**, acne unresponsive to prolonged courses of oral antibacterials, acne with scarring, or acne associated with psychological problems calls for early referral to a consultant dermatologist who may prescribe oral isotretinoin (section 13.6.2).

**Neonatal and infantile acne** Inflammatory papules, pustules, and occasionally comedones may develop at birth or within the first month; most neonates with acne do not require treatment. Acne developing at 3–6 months of age may be more severe and persistent; lesions are usually confined to the face. Topical preparations containing benzoyl peroxide (at the lowest strength possible to avoid irritation), azelaic acid, adapalene, or tretinoin may be used if treatment for infantile acne is necessary. In infants with inflammatory acne, oral erythromycin (section 5.1.5) is used because topical preparations for acne are not well tolerated. In cases of erythromycin-resistant acne, oral isotretinoin (section 13.6.2) can be given on the advice of a consultant dermatologist.

**Rosacea** The adult form of rosacea rarely occurs in children. Persistent or repeated use of potent topical corticosteroids may cause periorificial rosacea (steroid acne). The pustules and papules of rosacea may be treated for at least 6 weeks with a topical metronidazole preparation (section 13.10.1.2), or a systemic antibacterial such as erythromycin (section 5.1.5), or for a child over 12 years, oxytetracycline (section 5.1.3). Tetracyclines are contra-indicated in children under 12 years of age.

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### 13.6.1 Topical preparations for acne

In mild to moderate acne, comedones and inflamed lesions respond well to benzoyl peroxide (see below) or topical retinoids (see p.695). Alternatively, topical application of an antibacterial such as erythromycin or clindamycin may be effective for inflammatory acne. However, topical antibacterials are probably no more effective than benzoyl peroxide and may promote the emergence of resistant organisms. If topical preparations prove inadequate oral preparations may be needed (section 13.6.2). The choice of product and formulation (gel, solution, lotion, or cream) is largely determined by skin type, patient preference, and previous usage of acne products.

**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 a reduction in benzoyl peroxide concentration, frequency, and area of application. If the acne does not respond after 2 months then use of a topical antibacterial should be considered.

**Azelaic acid** has antimicrobial and anticomedonal properties. It may be used as an alternative to benzoyl peroxide or to a topical retinoid for treating mild to moderate comedonal acne, particularly of the face; azelaic acid is less likely to cause local irritation than benzoyl peroxide.
**BENZOYL PEROXIDE**

**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 reintroduce at reduced frequency).

**Licensed use**  
Quinoderm® is licensed for use in children; all other preparations, not licensed for use in treatment of infantile acne.

**Indication and dose**

**Acne vulgaris**

- **Child 12–18 years**: apply 1–2 times daily preferably after washing with soap and water, start treatment with lower-strength preparations.

  **Note**: May bleach clothing.

**Infantile acne**

- **Neonate**: apply 1–2 times daily; start treatment with lower-strength preparations.

- **Child 1 month–2 years**: apply 1–2 times daily; start treatment with lower-strength preparations.

**Acnecide®** (Galderma)

- **Gel**: benzoyl peroxide 5% in an aqueous gel basis, net price 60 g = £5.69  
  **Excipients**: include propylene glycol.

**Brevoxyl®** (Stiefel)

- **Cream**: benzoyl peroxide 4% in an aqueous basis, net price 40 g = £3.30  
  **Excipients**: include cetostearyl alcohol, fragrance, stearyl alcohol.

**PanOxyl®** (Stiefel)

- **Aquagel (= aqueous gel)**: benzoyl peroxide 2.5%, net price 40 g = £1.76; 5%, 40 g = £1.92; 10%, 40 g = £2.13  
  **Excipients**: include propylene glycol.

**AZELAIC ACID**

**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.

**Licensed use**  
Not licensed for use in infantile acne.

**Indication and dose**

**See under preparations**

**Finacea®** (Valeant)

- **Gel**: azelaic acid 15%, net price 30 g = £7.48  
  **Excipients**: include disodium edetate, polysorbate 80, propylene glycol.

**Skinoren®** (Valeant)

- **Cream**: azelaic acid 20%, net price 30 g = £3.74  
  **Excipients**: include propylene glycol.

**Dose**

- **Acne vulgaris, infantile acne**: apply twice daily (sensitive skin, once daily for first week). Extended treatment may be required but manufacturer advises period of treatment should not exceed 6 months.

**With antimicrobials**

**Duac® Once Daily** (Stiefel)

- **Gel**: benzoyl peroxide 5%, clindamycin 1% (as phosphate) in an aqueous basis, net price 25 g = £9.95, 50 g = £19.90  
  **Excipients**: include disodium edetate.

**Dose**

- **Acne vulgaris**: apply once daily in the evening.

- **Quinoderm®** (Ferndale)

  - **Cream**: benzoyl peroxide 5%, potassium hydroxyquinoline sulphate 0.5%, in an astringent vanishing-cream basis, net price 50 g = £2.21  
    **Excipients**: include cetostearyl alcohol, edetic acid (EDTA).

  - **Cream**: benzoyl peroxide 10%, potassium hydroxyquinoline sulphate 0.5%, in an astringent vanishing-cream basis, net price 25 g = £1.30, 50 g = £2.49  
    **Excipients**: include cetostearyl alcohol, edetic acid (EDTA).

**Dose**

- **Infantile acne, acne vulgaris, acneform eruptions, impetigo, folliculitis**: apply 2–3 times daily.
Topical antibacterials for acne

In the treatment of 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 children who wish to avoid oral antibacterials or who cannot tolerate them.

Topical preparations of erythromycin and clindamycin may be used to treat inflamed lesions in mild to moderate acne when topical benzoyl peroxide or tretinoin is ineffective or poorly tolerated. Topical benzoyl peroxide, azelaic acid, or retinoids used in combination with an antibacterial (topical or systemic) may be more effective than an antibacterial used alone. 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. 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 (but treatment with a topical preparation should be continued for at least 6 months).

### ANTIBACTERIALS

**Cautions** some manufacturers advise preparations containing alcohol are not suitable for use with benzoyl peroxide

**Indication and dose**

**Acne vulgaris** for dose, see under preparations

**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

**Zindaclin** (Crawford)

- **Gel**, clindamycin 1% (as phosphate), net price 30 g = £8.66
- **Excipients** include propylene glycol

**Dose**

- Child 12–18 years 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.

Tretinoin is used under specialist supervision to treat infantile acne, see Neonatal and Infantile Acne, p. 693.

Adapalene, a retinoid-like drug, is used for mild to moderate acne vulgaris and may also be used to treat infantile acne. It is less irritant 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. Topical retinoids should be used with caution on 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 (section 13.8.1) 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  Tretinoin is contra-indicated in children with personal or familial history of cutaneous epithelioma. Topical retinoids are contra-indicated in pregnancy; females of child-bearing age must use effective contraception (oral progestogen-only contraceptives not considered effective).

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 crusting of skin have been reported rarely.

### ADAPALENE

**Cautions**  see notes above  
**Contra-indications**  see notes above  
**Side-effects**  see notes above  
**Licensed use**  not licensed for use in infantile acne  
**Indication and dose**  
- **Infantile acne**  
- **Neonate**  apply thinly once daily at night  
- **Child 1 month–2 years**  apply thinly once daily at night

### TRETINOIN

**Note**  Tretinoin is the acid form of vitamin A  
**Cautions**  see notes above  
**Contra-indications**  see notes above  
**Side-effects**  see notes above  
**Licensed use**  Retin-A® not licensed for use in infantile acne  
**Indication and dose**  
- See under preparations  
- **Malignant disease (section 8.1.5)**

### 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. 699  
**Cautions**  (topical application only)  see notes above  
**Contra-indications**  (topical application only)  see notes above
**Indication and dose**

**Acne vulgaris**
- Apply thinly 1–2 times daily

**Isotrex** (Stiefel) Gel, isotretinoin 0.05%, net price 30 g = £6.18
- 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.

**NICOTINAMIDE**

- **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
- **Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

**Inflammatory acne vulgaris** see under preparations below

**Nicam** (Dermal) Gel, nicotinamide 4%, net price 60 g = £7.42
- Excipients none as listed in section 13.1.3

**Dose**
- Apply twice daily; reduce to once daily or on alternate days if irritation occurs

**SALICYLIC ACID**

- **Cautions** risk of significant systemic absorption in neonates; avoid contact with mouth, eyes, mucous membranes; systemic effects after excessive use
- **Side-effects** local irritation
- **Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

**Acne vulgaris** see under preparation

**Psoriasis** see section 13.5.2

**Warts and calluses** section 13.7

**Fungal nail infections** section 13.10.2

**Acnisal** (Alliance) Topical solution, salicylic acid 2% in a detergent and emollient basis, net price 177 mL = £4.03
- Excipients include benzyl alcohol

**Dose**
- Apply up to 3 times daily

**13.6.2 Oral preparations for acne**

**Oral antibacterials for acne**

Oral antibacterials may be used in moderate to severe inflammatory acne when topical treatment is not adequately effective or is inappropriate. Concomitant anticomedomal treatment with topical benzoyl peroxide or azelaic acid may also be required (section 13.6.1).

Tetracyclines should not be given to children under 12 years. In children over 12 years, 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 in children over 12 years. 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 for children over 12 years is an alternative for the management of moderate to severe acne with inflamed lesions, but propionibacteria strains resistant to erythromycin are becoming widespread and this may explain poor response. Infants with acne requiring oral treatment with erythromycin should be given 250 mg once daily or 125 mg twice daily; in cases of erythromycin-resistant *P. acnes* in infants, oral isotretinoin may be used on the advice of a consultant dermatologist.

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 females of childbearing age 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 females 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.

**CSM advice**

Venous thromboembolism occurs more frequently in women taking co-cyprindiol than those taking a low-dose combined oral contraceptive. The CSM has reminded prescribers that co-cyprindiol is licensed for use in women with severe acne which has not responded to oral antibacterials and for moderately severe hirsutism; it should not be used solely for contraception. It is contra-indicated in those with a personal or close family history of venous thromboembolism. Women with severe acne or hirsutism may have an inherently increased risk of cardiovascular disease.

### CO-CYPRINDIOL

A mixture of cyproterone acetate and ethinylestradiol in the mass proportions 2000 parts to 35 parts, respectively

**Cautions** see under Combined Hormonal Contraceptives, section 7.3.1

**Contra-indications** see under Combined Hormonal Contraceptives, section 7.3.1

**Side-effects** see under Combined Hormonal Contraceptives, section 7.3.1

**Licensed use** licensed for use in females of childbearing age

**Indication and dose**

Severe acne in females of childbearing age refractory to prolonged oral antibacterial therapy (but see notes above), moderately severe hirsutism

- **By mouth**
  - 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) (T)

Tablets, co-cyprindiol 2000/35 (cyproterone acetate 2 mg, ethinylestradiol 35 micrograms), net price 21-tab pack = £3.74

Brands include Acnocin®, Cicafem®, Clairette®, Diva®

**Dianette** (Schering Health) (T)

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, acne with scarring, or for acne which has not responded to an adequate course of a systemic antibacterial. Isotretinoin is used for the treatment of severe infantile acne resistant to erythromycin.

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 females 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. They must also be registered with a pregnancy prevention programme (see under Contra-indications 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

**Cautions** avoid blood donation during treatment and for at least 1 month after treatment; history of depression—monitor all patients for 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;

**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 emolient (including lip balm) preparations from the start of treatment

**Renal impairment** reduce initial dose and increase gradually, if necessary, up to max. 1 mg/kg daily as tolerated

**Contra-indications** hypervitaminosis A, hyperlipidaemia

**Hepatic impairment** avoid—further impairment may occur

**Pregnancy** (important teratogenic risk) exclude pregnancy before starting (perform pregnancy test 2–3 days before expected menstruation, start treatment on day 2 or 3 of menstrual cycle)—effective contraception must be practised at least 1 month before, during, and for at least 1 month after treatment (see also notes above)

**Breast-feeding** avoid

**Side-effects** dryness of skin (with dermatitis, scaling, thinning, erythema, pruritus), 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, diziness, 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
Isotretinoin (Non-proprietary) (Non-proprietary)

Roaccutane® (Roche) (Roche)
Capsules, isotretinoin 10 mg (brown-red), net price 30-cap pack = £17.46; 20 mg (brown-red/white), 30-cap pack = £25.02. Label: 10, patient information card, 11, 21

Excipients may include arachis (peanut) oil in Roaccutane® 20 mg capsules; Roaccutane® 5 mg capsules are discontinued, but those in circulation contain arachis (peanut) oil

Extemporaneous formulations available see Extemporaneous Preparations, p. 8

13.7 Preparations for warts and calluses

Warts (verruca vulgaris) are common, benign, self-limiting, and usually asymptomatic. They 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 and is required only if the warts are painful, unsightly, persistent, or cause distress. In immunocompromised children, warts may be more difficult to eradicate.

Preparations of salicylic acid, formaldehyde, gluteraldehyde or silver nitrate are used for the removal of warts on hands and feet. Salicylic acid is a useful keratolytic which may be considered first-line in the treatment of warts; it is also suitable for the removal of corns and calluses. Preparations of salicylic acid in a collodion basis are available but some children may develop an allergy to colophony in the formulation; collodion should be avoided in children allergic to elastic adhesive plaster. An ointment combining salicylic acid with podophyllum resin (Posafilin®) 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

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

Licensed use not licensed for use in children under 2 years

Indication and dose

Warts on hands and feet (plantar)
For dose see preparations; apply carefully to wart and 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

Psoriasis section 13.5.2

Acne section 13.6.1

Fungal nail infections section 13.10.2

Cuplex® (Crawford)
Gel, salicylic acid 11%, lactic acid 4%, in a collodion basis, net price 5 g = £2.23. Label: 15

Dose Apply twice daily

Note Contains colophony (see notes above)

Duofilm® (Stiefel)
Paint, salicylic acid 16.7%, lactic acid 16.7%, in flexible collodion, net price 15 mL (with applicator) = £2.25. Label: 15

Dose Apply daily

Occlusal® (Alliance)
Cutaneous solution, salicylic acid 26% in polyacrylic solution, net price 10 mL (with applicator) = £3.39. Label: 15

Dose Apply daily
### Formulations of Salicylic Acid Containing Preparations

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Description</th>
<th>Dose</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Salactol</strong>&lt;sup&gt;®&lt;/sup&gt; (Dermal) Paint</td>
<td>Salicylic acid 16.7%, lactic acid 16.7%, in flexible collodion, net price 10 mL (with applicator) = £1.79. Label: 15</td>
<td>Apply daily</td>
<td>Contains colophony (see notes above)</td>
</tr>
<tr>
<td><strong>Salatac</strong>&lt;sup&gt;®&lt;/sup&gt; (Dermal) Gel</td>
<td>Salicylic acid 12%, lactic acid 4% in a collodion basis, net price 8 g (with applicator) = £3.12. Label: 15</td>
<td>Apply daily</td>
<td></td>
</tr>
<tr>
<td><strong>Verrugon</strong>&lt;sup&gt;®&lt;/sup&gt; (Ransom) Ointment</td>
<td>Salicylic acid 50% in a paraffin basis, net price 6 g = £2.83</td>
<td>Apply daily</td>
<td></td>
</tr>
<tr>
<td><strong>With podophyllum</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Posalfilin</strong>&lt;sup&gt;®&lt;/sup&gt; (Norgine) Ointment</td>
<td>Podophyllum resin 20%, salicylic acid 25%, net price 10 g = £3.51</td>
<td>Apply daily</td>
<td></td>
</tr>
</tbody>
</table>

#### Formaldehyde

<table>
<thead>
<tr>
<th>Cautions</th>
<th>Side-effects</th>
<th>Licensed use</th>
<th>Indication and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protect surrounding skin; not for application to face, mucosa, or anogenital areas</td>
<td>Rashes, skin irritation (discontinue if severe); stains skin brown</td>
<td>Licensed for use in children (age range not specified by manufacturer)</td>
<td>Warts, particularly plantar warts for dose see preparation below</td>
</tr>
</tbody>
</table>

#### Glutaraldehyde

<table>
<thead>
<tr>
<th>Cautions</th>
<th>Side-effects</th>
<th>Licensed use</th>
<th>Indication and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protect surrounding skin; not for application to face, anogenital region, or large areas</td>
<td>Chemical burns on surrounding skin; stains skin and fabric</td>
<td>No age range specified by manufacturer</td>
<td>Warts, particularly plantar warts Apply twice daily</td>
</tr>
</tbody>
</table>

#### Silver Nitrate

<table>
<thead>
<tr>
<th>Cautions</th>
<th>Side-effects</th>
<th>Licensed use</th>
<th>Indication and dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protect surrounding skin and avoid broken skin; not suitable for application to face, anogenital region, or large areas</td>
<td>Chemical burns on surrounding skin; stains skin and fabric</td>
<td>No age range specified by manufacturer</td>
<td>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</td>
</tr>
</tbody>
</table>

#### Anogenital Warts

Anogenital warts (condylomata acuminata) in children are often asymptomatic and require only a simple barrier preparation. If treatment is required it should be
supervised by a hospital specialist. Persistent warts on genital skin may require treatment with cryotherapy or other forms of physical ablation under general anaesthesia.

Podophyllotoxin (the major active ingredient of podophyllum), or imiquimod are used to treat external anogenital warts; these preparations can cause considerable irritation of the treated area and are therefore suitable only for children who are able to cooperate with the treatment.

Severe systemic toxicity including gastro-intestinal, renal, haematological, and CNS effects may occur with excessive application of podophyllotoxin.

**IMIQUIMOD**

**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** no evidence of teratogenicity or toxicity in animal studies; manufacturer advises caution

**Breast-feeding** manufacturer advises no information available

**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; permanent hypopigmentation or hyperpigmentation reported

**Licensed use** not licensed for use in children

**Indication and dose**

**External genital and perianal warts** (for use under specialist supervision only)

Apply thinly 3 times a week at night until lesions resolve (max. 16 weeks)

**Important** Should be rubbed in and allowed to stay on the treated area for 6–10 hours 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**

Cream, imiquimod 5%, net price 12-sachet pack = £51.32. Label: 10, patient information leaflet

**Excipients** include benzyl alcohol, cetyl alcohol, hydroxybenzoates (parabens), polysorbate 60, stearyl alcohol

**Condoms** may damage latex condoms and diaphragms

**PODOPHYLLOTOXIN**

**Cautions** see notes above; avoid normal skin and open wounds; keep away from eyes; very irritant to eyes

**Contra-indications**

**Pregnancy** avoid

**Breast-feeding** avoid

**Side-effects** see notes above

**Licensed use** not licensed for use in children

**Indication and dose**

See under preparations (for use under specialist supervision only)

**Condyline**

**Solution**, podophyllotoxin 0.5% in alcoholic basis, net price 3.5 mL (with applicators) = £14.49.

Label: 15

**Dose**

Condylomata acuminata affecting the penis or the female external genitalia

**Child 2–18 years** (see notes above) 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 cm²

**Solution**, blue, podophyllotoxin 0.5% in alcoholic basis, net price 3 mL (with applicators—*Warticon* [for men]; with applicators and mirror—*Warticon Fem* [for women]) = £12.98. Label: 15

**Dose**

Condylomata acuminata affecting the penis or the female external genitalia

**Child 2–18 years** (see notes above) 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 cm²; max. 50 single applications (‘loops’) per session (consult product literature)
13.8 Sunscreens and camouflagers

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 aggravates) skin lesions of lupus erythematosus and may aggravate some other dermatoses. Certain drugs, such as demeclocycline, phenothiazines, or amiodarone, can cause photosensitivity. All these conditions (as well as sunburn) may occur after relatively short periods of exposure to the sun. Solar ultraviolet irradiation 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 UVB) 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. Protective clothing and sun avoidance (rather than the use of sunscreen preparations) are recommended for children under 6 months of age.

The sun protection factor (SPF, usually indicated in the preparation title) provides guidance on the degree of protection offered against UVB; it indicates the multiples of protection provided against burning, compared with unprotected skin; for example, an SPF of 8 should enable a child 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); products that achieve this requirement will be labelled with a UVA logo alongside the SPF classification. Preparations that also contain reflective substances, such as titanium dioxide, provide the most effective protection against UVA.

Sunscreen preparations may rarely cause allergic reactions.

Borderline substances The preparations marked ‘ACBS’ cannot be prescribed on the NHS except for skin protection against ultraviolet radiation in abnormal cutaneous photosensitivity resulting from genetic disorders 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 2.

For optimum photoprotection, sunscreen preparations should be applied thickly and frequently (approximately 2 hourly). In photodermatoses, they should be used from spring to autumn. As maximum protection from sunlight is desirable, preparations with the highest SPF should be prescribed.

Delph® (Fenton) Lotion (UVA and UVB protection; UVB-SPF 30), avobenzone 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), waterproof, titanium dioxide 6.4%, zinc oxide 16%, net price 150 mL = £7.09. ACBS

Excipients include hydroxybenzoates (parabens), isopropyl palmitate
SpectraBan® (Stiefel)
Ultra lotion (UVA and UVB protection; UVB-SPF 28), water resistant, avobenzone 2%, oxybenzone 3%, padi-
mate-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), octi-
noxate 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), avo-
benzone 5%, bisoctrizole 1.5%, octinoxate 7.5%, octocrilene 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), amilo-
ate 2%, avobenzone 5%, bisoctrizole 6%, octinoxate 10%, octocrilene 4%, titanium dioxide 4.8%, net price 125 mL = £8.45. ACBS
Excipients include disodium edetate, polysorbate 60, propy-
lene glycol

Lipscreen (UVA and UVB protection; UVB-SPF 50), avo-
benzone 5%, bemotrizinol 3%, octinoxate 10%, octocrilene 4%, titanium dioxide 3%, net price 5 g = £2.99. ACBS
Excipients include butylated hydroxytoluene, hydroxybenzo-
ates (parabens)

Photodamage

Actinic keratoses occur very rarely in healthy children; actinic cheilitis may occur on
the lips of adolescents following excessive sun exposure.

Diclofenac gel (Solaraze®) and fluorouracil cream are licensed for the treatment
of actinic keratoses but they are not licensed for use in children.

In children with photosensitivity disorders, such as erythropoietic protoporphyria,
specialists may use betacarotene, mepacrine, chloroquine or hydroxychloro-
quine (section 10.1.3) to reduce skin reactions.

BETACAROTENE

Note Betacarotene is a precursor to vitamin A

Cautions monitor vitamin A intake; interactions:
Appendix 1 (vitamins)
Renal impairment use with caution
Pregnancy partially converted to vitamin A, but does not give rise to abnormally high serum con-
centration; manufacturer advises use only if potential benefit outweighs risk
Breast-feeding use with caution, present in milk

Contra-indications

Hepatic impairment avoid

Side-effects loose stools; yellow discolouration of skin; rarely, bruising, arthralgia

Licensed use not licensed for use in UK

Indication and dose

Management of photosensitivity reactions in erythropoietic protoporphyria (specialist use
only)

• By mouth

Child 1–5 years 60–90 mg daily in single or divided doses
Child 5–9 years 90–120 mg daily in single or divided doses
Child 9–12 years 120–150 mg daily in single or divided doses
Child 12–16 years 150–180 mg daily in single or divided doses
Child 16–18 years 180–300 mg daily in single or divided doses

Note Protection not total—avoid strong sunlight and use sunscreen preparations; generally 2–6 weeks of treatment
(resulting in yellow coloration of palms and soles) necessary before increasing exposure to sunlight; dose should
be adjusted according to level of exposure to sunlight

Betacarotene (Non-proprietary)
Capsules, 15 mg, 25 mg are available from ‘special-
order’ manufacturers or specialist importing com-
panies, see p. 943. Label: 21

13.8.2 Camouflagers

Disfigurement of the skin can be very distressing and may have a marked
psychological effect, especially in children. Cosmetic preparations may be used
to camouflage unsightly scars, skin deformities, and pigment abnormalities, such
as vitiligo and birthmarks.

Opaque cover foundation or cream is used to mask skin pigment abnormalities;
careful application using a combination of dark- and light-coloured cover creams
set with powder helps to minimise the appearance of skin deformities.

Borderline substances The preparations marked ‘ACBS’ cannot be prescribed
on the NHS for postoperative scars and other deformities except as adjunctive
therapy in the relief of emotional disturbances due to disfiguring skin disease, such
as vitiligo.
**Shampoos and other preparations for scalp conditions**

The detergent action of shampoo removes grease (sebum) from hair. Prepubertal children produce very little grease and require shampoo less frequently than adults. Shampoos can be used as vehicles for medicinal products, but their usefulness is limited by the short time the product is in contact with the scalp and by their irritant nature.

Oils and ointments are very useful for scaly, dry scalp conditions; if a greasy appearance is cosmetically unacceptable, the preparation may be applied at night and washed out in the morning. Alcohol-based lotions are rarely used in children; alcohol causes painful stinging on broken skin and the fumes may exacerbate asthma.

Itchy, inflammatory, eczematous scalp conditions may be relieved by a simple emollient oil such as olive oil or coconut oil (arachis oil (ground nut oil, peanut oil) is best avoided in children under 5 years). In more severe cases a topical corticosteroid (section 13.4) may be required. Preparations containing coal tar are used for the common scaly scalp conditions of childhood including seborrhoeic dermatitis, dandruff (a mild form of seborrhoeic dermatitis), and psoriasis (section 13.5.2); salicylic acid is used as a keratolytic in some scalp preparations. Shampoos containing antimicrobials such as selenium sulphide or ketoconazole are used for seborrhoeic dermatitis and dandruff in which yeast infection has been implicated, and for tinea capitis (ringworm of the scalp, section 13.10.2). Bacterial infection affecting the scalp (usually secondary to eczema, head lice, or ringworm) may be treated with shampoos containing antimicrobials such as pyrithione zinc, cetrimide, or povidone–iodine.

In neonates and infants, cradle cap (which is also a form of seborrhoeic eczema) can be treated by massaging coconut oil or olive oil into the scalp; a bland emollient such as emulsifying ointment can be rubbed onto the affected area once or twice daily before bathing and a mild shampoo used.

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**Shampoos**

*Ketoconazole* (Non-proprietary) 2%

Cream—section 13.10.2

Shampoo, ketoconazole 2%, net price 120 mL = £3.26

Excipients include imidurea

Brands include Dandrazel® 2% Shampoo, Nizoral®

Dose

**Seborrhoeic dermatitis and dandruff**

- treatment, apply twice weekly for 2–4 weeks; prophylaxis, apply once every 1–2 weeks

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**Keromask®** (Lornamead)

- *Masking cream*, (2 shades), net price 15 mL = £5.67. ACBS

Excipients include butylated hydroxyanisole, hydroxybenzoates (parabens), wool fat, propylene glycol

Finishing powder, net price 20 g = £5.67. ACBS

Excipients include butylated hydroxyanisole, hydroxybenzoates (parabens)

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**Veil®** (Blake)

- *Cover cream* (40 shades), net price 19 g = £19.65, 44 g = £29.22, 70 g = £36.90. ACBS

Excipients include fragrance derivative

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### Alphosyl 2 in 1® (GSK Consumer Healthcare)
- **Shampoo**, alcoholic coal tar extract 5%, net price 125 mL = £1.81, 250 mL = £3.43
- **Excipients** include hydroxybenzoates (parabens), fragrance

**Dose**
- **Dandruff** use once or twice weekly as necessary
- **Psoriasis, seborrhoeic dermatitis, scaling and itching** use every 2–3 days

### Capasal® (Dermal)
- **Shampoo**, coal tar 1%, coconut oil 1%, salicylic acid 0.5%, net price 250 mL = £4.91
- **Excipients** none as listed in section 13.1.3

**Dose**
- **Scaly scalp disorders including psoriasis, seborrhoeic dermatitis, dandruff, and cradle cap** apply daily as necessary

### Ceanel Concentrate® (Ferndale)
- **Shampoo**, cetrimide 10%, undecenoic acid 1%, phenylethyl alcohol 7.5%, net price 150 mL = £3.40, 500 mL = £9.80
- **Excipients** none as listed in section 13.1.3

**Dose**
- **Scalp psoriasis, seborrhoeic dermatitis, dandruff** apply 3 times in first week then twice weekly

### Clinitar® (CHS)
- **Shampoo**, coal tar extract 2%, net price 100 g = £2.50
- **Excipients** include polysorbates, fragrance

**Dose**
- **Scalp psoriasis, seborrhoeic dermatitis, dandruff** apply up to 3 times weekly

### Dermax® (Dermal)
- **Shampoo**, benzalkonium chloride 0.5%, net price 250 mL = £5.95
- **Excipients** none as listed in section 13.1.3

**Dose**
- **Seborrhoeic scalp conditions associated with dandruff and scaling** apply as necessary

### Meted® (Alliance)
- **Shampoo**, salicylic acid 3%, sulphur 5%, net price 120 mL = £3.80
- **Excipients** include fragrance

**Dose**
- **Scaly scalp disorders including psoriasis, seborrhoeic dermatitis, and dandruff** apply at least twice weekly

### Pentrax® (Alliance)
- **Shampoo**, coal tar 4.3%, net price 120 mL = £3.80
- **Excipients** none as listed in section 13.1.3

**Dose**
- **Scaly scalp disorders including psoriasis, seborrhoeic dermatitis, and dandruff** apply at least twice weekly

### Polytar AF® (Stiefel)
- **Shampoo**, arachis (peanut) oil extract of coal tar 0.3%, cade oil 0.3%, coal tar solution 0.1%, pine tar 0.3%, pyrithione zinc 1%, net price 250 mL = £6.52
- **Excipients** include fragrance, imidurea

**Dose**
- **Scaly scalp disorders including psoriasis, seborrhoeic dermatitis, and dandruff** apply 2–3 times weekly for at least 3 weeks

### Psoriderm® (Dermal)
- **Scalp lotion** (= shampoo), coal tar 2.5%, lecithin 0.3%, net price 250 mL = £4.96
- **Excipients** include disodium edetate

**Dose**
- **Scalp psoriasis** 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**
  - Child 5–18 years: apply twice weekly for 2 weeks then once weekly for 2 weeks and then as necessary

### T/Gel® (J&J)
- **Shampoo**, coal tar extract 2%, net price 125 mL = £3.18, 250 mL = £4.78
- **Excipients** include fragrance, hydroxybenzoates (parabens), imidurea, tetrasodium edetate

**Dose**
- **Scalp psoriasis, seborrhoeic dermatitis, dandruff** apply up to 3 times weekly

### Other scalp preparations

#### Cocos®
Section 13.5.2

#### Polytar® (Stiefel)
- **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, imidurea, polysorbate 80

**Dose**
- **Scalp disorders including psoriasis, seborrhoea, eczema, pruritus, and dandruff** apply 1–2 times weekly

#### Polytar Plus® (Stiefel)
- **Liquid**, ingredients as Polytar® liquid with hydrolysed animal protein 3%, net price 500 mL = £3.91
- **Excipients** include fragrance, imidurea, polysorbate 80

**Dose**
- **Scalp disorders including psoriasis, seborrhoea, eczema, pruritus, and dandruff** apply 1–2 times weekly

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**Skin 13.9 Shampoos and other preparations for scalp conditions BNFC 2009**
13.10 Anti-infective skin preparations

13.10.1 Antibacterial preparations

Topical antibacterial preparations are used to treat localised bacterial skin infections caused by Gram-positive organisms (particularly by staphylococci or streptococci). Systemic antibacterial treatment (Table 1, section 5.1) is more appropriate for deep-seated skin infections.

Problems associated with the use of topical antibacterials include bacterial resistance, contact sensitisation, and superinfection. In order to minimise the development of resistance, antibacterials used systemically (e.g. fusidic acid) should not generally be chosen for topical use. Neomycin applied topically may cause sensitisation and cross-sensitivity with other aminoglycoside antibacterials such as gentamicin may occur. Topical antibacterials applied over large areas can cause systemic toxicity; ototoxicity with neomycin and with polymyxins is a particular risk for neonates and children with renal impairment.

Superficial bacterial infection of the skin may be treated with a topical antiseptic such as povidine–iodine (section 13.11.4) which also softens crusts.

Bacterial infections such as impetigo and folliculitis can be treated with a short course of topical fusidic acid; mupirocin should be used only to treat meticillin-resistant Staphylococcus aureus.

For extensive or long-standing impetigo, an oral antibacterial such as flucloxacillin (or erythromycin in children with penicillin-allergy), Table 1, section 5.1, should be used. A mild antiseptic such as povidine–iodine may help to soften crusts and clear exudate. Mild antiseptics may be useful in reducing the spread of infection, but there is little evidence to support the use of topical antiseptics alone in the treatment of impetigo.

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.

Staphylococcal scalded-skin syndrome requires urgent treatment with a systemic antibacterial, such as flucloxacillin.

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 antibacterials. 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 antiseptic, such as povidone–iodine, chlorhexidine, or alcohol, can be used (section 13.11); their use should be discussed with the local microbiologist.

Mupirocin ointment contains macrogol; extensive absorption of macrogol through the mucous membranes or through application to thin or damaged skin may result in renal toxicity, especially in neonates. Mupirocin nasal ointment is formulated in a paraffin base and may be more suitable for the treatment of MRSA-infected open wound in neonates.

Metronidazole gel is used topically in children to reduce the odour associated with anaerobic infections and for the treatment of periorificial rosacea (section 13.6); oral metronidazole (section 5.1.11) is used to treat wounds infected with anaerobic bacteria.
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. 4) 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 licensed for the prevention and treatment of infection in burns but the use of appropriate dressings may be more effective. Systemic effects may occur following extensive application of silver sulfadiazine; its use is not recommended in neonates.

### 13.10.1.1 Antibacterial preparations only used topically

#### MUPIROCIN

**Side-effects** local reactions including urticaria, pruritus, burning sensation, rash  
**Licensed use** *Bactroban* ointment licensed for use in children (age range not specified by manufacturer); *Bactroban* cream not recommended for use in children under 1 year

**Indication and dose**  
**Bacterial skin infections** (see also notes above)  
**Child 1 month–18 years** apply up to 3 times daily for up to 10 days

#### NEOMYCIN SULPHATE

**Cautions** large areas—if large areas of skin are being treated ototoxicity may be a hazard in children, particularly in those with renal impairment  
**Contra-indications** neonates  
**Side-effects** sensitisation (see also notes above)  
**Licensed use** *Neomycin Cream BPC*—no information available

**Indication and dose**  
**Bacterial skin infections** see under preparations

#### POLYMYXINS

**Cautions** large areas—if large areas of skin are being treated nephrotoxicity and neurotoxicity may be a hazard, particularly in children with renal impairment  
**Side-effects** sensitisation (see also notes above)  
**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**  
**Bacterial skin infections** see under preparation

#### RETAPAMULIN

**Contra-indications** contact with eyes and mucous membranes  
**Side-effects** local reactions including irritation, erythema, pain, and pruritus

**Indication and dose**  
**Superficial bacterial skin infections** (but see also notes above)  
**Child 9 months–18 years** apply thinly twice daily for 5 days; review treatment if no response within 2–3 days
SILVER SULFADIAZINE
(Silver sulphadiazine)

Cautions G6PD deficiency; may inactivate enzymatic debriding agents—concomitant use may be inappropriate; interactions: Appendix 1 (sulphonamides)

Hepatic impairment severe, use with caution (see Large Areas, below)

Renal impairment severe, use with caution (see Large Areas, below)

Pregnancy avoid in third trimester, risk of neonatal haemolysis and methaemoglobinemia

Breast-feeding small risk of kernicterus in jaundiced neonates and of haemolysis in G6PD deficient infant

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 baseline within a few days. Argyria may also occur if large areas of skin are treated (or if application is prolonged).

Contra-indications sensitivity to sulphonamides; neonates

Side-effects allergic reactions including burning, itching and rashes; argyria reported following prolonged use; leucopenia reported (monitor blood count)

Licensed use no age range specified by manufacturer but see contra-indications, above

Indication and dose

Prophylaxis and treatment of infection in burn wounds, for conservative management of finger-tip injuries see under preparation below

Adjunct to short-term treatment of infection in pressure sores, adjunct to prophylaxis of infection in skin graft donor sites and extensive abrasions consult product literature for details

Flamazine® (S&N Hlth.) Cream, silver sulfadiazine 1%, net price 20 g = £2.91, 50 g = £3.85, 250 g = £10.32, 500 g = £18.27

Excipients include cetyl alcohol, polysorbates, propylene glycol

Dose

Burns

Child 1 month–18 years apply daily or more frequently if very exudative

Finger-tip injuries

Child 1 month–18 years apply every 2–3 days

Note apply with sterile applicator

13.10.1.2 Antibacterial preparations also used systemically

Sodium fusidate is a narrow-spectrum antibacterial used for staphylococcal infections. For the role of sodium fusidate in the treatment of impetigo see p. 707.

Metronidazole is used topically to treat rosacea and to reduce the odour associated with anaerobic infections; oral metronidazole (section 5.1.11) is used to treat wounds infected with anaerobic bacteria.

Angular cheilitis An ointment containing sodium fusidate is used in the fissures of angular cheilitis when associated with staphylococcal infection. For further information on angular cheilitis, see p. 657.

FUSIDIC ACID

Cautions see notes above; avoid contact with eyes

Side-effects rarely hypersensitivity reactions

Licensed use licensed for use in children (age range not specified by manufacturer)

Indication and dose

Staphylococcal eye infections section 11.3.1

Fucidin® (LEO) Cream, fusidic acid 2%, net price 15 g = £2.00, 30 g = £3.79

Excipients include butylated hydroxyanisole, cetyl alcohol

Ointment, sodium fusidate 2%, net price 15 g = £2.23, 30 g = £3.79

Excipients include cetyl alcohol, wool fat

Dental prescribing on NHS May be prescribed as Sodium Fusidate ointment

METRONIDAZOLE

Cautions avoid exposure to strong sunlight or UV light

Side-effects skin irritation

Licensed use Metrotop® licensed for use in children (age range not specified by manufacturer); Acea® and Anabact® not licensed for use in children under 12 years; Noritate® not licensed for use in children under 16 years; Metrogel®, Metrosa®, Rosiced®, Rozex®, and Zyomet not licensed for use in children

Staphylococcal skin infections apply 3–4 times daily, usually for 7 days

Penicillin-resistant staphylococcal infections section 5.1.7

Ointment, sodium fusidate 2%, net price 15 g = £2.23, 30 g = £3.79

Excipients include cetyl alcohol, wool fat

Dental prescribing on NHS May be prescribed as Sodium Fusidate ointment

13Skin
### 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. Specimens of scale, nail or hair should be sent for mycological examination before starting treatment, unless the diagnosis is certain.

#### Dermatophytoses

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, onychomycosis). Tinea capitis is a common childhood infection that requires systemic treatment with an oral antifungal (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 scalp ringworm.
Tinea corporis and tinea pedis infections in children respond to treatment with a topical imidazole (clotrimazole, econazole, ketoconazole, miconazole, or sulconazole) or terbinafine cream. Nystatin is less effective against tinea.

Compound benzoic acid ointment (Whitfield’s ointment) has been used for ringworm infections but it is cosmetically less acceptable than proprietary preparations. Antifungal dusting powders are of little therapeutic value in the treatment of fungal skin infections and may cause skin irritation; they may have some role in preventing re-infection.

Antifungal treatment may not be necessary in asymptomatic children 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. Chronic paronychia on the fingers (usually due to a candidal infection) should be treated with topical clotrimazole or nystatin, but these preparations should be used with caution in children who suck their fingers. Chronic paronychia of the toes (usually due to dermatophyte infection) can be treated with topical terbinafine.

Pityriasis versicolor Pityriasis (tinea) versicolor can be treated with ketoconazole shampoo or selenium sulphide shampoo (section 13.9). Topical imidazole antifungals, clotrimazole, econazole, ketoconazole, miconazole, and sulconazole, 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 an azole antifungal (section 5.2). Relapse is common, especially in the immunocompromised.

Candidiasis Candidal skin infections can be treated with topical imidazole antifungals 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 dermatophytosis. Refractory candidiasis requires systemic treatment (section 5.2) generally with a triazole such as fluconazole; systemic treatment with griseofulvin or terbinafine is not appropriate for refractory candidiasis. For the treatment of oral candidiasis see section 12.3.2 and for the management of nappy rash see section 13.2.2.

Angular cheilitis Miconazole cream is used in the fissures of angular cheilitis when associated with Candida. For further information on angular cheilitis, see p. 657.

Cautions Contact with eyes and mucous membranes should be avoided.

Side-effects Occasional local irritation and hypersensitivity reactions include mild burning sensation, erythema, and itching. Treatment should be discontinued if symptoms are severe.

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 intertriginous eczema associated with candida.
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

Excipients: 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: Use with caution in child likely to suck affected digits.*

**BENZOIC ACID**

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

- **Ringworm (tinea)** but see notes above; dose under preparation

**Benzoic Acid Ointment, Compound, BP** (Whitfield’s ointment)

- **Ointment**, benzoic acid 6%, salicylic acid 3%, in emulsifying ointment
- **Excipients**: include cetostearyl alcohol

**Dose**

- **Child 1 month–18 years** apply twice daily

**CLOTRIMAZOLE**

**Cautions** see notes above

**Side-effects** see notes above

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

- **Fungal skin infections**: apply 2–3 times daily
- **Vaginal candidiasis**: section 7.2.2
- **Otitis externa**: section 12.1.1

**Clotrimazole** (Non-proprietary)

- **Cream**, clotrimazole 1%, net price 20 g = £1.92

**ECONAZOLE NITRATE**

**Cautions** see notes above

**Side-effects** see notes above

**Licensed use** *Ecostatin*® not licensed for use in children under 1 year; *Pevaryl*®, no age range specified by manufacturer

**Indication and dose**

- **Fungal skin infections**: apply twice daily
- **Fungal nail infections**: apply once daily under occlusive dressing

**Ecostatin**® (Squibb)

- **Cream**, econazole nitrate 1%, net price 15 g = £1.49; 30 g = £2.75
- **Excipients**: include butylated hydroxyanisole, fragrance

**Pevaryl**® (Janssen-Cilag)

- **Cream**, econazole nitrate 1%, net price 30 g = £2.65
- **Excipients**: include butylated hydroxyanisole, fragrance

**KETOCONAZOLE**

**Cautions** see notes above; do not use within 2 weeks of a potent topical corticosteroid for seborrhoeic dermatitis—risk of skin sensitisation

**Side-effects** see notes above

**Indication and dose**

- **Tinea pedis**: apply twice daily

**Other fungal infections**: apply 1–2 times daily

**Systemic or resistant fungal infections**: section 5.2

**Vulval candidiasis**: section 7.2.2
### 13.10.2 Antifungal preparations

#### KETOCONAZOLE (continued)

**Nizoral**® (Janssen-Cilag)  
*K 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 for the treatment of tinea pedis, tinea cruris, and candidal intertrigo

#### MICONAZOLE NITRATE

**Cautions** see notes above  
**Side-effects** see notes above  
**Licensed use** Licensed for use in children (age range not specified by manufacturer)  
**Indication and dose**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fungal skin infections</td>
<td><strong>Neonate</strong> apply twice daily continuing for 10 days after lesions have healed</td>
</tr>
<tr>
<td></td>
<td><strong>Child 1 month–18 years</strong> apply twice daily continuing for 10 days after lesions have healed</td>
</tr>
<tr>
<td>Fungal nail infections</td>
<td>apply 1–2 times daily</td>
</tr>
</tbody>
</table>

#### NYSTATIN

**Cautions** see notes above  
**Side-effects** see notes above  
**Licensed use** licensed for use in children (age range not specified by manufacturer)  
**Indication and dose**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin infections due to Candida spp. for dose, see preparations</td>
<td>Apply 2–3 times daily continuing for 7 days after lesions have healed</td>
</tr>
<tr>
<td>Intestinal candidiasis</td>
<td>section 5.2</td>
</tr>
<tr>
<td>Oral fungal infections</td>
<td>section 12.3.2</td>
</tr>
</tbody>
</table>

#### SALICYLIC ACID

**Cautions** avoid broken or inflamed skin  
Salicylate toxicity Salicylate toxicity can occur particularly if applied on large areas of skin  
**Contra-indications** children under 5 years  
**Side-effects** see notes above  
**Licensed use** not licensed for use in children under 5 years  
**Indication and dose**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dosage Details</th>
</tr>
</thead>
</table>
| Fungal nail infections, particularly tinea | Apply twice daily and after washing  
*Note* Use with caution in child likely to suck affected digits |
| Hyperkeratotic skin disorders           | section 13.5.2                                                                |

#### Shampoo—section 13.9

1. *Exempt* except for seborrhoeic dermatitis and pityriasis versicolor and endorsed ‘SLS’

#### Oral and intestinal fungal infections section 12.3.2

**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

#### Vaginal candidiasis section 7.2.2

**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

#### 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

#### Acne vulgaris section 13.6.1

#### Warts and calluses section 13.7

#### 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 13.1.3  
*Note* Flammable
SULCONAZOLE NITRATE

Cautions  see notes above
Side-effects  see notes above; also blistering

Indication and dose

Fungal skin infections
apply 1–2 times daily continuing for 2–3 weeks after lesions have healed

Exelderm® (Centrapharm)
Cream, sulconazole nitrate 1%, net price 30 g = £3.90
Excipients include cetyl alcohol, polysorbates, propylene glycol, stearyl alcohol

TERBINAFINE

Cautions  avoid contact with eyes
Pregnancy  manufacturer advises avoid—studies in animals suggest no adverse effects
Breast-feeding  manufacturer advises avoid—present in milk, but less than 5% of the dose is absorbed after topical application of terbinafine

Side-effects  see notes above

Licensed use  not licensed for use in children

Indication and dose

Fungal skin infections
Apply thinly 1–2 times daily 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

Lamisil® (Novartis Consumer Health)
Cream, terbinafine hydrochloride 1%, net price 15 g = £4.86, 30 g = £8.76
Excipients include benzyl alcohol, cetyl alcohol, polysorbate 60, stearyl alcohol

TIOCONAZOLE

Cautions  see notes above

Contra-indications
Pregnancy  manufacturer advises avoid

Side-effects  see notes above; also local oedema, dry skin, nail discoloration, periungual inflammation, nail pain, rash, exfoliation

Licensed use  licensed for use in children (age range not specified by manufacturer)

Indication and dose

Fungal nail infections
apply to nails and surrounding skin twice daily for up to 6 months (may be extended to 12 months)

Trosyl® (Pfizer)
Cutaneous solution, tioconazole 28%, net price 12 mL (with applicator brush) = £27.38
Excipients none as listed in section 13.1.3
Note Use with caution in child likely to suck affected digits

UNDECENOATES

Side-effects  see notes above

Licensed use  Monphytol® not licensed for use in children under 12 years; Mycota® licensed for use in children (age range not specified by manufacturer)

Indication and dose

See under preparations

Mycota® (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

Powder, zinc undecenoate 20%, undecenoic acid 2%, net price 70 g = £1.93
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

Spray application, undecenoic acid 2.5%, dichlorophen 0.25% (pressurised aerosol pack), net price 100 mL = £2.19
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
Antiviral preparations

See section 12.3.2 for drugs used in herpetic stomatitis, section 13.5.1 for eczema herpeticum, and section 11.3.3 for viral infections of the eye.

Aciclovir cream is used for the treatment of initial and recurrent labial, cutaneous, and genital herpes simplex infections in children; treatment should begin as early as possible. Systemic treatment is necessary for buccal or vaginal infections or if cold sores recur frequently (for details of systemic use see section 5.3.2.1).

**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.

### ACICLOVIR

*(Acyclovir)*

**Cautions** avoid contact with eyes and mucous membranes

**Side-effects** transient stinging or burning; occasionally erythema, itching or drying of the skin

**Licensed use** licensed for use in children (age range not specified by manufacturer)

**Indication and dose**

- **Herpes simplex infections**
  - Apply to lesions every 4 hours (5 times daily) for 5–10 days, starting at first sign of attack

- **Herpes simplex and varicella–zoster infections**
  - See section 5.3.2.1

### PENCICLOVIR

*(Non-proprietary)*

**Cautions** avoid contact with eyes and mucous membranes

**Side-effects** transient stinging, burning, numbness; hypersensitivity reactions also reported

**Licensed use** not licensed for use in children under 12 years

**Dose**

- **Herpes labialis**
  - Apply to lesions every 2 hours during waking hours for 4 days, starting at first sign of attack

Dental prescribing on NHS May be prescribed as Penciclovir Cream

### Parasiticidal preparations

**Suitable quantities of parasiticidal preparations**

<table>
<thead>
<tr>
<th>Skin creams</th>
<th>Lotions</th>
<th>Cream rinses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scalp (head lice)</td>
<td>—</td>
<td>50–100 mL</td>
</tr>
<tr>
<td>Body (scabies)</td>
<td>30–60 g</td>
<td>100 mL</td>
</tr>
<tr>
<td>Body (crab lice)</td>
<td>30–60 g</td>
<td>100 mL</td>
</tr>
</tbody>
</table>

These amounts are usually suitable for a child 12–18 years for single application

**Scabies**

Permethrin is used for the treatment of scabies (*Sarcoptes scabiei*); malathion can be used if permethrin is inappropriate.

Aqueous preparations are preferable; alcoholic lotions cause irritation of excoriated skin and the genitalia.

Benzyl benzoate is an irritant and should be avoided in children; it is less effective than malathion and permethrin.

Ivermectin (available from 'special-order' manufacturers or specialist importing
companies, see p. 943), is 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. Malathion and permethrin should be applied twice, one week apart. It is important to warn users to reapply treatment to the hands if they are washed. Children 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 (section 13.4) may help to reduce itch and inflammation after scabies has been treated successfully; however, persistent symptoms suggest failure of scabies eradication. Oral administration of a sedating antihistamine (section 3.4.1) at night may also be useful.

**Head lice**  Malathion and 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. Permethrin is effective against head lice but no suitable preparation for a contact time of 12 hours exists. 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 not recommended for use in children.

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 children, especially those with severe eczema or asthma. 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); permethrin is not licensed for treatment of crab lice in children under 18 years. 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).

Aqueous malathion lotion is effective for crab lice of the eye lashes [unlicensed use].

Parasiticidal preparations

Dimeticone coats head lice and interferes with water balance in lice by preventing excretion of water; it is less active against eggs and treatment should be repeated after 7 days.

Malathion is recommended for scabies, head lice and crab lice (see notes above). The risk of systemic effects associated with 1–2 applications of malathion is considered to be very low; however, except in the treatment of hyperkeratotic scabies (see notes above), applications of lotion repeated at intervals of less than 1 week or application for more than 3 consecutive weeks should be avoided since the likelihood of eradication of lice is not increased.

Permethrin is effective for scabies. It 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 is also effective against crab lice but it is not licensed for this purpose in children under 18 years.

Phenothrin is recommended for head lice and crab lice.

### DIMETICONE

- **Cautions**: avoid contact with eyes
- **Side-effects**: skin irritation
- **Licensed use**: not licensed for use in children under 6 months except under medical supervision

**Indication and dose**

**Head lice**

Rub into dry hair and scalp, allow to dry naturally, shampoo after 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 their hair away from fire and flames during treatment

### MALATHION

- **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; alcoholic lotions not recommended for head lice in children with severe eczema or asthma, or for scabies or crab lice (see notes above)
- **Side-effects**: skin irritation and hypersensitivity reactions; chemical burns also reported
- **Licensed use**: not licensed for use in children under 6 months except under medical supervision

**Indication and dose**

**Head lice**

Rub 0.5% preparation into dry hair and scalp, allow to dry naturally, remove by washing after 12 hours; repeat application after 7 days (see also notes above)

**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
MALATHION (continued)

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, malathion 1%, net price 40 g = £2.77

Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens), sodium edetate, wool fat

Note Head and crab lice, not recommended, therefore no dose stated (product too diluted in use and insufficient contact time)

Quellada M® (GSK Consumer Healthcare)

Liquid, malathion 0.5% in an aqueous basis, net price 50 mL = £1.85, 200 mL = £4.62

Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens)

For crab lice, head lice, and scabies

Cream shampoo, malathion 1%, net price 40 g = £2.18

Excipients include cetostearyl alcohol, fragrance, hydroxybenzoates (parabens), sodium edetate, wool fat

Note Head and crab lice, not recommended, therefore no dose stated (product too diluted in use and insufficient contact time)

PERMETHRIN

Cautions avoid contact with eyes; do not use on broken or secondarily infected skin

Side-effects pruritus, erythema, and stinging; rarely rashes and oedema

Licensed use Dermal Cream (scabies), not licensed for use in children under 2 months; children aged 2 months–2 years, medical supervision required; not licensed for treatment of crab lice in children under 18 years; Creme Rinse (head lice) not licensed for use in children under 6 months except under medical supervision

Indication and dose

See notes above

Scabies

Apply 5% preparation over whole body including face, neck, scalp, and ears; wash off after 8-12 hours; 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

Lyclear® Creme Rinse (Chefaro UK)

Creme 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

Note Head lice, not recommended, therefore no dose stated (product too diluted in use and 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

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; 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

Licensed use not licensed for use in children under 6 months except under medical supervision

Indication and dose

See notes above and under preparations

Full Marks® (SSL)

Liquid, 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

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)
Preparations for minor cuts and abrasions

Cetrimide cream is used to treat minor cuts and abrasions. Proflavine cream may be used to treat infected wounds or burns, but has now been largely superseded by other antiseptics or suitable antibacterials.

**Cetrimide Cream, BP**
Cream, cetrimide 0.5% in a suitable water-miscible basis such as cetostearyl alcohol 5%, liquid paraffin 50% in freshly boiled and cooled purified water, net price 50 g = £1.11

**Proflavine Cream, BPC**
Cream, proflavine hemisulphate 0.1%, yellow beeswax 2.5%, chlorocresol 0.1%, liquid paraffin 67.3%, freshly boiled and cooled purified water 25%, wool fat 5%, net price 100 mL = 68p
Excipients include beeswax, wool fat
Note Stains clothing

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 plasters and tape

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 = £149.50 (with dispensing pipettes and palate)

**Histoacryl® (Braun)**
Tissue adhesive, sterile, enbucrilate, net price 5 × 200-mg unit (blue) = £32.00, 10 × 200-mg unit (blue) = £67.20, 5 × 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

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

Soap or detergent is used with water to cleanse intact skin but they can irritate infantile 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 or irritated skin.

An antiseptic is used for skin that is infected or that is susceptible to recurrent infection. Detergent preparations containing chlorhexidine 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. On neonatal skin, regular use of povidone–iodine and of preparations containing alcohol should be avoided.
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 as a soak for exudative eczematous areas (section 13.5.1); treatment should be stopped when the skin becomes dry. Potassium permanganate can stain skin and nails especially with prolonged use.

13.11.1 Alcohols and saline

Alcohols and saline

Cautions: flammable; avoid broken skin; patients have suffered severe burns when diathermy has been preceded by application of alcoholic skin disinfectants.

Contra-indications: neonates, see section 13.1

Indication and dose

Skin preparation before injection
apply to skin as necessary

Industrial Methylated Spirit, BP
Solution, 19 volumes of ethanol and 1 volume approved wood naphtha, net price ‘66 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

13.11.2 Chlorhexidine salts

Chlorhexidine salts

Cautions: avoid contact with eyes, brain, meninges and middle ear; not for use in body cavities; alcoholic solutions not suitable before diathermy or for use on neonatal skin.

Side-effects: occasional sensitivity

Indication and dose
See under preparations

Bladder irrigation and catheter patency solutions section 7.4.4

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
CHLORHEXIDINE (continued)

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
  - Note Flammable
  - For pre-operative skin disinfection

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 × 25-mL sachet = £5.40; 10 × 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 × 25-mL sachet = £5.20; 10 × 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
    - Pre-operative skin preparation
      - Dilute 1 in 10 (0.5%) with alcohol 70%

13.11.3 Cationic surfactants and soaps

CETRIMIDE

Cautions
- Avoid contact with eyes; avoid use in body cavities

Side-effects
- Skin irritation and occasionally sensitisation

Indication and dose
- Skin disinfection

Preparations
- Ingredient of Tisept® and Travasept® 100, see above
13.11.4 Iodine

POVIDONE–IODINE

Cautions  broken skin (see below)
Renal impairment  avoid regular application to inflamed or broken skin or mucosa
Large open wounds  The application of povidone–iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatremia, and impairment of renal function
Contra-indications  preterm neonate gestational age under 32 weeks; infants body-weight under 1.5 kg; regular use in neonates; thyroid disorders; concomitant lithium treatment
Pregnancy  avoid regular use
Breast-feeding  avoid
Side-effects  rarely sensitivity; may interfere with thyroid function tests

Indication and dose
Skin disinfection  see preparations

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

Dose
Apply undiluted in pre-operative skin disinfection

Note  Flammable—caution in procedures involving hot wire cautery and diathermy; avoid use in neonates

Antiseptic solution, povidone–iodine 10% in aqueous solution, net price 500 mL = £2.50

Dose
Apply undiluted in pre-operative skin disinfection and general antisepsis

Surgical scrub, povidone–iodine 7.5% in aqueous solution, net price 500 mL = £2.50

Dose
Use as a pre-operative scrub for hand and skin disinfection

13.11.5 Phenolics

Triclosan has been used for disinfection of the hands and wounds, and for disinfection of the skin before surgery.

13.11.6 Oxidisers and dyes

HYDROGEN PEROXIDE

Cautions  large or deep wounds; avoid on healthy skin and eyes; bleaches fabric; incompatible with products containing iodine or potassium permanganate
Licensed use  licensed for use in children (age range not specified by manufacturer)

Indication and dose
Superficial bacterial skin infection  see under preparation below

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

Cautions  irritant to mucous membranes

Indication and dose
Cleansing and deodorising suppurating eczematous reactions (section 13.5.1) and wounds for wet dressings or baths, use approx. 0.01% (1 in 10 000) solution

Note  Stains skin and clothing

Potassium Permanganate Solution
Solution, potassium permanganate 0.1% (1 in 1000) in water

Note  to be diluted 1 in 10 to provide a 0.01% (1 in 10 000) solution
Preparations for promotion of wound healing

Desloughing agents  Alginate, hydrogel, and hydrocolloid dressings (BNF Appendix 8) are effective in wound debridement. Sterile larvae (maggots) (LarvE®, Zoobiotic) are also used for managing 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.

Growth factor  A topical preparation of becaplermin (recombinant human platelet-derived growth factor) is used as an adjunct treatment of full-thickness, neuropathic, diabetic ulcers. It enhances the formulation of granulation tissue, thereby promoting wound healing.

For further information on wound management products and elastic hosiery, see BNF Appendix 8.

BECAPLERMIN  (Recombinant human platelet-derived growth factor)

| 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 |
| Licensed use     | not licensed for use in children |

Indication and dose  Full-thickness, neuropathic, diabetic ulcers (no larger than 5 cm²)

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)

Regranex® (Janssen-Cilag)  Gel, becaplermin (recombinant human platelet-derived growth factor) 0.01%, net price 15 g = £255.75

Excipients  include hydroxybenzoates (parabens)

Antiperspirants

Aluminium chloride is a potent antiperspirant used in the treatment of axillary, palmar, and plantar hyperhidrosis. Aluminium salts are also incorporated in preparations used for minor fungal skin infections associated with hyperhidrosis.

In more severe cases specialists use tap water or glycopyrronium bromide (as a 0.05% solution) in the iontophoretic treatment of hyperhidrosis of palms and soles.

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 antihidrotic treatment; intradermal treatment is unlikely to be tolerated by most children and should be administered under hospital specialist supervision.

ALUMINIUM SALTS

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

Licensed use  licensed for use in children (age range not specified by manufacturer)
**Indication and dose**

Hyperhidrosis affecting axillae, hands or feet

Apply liquid formulation at night to dry skin, wash off the following morning, initially apply daily then reduce frequency as condition improves—do not bathe immediately before use.

Hyperhidrosis, bromidrosis, intertrigo, and prevention of tinea pedis and related conditions

Apply powder to dry skin.

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**Indication and dose**

Iontophoretic treatment of hyperhidrosis

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.

Other indications section 15.1.3

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**GLYCOPHYRRONIUM BROMIDE**

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

Licensed use licensed for use in children (age range not specified by manufacturer)

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**Topical circulatory preparations**

These preparations are used to improve circulation in conditions such as bruising and superficial thrombophlebitis but are of little value. First aid measures such as rest, ice, compression, and elevation should be used. Topical preparations containing heparinoids should not be used on large areas of skin, broken or sensitive skin, or mucous membranes. Chilblains are best managed by avoidance of exposure to cold; neither systemic nor topical vasodilator therapy is established as being effective.

**Hirudoid® (Genus) **

Cream, heparinoid 0.3% in a vanishing-cream basis, net price 50 g = £3.99

Excipients include cetostearyl alcohol, hydroxybenzoates (parabens)

Dose

Superficial thrombophlebitis, bruising, and haematoma

Child 5–18 years apply up to 4 times daily

**Gel, heparinoid 0.3%, net price 50 g = £3.99**

Excipients include propylene glycol, fragrance

Dose

Superficial thrombophlebitis, bruising, and haematoma

Child 5–18 years apply up to 4 times daily
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 a 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 children can safely receive the majority of vaccines. Vaccination may be postponed if the child is suffering from an acute illness, however, it is not necessary to postpone immunisation in children 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 children who have a confirmed anaphylactic reaction to a preceding dose of a vaccine containing the same antigens or vaccine component (such as antibacterials in viral vaccines). The
The presence of the following excipients in vaccines and immunological products has been noted under the relevant entries:

<table>
<thead>
<tr>
<th>Gelatin</th>
<th>Neomycin</th>
<th>Streptomycin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gentamicin</td>
<td>Penicillins</td>
<td>Thiomersal</td>
</tr>
<tr>
<td>Kanamycin</td>
<td>Polymyxin B</td>
<td></td>
</tr>
</tbody>
</table>

**Hypersensitivity to egg** with evidence of previous anaphylactic reaction, contraindicates influenza vaccine, tick-borne encephalitis vaccine, and yellow fever vaccine. See also Cautions under MMR vaccine.

See also Vaccines and HIV infection, below.

Live vaccines may be contra-indicated temporarily in children who are:

- immunosuppressed (see Impaired Immune Response, below);
- pregnant (see Pregnancy and Breast-feeding, below).

See also Contra-indications under individual vaccines.

**Impaired immune response** Immune response to vaccines may be reduced in immunosuppressed children and there is also a risk of generalised infection with live vaccines. Severely immunosuppressed children should not be given live vaccines (including those with severe primary immunodeficiency). Specialist advice should be sought for children being treated with high doses of corticosteroids (dose equivalents of prednisolone: **children**, 2 mg/kg (or more than 40 mg) daily for at least 1 week or 1 mg/kg daily for 1 month), or other immunosuppressive drugs, and for children with malignant conditions undergoing chemotherapy or generalised radiotherapy. For special reference to HIV infection, see below.


**Pregnancy and breast-feeding** Live vaccines should not be administered routinely during pregnancy because of the theoretical risk of fetal infection but where there is a significant risk of exposure to disease (e.g. to yellow fever), the need for vaccination usually outweighs any possible risk to the fetus. Termination of pregnancy following inadvertent immunisation is not recommended. Although there is a theoretical risk of live vaccine being present in breast milk, vaccination is not contra-indicated for women who are breast-feeding when there is significant risk of exposure to disease. There is no evidence of risk from vaccinating pregnant women, or those who are breast-feeding, with inactivated viral or bacterial vaccines or toxoids. For use of specific vaccines during pregnancy or breast-feeding, see under individual vaccines.

**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, asthenia, 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. 21).

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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. 756) and varicella-zoster immunoglobulin considered after exposure to chickenpox or herpes zoster (see p. 757).
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, below) 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 peri-natal 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.

### Post-immunisation pyrexia in infants

The parent should be advised that if pyrexia develops after childhood immunisation, the infant can be given a dose of paracetamol and, if necessary, a second dose given 6 hours later; ibuprofen may be used if paracetamol is unsuitable. The parent should be warned to seek medical advice if the pyrexia persists.

For post-immunisation pyrexia in an infant aged 2–3 months, the dose of paracetamol is 60 mg; the dose of ibuprofen is 50 mg (on doctor’s advice). An oral syringe can be obtained from any pharmacy to give the small volume required.

Further information on adverse effects associated with specific vaccines can be found under individual vaccines.

### Vaccines and HIV infection

HIV-positive children 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

and the following inactivated vaccines:

- anthrax, cholera (oral), diphtheria, haemophilus influenzae type b, hepatitis A, hepatitis B, human papilloma virus, influenza, meningococcal, pertussis, pneumococcal, poliomyelitis², rabies, tetanus, tick-borne encephalitis, typhoid (injection).

HIV-positive children should not receive:

- BCG, typhoid (oral), yellow fever³

**Note** The above advice differs from that for other immunocompromised children; 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 children or those with splenic dysfunction:

- haemophilus influenzae type b, influenza, meningococcal group C, pneumococcal.

For antibiotic prophylaxis in asplenia see p. 305.

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¹ Use of normal immunoglobulin should be considered after exposure to measles (see p. 756) and varicella–zoster immunoglobulin considered after exposure to chickenpox or herpes zoster (see p. 757).

² Inactivated poliomyelitis vaccine is now used instead of oral poliomyelitis vaccine for routine immunisation of children.

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 directly related to vaccines. However, for those in neonatal units with cardiorespiratory problems, and those infants who have had more than one apnoeic attack in the 24 hours prior to immunisation, it may be appropriate to monitor for apnoea for 48 hours after immunisation. 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)**

Vaccine given and dose schedule (for details of dose, see under individual vaccines)

<table>
<thead>
<tr>
<th>Neonates at risk only</th>
<th>Vaccine given and dose schedule (for details of dose, see under individual vaccines)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 months</td>
<td>- BCG Vaccine&lt;br&gt;See section 14.4, BCG Vaccines&lt;br&gt;- Hepatitis B Vaccine&lt;br&gt;See section 14.4, Hepatitis B Vaccine</td>
</tr>
<tr>
<td>3 months</td>
<td>- Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and Haemophilus Type b Conjugate Vaccine (Adsorbed)&lt;br&gt;First dose&lt;br&gt;- Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)&lt;br&gt;First dose</td>
</tr>
<tr>
<td>4 months</td>
<td>- Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated), and Haemophilus Type b Conjugate Vaccine (Adsorbed)&lt;br&gt;Third dose&lt;br&gt;- Meningococcal Group C Conjugate Vaccine&lt;br&gt;Second dose&lt;br&gt;- Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)&lt;br&gt;Second dose</td>
</tr>
<tr>
<td>12 months</td>
<td>- Haemophilus Type b Conjugate Vaccine and Meningococcal Group C Conjugate Vaccine&lt;br&gt;Single booster dose</td>
</tr>
<tr>
<td>13 months</td>
<td>- Measles, Mumps and Rubella Vaccine, Live (MMR)&lt;br&gt;First dose&lt;br&gt;- Pneumococcal Polysaccharide Conjugate Vaccine (Adsorbed)&lt;br&gt;Single booster dose</td>
</tr>
<tr>
<td>Between 3 years and 4 months, and 5 years</td>
<td>- Adsorbed Diphtheria (low dose), Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine or&lt;br&gt;Adsorbed Diphtheria, Tetanus, Pertussis (Acellular, Component) and Poliomyelitis (Inactivated) Vaccine or&lt;br&gt;Diphtheria, Tetanus, Pertussis (Acellular, Component) Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed)&lt;br&gt;Single booster dose&lt;br&gt;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</td>
</tr>
<tr>
<td>12–13 years (females only)</td>
<td>- Human Papilloma Virus Vaccine&lt;br&gt;3 doses; second dose 1–2 months, and third dose 6 months after first dose¹ ²</td>
</tr>
<tr>
<td>13–18 years</td>
<td>- Adsorbed Diphtheria (low dose), Tetanus, and Poliomyelitis (Inactivated) Vaccine&lt;br&gt;Single booster dose</td>
</tr>
<tr>
<td>During adult life Women of child-bearing age susceptible to rubella</td>
<td>- Measles, Mumps and Rubella Vaccine, Live (MMR)&lt;br&gt;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</td>
</tr>
<tr>
<td>During adult life If not previously immunised</td>
<td>- Adsorbed Diphtheria (low dose), Tetanus, and Poliomyelitis (inactivated) Vaccine&lt;br&gt;3 doses at intervals of 1 month&lt;br&gt;Booster dose at least 1 year after primary course and again 5–10 years later</td>
</tr>
</tbody>
</table>

¹ The two human papilloma virus vaccines are not interchangeable and one vaccine product should be used for the entire course; however, Department of Health (November 2008) states 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.

² For females aged 14 to under 18 years, see ‘Catch-Up’ Programme, p. 740.
Route of administration Vaccines should not be given intravenously. Most vaccines are given by the intramuscular route; some vaccines are given by other routes—the intradermal route for BCG vaccine, deep subcutaneous route for Japanese encephalitis and varicella vaccines, and the oral route for cholera, live poliomyelitis, rotavirus, and live typhoid vaccines. The intramuscular route should not be used in children 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 blood-borne infections, such as HIV.

High-risk groups
For information on high-risk groups, see section 14.4 under individual vaccines
BCG Vaccines, p. 730
Hepatitis A Vaccine, p. 736
Hepatitis B Vaccine, p. 737
Influenza Vaccine, p. 741
Pneumococcal Vaccines, p. 746
Tetanus Vaccines, p. 751

Children with unknown or incomplete immunisation history
For children born in the UK who present with an inadequate or unknown immunisation history, investigation into immunisations received should be carried out. Outstanding doses should be administered where the routine childhood immunisation schedule has not been completed.

For advice on the immunisation of children coming to the UK, consult the handbook Immunisation against Infectious Disease (2006) (available at www.dh.gov.uk)

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 antisera is applied to material prepared in animals. Because of serum sickness and other allergic-type reactions that may follow injections of antisera, 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 multi-dose 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. 47.

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 commercially available 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 rarely required for children. For further information see BNF section 14.4.

**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.

All children of 6 years and over 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 of 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 of children if BCG immunisation has not previously been carried out and they are negative for tuberculoprotein hypersensitivity:

- all neonates and infants (0–12 months) born in areas where the incidence of tuberculosis is greater than 40 per 100 000;

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1. List of countries or primary care trusts where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.hpa.org.uk
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 between them. 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.

For advice on chemoprophylaxis against tuberculosis, see section 5.1.9; for treatment of infection following vaccination, seek expert advice.

**BACILLUS CALMETTE-GUÉRIN VACCINE**

*BCG vaccine*

**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 children 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

**Indication and dose**

<table>
<thead>
<tr>
<th>Immunisation against tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutone 0.05 mL</td>
</tr>
<tr>
<td>Child 1 month–1 year 0.05 mL</td>
</tr>
<tr>
<td>Child 1–18 years 0.1 mL</td>
</tr>
</tbody>
</table>

**Intradermal**

**Bacillus Calmette-Guérin Vaccine (HBro)**

**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.

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

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1. List of countries or primary care trusts where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.hpa.org.uk
Two interferon gamma release assay (IGRA) tests are also available as an aid in the diagnosis of tuberculosis infection: QuantiFERON®-TB Gold and T-SPOT®.TB. Both tests measure T-cell mediated immune response to synthetic antigens. For further information on the use of interferon gamma release assay tests for tuberculosis, see www.hpa.org.uk.

**Tuberculin Purified ProteinDerivative (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**

**Mantoux test**

- By intradermal injection
  - 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)

**Important** 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 children 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 contraindications, 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 children 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 Botulim Antitoxin is not used because the preparation currently in use may have a different specification

**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**

**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

**Indication and dose**

- By mouth
  - **Child 2–6 years** 3 doses each separated by an interval of 1–6 weeks
  - **Child 6–18 years** 2 doses 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 children 6–18 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

**Administration** Dissolve effervescent sodium bicarbonate granules in a glassful of
water (approximately 150 mL). For child 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 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 children 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. Children 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). For children who have been vaccinated following a tetanus-prone wound, see Tetanus vaccines, p. 751.

Travel Children travelling 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 Advice on the management of cases of diphtheria, carriers, contacts and outbreaks must be sought from health protection units. The immunisation history of infected children 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 child, see Table 2, section 5.1.

DIPHTHERIA-CONTAINING VACCINES

Cautions see section 14.1; see also individual components of vaccines

Contra-indications see section 14.1; see also individual components of vaccines

Side-effects see section 14.1; also restlessness, sleep disturbances, and unusual crying in infants;

Licensed use Infanrix-IPV + Hib® not licensed for use in children over 36 months; Pediacel® not licensed in children over 4 years but Department
Diphtheria-containing vaccines for children over 10 years

A low dose of diphtheria toxoid is sufficient to recall immunity in older children previously immunised against diphtheria but whose immunity may have diminished with time; it is insufficient to cause serious reactions in a child who is already immune. Preparations containing low dose diphtheria should be used for children over 10 years, both for primary immunisation and booster doses.

Adsorbed Diphtheria [low dose], Tetanus and Inactivated Poliomyelitis Vaccine (Repevax)

Injection, suspension of diphtheria toxoid [low dose], tetanus toxoid and inactivated poliomyelitis vaccine components adsorbed on a mineral carrier, net price 0.5-mL prefilled syringe = £6.74

Excipients may include neomycin, polymyxin B and streptomycin

Dose

Primary immunisation

- By intramuscular injection
  Child 10–18 years 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 also be 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, above

Available as part of childhood immunisation schedule, from health organisations or Movianto; brands include Infanrix-IPV+Hib®, Pediacel®

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 (Table 2, section 5.1) and vaccine (see Contacts above, p. 733).

Diphtheria Antitoxin

Dip/Ser

Prophylaxis not recommended therefore no dose stated (see notes above)

Available from Centre for Infections (Tel (020) 8200 6868) or in Northern Ireland from Public Health Laboratory, Belfast City Hospital (Tel (028) 9032 9241).

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).

Diphtheria-containing vaccines for children under 10 years

Important Not recommended for children aged 10 years or over (see Diphtheria vaccines for children over 10)

Diphtheria, Tetanus, Pertussis (Acellular, Component), Poliomyelitis (Inactivated) and Haemophilus Type b Conjugate Vaccine (Adsorbed) (Pedvax)

Injection, suspension of diphtheria toxoid, tetanus toxoid, acellular pertussis, inactivated poliomyelitis and Haemophilus influenzae type b (conjugated to tetanus protein), net price 0.5-mL prefilled syringe = £19.94

Excipients may include neomycin, polymyxin B and streptomycin

Dose

Primary immunisation

- By intramuscular injection
  Child 2 months–10 years 3 doses each of 0.5 mL separated by intervals of 1 month; see also notes on booster doses, above

Available as part of childhood immunisation schedule, from health organisations or Movianto; brands include Infanrix-IPV+Hib®, Pediacel®

Adsorbed Diphtheria, Tetanus, Pertussis (Acellular, Component) and Inactivated Poliomyelitis Vaccine (Pedvax)

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 and polymyxin B

Dose

First booster dose

- By intramuscular injection
  Child 2 months–10 years 3 doses each of 0.5 mL separated by intervals of 1 month; see also notes on booster doses, above

Available as part of childhood immunisation schedule, from health organisations or Movianto; brands include Infanrix-IPV®

Adsorbed Diphtheria [low dose], Tetanus, Pertussis (Acellular, Component) and Inactivated Poliomyelitis Vaccine (Pedvax)

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 = £11.98

Excipients may include neomycin, polymyxin B and streptomycin

Dose

First booster dose

- By intramuscular injection
  Child 2 months–10 years 3 doses each of 0.5 mL separated by intervals of 1 month; see also notes on booster doses, above

Available as part of childhood immunisation schedule, from health organisations or Movianto; brands include Repevax®

of Health recommends that these be used for children up to 10 years

Indication and dose

See notes above and under preparations
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 is given in combination with diphtheria, tetanus, pertussis (acellular, component) and inactivated poliomyelitis vaccine, (see under Diphtheria-containing Vaccines) as a component of the primary course of childhood immunisation (see Immunisation schedule, section 14.1) 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.

Children 1–10 years who have not been immunised against Haemophilus influenzae type b need to receive only 1 dose of the 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 influenza type b disease, see Table 2, section 5.1

Asplenia or splenic dysfunction  Haemophilus influenzae type b vaccine is recommended for children with asplenia or splenic dysfunction. Immunised 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. 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**

**Cautions** see section 14.1

**Contra-indications** see section 14.1

**Side-effects** see section 14.1; also, atopic dermatitis, hypotonia

**Licensed use** Menitorix® is not licensed for use in children over 2 years

**Indication and dose**

- **Primary immunisation**, see under Diphtheria-containing vaccines
- **Available as part of the childhood immunisation schedule from Movianto**

**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.
  - CHILD over 1 year, with asplenia or splenic dysfunction (see notes above), 0.5 mL.

**Combined vaccines**

See also 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:
- residents of homes for those with severe learning difficulties;
- children with haemophilia treated with plasma-derived clotting factors;
- children with severe liver disease;
- children travelling to high-risk areas (see p. 759);
- adolescents who are at risk due to their sexual behaviour;
- parenteral drug abusers.

Immunisation should be considered for:
- children 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 of hepatitis A vaccine 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.

In children under 16 years, a single dose of the combined vaccine Ambirix® can be used to provide rapid protection against hepatitis A.

**HEPATITIS A VACCINE**

**Cautions** section 14.1

**Contra-indications** section 14.1

**Side-effects** section 14.1; for combination vaccines, see also Typhoid vaccines, p. 752

**Indication and dose**

Immunisation against hepatitis A infection for dose, see under preparations

**Single component**

**Avaxim®** (Sanofi Pasteur) (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

**Excipients** include neomycin

**Dose**

- **By intramuscular injection** (see note below)
  - **Child 16–18 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; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for children with bleeding disorders

**Epaxal®** (MASTA) (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

**Excipients** include neomycin

**Dose**

- **By intramuscular injection** (see note below)
  - **Child 1–15 years** 0.5 mL as a single dose; booster dose 0.5 mL 6–12 months after initial dose
  - **Child 16–18 years** 1 mL as a single dose; booster dose 1 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 Epaxal®. The deltoid region is the preferred site of injection. The subcutaneous route may be used for children with bleeding disorders (but immune response may be reduced)

**Vaqta® Paediatric** (Sanofi Pasteur) (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

**Excipients** include neomycin

**Dose**

- **By intramuscular injection** (see note below)
  - **Child 1–18 years** 0.5 mL as a single dose; booster dose 0.5 mL 6–18 months after initial dose
  - **Note** The deltoid region is the preferred site of injection. The subcutaneous route may be used for children with bleeding disorders (but immune response may be reduced)
**HEPATITIS A VACCINE (continued)**

### With hepatitis B vaccine

**Ambirix® (GSK) [HF]**

**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 hydroxide and aluminium phosphate, net price 1-mL prefilled syringe = £31.18

**Excipients** include neomycin and traces of thiomersal

**Dose**

- **By intramuscular injection**
  - **Child 1–15 years** primary course, 2 doses of 1 mL, the second 6–12 months after initial dose

**Note** Primary course should be completed with Ambirix® (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; antero-lateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for children with bleeding disorders (but immune response may be reduced)

**Important** Ambirix® not recommended for post-exposure prophylaxis following percutaneous (needle-stick), ocular, or mucous membrane exposure to hepatitis B virus

**Twinrix® (GSK) [HF]**

**Injection**, inactivated hepatitis A virus (grown in human diploid cells) 720 ELISA units absorbed onto aluminium hydroxide, and recombinant (DNA) hepatitis B surface antigen (grown in yeast cells) 20 micrograms/mL adsorbed onto aluminium hydroxide and aluminium phosphate, net price 1-mL prefilled syringe (Twinrix® Adult) = £27.76; 0.5-mL prefilled syringe (Twinrix® Paediatric) = £20.79

**Excipients** include neomycin and traces of thiomersal

**Dose**

- **By intramuscular injection**
  - **Child 1–15 years** primary course 3 doses of 0.5 mL, the second 1 month and the third 6 months after first dose
  - **Child 16–18 years** primary course, 3 doses of 1 mL, the second 1 month and the third 6 months after 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 older children; antero-lateral thigh is the preferred site in infants; not to be injected into the buttock (vaccine efficacy reduced); subcutaneous route used for children 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

**Hepatyrix® (GSK) [HF]**

**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**
  - **Child 15–18 years 1 mL as a single dose; booster doses, see under single component hepatitis A vaccine (above) and under polysaccharide typhoid vaccine, p. 752

**Note** The deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for children with bleeding disorders

**VIATIM® (Sanofi Pasteur) [HF]**

**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

**Dose**

- **By intramuscular injection**
  - **Child 16–18 years 1 mL as a single dose; booster doses, see under single component hepatitis A vaccine (above) and under polysaccharide typhoid vaccine, p. 752

**Note** The deltoid region is the preferred site of injection; not to be injected into the buttock (vaccine efficacy reduced). The subcutaneous route may be used for children with bleeding disorders

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**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, high-risk groups include:

- parenteral drug misusers, their sexual partners, and household contacts; other drug misusers who are likely to ‘progress’ to injecting;
- adolescents who are at risk from their sexual behaviour;
- close family contacts of a case or individual with chronic hepatitis B infection;
- 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. 757) 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 receive the immunoglobulin regardless of the mother’s e-antigen antibody status);

- children with haemophilia, those receiving regular blood transfusions or blood products, and carers responsible for the administration of such products;
- children with chronic renal failure including those on haemodialysis. Children receiving haemodialysis should be monitored for antibodies annually and re-immunised if necessary. Home carers (of dialysis patients) should be vaccinated;
- children with chronic liver disease;
- patients of day-care or residential accommodation for those with severe learning difficulties;
- children in custodial institutions;
- children travelling to areas of high or intermediate prevalence who are at increased risk or who plan to remain there for lengthy periods (see p. 759);
- 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); 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). Generally, three or four doses are required for primary immunisation. 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 initial 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

Cautions  section 14.1
Contra-indications  section 14.1
Side-effects  section 14.1
Indication and dose  

**Immunisation against hepatitis B infection**
for dose see under preparations

- Single component
- **Engerix B® (GSK)**

**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) prefilled syringe = £9.67, 1-mL vial = £12.34, 1-mL prefilled syringe = £12.99

Excipients include traces of thiomersal

<table>
<thead>
<tr>
<th>Dose</th>
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<tbody>
<tr>
<td>By intramuscular injection</td>
<td>(see note below)</td>
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<tr>
<td>Neonate (except if born to hepatitis B surface antigen-positive mother, see below). 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose</td>
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HEPATITIS B VACCINE (continued)

**Child 1 month–16 years** 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose

**Child 16–18 years** 3 doses of 20 micrograms, second dose 1 month and third dose 6 months after first dose. Accelerated schedule (all age groups), second dose 1 month after first dose, third dose 2 months 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)

Infant born to hepatitis B surface antigen-positive mother (see also notes above)
- By intramuscular injection (see note below)

**Neonate** 4 doses of 10 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 first dose

Renal insufficiency (including haemodialysis patients)
- By intramuscular injection (see note below)

**Neonate** (except if born to hepatitis B surface antigen-positive mother, see above), 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

**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

**Child 16–18 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

**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

**Child 16–18 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

**Note** Deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in neonates, infants and young children; not to be injected into the buttock (vaccine efficacy reduced)

Fendrix® (GSK) Injection, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 40 micrograms/mL adsorbed onto aluminium hydroxyphosphate sulphate, net price 0.5-mL prefilled syringe = £38.10. Excipients include traces of thiomersal

**Dose**

**Renal insufficiency patients (including pre-haemodialysis and haemodialysis patients)**
- By intramuscular injection (see note below)

**Child 15–18 years** 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 buttock (vaccine efficacy reduced)

HBraxPRO® (Sanofi Pasteur) Injection, suspension of hepatitis B surface antigen (prepared from yeast cells by recombinant DNA technique) 10 micrograms/mL adsorbed onto aluminium hydroxyphosphate 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)

**Neonate** (except if born to hepatitis B surface antigen-positive mother, see below), 3 doses of 5 micrograms, second dose 1 month and third dose 6 months after first dose

**Child 1 month–16 years** 3 doses of 5 micrograms, second dose 1 month and third dose 6 months after first dose

**Child 16–18 years** 3 doses of 10 micrograms, second dose 1 month and third dose 6 months after first dose. Accelerated schedule (all age groups), second dose 1 month after first dose, third dose 2 months after first dose with fourth dose at 12 months.

**Note** Booster doses may be required in immunocompromised patients with low antibody concentration

**Infant born to hepatitis B surface antigen-positive mother** (see also notes above)
- By intramuscular injection (see note below)

**Neonate** 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

**Chronic haemodialysis patients**
- By intramuscular injection (see note below)

**Child 16–18 years** 3 doses of 40 micrograms, second dose 1 month and third dose 6 months after first dose; booster doses may be required in those with low antibody concentration

**Note** Deltoid muscle is preferred site of injection in older children; anterolateral thigh is preferred site in neonates and infants; not to be injected into the buttock (vaccine efficacy reduced)

**With hepatitis A vaccine**

**See Hepatitis A Vaccine**
Human papilloma virus vaccine is available as a bivalent vaccine (Cervarix®) or a quadrivalent vaccine (Gardasil®). Cervarix® is licensed for use in females for the prevention of cervical cancer and other 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 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 vaccination, 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 papillomavirus 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 primary course.

### Cervarix® (GSK) TA
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

### Gardasil® (Sanofi Pasteur) TA
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

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**HUMAN PAPILLOMA VIRUS VACCINES**

**Cautions** see section 14.1  
**Contra-indications** see section 14.1  
**Side-effects** see section 14.1  

**Indication and dose**

<table>
<thead>
<tr>
<th>Cervarix® (GSK)</th>
<th>Gardasil® (Sanofi Pasteur)</th>
</tr>
</thead>
<tbody>
<tr>
<td>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</td>
<td></td>
</tr>
<tr>
<td>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</td>
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</tbody>
</table>

**Dose**

**Prevention of premalignant genital lesions and cervical cancer (see notes above)**

- By intramuscular injection into deltoid region
  - **Child 10–18 years** 3 doses of 0.5 mL, the second 1 month and the third 6 months after the first dose

**Note** To avoid confusion, prescribers should specify the brand to be dispensed

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**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 [January 2009 in Wales] 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)

**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 (continued)

recombinant DNA technique) adsorbed onto aluminium hydroxyphosphate sulphate, net price 0.5-mL prefilled syringe = £80.50

Note To avoid confusion, prescribers should specify the brand to be dispensed.

Influenza vaccine

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 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 children (including infants that were preterm or low birth-weight) 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 chemotherapy and prolonged corticosteroid treatment);
- HIV infection (regardless of immune status).

Influenza immunisation is also recommended for children living in long-stay facilities. Influenza immunisation should also be considered for household contacts of immunocompromised individuals.

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.

Information on pandemic influenza and avian influenza may be found at www.dh.gov.uk/pandemicflu and www.hpa.org.uk.

**INFLUENZA VACCINES**

**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

**Licensed use** Inactivated Influenza Vaccine (Surface Antigen) and Fluvirin® are not licensed for use in children under 4 years

**Indication and dose**

**Annual immunisation against influenza**

- **By intramuscular injection**
  - Child 6 months–3 years 0.25–0.5 mL (repeated after 4–6 weeks in children not previously vaccinated)

**Prevention of premalignant genital lesions, cervical cancer and genital warts (see notes above)**

- **By intramuscular injection preferably into deltoid region or higher anterolateral thigh**
  - Child 9–18 years 3 doses of 0.5 mL, the second 2 months and the third 6 months after the first dose
  - Alternative schedule for Child 9–18 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

**Dose**

**Inactivated Influenza Vaccine (Split Virion)**

- **Flu Injection**, suspension of formaldehyde-inactivated influenza virus (split virion) grown in fertilised hens’ eggs, net price 0.25-mL prefilled syringe = £6.29, 0.5-mL prefilled syringe = £6.29

**Excipients** may include neomycin and polymyxin

Available from Sanofi Pasteur

**BNFC 2009**

14.4 Vaccines and antisera

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Immunological products and vaccines
**INFLUENZA VACCINES (continued)**

**Inactivated Influenza Vaccine (Surface Antigen)**

**Flu or Flu(Adj)**

*Injection*, suspension of propiolactone-inactivated influenza virus (surface antigen) grown in fertilised hens’ eggs, net price 0.5-mL prefilled syringe = £4.40

*Excipients* may include neomycin, polymyxin B and traces of thiomersal

Available from Novartis Vaccines

**Agrippal® (Novartis Vaccines)**

*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)**

*Injection*, suspension of formaldehyde-inactivated influenza virus (split virion) grown in fertilised hens’ eggs, net price 0.5-mL prefilled syringe = £5.85

*Excipients* include polymyxin B

**Enzira® (Wyeth)**

*Injection*, suspension of inactivated influenza virus (split virion) grown in fertilised hens’ eggs, net price 0.5-mL prefilled syringe = £6.59

*Excipients* include neomycin and polymyxin B

**Fluarix® (GSK)**

*Injection*, suspension of formaldehyde-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)**

*Injection*, suspension of formaldehyde-inactivated influenza virus (surface antigen) grown in fertilised hens’ eggs, net price 0.5mL prefilled syringe = £5.55

*Excipients* include neomycin, polymyxin B, and traces of thiomersal

**Imuvac® (Solvay)**

*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)**

*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)**

*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)**

*Injection*, suspension of inactivated influenza virus (surface antigen, virosome) grown in fertilised hens’ eggs, net price 0.5-mL prefilled syringe = £6.59

*Excipients* include neomycin and polymyxin B

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**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, below

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**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 the initial dose.

MMR vaccine should be used to protect against rubella in seronegative females of child-bearing age (see Immunisation schedule, section 14.1). MMR vaccine may also be offered to previously unimmunised and seronegative post-partum mothers—vaccination a few days after delivery is important because about 60% of congenital abnormalities from rubella infection occur in babies of mothers 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 including babies 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, p. 755) after exposure to measles; routine MMR immunisation should then be given 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 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 children over 6 months of age travelling 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, arthropathy 2 to 3 weeks after immunisation. Adverse reactions are considerably less frequent after the second dose of MMR vaccine than after the first dose.

Idiopathic thrombocytopenic purpura has occurred rarely following MMR vaccination, usually within 6 weeks of the first dose. The risk of developing idiopathic thrombocytopenic purpura after MMR vaccine is much less than the risk of developing it after infection with wild measles or rubella virus. The CSM has recommended that children who develop idiopathic thrombocytopenic purpura within 6 weeks of the first dose of MMR should undergo serological testing before the second dose is due; if the results suggest incomplete immunity against measles, mumps or rubella then a second dose of MMR is recommended. The Specialist and Reference Microbiology Division, Health Protection Agency offers free serological testing for children who develop idiopathic thrombocytopenic purpura within 6 weeks of the first dose of MMR.

Post-vaccination aseptic meningitis was reported (rarely and with complete recovery) following vaccination with MMR vaccine containing Urabe mumps
vaccine, which has now been discontinued; no cases have been confirmed in association with the currently used Jeryl Lynn mumps vaccine. Children with post-vaccination symptoms are not infectious.

Reviews undertaken on behalf of the CSM, the Medical Research Council, and the Cochrane Collaboration, have not found any evidence of a link between MMR vaccination and bowel disease or autism. The Chief Medical Officers have advised that the MMR vaccine is the safest and best way to protect children against measles, mumps, and rubella. Information (including fact sheets and a list of references) may be obtained from: www.immunisation.nhs.uk and www.immunisation.nhs.uk/Vaccines/MMR

### MEASLES, MUMPS AND RUBELLA VACCINE, LIVE

**Cautions** see section 14.1; also after immunoglobulin administration or blood transfusion, leave an interval of at least 3 months before MMR immunisation as antibody response to measles component may be reduced; **interactions:** Appendix 1 (vaccines)

**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 egg is not a contraindication). 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

**Pregnancy** avoid vaccination during pregnancy; avoid pregnancy for at least 1 month after vaccination

**Side-effects** see section 14.1 and notes above; also less commonly sleep disturbance, unusual crying in infants, also reported peripheral and optic neuritis.

**Licensed use** Priorix® not licensed for use in children under 9 months, and MMRvaxPro® not licensed for use in children under 1 year

**Indication and dose**

Immunisation against measles, mumps, and rubella

- **By intramuscular or deep subcutaneous injection**
- **CHILD 6 months–18 years** primary immunisation, 2 doses each of 0.5 mL, see Immunisation schedule, section 14.1, p. 728; 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 (Enders’ Edmonston strain) and mumps virus (Jeryl Lynn [Level B] 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 meningococcal 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 dose 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. 728). 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.

**Meningococcal group C conjugate vaccine in patients with asplenia or splenic dysfunction** Meningococcal group C conjugate vaccine is recommended for children with asplenia or splenic dysfunction. Children under 1 year should be
vaccinated according to the Immunisation Schedule (section 14.1). Unimmunised 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 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**  
Children 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 the child 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.

Vaccination is particularly important for those living with local people or visiting an area of risk during outbreaks.

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 outbreaks and epidemics of meningococcal 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 Guidelines 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.

### MENINGOCOCCAL VACCINES

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<tr>
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<tbody>
<tr>
<td>Contra-indications</td>
<td>see section 14.1</td>
</tr>
<tr>
<td>Side-effects</td>
<td>see section 14.1; also rarely symptoms of meningitis reported (but no evidence that vaccine causes meningococcal C meningitis)</td>
</tr>
</tbody>
</table>

**Licensed use**  
*ACWVYVax* not licensed in children under 2 years

**Indication and dose**  
Immunisation against *Neisseria meningitidis* for dose, see under preparations

#### Meningococcal Group C conjugate vaccine

**Meningitec®** (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  
  Child 2 months–1 year for routine immunisation, 0.5 mL, see notes above and Immunisation schedule, section 14.1  
  Child 1–18 years 0.5 mL as a single dose  
  **Note** Subcutaneous route used for children with bleeding disorders

**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 vials

**Dose**  
• By intramuscular injection  
  Child 2 months–1 year for routine immunisation, 0.5 mL, see notes above and Immunisation schedule, section 14.1  
  Child 1–18 years 0.5 mL as a single dose  
  **Note** Subcutaneous route used for children with bleeding disorders

**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  
  Child 3 months–1 year for routine immunisation, 0.5 mL, see notes above and Immunisation schedule, section 14.1  
  Child 1–18 years 0.5 mL as a single dose

Available from Movianto

Available as part of childhood immunisation schedule from Movianto
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) T A
Injection, powder for reconstitution, capsular polysaccharide antigens of Neisseria meningitidis

Injection, powder for reconstitution, capsular polysaccharide antigens of Neisseria meningitidis A, C, W135 and Y, net price single-dose vial (with syringe containing diluent) = £16.73

Dose

- By deep subcutaneous injection
  - Child 3 months–2 years 2 doses (each of 0.5 mL) separated by an interval of 3 months; antibody response may be suboptimal in this age group
  - Child 2–18 years 0.5 mL as a single dose; booster dose for those at continued risk; 0.5 mL 5 years after initial dose (children under 5 years when first vaccinated, should be given a booster dose after 2–3 years)

Mumps vaccine

- Single antigen vaccine
  - No longer available in the UK
- Combined vaccines
  - See MMR Vaccine, p. 742

Pertussis vaccine

Pertussis vaccine is given as a combination preparation containing other vaccines (see Diphtheria 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, p. 728), 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 schedule 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. 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 vaccines

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 pneumococci whereas pneumococcal polysaccharide...
**conjugated vaccine** (adsorbed) contains polysaccharide from 7 capsular types, the polysaccharide being conjugated to protein.

The conjugate vaccine is used for childhood immunisation. 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:

- child under 5 years with a history of invasive pneumococcal disease;
- 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;
- 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 could occur.

Where possible, the vaccine should be given at least 2 weeks before splenectomy, cochlear implant surgery, and chemotherapy; children and carers should be given advice about increased risk of pneumococcal infection. Prophylactic antibacterial therapy against pneumococcal infection (Table 2, section 5.1, p. 305) 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 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 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 VACCINES

Cautions  see section 14.1
Contra-indications  see section 14.1
Side-effects  see section 14.1; also Revaccination, above

Indication and dose

Immunisation against pneumococcal infection
for dose see under preparations

Pneumococcal polysaccharide vaccines

Pneumovax® II (Sanofi Pasteur)
Injection, polysaccharide from each of 23 capsular
types of pneumococcus, net price 0.5-mL vial = £8.83

Dose
- By subcutaneous or intramuscular injection
  Child 2–18 years 0.5 mL; revaccination, see notes above

Pneumococcal polysaccharide conjugate vaccine (adsorbed)
Prevenar® (Wyeth) ▼ (FH)
Injection, polysaccharide from each of 7 capsular
types of pneumococcus (conjugated to diphtheria
 toxoid) 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 BNF for Children may differ from that in
  product literature

Poliomyelitis vaccines

There are two types of poliomyelitis vaccine (containing strains of poliovirus
types 1, 2, and 3) available, inactivated poliomyelitis vaccine (for injection) and
live (oral) poliomyelitis vaccine. Inactivated poliomyelitis vaccine, only avail-
able in combined preparation (see under Diphtheria vaccines, combined), is
recommended for routine immunisation; it is given by injection and contains
inactivated strains of human poliovirus types 1, 2 and 3.

A course of primary immunisation consists of 3 doses of a combined preparation
containing inactivated poliomyelitis vaccine starting at 2 months of age with
intervals of 1 month between doses (see Immunisation schedule, section 14.1). A
course of 3 doses should also be given to all unimmunised children; no child
should remain unimmunised against poliomyelitis.

Two booster doses of a preparation containing inactivated poliomyelitis vaccine
are recommended, the first before school entry and the second before leaving
school (see Immunisation schedule, section 14.1). Further booster doses should
be given every 10 years only to individuals at special risk.

Preparations containing inactivated poliomyelitis vaccine can be used to com-
plete an immunisation course initiated with the live (oral) poliomyelitis vaccine.
Live (oral) poliomyelitis vaccine is available only for use during outbreaks. The
live (oral) vaccine poses a very rare risk of vaccine-associated paralytic polio
because the attenuated strain of the virus can revert to a virulent form. For this
reason the live (oral) vaccine must not be used for immunosuppressed individuals
or their household contacts. The use of inactivated poliomyelitis vaccine removes
the risk of vaccine-associated paralytic polio altogether.

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, p.760 (www.nathnac.org).

POLIOMYELITIS VACCINES

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

Indication and dose
See under preparations

Combined vaccines
See under Diphtheria-containing Vaccines

Inactivated (Salk) Vaccine
See under Diphtheria-containing Vaccines
Poliomyelitis Vaccine, Live (Oral) (GSK) (OPV)

A suspension of suitable live attenuated strains of poliomyelitis virus, types 1, 2, and 3. Available in single-dose and 10-dose containers

Excipients include neomycin and polymyxin B

Dose

Control of outbreaks

- By mouth
  - Child 1 month–18 years 3 drops; may be given on a lump of sugar; not to be given with foods which contain preservatives

Note: Live poliomyelitis vaccine loses potency once the container has been opened—any vaccine remaining at the end of an immunisation session should be discarded; whenever possible sessions should be arranged to avoid undue wastage.

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 children at high risk of exposure to rabies—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. Transmission of rabies by humans has not been recorded but it is advised that those caring for children with the disease should be vaccinated.

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.

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 child 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 child was not at risk.
RABIES VACCINE

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

Indication and dose

Pre-exposure immunisation against rabies
• By intramuscular injection in deltoid region or anterolateral thigh in infants
Child 1 month–18 years  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 immunisation against rabies
Child 1 month–18 years  1 mL (see notes above)

Rabies Vaccine (Sanofi Pasteur)  
Rab
Injection, powder for reconstitution, freeze-dried inactivated Wistar rabies virus strain PM/ WI38 1503-3M cultivated in human diploid cells, net price single-dose vial with syringe containing diluent = £24.40
Excipients include neomycin

Rabipur® (Novartis Vaccines)  
Injection, powder for reconstitution, freeze-dried inactivated Flury LEP rabies virus strain cultivated in chick embryo cells, net price single-dose vial = £24.40
Excipients include neomycin

Rotavirus vaccine

Rotavirus vaccine is a live, oral vaccine 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 immunosuppressed 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

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

Indication and dose

Immunisation against gastro-enteritis caused by rotavirus infection
• 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
Excipients include neomycin

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 the combined live measles, mumps and rubella vaccine is a suitable alternative.

Single antigen vaccine
No longer available in the UK; see MMR vaccine, p. 742

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 number of 5 doses of tetanus vaccine is considered sufficient for long-term protection.

For primary immunisation of 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 a child 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; carers of children awaiting elective surgery should be asked about the child’s tetanus immunisation status and the child should be 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.

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 manure) or show much devitalised tissue or are septic or are 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.
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 living in or visiting high-risk areas (see International Travel, section 14.6). Children 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.

Typhoid vaccines

Typhoid vaccine is available as Vi capsular polysaccharide injectable vaccine (from Salmonella typhi) for injection; and as live attenuated Salmonella typhi vaccine for oral use.

Typhoid immunisation is advised for children travelling to:

- areas where typhoid is endemic, especially if staying with or visiting local people
- endemic areas where frequent or prolonged exposure to poor sanitation and poor food hygiene is likely

Typhoid vaccination is not a substitute for scrupulous personal hygiene (see p. 759).

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;
- 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**

**Cautions** 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

**Indication and dose**

Immunisation against typhoid fever

For dose see under preparations

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**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
  - **Child under 2 years** [unlicensed use], 0.5 mL, at least 2 weeks before potential exposure to typhoid infection; response may be suboptimal (see notes above)
  - **Child 2–18 years** 0.5 mL, at least 2 weeks before potential exposure to typhoid infection

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**Poly saccharide vaccine with hepatitis A vaccine**

See Hepatitis A Vaccine

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**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**

- By mouth
  - **Child 6–18 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

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**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.

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 females;
- individuals at high risk of severe varicella, including those with immunodeficiency or those receiving immunosuppressive therapy.

**Varicella–zoster immunoglobulin** is used to protect susceptible children at increased risk of varicella infection, see p. 758

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**VARICELLA–ZOSTER VACCINES**

**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

- **Pregnancy** avoid pregnancy for 3 months after vaccination

**Side-effects** see section 14.1; also varicella-like rash; rarely thrombocytopenia

**Indication and dose**

Immunisation against varicella infection (see notes above)

For dose, see under preparations

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**Varilrix**® (GSK) ✧

Injection, powder for reconstitution, live attenuated varicella–zoster virus (Oka strain) propagated in human diploid cells, net price 0.5-mL vial (with diluent) = £27.31

**Excipients** include neomycin

**Dose**

- By subcutaneous injection preferably into deltoid region
  - **Child 1–18 years** (see notes above), 2 doses of 0.5 mL, separated by an interval of at least 6 weeks (minimum 4 weeks)
Yellow fever vaccine

Live yellow fever vaccine is indicated for those travelling to or living in areas where infection is endemic (see p. 758). 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 rarely 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 have usually 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.

Immune globulins

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) and in the Health Protection Agency’s *Immunoglobulin Handbook*: www.hpa.org.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**.

**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).

<table>
<thead>
<tr>
<th>CHM advice</th>
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<tr>
<td>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.</td>
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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 children with congenital agammaglobulinaemia and hypogammaglobulinaemia, for the treatment of idiopathic thrombocytopenic purpura and Kawasaki syndrome (see section 2.9), 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 children at risk of infection (see p.736) 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 children, 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 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 females 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 individual, when it should be given as soon as possible after exposure. Serological follow-up of recipients is essential. For routine prophylaxis, see MMR vaccine (p. 742).

### For intramuscular use

**Normal Immunoglobulin**

Normal immunoglobulin injection. 250-mg vial; 750-mg vial

**Dose**

To control outbreaks of hepatitis A (see notes above)

- By deep intramuscular injection
  - Child under 10 years 250 mg
  - Child 10–18 years 500 mg

Measles prophylaxis or to attenuate an attack

- By deep intramuscular injection
  - Child under 1 year 250 mg
  - Child 1–3 years 500 mg
  - Child 3–18 years 750 mg

Rubella in pregnancy, prevention of clinical attack

- By deep intramuscular injection
  - 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)**

Normal immunoglobulin injection, net price 5-mL vial = £32.56, 10-mL vial = £65.12

**Dose**

Antibody deficiency syndromes

- By subcutaneous injection
  - Consult product literature

**Note** May be administered by intramuscular injection (if subcutaneous route not possible) but **not** for patients with bleeding disorders

**Subgam® (BPL)**

Normal immunoglobulin injection, net price 250-mg vial = £11.20, 750-mg vial = £28.50, 1.5-g vial = £57.00

**Dose**

Antibody deficiency syndromes

- By subcutaneous injection
  - Consult product literature

**Note** May be administered by intramuscular injection (if subcutaneous route not possible) but **not** for patients with bleeding disorders

**Vivaglobin® (CSL Behring)**

Normal immunoglobulin injection, net price 3-mL vial £17.76, 10-mL vial = £59.20, 20-mL vial = £118.40

**Dose**

Antibody deficiency syndromes

- By subcutaneous injection
  - Consult product literature
For intravenous use

Normal Immunoglobulin for Intravenous Use
Brands include Flebogamma®, 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 (6 g, 12 g); Vigam® S (2.5 g, 5 g); Vigam® Liquid (2.5 g, 5 g, 10 g)

Dose

Kawasaki syndrome
- By intravenous infusion
  Child 1 month–12 years 2 g/kg as a single dose within 10 days of onset of symptoms (but children with a delayed diagnosis may also benefit)

Other indications 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 infants born to mothers who have become infected with this virus in pregnancy or who are high-risk carriers (see Hepatitis B Vaccine, p. 737).

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 should be 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, BNF section 14.4).

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 5.1.11) 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:
- neontes 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 of 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 (or more than 40 mg) for at least 1 week or 1 mg/kg daily for 1 month.

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)
  Neonate 200 units as soon as possible after birth; for full details consult Immunisation against Infectious Disease
  Child 1 month–5 years 200 units
  Child 5–10 years 300 units

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)
  Neonate 200 units as soon as possible after birth; for full details consult Immunisation against Infectious Disease
  Child 1 month–5 years 200 units
  Child 5–10 years 300 units

Available from selected Health Protection Agency and NHS laboratories (except for Transplant Centres, see p. 755), also available from BPL and SNBTS (as Liberin HB®)

Note Hepatitis B immunoglobulin for intravenous use is available from BPL on a named-patient basis.
14.6 International travel

**Rabies**

**Rabies Immunoglobulin** *(Antirabies Immunoglobulin Injection)*

See notes above

**Dose**

20 units/kg, by infiltration in and around the cleansed wound; if the 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)

**Tetanus**

**Tetanus Immunoglobulin** *(Antitetanus Immunoglobulin Injection)*

See notes above

**Dose**

**Prophylaxis**

- By intramuscular injection
  
  250 units, increased to 500 units if more than 24 hours have elapsed or there is risk of heavy contamination or following burns

**Therapeutic**

- By intramuscular injection
  
  150 units/kg (multiple sites)

Available from BPL

**Note** May be difficult to obtain

**Varicella–zoster**

**Varicella–Zoster Immunoglobulin** *(Antivaricella–zoster Immunoglobulin)*

See notes above

**Dose**

**Prophylaxis (as soon as possible—not later than 10 days after exposure)**

- By deep intramuscular injection

  **Neonate** 250 mg

  **Child 1 month–6 years** 250 mg

  **Child 6–11 years** 500 mg

  **Child 11–15 years** 750 mg

  **Child 15–18 years** 1 g

  Give second dose if further exposure occurs more than 3 weeks after first dose

**Note** No evidence that effective in treatment of severe disease. Normal immunoglobulin for intravenous use may be used in those unable to receive intramuscular injection.

Available from selected Health Protection Agency and NHS laboratories (also from BPL)

**Anti-D (Rho(D)) immunoglobulin**

This section is not included in *BNF for Children*. See BNF for use of Anti-D (Rho(D)) immunoglobulin

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**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 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. BCG immunisation is recommended for travellers aged under 16 years 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; it should preferably be given three months or more before departure.

Yellow fever immunisation 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).

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1. List of countries where the incidence of tuberculosis is greater than 40 cases per 100 000 is available at www.hpa.org.uk
Immunisation against meningococcal meningitis is recommended for a number of areas of the world (for details, see p. 744).

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. 736) 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. 755). Special care must also be taken with food hygiene (see below).

**Hepatitis B** vaccine (see p. 737) is recommended for those travelling to areas of high prevalence 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 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 Rabies Vaccine, BNF section 14.4) 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. 733), even if they have received 5 doses of a tetanus-containing vaccine previously.

**Typhoid vaccine** is indicated for travellers to those countries where typhoid is endemic but the vaccine is no substitute for personal precautions (see below).

There is no requirement for cholera vaccination as a condition for entry into any country, but oral cholera vaccine (see p. 732) 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, on Japanese encephalitis (vaccine available on named-patient basis from Sanofi Pasteur and MASTA) and on tick-borne encephalitis 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.

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1. Japanese encephalitis vaccine not prescribable on the NHS; health authorities may investigate circumstances under which vaccine prescribed
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  
(08.30 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
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

15.1.5 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

15.2 Local anaesthesia

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 topical 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 children 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 (section 15.1.4) 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 child is (or has been) taking.

Children 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 postoperative period. Anaesthetists must therefore know whether a child is, or has been, receiving corticosteroids (including high-dose inhaled corticosteroids).
Other drugs that should normally not be stopped before surgery include drugs for epilepsy, asthma, immunosuppression, and metabolic, endocrine and cardiovascular disorders (but see potassium sparing diuretics, below). Expert advice is required for children receiving antivirals for HIV infection. For general advice on surgery in children with diabetes, see section 6.1.1.

Children 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). If antidepressants need to be stopped, they should be withdrawn gradually to avoid withdrawal symptoms. 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.

**Anaesthesia and skilled tasks** Children and their carers should be very carefully warned about the risk of undertaking skilled tasks after the use of sedatives and analgesics during minor outpatient procedures. For intravenous benzodiazepines and for a short general anaesthetic the risk extends to at least 24 hours after administration. Responsible persons should be available to take children 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, during emergency surgery and in gastro-oesophageal reflux disease; prophylaxis against acid aspiration may be required in children.

An H₂-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 H₂-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).

**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 Clinical Effectiveness Programme, May 2006.

**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.

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. Extreme care is required in surgery of the mouth, pharynx, or larynx and in children with acute circulatory failure (shock) or fixed cardiac output.

To facilitate tracheal intubation, induction is usually followed by a neuromuscular blocking drug (section 15.1.5) or short-acting opioid (section 15.1.4.3).

Total intravenous anaesthesia This is a technique in which 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; specific models with paediatric pharmacokinetic data should be used for children.

Anaesthesia and skilled tasks See section 15.1.

Drugs used for intravenous anaesthesia

Propofol is associated with rapid recovery without a hangover effect and it is very 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 has been associated with bradycardia, occasionally profound; intravenous administration of an antimuscarinic drug may prevent this.

Thiopental sodium (thiopentone sodium) is a barbiturate that 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 particularly in neonates, and recovery is much slower.

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 may suppress adrenocortical function, particularly on continuous administration, and it should not be used for maintenance of anaesthesia.

Ketamine has good analgesic properties at sub-anaesthetic dosage and it causes less hypotension than thiopental and propofol during induction. It is often used in children requiring repeat anaesthesia (such as for serial burns dressings), however 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 psychotic effects; these can be reduced by a benzodiazepine, such as diazepam or midazolam. Ketamine also has abuse potential and may lead to dependence.
ETOMIDATE

Cautions see notes above; avoid in acute porphyria (section 9.8.2); interactions: Appendix 1 (anaesthetics, general)

Hepatic impairment reduce dose in liver cirrhosis

Pregnancy depresses neonatal respiration in third trimester

Breast-feeding avoid for 24 hours after administration

Contra-indications see notes above

Side-effects see notes above; also coughing, hiccups, shivering, allergic reactions (including bronchospasm and anaphylaxis); respiratory depression, arrhythmias, and convulsions also reported

Indication and dose See under preparations

Etomidate-Lipuro® (Braun) (NW)

Injection (emulsion), etomidate 2 mg/mL, net price 10-mL amp = £1.53

Dose

Induction of anaesthesia

- By slow intravenous injection
  Child 1 month–18 years 150–300 micrograms/kg; child under 10 years may need up to 400 micrograms/kg

Hypnomidate® (Janssen-Cilag) (NW)

Injection, etomidate 2 mg/mL, net price 10-mL amp = £1.47

Excipients include propylene glycol (see Excipients, p. 3)

Dose

Induction of anaesthesia

- By slow intravenous injection
  Child 1 month–18 years 300 micrograms/kg; max. total dose 60 mg

KETAMINE

Cautions see notes above; increased cerebrospinal fluid pressure; predisposition to hallucinations or nightmares; interactions: Appendix 1 (anaesthetics, general)

Pregnancy depresses neonatal respiration in third trimester

Contra-indications see notes above; 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, diplopia, nystagmus, raised intra-ocular pressure; rashes, injection-site reactions; anaphylaxis also reported

Indication and dose

Premedication prior to invasive or painful procedures

- By intravenous injection
  Child 1 month–18 years 1–2 mg/kg as a single dose

Induction and maintenance of anaesthesia (short procedures)

- By intravenous injection over at least 60 seconds
  Neonate 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response
  Child 1 month–12 years 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response
  Child 12–18 years 1–4.5 mg/kg (usually 2 mg/kg) produces 5–10 minutes of surgical anaesthesia, adjusted according to response

Induction and maintenance of anaesthesia (longer procedures)

- By continuous intravenous infusion
  Neonate initially 0.5–2 mg/kg followed by a continuous intravenous infusion of 500 micrograms/kg/hour adjusted according to response; up to 2 mg/kg/hour may be used to produce deep anaesthesia
  Child 1 month–18 years initially 0.5–2 mg/kg followed by a continuous intravenous infusion of 0.6–2.7 mg/kg/hour adjusted according to response

Administration for continuous intravenous infusion, dilute to a concentration of 1 mg/mL with Glucose 5% or Sodium Chloride 0.9%; use microdrop infusion for maintenance of anaesthesia

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

Ketalar® (Pfizer) (NW)

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
**PROPOFOL**

**Cautions** see notes above; cardiac impairment; respiratory impairment; hypovolaemia; epilepsy; hypotension; raised intracranial pressure; monitor blood-lipid concentration if risk of fat overload or if sedation longer than 3 days; interactions: Appendix 1 (anaesthetics, general)

**Hepatic impairment** use with caution

**Renal impairment** use with caution

**Pregnancy** depresses neonatal respiration in third trimester, for maintenance of anaesthesia, doses of propofol should not exceed 6 mg/kg/hour

**Breast-feeding** present in milk but amount probably too small to be harmful

**Contra-indications** see notes above; cardiac impairment; hepatic impairment

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**Licensed use** Diprivan® 2%, Propofol-Lipuro® 2%, and Propoven® 2% not licensed for use in children under 3 years; Diprivan® TCI (‘target controlled infusion’) system not licensed for use in children

**Indication and dose**

**Induction of anaesthesia**

- By intravenous injection or by intravenous infusion
  - Child 1 month–3 years 2.5–4 mg/kg administered slowly until response (using Diprivan® 1%, Propofol-Lipuro® 1%, and Propoven® 1% only)
  - Child 3–8 years 2.5–4 mg/kg administered slowly until response
  - Child 8–12 years 2.5 mg/kg administered slowly until response
  - Child 12–18 years 1.5–2.5 mg/kg at a rate of 20–40 mg every 10 seconds until response

**Maintenance of anaesthesia**

- By continuous intravenous infusion
  - Child 1 month–3 years 9–15 mg/kg/hour (using Diprivan® 1%, Propofol-Lipuro® 1%, and Propoven® 1% only), adjusted according to response

**Propofol (Non-proprietary)**

- 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) 1% injection (emulsion), propofol 10 mg/mL, net price 20-mL amp = £3.88, 50-mL prefilled syringe (for use with Diprivan® TCI system) = £10.67
- 2% injection (emulsion), propofol 20 mg/mL, net price 50-mL prefilled syringe (for use with Diprivan® TCI system) = £20.37

**Administration** for continuous intravenous infusion; microbiological filter not recommended; 1% emulsion may be infused undiluted using a suitable infusion pump; may also be administered via a Y-piece close to injection site co-administered with Glucose 5% or Sodium Chloride 0.9%; alternatively dilute to a concentration not less than 2 mg/mL with Glucose 5% (or Sodium Chloride 0.9% for Propofol-Lipuro®, Propoven®, Braun, and Fresenius Kabi brands); 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

2% emulsion do not dilute; may be administered via a Y-piece close to injection site co-administered with Glucose 5% or Sodium Chloride 0.9%

**Maintenance of sedation for surgical and diagnostic procedures (1% emulsion only)**

- By intravenous infusion
  - Child 17–18 years 1.5–4.5 mg/kg/hour (additionally if rapid increase in sedation required, by intravenous injection 10–20 mg)

**Sedation of ventilated children in intensive care**

- By continuous intravenous infusion
  - Child 17–18 years 0.3–4 mg/kg/hour, adjusted according to response

**Induction of sedation for surgical and diagnostic procedures (1% emulsion only)**

- By intravenous injection over 1–5 minutes
  - Child 17–18 years 0.5–1 mg/kg

**Hepatic impairment** reduce induction dose in severe liver disease

**Pregnancy** depresses neonatal respiration in the third trimester—dose should not exceed 250 mg
Contra-indications see notes above; acute porphyria (section 9.8.2); myotonic dystrophy

Breast-feeding present in milk—manufacturer advises avoid

Side-effects hypotension, arrhythmias, myocardial depression, laryngeal spasm, cough, sneezing; hypersensitivity reactions; rash, injection-site reactions; excessive doses associated with hypothermia and profound reduction in cerebral function

Licensed use not licensed for use in status epilepticus; not licensed for use by intravenous infusion

Indication and dose

Induction of anaesthesia

- By slow intravenous injection

Neonate initially up to 2 mg/kg, then 1 mg/kg repeated as necessary (max. total dose 4 mg/kg)

Child 1 month–18 years initially up to 4 mg/kg, then 1 mg/kg repeated as necessary (max. total dose 7 mg/kg)

Administration For intravenous injection, dilute to a concentration of 25 mg/mL with Water for Injections, and give over at least 10–15 seconds; for intravenous infusion dilute to a concentration of 2.5 mg/mL with Sodium Chloride 0.9%

Thiopental (Link) Injection, powder for reconstitution, thiopental sodium, net price 500-mg vial = £3.06

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 anaesthetics are administered using calibrated vaporisers, 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 children 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 with nitrous oxide, see Nitrous oxide, p. 768.

Anaesthesia and skilled tasks 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. 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 can 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 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 sevoflurane-induced permanent renal injury have been reported and the carbon dioxide absorbents used in the UK produce very low concentrations of compound A.

**Halothane** is a volatile liquid anaesthetic. It has largely been superceded by newer agents, but is used by very specialised paediatric anaesthetists to manage difficult airways (with careful monitoring for cardiorespiratory depression and arrhythmias). Its advantages are that it is potent, induction is smooth, and the vapour is non-irritant and seldom induces coughing or breathholding. 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 children 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.

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**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.
Breast-feeding

Contra-indications see notes above

Side-effects see notes above

Indication and dose

Induction of anaesthesia
- By inhalation through specifically calibrated vaporiser
  Child 1 month–18 years initially 0.5% then increased gradually according to response to 2–4% in oxygen or nitrous oxide–oxygen

Halothane (Non-proprietary) [PH]
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943

ISOFLURANE

Cautions see notes above; interactions: Appendix 1 (anaesthetics, general)

Pregnancy depresses neonatal respiration in third trimester

Contra-indications see notes above

Side-effects see notes above

Indication and dose

Induction of anaesthesia
- By inhalation through specifically calibrated vaporiser

Neonate increased gradually according to response from 0.5–3% in oxygen or nitrous oxide–oxygen

Child 1 month–18 years increased gradually according to response from 0.5–3% in oxygen or nitrous oxide–oxygen

Maintenance of anaesthesia
- By inhalation through specifically calibrated vaporiser
  Child 1 month–18 years 0.5–2% in oxygen or nitrous oxide–oxygen

Isoflurane (Abbott)
Isoflurane, net price 250 mL = £47.50

AErrane® (Baxter)
Isoflurane, net price 250 mL = £27.00

SEVOFLURANE

Cautions see notes above; interactions: Appendix 1 (anaesthetics, general)

Renal impairment manufacturer advises use with caution

Pregnancy depresses neonatal respiration in third trimester

Contra-indications see notes above

Side-effects see notes above; also agitation; hepatitis and seizures also reported

Indication and dose

Induction of anaesthesia
- By inhalation through specifically calibrated vaporiser

Neonate up to 4% in oxygen or nitrous oxide–oxygen, according to response

Child 1 month–18 years initially 0.5–1% then increased gradually up to 8% in oxygen or nitrous oxide–oxygen, according to response

Maintenance of anaesthesia
- By inhalation through specifically calibrated vaporiser
  Neonate 0.5–2% in oxygen or nitrous oxide–oxygen, according to response
  Child 1 month–18 years 0.5–3% in oxygen or nitrous oxide–oxygen, according to response

Sevoflurane (Non-proprietary) [PH]
Sevoflurane, net price 250 mL = £123.00

Nitrous oxide

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 may be used in children who are able to self-regulate their intake (usually over 5 years of age) for painful dressing changes, as an aid to postoperative physiotherapy, for wound debridement and in emergency ambulances.

Nitrous oxide may have a deleterious effect if used in children 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. Hypoxia can occur immediately following the administration of nitrous oxide; additional oxygen should always be given for several minutes after stopping the flow of nitrous oxide.

Exposure of children 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 B$_{12}$; 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$_{12}$ concentration should be considered before nitrous oxide anaesthesia in children at risk of deficiency, including children who have a poor or vegetarian diet and children 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.

### NITROUS OXIDE

**Cautions** see notes above; **interactions:** Appendix 1 (anaesthetics, general)

**Pregnancy** depresses neonatal respiration in third trimester

**Side-effects** see notes above

**Indication and dose**

<table>
<thead>
<tr>
<th>Maintenance of light anaesthesia</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>● By inhalation using suitable anaesthetic apparatus</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neonate</th>
<th>up to 66% in oxygen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–18 years</td>
<td>up to 66% in oxygen</td>
</tr>
</tbody>
</table>

**Analgesia**

- By inhalation using suitable anaesthetic apparatus (see also notes above)

<table>
<thead>
<tr>
<th>Neonate</th>
<th>up to 50% in oxygen, according to the child’s needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Child 1 month–18 years</td>
<td>up to 50% in oxygen, according to the child’s needs</td>
</tr>
</tbody>
</table>

### 15.1.3 Antimuscarinic drugs

Antimuscarinic drugs are used (less commonly nowadays) as premedicants to dry bronchial and salivary secretions which are increased by intubation, upper airway surgery, or some inhalational anaesthetics, but they should not be used for this indication in children with cystic fibrosis. Antimuscarinics are also used before or with neostigmine (section 15.1.6) to prevent bradycardia, excessive salivation, and other muscarinic actions of neostigmine. They also prevent bradycardia and hypotension associated with drugs such as halothane, propofol, and suxamethonium.

**Atropine sulphate** is now rarely used for premedication but still has an emergency role in the treatment of vagotonic side-effects. For its role in cardiopulmonary resuscitation, see section 2.7.3.

**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 children hyoscine may cause the central anti-cholinergic 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 muscle relaxants (section 15.1.5). Glycopyrronium or hyoscine hydrobromide are also used to control excessive secretions in upper airways or hypersalivation in palliative care and in children.
unable to control posture or with abnormal swallowing reflex; effective dose varies and tolerance may develop. The intramuscular route should be avoided if possible. Hyoscine transdermal patches may also be used (section 4.6).

## ATROPINE SULPHATE

**Cautions**  
Down’s syndrome; gastro-oesophageal reflux disease, diarrhoea, ulcerative colitis, paralytic ileus, pyloric stenosis, cardiovascular disease, hypertension, conditions characterised by tachycardia (including hyperthyroidism, cardiac insufficiency, cardiac surgery), myasthenia gravis, pyrexia, urinary retention, individuals susceptible to angle-closure glaucoma; **interactions:** Appendix 1 (antimuscarinics)  
**Pregnancy**  
not known to be harmful; manufacturer advises caution  
**Breast-feeding**  
small amount present in milk—manufacturer advises caution  
**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**  
constipation, tachycardia, 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, dryness of the skin; *less commonly* nausea, vomiting, giddiness, confusion

**Licensed use**  
not licensed for use by oral route; not licensed for use in children under 12 years for intra-operative bradycardia

### Indication and dose

#### Premedication
- **By mouth** 1–2 hours before induction  
  - **Neonate** 20–40 micrograms/kg  
  - **Child 1 month–12 years** 20–40 micrograms/kg (max. 900 micrograms)  
- **By subcutaneous or intramuscular injection** 30–60 minutes before induction  
  - **Neonate** 10–15 micrograms/kg (subcutaneous route recommended)  
  - **Child 1 month–12 years** 10–30 micrograms/kg (minimum 100 micrograms, max. 600 micrograms)  
  - **Child 12–18 years** 300–600 micrograms

#### Intra-operative bradycardia
- **By intravenous injection**  
  - **Neonate** 20 micrograms/kg  
  - **Child 1 month–12 years** 20 micrograms/kg (max. 600 micrograms)  
  - **Child 12–18 years** 0.6–1.2 mg

### Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block
- **By intravenous injection**  
  - **Neonate** 20 micrograms/kg  
  - **Child 1 month–12 years** 20 micrograms/kg (max. 600 micrograms)  
  - **Child 12–18 years** 0.6–1.2 mg

### Control of muscarinic side-effects of edrophonium in reversal of competitive neuromuscular block
- **By intravenous injection**  
  - **Child 1 month–18 years** 7 micrograms/kg (max. 600 micrograms)

### Cycloplegia, anterior uveitis (section 11.5)

#### Administration
  for administration *by mouth*, injection solution may be given orally

1. **Atropine (Non-proprietary)**  
  **Injection**  
  - atropine sulphate 600 micrograms/mL, net price 1-mL amp = £0.60
  - Other strengths also available  
  **Injection**  
  - prefilled disposable syringe, atropine sulphate 100 micrograms/mL, net price 5 mL = £4.58, 10 mL = £5.39, 30 mL = £8.95
  - prefilled disposable syringe, atropine sulphate 200 micrograms/mL, net price 5 mL = £5.37, 300 micrograms/mL, 10 mL = £5.37, 600 micrograms/mL, 1 mL = £4.67
  - Oral solution, atropine sulphate 100 micrograms/mL available from ’special-order’ manufacturers or specialist importing companies, see p. 943

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

1. *[^1]* restriction does not apply where administration is for saving life in emergency

## GLYCOPYRRONIUM BROMIDE

(Glycopyrrolate)

**Cautions**  
see under Atropine Sulphate; **interactions:** Appendix 1 (antimuscarinics)  
**Side-effects**  
see under Atropine Sulphate  
**Licensed use**  
not licensed for use in control of upper airways secretion and hypersalivation

### Indication and dose

#### Premedication at induction
- **By intravenous or intramuscular injection**  
  - **Neonate** 5 micrograms/kg  
  - **Child 1 month–18 years** 4–8 micrograms/kg (max. 200 micrograms)
Intra-operative bradycardia

- By intravenous injection
  - Neonate: 10 micrograms/kg, repeated if necessary
  - Child 1 month–18 years: 4–8 micrograms/kg (max. 200 micrograms), repeated if necessary

Control of muscarinic side-effects of neostigmine in reversal of competitive neuromuscular block

- By intravenous injection
  - Neonate: 10 micrograms/kg
  - Child 1 month–18 years: 10 micrograms/kg (max. 500 micrograms)

Control of upper airways secretion and hypersalivation

- By mouth
  - Child 1 month–18 years: 40–100 micrograms/kg 3–4 times daily, adjusted according to response (max. 2 mg)
- By subcutaneous infusion
  - Child 1 month–12 years: 12–40 micrograms/kg/24 hours (max. 1.2 mg)
  - Child 12–18 years: 0.6–1.2 mg/24 hours

### HYOSCINE HYDROBROMIDE
(Scopolamine hydrobromide)

**Cautions** see under Hyoscine hydrobromide (section 4.6); also paralytic ileus, myasthenia gravis, epilepsy, susceptibility to angle-closure glaucoma

**Side-effects** see under Atropine Sulphate; also bradycardia

**Indication and dose**

**Premedication**

- By subcutaneous or intramuscular injection 30–60 minutes before induction
  - Child 1–12 years: 15 micrograms/kg (max. 600 micrograms)

**Administration** for administration by mouth, injection solution may be given or crushed tablets suspended in water

**Glycopyrronium bromide** (Non-proprietary)

- Tablets, glycopyrronium bromide 1 mg and 2 mg
  - Available on a named-patient basis from specialist importing companies, p. 943

**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

### 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**

**Premedication** These drugs are given to allay fear and anxiety in the pre-operative period (including the night before an operation), to relieve pain and discomfort when present, and to augment the action of subsequent anaesthetic agents. A number of the drugs used also provide some degree of pre-operative amnesia. The choice will vary with the individual child, the nature of the operative procedure, the anaesthetic to be used, and other prevailing circumstances such as outpatients, obstetrics, and recovery facilities. The choice also varies between elective and emergency operations. Oral administration is preferred where possible; the rectal route should only be used in exceptional circumstances.

The use of anxiolytic or sedative drugs as premedication in children is declining, but can be useful in selected cases. Sedative premedication should be avoided in
children with a compromised airway, CNS depression, or a history of sleep apnoea.

Application of a local anaesthetic (section 15.2) to the injection site can help to prevent pain.

**Sedation for clinical procedures** Anxiety about a clinical procedure can be minimised by using a sedative drug, usually a benzodiazepine, for its anxiolytic and amnestic effect. The child should be monitored carefully as soon as the sedative is given until recovery after the procedure; concomitant use of sedatives potentiates the CNS depressant effects of analgesics. For a painful procedure, the sedative may be given with a local anaesthetic (administered topically, by infiltration or as a nerve block as appropriate) and an analgesic such as paracetamol or an NSAID.

Oral **midazolam** is the most common premedicant for children. Midazolam is suitable for sedating a child for a procedure lasting no longer than 20 minutes; it is given by mouth 30–60 minutes before the procedure. Alternatively, **temazepam** may be given by mouth 60–90 minutes before the procedure. If the procedure is likely to last 20–60 minutes, **chloral hydrate** or **triclofos** (section 4.1.1) by mouth are effective, especially in children of pre-school age; secobarbital (quinalbarbitone) can be used in older children but the risk of excessive sedation and cardiorespiratory depression is greater. The antihistamine **alimemazine** (trimeprazine, section 3.4.1) is occasionally used orally as a premedicant, but when given alone it may cause postoperative restlessness in the presence of pain. Alimemazine also has antiemetic properties though it is rarely used for this indication.

If deep sedation is required a general anaesthetic (e.g. propofol or ketamine), or a potent opioid (e.g. fentanyl) can be used, however they should be used only under the supervision of a specialist experienced in the use of these drugs.

**Dental procedures** Anxiolytics diminish tension, anxiety and panic, and may benefit anxious children, however they should be used under specialist supervision only. Children and their carers should be carefully warned about the risk of undertaking skilled tasks (**important**: for general advice on anaesthesia and skilled tasks, see p. 762). For further information on hypnotics and anxiolytics, see p. 211. For further information on hypnotics used for dental procedures, see p. 212.

**Anaesthesia and skilled tasks** See section 15.1.

### 15.1.4.1 Anxiolytics and neuroleptics

#### Benzodiazepines

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 in adolescents). 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 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 also painful and absorption is erratic; administration by the intramuscular route is not recommended. 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.

Temazepam is given by mouth in older children 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 by intravenous injection in preference to intravenous diazepam; it has a quick onset of action and recovery is faster than from diazepam, making it suitable for day cases. Midazolam can be given by mouth but its bitter acidic taste may need to be disguised. It can also be given buccally and intranasally; use of the intranasal route is limited by nasal discomfort and is not recommended. Midazolam is associated with profound sedation when high doses are given or when used with certain other drugs. It can cause severe disinhibition and restlessness in some children. Midazolam is not recommended for prolonged sedation in neonates; drug accumulation is likely to occur.

There have been reports of overdosage in adults when high strength midazolam injection 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**

**Cautions** see notes above and section 4.8.2

**Contra-indications** see section 4.8.2

**Side-effects** see notes above and section 4.8.2

**Indication and dose**

**Premedication and sedation for clinical procedures** (but see notes above)

- **By mouth** 45–60 minutes before procedure
  - Child 1 month–12 years 200–300 micrograms/kg (max. 10 mg)
  - Child 12–18 years 200–300 micrograms/kg (max. 20 mg)

- **By intravenous injection** over 2–4 minutes into large vein (specialist use only); emulsion preparation preferred
  - Child 1 month–12 years 100–200 micrograms/kg (max. 5 mg) immediately before procedure
  - Child 12–18 years 100–200 micrograms/kg (max. 20 mg) immediately before procedure

- **By rectum** (as rectal solution) approximately 30 minutes before procedure
  - Child 1–3 years 5 mg
  - Child 3–12 years 5–10 mg
  - Child 12–18 years 10 mg

- **Status epilepticus** section 4.8.2

- **Febrile convulsions** section 4.8.3

- **Muscle spasm** section 10.2.2

**Diazepam** (Non-proprietary) Tablets, diazepam 2 mg, net price 28 = 95p; 5 mg, 28 = 98p; 10 mg, 28 = £1.08. Label: 2 or 19

Brands include Rimapam®, 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®

Dental prescribing on NHS Diazepam Tablets or Diazepam Oral Solution 2 mg/5 mL may be prescribed

▲ Parenteral preparations and rectal solution

Section 4.8.2
LORAZEPAM

Cautions see notes above and section 4.8.2
interactions: Appendix 1 (anxiolytics and hypnotics)
Contra-indications see under Diazepam (section 4.8.2)
Side-effects see notes above and under Diazepam (section 4.8.2)
Licensed use not licensed for use in children under 5 years by mouth; not licensed for use in children under 12 years by intravenous injection

Indication and dose
Status epilepticus section 4.8.2

Premedication
• By mouth
  Child 1 month–12 years 50–100 micrograms/kg (max. 4 mg) at least 1 hour before surgery
  Child 12–18 years 1–4 mg at least 1 hour before surgery
  Note Same dose may be given the night before surgery in addition to, or to replace, dose before surgery

• By intravenous injection
  Child 1 month–18 years 50–100 micrograms/kg (max. 4 mg)
  Note Give intravenous injection 30–45 minutes before surgery

Administration for intravenous injection, dilute injection solution with an equal volume of Sodium Chloride 0.9% or Water for Injections; give over 3–5 minutes; max. rate 50 micrograms/kg over 3 minutes

Lorazepam (Non-proprietary) [774]
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 (avoid in neonates see Excipients, p. 3), propylene glycol
Brands include Ativan®
Extemporaneous formulations available see Extemporaneous Preparations, p. 8

MIDAZOLAM

Cautions see notes above; cardiac disease; respiratory disease; myasthenia gravis; neonates; history of drug or alcohol abuse; reduce dose if debilitated; risk of severe hypotension in hypovolaemia, vasoconstriction, hypothermia; avoid prolonged use (and abrupt withdrawal thereafter); interactions: Appendix 1 (anxiolytics and hypnotics)

Hepatic impairment can precipitate coma
Renal impairment start with small doses in severe renal impairment; increased cerebral sensitivity
Pregnancy use only if clear indication such as seizure control (high doses during late pregnancy or labour may cause neonatal hypothyroidism, hypotonia, and respiratory depression)
Breast-feeding present in milk—manufacturer advises avoid breast-feeding for 24 hours after administration

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), fatigue, dizziness, vertigo, involuntary movements, paradoxical excitement and aggression, dysarthria; urinary retention, incontinence; blood disorders; muscle weakness; visual disturbances; salivation changes; skin reactions; injection-site reactions; with intranasal administration burning sensation, lacrimation, and severe irritation of nasal mucosa under 6 months for premedication and conscious sedation; not licensed for use by mouth, or by buccal administration

Indication and dose
Sedation (but see notes above)
• By mouth
  Child 1 month–18 years 500 micrograms/kg (max. 20 mg) 30–60 minutes before procedure

• By buccal administration
  Child 6 months–10 years 200–300 micrograms/kg (max. 5 mg)
  Child 10–18 years 6–7 mg (max. 8 mg if 70 kg or over)

• By rectum
  Child 6 months–12 years 300–500 micrograms/kg 15–30 minutes before procedure

• By intravenous injection over 2–3 minutes 5–10 minutes before procedure
  Child 1 month–6 years initially 25–50 micrograms/kg, increased if necessary in small steps (max. total dose 6 mg)
  Child 6–12 years initially 25–50 micrograms/kg, increased if necessary in small steps (max. total dose 10 mg)
  Child 12–18 years initially 25–50 micrograms/kg, increased if necessary in small steps (max. total dose 7.5 mg)

Premedication (but see notes above)
• By mouth
  Child 1 month–18 years 500 micrograms/kg (max. 20 mg) 15–30 minutes before the procedure
MIDAZOLAM (continued)

- By rectum
  Child 6 months–12 years 300–500 micrograms/kg 15–30 minutes before induction
- By intravenous injection
  Child 12–18 years 25–50 micrograms/kg repeated as required (max. total dose 7.5 mg)

Induction of anaesthesia (but rarely used)
- By slow intravenous injection
  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 in intensive care
- By intravenous injection and continuous intravenous infusion
  Neonate less than 32 weeks gestational age
  30 micrograms/kg/hour by continuous intravenous infusion adjusted according to response
  Neonate over 32 weeks gestational age
  60 micrograms/kg/hour by continuous intravenous infusion adjusted according to response
- By intravenous injection
  Child 1–6 months 60 micrograms/kg/hour by continuous intravenous infusion adjusted according to response
  Child 6 months–12 years initially 50–200 micrograms/kg by slow intravenous injection over at least 3 minutes followed by 30–120 micrograms/kg/hour by continuous intravenous infusion adjusted according to response
  Child 12–18 years initially 30–300 micrograms/kg by slow intravenous injection given in steps of 1–2.5 mg every 2 minutes followed by 30–200 micrograms/kg/hour by continuous intravenous infusion adjusted according to response

Note: Initial dose may not be required and lower maintenance doses needed if opioid analgesics also used; reduce dose (or reduce or omit initial dose) in hypovolaemia, vasoconstriction, or hypothermia

Status epilepticus section 4.8.2

Administration for administration by mouth, injection solution may be diluted with apple or black currant juice, chocolate sauce, or cola
For buccal administration, administer half of the dose between the upper lip and gum on each side of the mouth using an oral syringe; retain in the mouth for at least 5 minutes then swallow.
For continuous intravenous infusion, dilute with Glucose 5% or Sodium Chloride 0.9%; for neonates and children under 15 kg body-weight, dilute to a max. concentration of 1 mg/mL.
Neonatal intensive care; body-weight under 3.3 kg, dilute 15 mg/kg body-weight to a final volume of 50 mL with infusion fluid; an intravenous infusion rate of 0.1 mL/hour provides a dose of 30 micrograms/kg/hour; body-weight over 3.3 kg, dilute 50 mg to final volume of 50 mL with infusion fluid, max. concentration of 1 mg/mL; an intravenous infusion rate of 0.05–0.1 mL/kg/hour provides a dose of 50–100 micrograms/kg/hour.
For rectal administration of the injection solution, attach a plastic applicator onto the end of a syringe; if the volume to be given rectally is too small, dilute with Water for Injections

Midazolam (Non-proprietary) [C]
Oral liquid, midazolam 2.5 mg/mL, 100 mL
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943
Buccal liquid, midazolam 10 mg/mL, 5 mL and 25 mL
Available from ‘special-order’ manufacturers or specialist importing companies, see p. 943 (Epistatus® and Consed®)
Injection, midazolam (as hydrochloride) 1 mg/mL, net price 2-mL amp = 50p, 5-mL amp = 60p, 50-mL vial = £7.87; 2 mg/mL, 5-mL amp = 65p; 5 mg/mL, 2-mL amp = 58p, 10-mL amp = £2.50
Hypnovel® (Roche) [C]
Injection, midazolam (as hydrochloride) 2 mg/mL, net price 5-mL amp = 75p; 5 mg/mL, 2-mL amp = 90p

15 Anaesthesia

TEMAZEPAM

Cautions see notes above and under Diazepam (section 4.8.2); interactions: Appendix 1 (anxiolytics and hypnotics)
Contra-indications see under Diazepam (section 4.8.2)
Side-effects see notes above and under Diazepam (section 4.8.2)
Licensed use tablets not licensed for use in children
Indication and dose
Premedication and sedation for clinical procedures
- By mouth
  Child 1–12 years 1 mg/kg (max. 30 mg) 1 hour before surgery

Child 12–18 years 20–30 mg 1 hour before surgery

Temazepam (Non-proprietary) [C]
Tablets, temazepam 10 mg, net price 28-tab pack = £3.89, 20 mg, 28-tab pack = £1.64. Label: 19
Oral solution, temazepam 10 mg/5 mL, net price 300 mL = £18.96. Label: 19
Note Sugar-free versions are available and can be ordered by specifying ‘sugar-free’ on the prescription
Dental prescribing on NHS Temazepam Tablets or Oral Solution may be prescribed
Note See p. 17 for prescribing requirements of controlled drugs
15.1.4.2 Non-opioid analgesics

Since non-steroidal anti-inflammatory drugs (NSAIDs) do not depress respiration, do not impair gastro-intestinal 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.

Diclofenac, ibuprofen (section 10.1.1), paracetamol (section 4.7.1), and ketorolac are used to relieve postoperative pain in children; diclofenac and paracetamol can be given parenterally and rectally as well as by mouth. Intramuscular injections of diclofenac 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 irritating on intramuscular injection but pain has been reported; it can also be given by mouth or by intravenous injection.

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 children 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 when monitoring of the child might be less intensive. Alfentanil, fentanyl, and remifentanil can cause muscle rigidity, particularly of the chest wall muscle or jaw muscle, which can be managed by the use of neuromuscular blocking drugs.

In contrast to other opioids which are metabolised in the liver, remifentanil undergoes rapid metabolism by non-specific blood and tissue esterases; its short duration of action allows prolonged administration at high dosage, without accumulation, and with little risk of residual postoperative respiratory depression. Remifentanil should not be given by intravenous injection intra-operatively, but it is well suited to continuous infusion; a supplementary analgesic is given before stopping the infusion of remifentanil.

**Neonates**  The half-life of fentanyl and alfentanil is prolonged in neonates and accumulation is likely with prolonged use.

### Alfentanil

#### Indication and dose

- **Analgesia especially during short procedures; enhancement of anaesthesia**
  - By intravenous injection over 30 seconds (with assisted ventilation)
  - Neonate initially 5–20 micrograms/kg; supplemental doses up to 10 micrograms/kg
  - Child 1 month–18 years initially 10–20 micrograms/kg; supplemental doses up to 10 micrograms/kg

#### Administration

- **By intravenous infusion (with assisted ventilation)**
  - Neonate initially 10–50 micrograms/kg over 10 minutes followed by 30–60 micrograms/kg/hour
  - Child 1 month–18 years initially 50–100 micrograms/kg over 10 minutes followed by 30–60 micrograms/kg/hour

### Fentanyl

#### Indication and dose

- **Analgesia during operation, enhancement of anaesthesia with spontaneous respiration**
  - By intravenous injection over at least 30 seconds
  - Child 12–18 years initially 50–200 micrograms, then 50 micrograms as required

#### Administration

- **By intravenous injection over at least 30 seconds**
  - Neonate initially 1–5 micrograms/kg, then 1–3 micrograms/kg as required
  - Child 1 month–12 years initially 1–5 micrograms/kg, then 1–3 micrograms/kg as required
  - Child 12–18 years initially 0.3–3.5 mg, then 100–200 micrograms as required
Analgesia and respiratory depressant with assisted ventilation in intensive care

- By intravenous infusion

**Neonate** initially 1–5 micrograms/kg, then adjusted according to response

**Child 1 month–18 years** initially 1–5 micrograms/kg, then adjusted according to response

Analgesia in other situations section 4.7.2

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**REMIFENTANIL**

**Cautions** section 4.7.2 (but no dose adjustment necessary in renal impairment) and notes above

**Contra-indications** section 4.7.2 and notes above; left ventricular dysfunction

**Side-effects** section 4.7.2 and notes above; also hypertension, hypoxia; very rarely asystole and anaphylaxis

**Indication and dose**

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

**Enhancement and maintenance of anaesthesia**

- By intravenous injection and by continuous intravenous infusion

**Neonate** by intravenous infusion 24–60 micrograms/kg/hour; additional doses of 1 microgram/kg can be given by intravenous injection during the intravenous infusion

**Child 1–12 years** initially by intravenous injection 0.1–1 micrograms/kg over at least 30 seconds (omitted if not required) then by intravenous infusion 3–80 micrograms/kg/hour according to anaesthetic technique and adjusted according to response; additional doses can be given by intravenous injection during the intravenous infusion

**Child 12–18 years** initially by intravenous injection 0.1–1 micrograms/kg over at least 30 seconds (omitted if not required) then by intravenous infusion 3–120 micrograms/kg/hour according to anaesthetic technique and adjusted according to response; additional doses can be given by intravenous injection during the intravenous infusion

**Administration** for intravenous infusion, injection solution may be diluted in Glucose 5% or Sodium Chloride 0.9%

**Fentanyl (Non-proprietary)**

- **Injection**, fentanyl (as citrate) 50 micrograms/mL, net price 2-mL amp = £5.40, 10-mL amp = £1.65

**Sublimaze® (Janssen-Cilag)**

- **Injection**, fentanyl (as citrate) 50 micrograms/mL, net price 2-mL amp = 22p, 10-mL amp = £1.11

**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

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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.

Children 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, which includes 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 children 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 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 children with myasthenia gravis and in hypothermia, therefore 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 in these children is unpredictable. Resistance may develop in children with burns who may require increased doses; low plasma cholinesterase activity in these children 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 children with hepatic or renal impairment. Cardiovascular effects are associated with significant histamine release. Neonates may be more sensitive to the effects of atracurium and lower doses may be required.

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. In children aged 1 month to 12 years, cisatracurium has a shorter duration of action and produces faster spontaneous recovery.

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. In children under 12 years mivacurium has a faster onset, shorter duration of action, and produces more rapid spontaneous recovery.

Pancuronium, an aminosteroid neuromuscular blocking drug, has a long duration of action and is often used in children 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. The half-life of pancuronium is prolonged in neonates; neonates should receive post-operative intermittent positive pressure ventilation.

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. In children under 12 years, rocuronium has a faster onset and shorter duration of action.

Vecuronium, an aminosteroid neuromuscular blocking drug, has an intermediate duration of action. It does not generally produce histamine release and lacks
cardiovascular effects. In neonates and infants, vecuronium has a faster onset and a longer duration of action; recovery is longer in these children. Unexpected sustained neuromuscular blockade may occur in neonates.

**ATRACURIUM BESILATE**

*(Atracurium besylate)*

**Cautions**

- **Pregnancy** does not cross placenta in significant amounts but manufacturer advises use only if potential benefit outweighs risk
- **Breast-feeding** unlikely to be harmful following recovery from neuromuscular block; some manufacturers advise avoiding breast-feeding for 24 hours after administration

**Side-effects** seen above; seizures also reported

**Licensed use** not licensed for use in neonates

**Indication and dose**

Neuromuscular blockade (short to intermediate duration) for surgery or during intensive care

- **Neonate** initially by *intravenous injection* 300–500 micrograms/kg followed either by *intravenous injection*, 100–200 micrograms/kg repeated as necessary or by *intravenous infusion*, 300–400 micrograms/kg/hour adjusted according to response

**Child 1 month–18 years** initially by *intravenous injection* 300–600 micrograms/kg then 100–200 micrograms/kg repeated as necessary or initially by *intravenous injection* 200–600 micrograms/kg followed by *intravenous infusion*, 300–600 micrograms/kg/hour adjusted to response; higher doses may be necessary in intensive care

**Administration** for *continuous intravenous infusion*, dilute to a concentration of 0.5–5 mg/mL with Glucose 5% or Sodium Chloride 0.9% or Ringer’s solution or Compound Sodium Lactate; stability varies with diluent.

**Neonatal intensive care**, dilute 60 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; minimum concentration of 500 micrograms/mL, max. concentration of 5 mg/mL; an intravenous infusion rate of 0.1 mL/hour provides a dose of 120 micrograms/kg/hour

**Atracurium** (Non-proprietary) (ATRACURIUM BESILATE) (Atracurium besylate) 10 mg/mL, net price 2.5-mL amp = £1.85; 5-mL amp = £3.37; 25-mL amp = £14.45

**Tracrium** (GSK) (ATRACURIUM BESILATE) (Atracurium besylate) 10 mg/mL, net price 2.5-mL amp = £1.66; 5-mL amp = £3.00; 25-mL amp = £12.91

**CISATRACURIUM**

**Cautions** see notes above

- **Pregnancy** manufacturer advises avoid—no information available
- **Breast-feeding** no information available

**Side-effects** see notes above

**Indication and dose**

Neuromuscular blockade (intermediate duration) for intubation and during surgery

- **Child 1 month–2 years** initially 150 micrograms/kg, then 30 micrograms/kg repeated approx. every 20 minutes as necessary
- **Child 2–12 years** initially 150 micrograms/kg (80–100 micrograms/kg if not for intubation), then 20 micrograms/kg repeated approx. every 10 minutes as necessary
- **Child 12–18 years** initially 150 micrograms/kg, then 30 micrograms/kg repeated approx. every 20 minutes as necessary

**Administration** for *continuous intravenous infusion*, dilute to a concentration of 0.1–2 mg/mL with Glucose 5% or Sodium Chloride 0.9%; solutions of 2 mg/mL and 5 mg/mL may be infused undiluted

**Nimbex** (GSK) (CISATRACURIUM) (Cisatracurium) (as besilate) 2 mg/mL, net price 10-mL amp = £7.55

**Forte injection** (CISATRACURIUM) (Cisatracurium) (as besilate) 5 mg/mL, net price 30-mL vial = £31.09

**MIVACURIUM**

**Cautions** see notes above; low plasma cholinesterase activity

- **Hepatic impairment** reduce dose in severe impairment
- **Renal impairment** clinical effect prolonged in renal failure—reduce dose according to response

**Pregnancy** manufacturer advises avoid—no information available

**Hepatic impairment** reduce dose in severe impairment

**Renal impairment** clinical effect prolonged in renal failure—reduce dose according to response

**Pregnancy** manufacturer advises avoid—no information available
MIVACURIUM (continued)

Side-effects  see notes above

Indication and dose
To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (short duration) during surgery
• By intravenous administration
  Child 2–6 months by intravenous injection initially 150 micrograms/kg, then either by intravenous injection 100 micrograms/kg repeated every 6–9 minutes as necessary or by intravenous infusion, 8–10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose 11–14 micrograms/kg/minute
  Child 6 months–12 years by intravenous injection initially 200 micrograms/kg, then either by intravenous injection 100 micrograms/kg repeated every 6–9 minutes as necessary or by intravenous infusion, 8–10 micrograms/kg/minute, adjusted if necessary every 3 minutes by 1 microgram/kg/minute to usual dose 11–14 micrograms/kg/minute
  Child 12–18 years by intravenous injection initially 70–250 micrograms/kg, then either by intravenous injection 100 micrograms/kg repeated every 15 minutes as necessary or by intravenous infusion, 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

Administration for intravenous injection, give undiluted or dilute in Glucose 5% or Sodium Chloride 0.9%. Doses up to 150 micrograms/kg may be given over 5–15 seconds, higher doses should be given over 30 seconds. In asthma, cardiovascular disease or in those sensitive to reduced arterial blood pressure, give over 60 seconds.

Mivacron® (GSK)
Injection, mivacurium (as chloride) 2 mg/mL, net price 5-mL amp = £2.79; 10-mL amp = £4.51

PANCURONIUM BROMIDE

Cautions  see notes above
  Hepatic impairment  possibly slower onset, higher dose requirement, and prolonged recovery time
  Renal impairment  manufacturer advises caution; prolonged duration of block
  Pregnancy  crosses placenta in small amounts—manufacturer advises avoid
  Breast-feeding  no information available—manufacturer advises avoid

Side-effects  see notes above

Indication and dose
To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (long duration) during surgery
• By intravenous injection
  Neonate initially 100 micrograms/kg, then 50 micrograms/kg repeated as necessary
  Child 1 month–18 years initially 100 micrograms/kg, then 20 micrograms/kg repeated as necessary

Administration for intravenous injection, give undiluted or dilute in Glucose 5% or Sodium Chloride 0.9%

Pancuronium (Non-proprietary)
Injection, pancuronium bromide 2 mg/mL, net price 2-mL amp = £1.20

ROCURONIUM BROMIDE

Cautions  see notes above
  Hepatic impairment  reduce dose
  Renal impairment  reduce maintenance dose; prolonged paralysis
  Pregnancy  manufacturer advises caution
  Breast-feeding  present in milk in animal studies—manufacturer advises avoid unless potential benefit outweighs risk

Side-effects  see notes above

Indication and dose
To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

Neuromuscular blockade (intermediate duration) during surgery
• By intravenous administration
  Child 1 month–18 years initially by intravenous injection 600 micrograms/kg, then either by intravenous injection, 150 micrograms/kg repeated as required or by intravenous infusion, 300–600 micrograms/kg/hour adjusted according to response

Administration for continuous intravenous infusion or via drip tubing, may be diluted with Glucose 5% or Sodium Chloride 0.9%

Esmeron® (Organon)
Injection, rocuronium bromide 10 mg/mL, net price 5-mL vial = £3.01, 10-mL vial = £6.01
**VECURONIUM BROMIDE**

**Cautions** see notes above

**Pregnancy** manufacturer advises avoid unless potential benefit outweighs risk—no information available

**Breast-feeding** no information available

**Side-effects** see notes above

**Licensed use** not licensed for assisted ventilation in intensive care; not licensed without a test dose in children under 5 months for neuromuscular blockade during surgery

**Indication and dose**

To avoid excessive dosage in obese children, dose should be calculated on the basis of ideal weight for height

**Neuromuscular blockade (intermediate duration) during surgery**

- **By intravenous administration**

  **Neonate** by intravenous injection initially 80–100 micrograms/kg, then 30–50 micrograms/kg adjusted according to response

  **Child 1 month–18 years** by intravenous injection initially 80–100 micrograms/kg, then either by intravenous injection, 20–30 micrograms/kg repeated as required or by intravenous infusion, 50–80 micrograms/kg/hour, adjusted according to response

**Assisted ventilation in intensive care**

- **By intravenous injection**

  **Neonate** initially 80–100 micrograms/kg, then 30–50 micrograms/kg adjusted according to response usually every 2–4 hours

  **Child 1 month–18 years** initially 80–100 micrograms/kg then 50–80 micrograms/kg/hour, adjusted according to response; up to 200 micrograms/kg/hour may be required

- **By intravenous infusion**

  **Child 1 month–18 years** initially 80–100 micrograms/kg then 50–80 micrograms/kg/hour, adjusted according to response; up to 200 micrograms/kg/hour may be required

**Administration** 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 or Ringer’s solution—unsuitable for further dilution if not reconstituted with Water for Injections.

For continuous intravenous infusion, dilute reconstituted solution to a concentration up to 40 micrograms/mL with Glucose 5% or Sodium Chloride 0.9% or Ringer’s solution; reconstituted solution can also be given via drip tubing

**Norcuron®** (Organon)

Injection, powder for reconstitution, vecuronium bromide, net price 10-mg vial = £3.95 (with water for injections)

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**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. Neonates and young children are less sensitive to suxamethonium and a higher dose may be required.

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 painful muscle fasciculations. Bradycardia may occur; premedication with atropine (section 15.1.3) 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. Children 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)

**Cautions** see notes above; hypersensitivity to other neuromuscular blocking drugs; patients with cardiac, respiratory or neuromuscular disease; raised intra-ocular pressure (avoid in penetrating eye injury); severe sepsis (risk of hyperkalaemia); **interactions**: Appendix 1 (muscle relaxants)

**Pregnancy** mildly prolonged maternal paralysis may occur

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**15 Anaesthesia**

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**SUXAMETHONIUM CHLORIDE (continued)**

**Contra-indications**

- Family history of malignant hyperthermia, hyperkalaemia; major trauma, severe burns, neurological disease involving acute wasting of major muscle, prolonged immobilisation—risk of hyperkalaemia, personal or family history of congenital myotonic disease, Duchenne muscular dystrophy, low plasma-cholinesterase activity (including severe liver disease, see below)
- **Hepatic impairment** prolonged apnoea may occur in severe liver disease because of reduced hepatic synthesis of pseudocholinesterase

**Side-effects**

- See notes above; also increased gastric pressure; hyperkalaemia; postoperative muscle pain, myoglobinuria, myoglobinæmia; 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

**Indication and dose**

**Neuromuscular blockade during surgery**

- **By intravenous injection**
  - **Neonate** 2 mg/kg produces 5-10 minutes paralysis; 3 mg/kg results in full neuromuscular block
  - **Child 1 month–1 year** initially 2 mg/kg, maintenance usually 1–2 mg/kg at 5–10 minute intervals as necessary
  - **Child 1–18 years** initially 1 mg/kg, then 0.5–1 mg/kg repeated every 5–10 minutes as necessary

- **By intramuscular injection**
  - **Neonate** up to 4–5 mg/kg produces 10–30 minutes paralysis (after 2–3 minute delay)
  - **Child 1 month–1 year** up to 4–5 mg/kg (paralysis after 2–3 minute delay)
  - **Child 1–12 years** up to 4 mg/kg (paralysis after 2–3 minute delay); max. 150 mg

**Administration**

- For *intravenous injection*, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9%

**Suxamethonium Chloride (Non-proprietary)**

- **Injection**, suxamethonium chloride 50 mg/mL, net price 2-mL amp = 64p, 2-mL prefilled syringe = £7.35

**Anectine (GSK)**

- **Injection**, suxamethonium chloride 50 mg/mL, net price 2-mL amp = 71p

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**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 of edrophonium; it is also used in the diagnosis of myasthenia gravis (section 10.2.1).

**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.

**EDROPHONIUM CHLORIDE**

**Cautions** section 10.2.1; atropine should also be given

**Contra-indications** section 10.2.1

**Side-effects** section 10.2.1

**Indication and dose**

- **Brief reversal of non-depolarising neuromuscular blockade**
  - **By intravenous injection over several minutes**
    - **Child 1 month–1 year** 500–700 micrograms/kg (after or with atropine)

**Myasthenia gravis** (section 10.2.1)

**Edrophonium** (Cambridge)

- **Injection**, edrophonium chloride 10 mg/mL, net price 1-mL amp = £6.55
NEOSTIGMINE METILSULFATE
(Neostigmine methylsulphate)

Cautions section 10.2.1; glycopyrronium or atropine should also be given

Contra-indications section 10.2.1

Side-effects section 10.2.1

Indication and dose

Reversal of non-depolarising muscle block

- Neonate 50–80 micrograms/kg, after or with glycopyrronium or atropine
- Child 1 month–12 years 50–80 micrograms/kg (max. 2.5 mg) after or with glycopyrronium or atropine
- Child 12–18 years 50–80 micrograms/kg (max. 5 mg) after or with glycopyrronium or atropine

Myasthenia gravis section 10.2.1

Administration for intravenous injection, give undiluted or dilute with Glucose 5% or Sodium Chloride 0.9% or Water for Injections

Neostigmine (Non-proprietary)

Injection, neostigmine metilsulfate 2.5 mg/mL, net price 1-mL amp = 58p

With glycopyrronium

Robinul-Neostigmine® (Anpharm) Injection, neostigmine metilsulfate 2.5 mg, glycopyrronium bromide 500 micrograms/mL, net price 1-mL amp = £1.15

Dose

Reversal of non-depolarising neuromuscular blockade

- By intravenous injection over 10–30 seconds
  - Child 1 month–18 years 0.02 mL/kg (or 0.2 mL/kg of a 1 in 10 dilution), dose may be repeated if required (total max. 2 mL)

Administration for intravenous injection, may be diluted with Sodium Chloride 0.9% or Water for Injections

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 (section 15.1.5).

SUGAMMADEX

Cautions recurrence of neuromuscular blockade—monitor respiratory function until fully recovered; recovery may be delayed in cardiovascular disease; wait 24 hours before re-administering rocuronium; interactions: Appendix 1 (sugammadex)

Renal impairment avoid if estimated glomerular filtration rate less then 30 mL/minute/1.73 m²

Pregnancy manufacturer advises caution—no information available

Side-effects taste disturbances; less commonly allergic reactions; bronchospasm also reported

Indication and dose

Routine reversal of neuromuscular blockade induced by rocuronium

- By intravenous injection
  - Child 2–18 years 2 mg/kg (consult product literature)

Administration for intravenous injection dose may be diluted to a concentration of 10 mg/mL with Sodium Chloride 0.9%

Bridion® (Schering-Plough) 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 an opioid antagonist. Naloxone given intravenously immediately reverses opioid-induced respiratory depression but the dose may have to be repeated because of its short duration of action. Intramuscular injection of naloxone produces a more gradual and prolonged effect but absorption may be erratic. Care is required in children requiring pain relief because naloxone also antagonises the analgesic effect of opioids.

Neonates Naloxone is used in newborn infants to reverse respiratory depression and sedation resulting from the use of opioids by the mother, usually for pain during labour. In neonates the effects of opioids may persist for up to 48 hours and in such cases naloxone is often given by intramuscular injection for its prolonged effect. In severe respiratory depression after birth, breathing should first be established (using artificial means if necessary) and naloxone administered only if use of opioids by the mother is thought to cause the respiratory depression; the
infant should be monitored closely and further doses of naloxone administered as necessary.

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 and midazolam, so children may become resedated.

Doxapram (section 3.5.1) is a central and respiratory stimulant but is of limited value in anaesthesia.

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**FLUMAZENIL**

**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 children and following major surgery; head injury (rapid reversal of benzodiazepine sedation may cause convulsions)

**Hepatic impairment** carefully titrate dose

**Pregnancy** may cross placenta in small amounts—manufacturer advises avoid unless potential benefit outweighs risk

**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

**Licensed use** not licensed for use in children

**Indication and dose** Reversal of sedative effects of benzodiazepines

- By intravenous injection over 15 seconds (question aetiology if no response to repeated injection)

- Neonate 10 micrograms/kg, repeat at 1-minute intervals if required

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**NALOXONE HYDROCHLORIDE**

**Cautions** cardiovascular disease or those receiving cardiotoxic drugs (serious adverse cardiovascular effects reported); maternal physical dependence on opioids (may precipitate withdrawal in newborn); pain (see also under Titration of Dose, below); has short duration of action (see notes above)

**Titration of dose** In postoperative use, the dose should be titrated for each child in order to obtain sufficient respiratory response; however, naloxone antagonises analgesia

**Pregnancy** manufacturer advises use only if potential benefit outweighs risk

**Side-effects** hypotension, hypertension, ventricular tachycardia and fibrillation, cardiac arrest; hyperventilation, dyspnoea, pulmonary oedema; less commonly agitation, excitement, paraesthesia

**Indication and dose** Reversal of respiratory and CNS depression in neonate following maternal opioid use during labour

- By intramuscular injection

- Neonate 200 micrograms (60 micrograms/kg) as a single dose at birth

- By intravenous or subcutaneous injection

- Neonate 10 micrograms/kg, repeated every 2–3 minutes if required
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 the 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 children 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

**Cautions**
- avoid extravasation (risk of tissue necrosis);
- interactions: Appendix 1 (muscle relaxants);
- Pregnancy: use only if potential benefit outweighs risk
- Breast-feeding: present in milk—manufacturer advises use only if potential benefit outweighs the risk

**Side-effects**
- hepatotoxicity, pulmonary oedema, dizziness, weakness, and injection-site reactions including erythema, rash, swelling, and thrombophlebitis

**Indication and dose**

**Malignant hyperthermia**

- By rapid intravenous injection
  - Child 1 month–18 years initially 2–3 mg/kg, then 1 mg/kg repeated as required (total max. dose 10 mg/kg)

**Chronic severe spasticity of voluntary muscle**

see section 10.2.2

**Dantrium 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 child’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 for major surgery in children, including orthopaedic and 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, circu-
moral 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 ester-type local anaes-
thetics such as benzocaine, procaine, and tetracaine (amethocaine); reactions are less frequent with the amide types such as lidocaine (lignocaine), bupivacaine, leviobupivacaine, prilocaine, and ropivacaine. Local anaesthetics may be asso-
ciated with methaemoglobinemia; prilocaine and benzocaine have been impli-
cated.

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 ototoxic and should **not** be applied to the middle ear.

**Use of vasoconstrictors** Most local anaesthetics 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 400 000–1 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 necro-
sis.

When adrenaline is included the final concentration should be no more than 1 in 200 000 (5 micrograms/mL), but see also Dental Anaesthesia, below. The total dose of adrenaline should **not** exceed 5 micrograms/kg (1 mL/kg of a 1 in 200 000 solution). 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 20 000 (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 children with severe hypertension or unstable cardiac rhythm, the use of adrenaline in a local anaesthetic may be hazardous. For these children prilocaine with or without felypressin can be used but there is no evidence that it is any safer. 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.

Application of a mixture of lidocaine and prilocaine (EMLA®) under an occlusive dressing provides surface anaesthesia for 1–2 hours. EMLA® does not appear to be effective in providing local anaesthesia for heel lancing in neonates.

**LIDOCaine HYDROCHLORIDE**

*(Lignocaine hydrochloride)*

**Cautions** see notes above; see section 2.3.2 for effects on heart; also epilepsy, respiratory impairment, impaired cardiac conduction, bradycardia, severe shock; acute porphyria (section 9.8.2); myasthenia gravis; reduce dose in debilitated; resuscitative equipment should be available; *interactions*: Appendix 1 (lidocaine)

**Hepatic impairment** manufacturer advises caution—increased risk of side-effects

**Renal impairment** possible accumulation of lidocaine and active metabolite; manufacturers advise caution in severe impairment

**Pregnancy** with large doses, neonatal respiratory depression, hypotonia and bradycardia after paracervical or epidural block

**Breast-feeding** amount too small to be harmful

**Contra-indications** see notes above; also 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); hypersensitivity reported

**Licensed use** EMLA® cream not licensed for use in children under 1 year

**Indication and dose**

**Local anaesthesia**

*By local infiltration* (see also Administration p. 787 and Safe Practice warning below)

- **Neonate** according to nature of procedure, up to 3 mg/kg (0.3 mL/kg of 1% solution), repeated not more often than every 4 hours
- **Child 1 month–12 years** according to nature of procedure, up to 3 mg/kg (0.3 mL/kg of 1% solution), repeated not more often than every 4 hours
- **Child 12–18 years** according to nature of procedure, up to 200 mg, repeated not more often than every 4 hours

*Ventricular arrhythmias* section 2.3.2

**Intravenous regional anaesthesia and nerve blocks** seek expert advice

**Dental anaesthesia** seek expert advice

**Safe Practice** The licensed doses stated above may not be appropriate in some settings and expert advice should be sought

**Lidocaine hydrochloride injections**

**Lidocaine** (Non-proprietary)

- **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 = £4.53; 20-mL amp = 78p
- **Injection 2%**, lidocaine hydrochloride 20 mg/mL, net price 2-mL amp = 27p; 5-mL amp = 28p

**Xylocaine®** (AstraZeneca)

- **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 are available in dental cartridges; brand names include Lignospan Special®, Rexocaine®, Xylocaine®, and Xylotox®.

**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**

- **Child** rub gently into dry gum
LIDOCAINE HYDROCHLORIDE (continued)

Pain relief (in anal fissures, haemorrhoids, pruritus ani, pruritus vulvae, herpes zoster)
Child 1–2 mL applied when necessary; avoid long-term use

Solution, lidocaine hydrochloride 4%, net price 25 mL = £1.35

Dose

Biopsy in mouth
Child up to 3 mg/kg with suitable spray or swab (with adrenaline if necessary); max. 5 mL

Puncture of maxillary sinus or polyectomy
Child up to 3 mg/kg; apply with swab for 2–3 minutes (with adrenaline)

Bronchoscopy and bronchography
Child up to 3 mg/kg; 2–3 mL with suitable spray

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 = £1.73
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, 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. 791)
Side-effects include administration site reactions such as transient paleness, redness, oedema, itching, burning sensation, and localised lesions

Dose

Anaesthesia before minor skin procedures including venepuncture
Neonate apply max. 1 g under occlusive dressing for max. 1 hour before procedure; max. 1 dose in 24 hours
Child 1–3 months or body-weight less than 5 kg apply max. 1 g under occlusive dressing for max. 1 hour before procedure; max. 1 dose in 24 hours
Child 3 months–1 year and body weight over 5 kg apply max. 2 g under occlusive dressing for max. 4 hours before procedure; max. 2 doses in 24 hours
Child 1–2 years apply thick layer under occlusive dressing 1–5 hours before procedure (2–5 hours before procedures on large areas e.g. split skin grafting); max. 2 doses in 24 hours for child 1–12 years

Note Shorter application time of 15–30 minutes is recommended for children with atopic dermatitis

Instillagel® (CliniMed)
Gel, lidocaine hydrochloride 2%, chlorhexidine gluconate solution 0.25%, in a sterile lubricant basis in disposable syringe, net price 6-mL syringe = £1.41, 11-mL syringe = £1.58
Excipients include hydroxybenzoates (parabens)

Laryngojet® (UCB Pharma) Jet spray 4% (disposable kit for laryngotraceal anaesthesia), lidocaine hydrochloride 40 mg/mL, net price per unit (4-mL vial and disposable sterile cannula with cover and vial injector) = £5.10
Cautions may be rapidly and almost completely absorbed from respiratory tract and systemic side-effects may occur; extreme caution if mucosa has been traumatized or if sepsis present

Dose

Bronchoscopy, laryngoscopy, oesophagoscopy, endotracheal intubation, and biopsy
Child up to 0.075 mL/kg (3 mg/kg) as a single dose instilled as jet spray or applied with a swab; max. 5 mL (200 mg)

LMX 4® (Femdale)
Cream lidocaine 4%, net price 5-g tube = £2.98, 5 × 5-g tube with 10 occlusive dressings = £16.90
Excipients include benzyl alcohol and propylene glycol
Cautions not for wounds, mucous membranes or atopic dermatitis, avoid use near eyes or middle ear; although systemic absorption low, caution in severe hepatic impairment, acutely ill or debilitated children
Side-effects irritation and rash

Dose

Anaesthesia before venous cannulation or venepuncture
Child 1 month–18 years apply thick layer (1–2.5 g; child under 1 year max 1 g) to small area (2.5 cm × 2.5 cm) of non-irritated skin at least 30 minutes before procedure (max 60 minutes); remove cream with gauze and perform procedure after approximately 5 minutes

Rapydan® (EUSA Pharma) Medicated plasters, lidocaine 70 mg, tetracaine 70 mg, net price 100 = £98.00
Excipients include hydroxybenzoates (parabens)

Dose

Needle puncture
Child 3–18 years apply 1–2 plasters to intact skin 30 minutes before needle puncture; max. 2 plasters daily

Xylocaine® (AstraZeneca)
Spray (= pump spray), lidocaine 10% (100 mg/g) supplying 10 mg lidocaine/dose; 500 spray doses per container, net price 50-mL bottle = £3.13
Dose

Bronchoscopy, laryngoscopy, oesophagoscopy, endotracheal intubation
Child up to 18 years up to 3 mg/kg

Note Lidocaine can damage plastic cuffs of endotracheal 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 (3–7 hours). 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**

**Cautions** see under Lidocaine Hydrochloride and notes above; myocardial depression may be more severe and more resistant to treatment; **interactions**: Appendix 1 (bupivacaine)

**Hepatic impairment** manufacturer advises caution in severe impairment

**Renal impairment** manufacturer advises caution

**Pregnancy** large doses during the third trimester can cause neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block; lower doses for intrathecal use during late pregnancy

**Breast-feeding** amount too small to be harmful

**Contra-indications** see under Lidocaine Hydrochloride and notes above; intravenous regional anaesthesia (Bier’s block)

**Side-effects** see under Lidocaine Hydrochloride and notes above

**Indication and dose**

Adjusted according to child’s physical status and nature of procedure, seek expert advice—**important**: see also under Administration, p. 787

**Bupivacaine (Non-proprietary)**

**Injection**, anhydrous bupivacaine hydrochloride 2.5 mg/mL (0.25%), net price 10 mL = 82p; 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

**Marcain® (AstraZeneca)**

**Injection**, anhydrous bupivacaine hydrochloride 2.5 mg/mL (Marcain® 0.25%), net price 10-mL Polyamp® = £1.06; 5 mg/mL (Marcain® 0.5%), 10-mL Polyamp® = £1.21

**Marcain Heavy® (AstraZeneca)**

**Injection**, anhydrous bupivacaine hydrochloride 5 mg, glucose 80 mg/mL, net price 4-mL amp = £1.21

**With adrenaline**

**Bupivacaine and Adrenaline (Non-proprietary)**

**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

**Marcain**

**Injection**, anhydrous bupivacaine hydrochloride 2.5 mg/mL (Marcain® 0.25%), net price 10-mL Polyamp® = £1.06; 5 mg/mL (Marcain® 0.5%), 10-mL Polyamp® = £1.21

**Marcain Heavy**

**Injection**, anhydrous bupivacaine hydrochloride 5 mg, glucose 80 mg/mL, net price 4-mL amp = £1.21

**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

**Levobupivacaine**

Levobupivacaine, an isomer of bupivacaine, has anaesthetic and analgesic properties similar to bupivacaine but is thought to have fewer adverse effects.

**LEVOBUPIVACINE**

**Note** Levobupivacaine is an isomer of bupivacaine

**Cautions** see under Lidocaine Hydrochloride and notes above; **interactions**: Appendix 1 (levobupivacaine)

**Hepatic impairment** manufacturer advises caution

**Pregnancy** large doses during the third trimester can cause neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block; manufacturer advises avoid if possible—toxicity in animal studies

**Breast-feeding** likely to be present in milk but risk to infant minimal

**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

**Licensed use** not licensed for use in children by epidural infusion

**Indication and dose**

Adjusted according to child’s physical status and nature of procedure, seek expert advice—**important**: see also under Administration, p. 787

**Chirocaine® (Abbott)**

**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

**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
**Prilocaine**

Prilocaine is a local anaesthetic of low toxicity which is similar to lidocaine (lignocaine). If used in high doses, methaemoglobinaemia may occur which can be treated with intravenous injection of methylthioninium chloride (methylene blue) 1% using a dose of 1 mg/kg. Neonates and infants under 6 months are particularly susceptible to methaemoglobinaemia.

**PRILOCAINE HYDROCHLORIDE**

**Cautions** see under Lidocaine Hydrochloride and notes above; severe or untreated hypertension, severe heart disease; concomitant drugs which cause methaemoglobinemia; hepatic impairment; renal impairment; interactions: Appendix 1 (prilocaine)

**Hepatic impairment** manufacturer advises caution

**Renal impairment** manufacturer advises caution

**Pregnancy** large doses during the third trimester can cause neonatal respiratory depression, hypotonia, and bradycardia after paracervical or epidural block; neonatal methaemoglobinemia reported after paracervical block or pudendal block

**Breast-feeding** present in milk but not known to be harmful

**Contra-indications** see under Lidocaine Hydrochloride and notes above; anaemia or congenital or acquired methaemoglobinaemia

**Side-effects** see under Lidocaine Hydrochloride and notes above; ocular toxicity (including blindness) reported with excessively high strengths used for ophthalmic procedures

**Indication and dose**

**Infiltration anaesthesia (higher strengths for dental use only), nerve block**

See under preparations below, seek expert advice—important: see also under Administration, p. 787

**Citanest® (AstraZeneca)**

Injection 1%, prilocaine hydrochloride 10 mg/mL, net price 50-mL multidose vial = £2.01

**Dose**

**Child 6 months–12 years** up to 5 mg/kg adjusted according to site of administration and response; max. 400 mg

**Child 12–18 years** 100–200 mg/minute, or in incremental doses, to max. total dose 400 mg (adjusted according to site of administration and response)

**With lidocaine**

**EMLA®**

See Lidocaine, p. 789

**For dental use**

**Note** Consult expert dental sources for specific advice in relation to dose of prilocaine for dental anaesthesia

**Citanest® (Dentsply)**

Injection 4%, prilocaine hydrochloride 40 mg/mL, net price 2.2-mL cartridge = 17p

**Citanest 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) = 15p

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**Ropivacaine**

Ropivacaine is an amide-type local anaesthetic agent similar to bupivacaine. It is less cardiotoxic than bupivacaine, but also less potent.

**ROPIVACAINE HYDROCHLORIDE**

**Cautions** see under Lidocaine Hydrochloride and notes above; interactions: Appendix 1 (ropivacaine)

**Hepatic impairment** manufacturer advises caution in severe impairment

**Renal impairment** manufacturer advises caution in severe impairment

**Pregnancy** safety not established but not known to be harmful

**Breast-feeding** not known to be harmful

**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

**Licensed use** not licensed for use in children by epidural infusion

**Indication and dose**

Adjust according to child’s physical status and nature of procedure, seek expert advice—important: see also under Administration, p. 787

**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

**Epidural infusion**, ropivacaine hydrochloride 2 mg/mL, net price 200-mL Polybag® = £14.45
Tetracaine

Tetracaine (amethocaine) is an effective local anaesthetic for topical application; a 4% gel is indicated for anaesthesia prior to venepuncture or venous cannulation. Tetracaine remains effective for 4–6 hours after a single application in most children. It does not appear to be effective prior to neonatal heel lancing.

Tetracaine 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)

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)

Licensed use not licensed for use in neonates

Ametop® (S&N Hlth.)

Gel, tetracaine 4%, net price 1.5-g tube = £1.08

Dose

**Neonate** apply contents of tube (or appropriate proportion) 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

**Child 1 month–18 years** apply contents of tube (or appropriate proportion) 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** Child over 5 years, contents of max. 5 tubes applied at separate sites at a single time, child 1 month–5 years, contents of max. 1 tube applied at separate sites at a single time

With lidocaine

Rapydan®

see Lidocaine, p. 789
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. anti-coagulants, antihypertensives, and antidiabetics) are most often involved.

Patients at increased risk from drug interactions include 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.

List of drug interactions

The following is an alphabetical list of drugs and their interactions; to avoid excessive cross-referencing each drug or group is listed twice: in the alphabetical list and also against the drug or group with which it interacts.

For explanation of symbol • see above

Abacavir

Analgesics: abacavir possibly reduces plasma concentration of methadone
Antibacterials: plasma concentration of abacavir possibly reduced by rifampicin
Antiepileptics: plasma concentration of abacavir possibly reduced by phenytoin
Antivirals: plasma concentration of abacavir reduced by tipranavir
Barbiturates: plasma concentration of abacavir possibly reduced by phenobarbital

Abatacept

Adalimumab: increased risk of side-effects when abatacept given with adalimumab
Etanercept: increased risk of side-effects when abatacept given with etanercept
Infliximab: increased risk of side-effects when abatacept given with infliximab
Vaccines: avoid concomitant use of abatacept with live vaccines (see p. 725)

Acarbose see Antidiabetics

ACE Inhibitors

Alcohol: enhanced hypotensive effect when ACE inhibitors given with alcohol
Aldesleukin: enhanced hypotensive effect when ACE inhibitors given with aldesleukin
Allopurinol: increased risk of leucopenia and hypersensitivity reactions when ACE inhibitors given with allopurinol especially in renal impairment

Alpha-blockers: enhanced hypotensive effect when ACE inhibitors given with alpha-blockers
Anaesthetics, General: enhanced hypotensive effect when ACE inhibitors given with general anaesthetics
Antibacterials: increased risk of renal impairment when ACE inhibitors given with NSAIDs, also hypotensive effect antagonised
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
Antibacterials: plasma concentration of active metabolite of imidapril reduced by rifampicin (reduced antihypertensive effect); quinapril tablets reduce absorption of tetracyclines (quinapril tablets contain magnesium carbonate)
Anticoagulants: increased risk of hyperkalaemia when ACE inhibitors given with heparins
Antidepressants: 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
**ACE Inhibitors (continued)**

- Anxiolytics and Hypnotics: enhanced hypotensive effect when ACE inhibitors given with anxiolytics and hypnotics
- 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
- Cardiac Glycosides: captopril possibly increases plasma concentration of digoxin
- Ciclosporin: increased risk of hyperkalaemia when ACE inhibitors given with ciclosporin
- 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)
- Methylprednisolone: enhanced hypotensive effect when ACE inhibitors given with methylprednisolone
- 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
- Prostaglandins: enhanced hypotensive effect when ACE inhibitors given with prostaglandins
- Vasodilator Antihypertensives: enhanced hypotensive effect when ACE inhibitors given with hydralazine, minoxidil or sodium nitroprusside

**Acetbutolol** see Beta-blockers

**Acetclofenac** see NSAIDs

**Acemetacin** see NSAIDs

**Aclonocoumarol (nicoumalone)** see Coumarins

**Acetazolamide** see Diuretics

**Aciclovir** see Antivirals

**Aciclovir interactions as for aciclovir**

- 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
- Cardiac Glycosides: increased risk of severe hyperkalaemia when aciclovir given with ciclosporin
- Cytotoxics: plasma concentration of aciclovir increased by mycophenolate, also plasma concentration of inactive metabolite of mycophenolate increased
- Probenecid: excretion of aciclovir reduced by probenecid (increased plasma concentration)
- Tacrolimus: possible increased risk of nephrotoxicity when aciclovir given with tacrolimus
- Valaciclovir interactions as for aciclovir

**Adalimumab**

- Abatacept: increased risk of side-effects when adalimumab given with abatacept
- Anakinra: avoid concomitant use of adalimumab with anakinra
- Vaccines: avoid concomitant use of adalimumab with live vaccines (see p. 725)

**Adefovir**

- Antivirals: avoidance of adefovir advised by manufacturer of tenofovir

**Adenosine**

- Note. Possibility of interaction with drugs tending to impair myocardial conduction
- 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
- Diprydiamole: effect of adenosine enhanced and extended by diprydiamole (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
- Anaesthetics, General: enhanced hypotensive effect when adrenergic neurone blockers given with general anaesthetics
- Analgesics: 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
- Antidepressants: enhanced hypotensive effect when adrenergic neurone blockers given with MAOIs; hypotensive effect of adrenergic neurone blockers antagonised by tricyclics
- Antipsychotics: hypotensive effect of adrenergic neurone blockers antagonised by haloperidol; hypotensive effect of adrenergic neurone blockers antagonised by higher doses of 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
- Beta-blockers: 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
Appendix 1: Interactions

Adrenergic Neurone Blockers (continued)

Methyldopa: enhanced hypotensive effect when adrenergic neurone blockers with methyldopa
Moxisylyte (thymoxamine): enhanced hypotensive effect when adrenergic neurone blockers given with moxisylyte

Moxonidine: enhanced hypotensive effect when adrenergic neurone blockers given with moxonidine

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

Oestrogens: hypotensive effect of adrenergic neurone blockers antagonised by oestrogens

Pizotifen: hypotensive effect of adrenergic neurone blockers antagonised by pizotifen

Prostaglandins: enhanced hypotensive effect when adrenergic neurone blockers given with alprostadil

* Sympathomimetics: hypotensive effect of adrenergic neurone blockers antagonised byephedrine, isomethyptene, metaraminol, methylphenidate, noradrenaline (norepinephrine), oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline

Vasodilator Antihypertensives: enhanced hypotensive effect when 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)

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

Analgesics: enhanced hypotensive and sedative effects when alcohol given with opioid analgesics

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when alcohol given with angiotensin-II receptor antagonists

Antibacterials: disulfiram-like reaction when alcohol given with metronidazole; possibility of disulfiram-like reaction when alcohol given with tindazole; increased risk of convulsions when alcohol given with cycloserine

Anticoagulants: major changes in consumption of alcohol may affect anticoagulant control with coumarins or ephrinindione

Antidepressants: some beverages containing alcohol and some dealkalised 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 mirtazapine, tricyclic-related antidepressants or tricyclics

Antidiabetics: alcohol enhances hypoglycaemic effect of antidiabetics; increased risk of lactic acidosis when alcohol given with metformin; flushing, in Alcohol

Antidiabetics (continued)
susceptible subjects, when alcohol given with chlorpropamide

Antiepileptics: alcohol possibly increases CNS side-effects of carbamazepine; 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)

Antimuscarnic: 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

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 procarbazine

Diazoxide: enhanced hypotensive effect when alcohol given with diazoxide

Disulfiram: disulfiram reaction when alcohol given with disulfiram (see BNF section 4.10)

Diuretics: enhanced hypotensive effect when alcohol given with diuretics

Dopaminergics: alcohol reduces tolerance to bromocriptine

Leveramsole: 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

Nicardil: alcohol possibly enhances hypotensive effect of nicardil

Nitrites: enhanced hypotensive effect when alcohol given with nitrites

Paraldehyde: increased sedative effect when alcohol given with paraldehyde

Retinoids: presence of alcohol causes etretinate 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

Aldesleukin

ACE Inhibitors: enhanced hypotensive effect when aldesleukin given with ACE inhibitors

Alpha-blockers: enhanced hypotensive effect when aldesleukin given with alpha-blockers

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when aldesleukin given with angiotensin-II receptor antagonists

Beta-blockers: enhanced hypotensive effect when aldesleukin given with beta-blockers

Calcium-channel Blockers: enhanced hypotensive effect when aldesleukin given with calcium-channel blockers

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Almotriptan

Cytotoxics: allopurinol enhances effects and increases toxicity.

Antivirals: allopurinol increases plasma concentration of theophylline.

see Alkylating Drugs

see Aliskiren

Alimemazine (trimeprazine) see Antihistamines

Alfentanil see Opioid Analgesics

Alfuzosin see Alpha-blockers

Alimemazine (trimipramine) see Antidepressants

Aliskiren

Angiotensin-II Receptor Antagonists: plasma concentration of aliskiren possibly reduced by irbesartan.

Anticoagulants: increased risk of hypersensitivity when allopurinol given with clopidogrel.

ACE Inhibitors: increased risk of hyperkalaemia when aliskiren given with heparin.

Antifungals: plasma concentration of aliskiren increased by ketoconazole.

Diuretics: aliskiren reduces plasma concentration of furosemide (frusamide); 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

Alkylating Drugs see Busulfan, Carmustine, Cyclophosphamide, Ifosfamide, Lomustine, Melphalan, and Thiotepa

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 anticoagulant effect of coumarins.

Antivirals: allopurinol increases plasma concentration of didanosine (risk of toxicity)—avoid concomitant use.

Ciclosporin: allopurinol possibly increases plasma concentration of ciclosporin (risk of nephrotoxicity).

Cytoxotics: 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 capetabine.

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.

Almotriptan see 5HT1 Agonists

Alpha-2-adrenoreceptor Stimulants see Apraclonidine, Brimonidine, Clonidine and Methylxypil

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 indomethin given with alcohol.

Aldesleukin: enhanced hypotensive effect when alpha-blockers given with aldesleukin.

Alpha-blockers (continued)

- 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 indomethin advises avoid concomitant use with MAOIs.

- Antipsychotics: enhanced hypotensive effect when alpha-blockers given with antipsychotics.

- Antivirals: plasma concentration of alfuzosin possibly increased by antivirals—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 beta-blockers, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin.

- Calcium-channel 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.

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.

Diazoxide: 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 dopaminergics.

Methylxypil: enhanced hypotensive effect when alpha-blockers given with methylxypil.

Moxisylyte (thymoxamine): possible severe postural hypotension when alpha-blockers given with moxisylyte.

Moxonidine: enhanced hypotensive effect when alpha-blockers given with moxonidine.

Muscle Relaxants: enhanced hypotensive effect when alpha-blockers given with baclofen or tizanidine.

Nitrates: 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 prostaglandins.

Silodosin: enhanced hypotensive effect when alpha-blockers given with silodosin (avoid alpha-blockers for 4 hours after sildenafil).

Sympathomimetics and anxiolytics and hypnotics: avoid concomitant use of beta-blockers with anxiolytics and hypnotics—avoid concomitant use.

Uterine Relaxants: enhanced hypotensive effect when alpha-blockers given with uterine Relaxants.

Vardenafil: enhanced hypotensive effect when alpha-blockers given with vardenafil—avoid vardenafil for 6 hours after alpha-blockers.

Alpha-blockers (post-synaptic) see Alpha-blockers

Appendix 1: Interactions
Amiloride

see

Amikacin

Tacrolimus: increased risk of nephrotoxicity when amikacin given with tacrolimus.

Muscle Relaxants: aminoglycosides enhance effects of muscle relaxants.

Memantine: increased risk of CNS toxicity when amikacin given with memantine (manufacturer of memantine advises avoid concomitant use); effects of dopaminergics possibly enhanced by memantine.

Methyldopa: increased risk of extrapyramidal side-effects when amikacin given with methyldopa; antiparkinsonian effect of dopaminergics antagonised by methyldopa.

Metoclopramide: increased risk of extrapyramidal side-effects when amikacin given with metoclopramide.

Tetrabenazine: increased risk of extrapyramidal side-effects when amikacin given with tetrabenazine.

Amikacin see Aminoglycosides

Aminoglycosides

Agalsidase Alfa and Beta: gentamicin possibly inhibits effects of agalsidase alfa and beta (manufacturers of agalsidase alfa and beta advise avoid concomitant use).

Analgesics: plasma concentration of amikacin and gentamicin in neonates possibly increased by indomethacin.

Antibacterials: neomycin reduces absorption of phenoxymethylpenicillin; increased risk of nephrotoxicity when aminoglycosides given with colistin or polymyxin; 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 warfarin or phenindione.

Antidiabetics: neomycin possibly enhances hypoglycaemic effect of acarbose, also severity of gastrointestinal effects increased.

Antifungals: increased risk of nephrotoxicity when aminoglycosides given with amphotericin.

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 otoxicity when aminoglycosides given with loop 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 478).

Parasympathomimetics: aminoglycosides antagonise effects of neostigmine and pyridostigmine.

Tacrolimus: increased risk of nephrotoxicity when aminoglycosides given with tacrolimus.

Anticoagulants: amiodarone inhibits metabolism of coumarins and phenindione (enhanced anticoagulant effect); amiodarone increases plasma concentration of dabigatran etexilate (reduce dose of dabigatran etexilate).

Antidepressants: increased risk of ventricular arrhythmias when amiodarone given with parenteral tricyclics; avoid concomitant use.

Antihistamines: increased risk of ventricular arrhythmias when amiodarone given with levofloxacin or moxifloxacin—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with sulfamethoxazole and trimethoprim (as co-trimoxazole)—avoid concomitant use of co-trimoxazole.

Anticoagulants: amiodarone inhibits metabolism of coumarins and phenindione (enhanced anticoagulant effect); amiodarone increases plasma concentration of dabigatran etexilate (reduce dose of dabigatran etexilate).

Antidepressants: increased risk of ventricular arrhythmias when amiodarone given with tricyclics—avoid concomitant use.

Antiepileptics: amiodarone inhibits metabolism of phenytoin (increased plasma concentration).

Antihistamines: increased risk of ventricular arrhythmias when amiodarone given with mizolastine—avoid concomitant use.

Antimalarials: avoidance of amiodarone advised by manufacturer of artemether/lumefantrine (risk of ventricular arrhythmias); increased risk of ventricular arrhythmias when amiodarone given with chloroquine and hydroxychloroquine, mefloquine or quinine—avoid concomitant use.

Antipsychotics: increased risk of ventricular arrhythmias when amiodarone given with olanzapine; plasma concentration of olanzapine possibly reduced when amiodarone given with olanzapine (reduce dose of olanzapine).

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 ventricular arrhythmias when amiodarone given with benperidol—manufacturer of benperidol advises avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with amnulpride, haloperidol, phenothiazines, pimozide, serindole or zoelopenthixol—avoid concomitant use; increased risk of ventricular arrhythmias when amiodarone given with sulpiride.

Antivirals: plasma concentration of amiodarone possibly increased by atazanavir; plasma concentration...
Amphotericin (continued)
- Corticosteroids: increased risk of hypokalaemia when amphotericin given with corticosteroids—avoid concomitant use unless corticosteroids needed to control reactions
Diuretics: increased risk of hypokalaemia when amphotericin given with loop diuretics or thiazides and related diuretics
Pentamidine isetionate: possible increased risk of nephrotoxicity when amphotericin given with pentamidine isetionate
- Tacrolimus: increased risk of nephrotoxicity when amphotericin given with tacrolimus

Ampicillin see Penicillins

Anabolic Steroids

Anticoagulants: anabolic steroids enhance anticoagulant effect of coumarins and phenindione
Antidiabetics: anabolic steroids possibly enhance hypoglycaemic effect of antidiabetics

Anaesthetics, General

Note. See also Surgery and Long-term Medication, p. 761
ACE Inhibitors: enhanced hypertensive effect when general anaesthetics with ACE inhibitors
- Adrenergic Neurone Blockers: enhanced hypertensive effect when general anaesthetics with adrenergic neurone blockers
- Alpha-blockers: enhanced hypertensive effect when general anaesthetics given with alpha-blockers
Angiotensin-II Receptor Antagonists: enhanced hypertensive effect when general anaesthetics given with angiotensin-II receptor antagonists
Antibacterials: general anaesthetics possibly potentiate hepatotoxicity of isoniazid; effects of thiopenthal enhanced by sulphonamides; hypersensitivity-like reactions can occur when general anaesthetics given with intravenous vancomycin
- Antidepressants: Because of hazardous interactions between general anaesthetics and MAOIs, MAOIs should normally be stopped 2 weeks before surgery; increased risk of arrhythmias and hypotension when general anaesthetics given with tricyclics
- Antipsychotics: enhanced hypertensive effect when general anaesthetics given with antipsychotics
Anxiolytics and Hypnotics: increased sedative effect when general anaesthetics given with anxiolytics and hypnotics
- Beta-blockers: enhanced hypertensive effect when general anaesthetics given with beta-blockers
- Calcium-channel Blockers: enhanced hypertensive effect when general anaesthetics or isoflurane given with calcium-channel blockers; general anaesthetics enhance hypertensive effect of verapamil (also AV delay)
- Clonidine: enhanced hypertensive effect when general anaesthetics given with clonidine
- Cytotoxics: nitrous oxide increases antifolate effect of methotrexate—avoid concomitant use
Diazoxide: enhanced hypertensive effect when general anaesthetics given with diazoxide
Diuretics: enhanced hypertensive 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)
Methyldopa: enhanced hypertensive effect when general anaesthetics given with methyldopa
Moxonidine: enhanced hypertensive effect when general anaesthetics given with moxonidine
- Muscle Relaxants: increased risk of myocardial depression and bradycardia when propofol given with suxamethonium; volatile liquid general anaest-

Appendix 1: Interactions
Anaesthetics, General
- Muscle Relaxants (continued) thetics enhance effects of non-depolarising muscle relaxants and suxamethonium; ketamine enhances effects of atracurium
Nitrates: enhanced hypertensive effect when general anaesthetics given with nitrates
Oxytocin: oxytocic effect possibly reduced, also enhanced hypertensive effect and risk of arrhythmias when volatile liquid general anaesthetics given with oxytocin
Probenecid: effects of thiopental possibly enhanced by probenecid
- Symptomimetics: increased risk of arrhythmias when volatile liquid general anaesthetics given with
  - adrenaline (epinephrine); increased risk of hypertension 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 hypertensive effect when general anaesthetics given with hydrazine, minoxidil or sodium nitroprusside

Anaesthetics, General (intravenous) see Anaesthetics, General
Anaesthetics, General (volatile liquids) see Anaesthetics, General

Anaesthetics, Local see Bupivacaine, Levobupivacaine, Lidocaine (lignocaine), Prilocaine, Procaine, and Ropivacaine

Anagrelide
- Clostazol: manufacturer of anagrelide advises avoid concomitant use with clostazol
- Phosphodiesterase Inhibitors: manufacturer of anagrelide advises avoid concomitant use with enoximone and mirlimonne

Anakinra
- Adalimumab: avoid concomitant use of anakinra with adalimumab
- Etanercept: increased risk of side-effects when anakinra given with etanercept—avoid concomitant use
- Infliximab: avoid concomitant use of anakinra with infliximab
- Vaccines: avoid concomitant use of anakinra with live vaccines (see p. 725)

Analgesics see Aspirin, Nefopam, NSAIDs, Opioid Analgesics, and Paracetamol

Angiotensin-II Receptor Antagonists
ACE Inhibitors: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with ACE inhibitors
Adrenergic Neurone Blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with adrenergic neurone blockers
Alcohol: enhanced hypertensive effect when angiotensin-II receptor antagonists given with alcohol
Aldesleukin: enhanced hypertensive effect when angiotensin-II receptor antagonists given with aldesleukin
Aliskiren: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with aliskiren
Alpha-blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with alpha-blockers

Anaesthetics, General: enhanced hypertensive 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 hypertensive effect antagonised
Anticoagulants: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with heparin

Angiotensin-II Receptor Antagonists (continued)
Antidepressants: hypertensive effect of angiotensin-II receptor antagonists possibly enhanced by MAOIs
Antipsychotics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with antipsychotics
Anxiolytics and Hypnotics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with anxiolytics and hypnotics
Beta-blockers: enhanced hypertensive effect when angiotensin-II receptor antagonists given with beta-blockers
Calcium-channel Blockers: enhanced hypertensive 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 hypertensive effect when angiotensin-II receptor antagonists given with clonidine
Corticosteroids: hypertensive effect of angiotensin-II receptor antagonists antagonised by corticosteroids
Diazoxide: enhanced hypertensive effect when angiotensin-II receptor antagonists given with diazoxide
Diuretics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with diuretics
Dopaminergics: enhanced hypertensive effect when angiotensin-II receptor antagonists given with levodopa
Lithium: angiotensin-II receptor antagonists reduce excretion of lithium (increased plasma concentration)
Methyl dopa: enhanced hypertensive effect when angiotensin-II receptor antagonists given with methyl dopa
Moxisylyte (thymoxamine): enhanced hypertensive effect when angiotensin-II receptor antagonists given with moxisylyte
Moxonidine: enhanced hypertensive effect when angiotensin-II receptor antagonists given with moxonidine
Muscle Relaxants: enhanced hypertensive effect when angiotensin-II receptor antagonists given with moxonidine
Potassium Salts: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with potassium salts
Nitrates: enhanced hypertensive effect when angiotensin-II receptor antagonists given with nitrates
Oestrogens: hypertensive effect of angiotensin-II receptor antagonists antagonised by oestrogens
Potassium Salts: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with potassium salts
Prostaglandins: enhanced hypertensive effect when angiotensin-II receptor antagonists given with alprostadil
Tacroliimus: increased risk of hyperkalaemia when angiotensin-II receptor antagonists given with tacrolimus
Vasodilator Antihypertensives: enhanced hypertensive effect when angiotensin-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 of ACE inhibitors: antacids possibly reduce absorption of ACE inhibitors; antacids 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, ceftodoxime, ciprofloxacin, isoniazid, levofloxacin, moxifloxacin, norfloxacin, ofloxacin, rifampicin and tetracyclines; oral
Anticoagulants: anticoagulants possibly decrease anticoagulant effect of coumarins.

Antidepressants: avoidance of fluvoxamine advised by manufacturer of reboxetine; possible increased serotoninergic effects when SSRIs given with duloxetine; fluvoxamine inhibits metabolism of duloxetine—avoid concomitant use; citalopram, escitalopram, fluvoxamine or paroxetine 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); antidepressants are possible 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 tricyclics.

Antidepressants: SSRIs may antagonise anticonvulsant effect of zipropitant.

Antidepressants: SSRIs increase plasma concentration of paroxetine and fluoxetine; citalopram possibly increases plasma concentration of risperidone; paroxetine possibly increases plasma concentration of tamoxifen; SSRIs increase plasma concentration of escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs antagonise antidepressant effect of SSRIs possibly antagonised by cyproheptadine.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.

Antidepressants: plasma concentration of escitalopram, fluvoxamine or paroxetine should not be started until at least 5 weeks after stopping fluoxetine; after stopping fluoxetine do not start escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs antagonised by cyproheptadine.

Antidepressants: SSRIs increase plasma concentration of paroxetine and fluoxetine; increased by fluvoxamine; MAOIs should not be started until at least 1 week 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); antidepressants are possible 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 tricyclics.

Antidepressants: SSRIs antagonise anticonvulsant effect of zipropitant.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.

Antidepressants: plasma concentration of escitalopram, fluvoxamine or paroxetine should not be started until at least 5 weeks after stopping fluoxetine; after stopping fluoxetine do not start escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs antagonise antidepressant effect of SSRIs possibly antagonised by cyproheptadine.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.

Antidepressants: plasma concentration of escitalopram, fluvoxamine or paroxetine should not be started until at least 5 weeks after stopping fluoxetine; after stopping fluoxetine do not start escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs increased by MAOIs (risk of serious toxicity); antidepressants are possible 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 tricyclics.

Antidepressants: SSRIs antagonise anticonvulsant effect of zipropitant.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.

Antidepressants: plasma concentration of escitalopram, fluvoxamine or paroxetine should not be started until at least 5 weeks after stopping fluoxetine; after stopping fluoxetine do not start escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs increased by MAOIs (risk of serious toxicity); antidepressants are possible 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 tricyclics.

Antidepressants: SSRIs antagonise anticonvulsant effect of zipropitant.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.

Antidepressants: plasma concentration of escitalopram, fluvoxamine or paroxetine should not be started until at least 5 weeks after stopping fluoxetine; after stopping fluoxetine do not start escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs increased by MAOIs (risk of serious toxicity); antidepressants are possible 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 tricyclics.

Antidepressants: SSRIs antagonise anticonvulsant effect of zipropitant.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.

Antidepressants: plasma concentration of escitalopram, fluvoxamine or paroxetine should not be started until at least 5 weeks after stopping fluoxetine; after stopping fluoxetine do not start escitalopram, fluvoxamine or paroxetine; CNS effects of SSRIs increased by MAOIs (risk of serious toxicity); antidepressants are possible 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 tricyclics.

Antidepressants: SSRIs antagonise anticonvulsant effect of zipropitant.

Antidepressants: SSRIs antagonise anticonvulsant effect of paroxetine; plasma concentration of paroxetine possibly increased when sertraline given with fluvoxamine.
Appendix 1: Interactions

Antidepressants, SSRI (continued)

Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine; fluoxetine and paroxetine possibly inhibit metabolism of atomoxetine

Barbiturates: SSRIs antagonise anticonvulsant effect of barbiturates (convulsive threshold lowered); plasma concentration of paroxetine reduced by phenobarbital

Beta-blockers: paroxetine possibly increases plasma concentration of metoprolol (enhanced effect); citalopram and escitalopram increase plasma concentration of metoprolol; fluvoxamine increases plasma concentration of propranolol

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; 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 CNS toxicity when SSRIs given with rasagiline; fluvoxamine should not be started until 2 weeks after stopping rasagiline; increased risk of hypertension 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 hypertension 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 not be started until 5 weeks after stopping fluoxetine, avoid fluoxetine for 2 weeks after stopping selegiline); theoretical risk of serotonin syndrome if citalopram given with selegiline (especially if dose of selegiline exceeds 10 mg daily); manufacturer of escitalopram advises caution with selegiline

SHT: Agonists: fluvoxamine inhibits the metabolism of frovatriptan; possible increased serotonergic effects when SSRIs given with frovatriptan; 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 (reduce dose of zolmitriptan)

Lithium: Increased risk of CNS effects when SSRIs given with lithium (lithium toxicity reported)

Muscle Relaxants: fluvoxamine increases plasma concentration of tizanidine (increased risk of toxicity)—avoid concomitant use

Parasympathomimetics: paroxetine increases plasma concentration of galantamine

Sibutramine: increased risk of CNS toxicity when SSRIs given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

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)

Ulceraellular Drugs: plasma concentration of citalopram, escitalopram and sertraline increased by cimetidine; fluvoxamine possibly increases plasma concentration of citalopram, escitalopram and sertraline increased by cimetidine; fluvoxamine possibly increases plasma concentration of citalopram, escitalopram and sertraline increased by cimetidine.

Antidepressants, SSRI (related)

Ulcer-healing Drugs (continued) concentration of lansoprazole; plasma concentration of escitalopram increased by omeprazole

Antidepressants, SSRI (related) see Duloxetine and Venlafaxine

Antidepressants, Tricyclic

Adrenergic Neurone Blockers: tricyclics antagonise hypotensive effect of adrenergic neurone blockers

Alcohol: increased sedative effect when tricycles given with alcohol

Alpha-2-adrenoceptor Stimulants: avoidance of tricyclics advised by manufacturer of apraclonidine and brimonidine

Anaesthetics, General: increased risk of arrhythmias and hypotension when tricycles given with general anaesthetics

Analgesics: increased risk of CNS toxicity when tricycles given with tramadol; side-effects possibly increased when tricycles given with nefopam; sedative effects possibly increased when tricycles given with opioid analgesics

Anti-arrhythmics: increased risk of ventricular arrhythmias when tricycles given with amiodarone—avoid concomitant use; increased risk of ventricular arrhythmias when tricycles given with disopyramide or lecainide; increased risk of arrhythmias when tricycles given with propafenone

Antibacterials: increased risk of ventricular arrhythmias when tricycles given with moxifloxacin—avoid concomitant use; plasma concentration of tricycles possibly reduced by rifampicin

Anticoagulants: tricycles may enhance or reduce anticoagulant effect of coumarins

Antidepressants: possible increased serotonergic effects when amitriptyline or clomipramine given with duloxetine; increased risk of hypertension and CNS excitation when tricycles given with MAOIs, tricycles 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 tricycles (3 weeks in the case of clomipramine or imipramine); after tricycles do not start moclobemide for at least 1 week; plasma concentration of some tricycles increased by SSRIs; plasma concentration of amitriptyline reduced by St John’s wort

Antiepileptics: tricycles antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); metabolism of tricycles accelerated by carbamazepine (reduced plasma concentration and reduced effect); plasma concentration of tricycles possibly reduced by phenytoin; tricycles antagonise anticonvulsant effect of primidone (convulsive threshold lowered), also metabolism of tricycles possibly accelerated (reduced plasma concentration) Antifungals: plasma concentration of imipramine and nortriptyline possibly increased by terbinafine Antihistamines: increased antimuscarinic and sedative effects when tricycles given with antihistamines

Antimalarials: avoidance of antidepressants advised by manufacturer of artemether/lumefantrine

Antimuscarinics: increased risk of antimuscarinic side-effects when tricycles given with antimuscarinics

Antipsychotics: plasma concentration of tricycles increased by antipsychotics—possibly increased risk of ventricular arrhythmias; possibly increased antimuscarinic side-effects when tricycles given with clozapine; increased risk of antimuscarinic side-effects when tricycles given with phenothiazines; increased risk of ventricular arrhythmias when tricycles given with pimozide—avoid concomitant use

Antivirals: side-effects of tricycles possibly increased by fosamprenavir; plasma concentration of tricycles possibly increased by ritonavir
Antidepressants, Tricyclic (continued)

Anxiolytics and Hypnotics: increased sedative effect when tricyclics given with anxiolytics and hypnotics

- Atomoxetine: increased risk of ventricular 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 ventricular arrhythmias when tricyclics given with betablockers
- 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
- Diazepam: metabolism of tricyclics inhibited by disulfram (increased plasma concentration); concomitant amitriptyline reported to increase disulfram reaction with alcohol
- Diuretics: increased risk of postural hypotension when tricyclics given with diuretics
- Dopaminergics: caution with tricyclics advised by dopamine manufacturer of entacapone; increased risk of CNS toxicity when tricyclics given with entacapone; 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: antidepressant effect of tricyclics antagonised by oestrogens (but side-effects of tricyclics possibly increased due to increased plasma concentration)
- Pentamidine Isetionate: increased risk of ventricular 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 Oxygenate: increased risk of side-effects when tricyclics given with sodium oxygenate
- Sympathomimetics: increased risk of hypertension and arrhythmias when tricyclics given with adrenaline (epinephrine) (but local anaesthetics with adrenaline appear to be safe); metabolism of tricyclics possibly inhibited by methylphenidate; increased risk of hypertension and arrhythmias when tricyclics given with adrenaline (norepinephrine)
- 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
- Alpha2-adrenoceptor Stimulants: avoidance of tricyclic-related antidepressants advised by manufacturer of apraclonidine and brimonidine
- Anxiolytics and Hypnotics: increased sedative effect when tricyclic-related antidepressants given with anxiolytics and hypnotics
- Atomoxetine: increased risk of ventricular arrhythmias when tricyclics given with atomoxetine
- Antiepileptics: tricyclic-related antidepressants possibly antagonise anticonvulsant effect of antiepileptics (convulsive threshold lowered); plasma concentration of mianserin reduced by antiepileptics and metabolism of mianserin accelerated by phenytoin (reduced plasma concentration)
- Barbiturates: tricyclic-related antidepressants possibly antagonise anticonvulsant effect of barbiturates (convulsive threshold lowered); metabolism of mianserin accelerated by primidone (reduced plasma concentration)
- Diazepam: metabolism of tricyclics inhibited by disulfram (increased plasma concentration)
- Diazoxide: enhanced hypotensive effect when tricyclic-related antidepressants given with diazoxide
- Nitrites: tricyclic-related antidepressants possibly reduce effects of sublingual tablets of nitrites (failure to dissolve under tongue owing to dry mouth)
- Nitrates: increased risk of CNS toxicity when tricyclic-related antidepressants given with nitrates
- 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 antidiabetics enhanced by alcohol; increased risk of lactic acidosis when metformin given with alcohol; flushings in susceptible subjects, when chlorpropamide given with alcohol

Anabolic Steroids: hypoglycaemic effect of antidiabetics possibly enhanced by anabolic steroids

Analgesia: effects of sulphonylureas possibly enhanced by NSAIDs; effects of tobutamide enhanced by azapropazone (avoid concomitant use)
Antidiabetics
- Antibacterials (continued): considering increasing dose of rosiglitazone; effects of sulphonylureas enhanced by chloramphenicol; metabolism of sulphonylureas possibly accelerated by rifampicins (reduced effect); metabolism of chlorpropamide and tolbutamide accelerated by rifampicins (reduced effect), effects of sulphonylureas rarely enhanced by sulphonamides and trimethoprim; hypoglycaemic effect of repaglinide possibly enhanced by trimethoprim—manufacturer advises avoid concomitant use
- Anticoagulants: exenatide possibly enhances anticoagulant effect of warfarin; hypoglycaemic effect of sulphonylureas possibly enhanced by coumarins, 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 glibenclamide possibly reduced by topiramate
- Antifungals: plasma concentration of sulphonylureas increased by fluconazole and miconazole; hypoglycaemic effect of gliclazide and glipizide enhanced by miconazole—avoid concomitant use; hypoglycaemic effect of nateglinide possibly enhanced by fluconazole; hypoglycaemic effect of repaglinide possibly enhanced by itraconazole; hypoglycaemic effect of glipizide 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)
- Antipsychotics: 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 given with beta-blockers; hypoglycaemic effect of insulin enhanced by beta-blockers
- Bosentan: increased risk of hepatotoxicty when glibenclamide given with bosentan—avoid concomitant use
- Calcium-channel Blockers: glucose tolerance occasionally impaired when insulin given with nifedipine
- Cardiac Glycosides: acarbose possibly reduces plasma concentration of digoxin; sitagliptin increases 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 gliclazide possibly impaired by paclitaxel
- Deferasirox: plasma concentration of repaglinide increased by deferasirox
- Diazoxide: hypoglycaemic effect of antidiabetics antagonised by diazoxide
- Diuretics: hypoglycaemic effect of antidiabetics antagonised by loop diuretics and thiazides and related diuretics; increased risk of hyponatraemia 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, repaglinide and sulphonylureas possibly reduced by lanreotide; requirements for insulin, metformin, repaglinide and sulphonylureas possibly reduced by octreotide
- Lipid-regulating Drugs: hypoglycaemic effect of tolbutamide possibly enhanced by leflunomide
- Leflunomide: hypoglycaemic effect of tolbutamide possibly enhanced by leflunomide
- Oestrogens: hypoglycaemic effect of antidiabetics antagonised by oestrogens
- Orlistat: avoidance of acarbose advised by manufacturer of orlistat
- Pancreatin: hypoglycaemic effect of acarbose antagonised by pancreatin
- 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: excretion of metformin reduced by Pancreatin
- Amphotericin: Antifungals, Imdazole; Antifungals, Triazole; Caspofungin; Flucytosine; Griseofulvin; Micafungin; Terbinafine
- Alikiren: ketoconazole increases plasma concentration of alikiren
- Analgesics: ketoconazole inhibits metabolism of buprenorphine (reduce dose of buprenorphine)
- Antacids: absorption of ketoconazole reduced by antacids
- Anti-arrhythmics: increased risk of ventricular arrhythmias when ketoconazole given with disopyramide—avoid concomitant use
- Antibacterials: metabolism of ketoconazole accelerated by rifampicin (reduced plasma concentration), also plasma concentration of rifampicin may be reduced by ketoconazole; plasma concentration of ketoconazole possibly reduced by isoniazid; avoidance of concomitant ketoconazole in severe renal and hepatic impairment advised by manufacturer of telithromycin
- Anticoagulants: ketoconazole enhances anticoagulant effect of coumarins; miconazole enhances anticoagulant effect of coumarins (miconazole oral gel and possibly vaginal formulations absorbed); ketoconazole increases plasma concentration of warfarin—avoid concomitant use
- Antidepressants: avoidance of imidazoles advised by manufacturer of reboxetine; ketoconazole increases plasma concentration of mirtazapine
- Antidiabetics: miconazole enhances hypoglycaemic effect of gliclazide and glipizide—avoid concomitant use; miconazole increases plasma concentration of sulphphonylureas
Antifungals, Imidazole
- • 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)
- • Antihistamines: manufacturer of loratadine advises ketoconazole possibly increases plasma concentration of loratadine; imidazoles possibly inhibit metabolism of emizolastine (avoid concomitant use); ketoconazole inhibits metabolism of emizolastine—avoid concomitant use
- • Antimalarials: avoidance of imidazoles advised by manufacturer of artesether/ lumefantrine
- • Antimuscarnics: absorption of ketoconazole reduced by antimuscarinics; ketoconazole increases plasma concentration of darifenacin—avoid concomitant use; manufacturer of fosoterodine advises dose reduction when ketoconazole given with fosoterodine—consult fosoterodine product literature; 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 pimozide—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
- • Antioxidants and Hypnotics: ketoconazole increases plasma concentration of alprazolam; ketoconazole increases plasma concentration of midazolam (risk of prolonged sedation)
- • Aprepitant: ketoconazole increases plasma concentration of aprepitant
- • Bosantan: ketoconazole increases plasma concentration of bosantan
- • Calcium-channel Blockers: ketoconazole inhibits metabolism of efedrinol (increased plasma concentration); avoidance of ketoconazole advised by manufacturer of lercanidipine; 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)
- • Clofazimine: ketoconazole possibly increases plasma concentration of clofazimine—avoid concomitant use
- • Calcineurin: ketoconazole inhibits metabolism of calcineurin (increased plasma concentration)
- • Cytotoxic Drugs: ketoconazole possibly increases plasma concentration of ciclosporin; ketoconazole increases metabolism of methylprednisolone; ketoconazole increases plasma concentration of inhaled mometasone
- • Cytotoxics: ketoconazole inhibits metabolism of erlotinib and sunitinib (increased plasma concentration); ketoconazole increases plasma concentration of bortezomib and imatinib; ketoconazole increases plasma concentration of lapatinib and nilotinib—avoid concomitant use; ketoconazole increases plasma concentration 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 tritocaferol (but concentration of active metabolite of tritocaferol increased)—avoid concomitant use
- • Diuretics: ketoconazole increases plasma concentration of spironolactone—avoid concomitant use
- • Domperidone: ketoconazole possibly increases risk of arrhythmias with domperidone
- • Ergot Alkaloids: increased risk of ergotism when imidazoles given with ergotamine and methysergide—avoid concomitant use
- • 5HT3, Agonists: ketoconazole increases plasma concentration of almotriptan (increased risk of toxicity); ketoconazole increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use
- • Ivabradine: ketoconazole increases plasma concentration of ivabradine—avoid concomitant use
- • Lanthanum: absorption of ketoconazole possibly reduced by lanthanum (give at least 2 hours apart)
- • Lipid-lowering Drugs: possible increased risk of myopathy when imidazoles with atorvastatin or simvastatin; increased risk of myopathy when ketoconazole given with atorvastatin or simvastatin (avoid concomitant use; possible increased risk of myopathy when miconazole given with simvastatin—avoid concomitant use
- • Oestrogens: anecdotal reports of contraceptive failure when miconazole or ketoconazole given with oestrogens
- • Parasympathomimetics: ketoconazole increases plasma concentration of galantamine
- • Retinoids: ketoconazole increases plasma concentration of alitretinoin
- • Rimonabant: ketoconazole increases plasma concentration of rimonabant; increase initial dose of rimonabant
- • 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 decreases plasma concentration of tacrolimus
- • 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
- • Vardenafil: ketoconazole increases plasma concentration of vardenafil (halve dose of vardenafil); vorico...
Antifungals, Triazole

- **Antalminials**: avoidance of triazoles advised by manufacturer of artemether/lumefantrine
- **Antimuscarinics**: avoidance of itraconazole advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when itraconazole given with fesoterodine—consult fesoterodine product literature; itraconazole increases plasma concentration of tolterodine and tolterodine—avoid concomitant use
- **Antipsychotics**: itraconazole possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); increased risk of ventricular arrhythmias when triazoles given with pimozide—avoid concomitant use; triazoles possibly increase plasma concentration of quetiapine (reduce dose of quetiapine); increased risk of ventricular arrhythmias when itraconazole given with erthropine—avoid concomitant use; possible increased risk of ventricular arrhythmias when triazoles given with erthropine—avoid concomitant use

Antidepressants: avoidance of triazoles advised by clarithromycin; triazoles possibly increase plasma concentration of efavirenz (consider increasing efavirenz dose and reducing efavirenz dose); plasma concentration of itraconazole possibly increased by ritonavir—avoid concomitant use; combination of itraconazole with ritonavir may increase plasma concentration of efavirenz and ritonavir—avoid concomitant use; plasma concentration of voriconazole reduced by nefazodone; voriconazole possibly increased when itraconazole given with nefazodone; voriconazole increases 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 midazolam (risk of prolonged sedation); itraconazole increases plasma concentration of buspirone (reduce dose of buspirone)

Barbiturates: plasma concentration of voriconazole possibly reduced by phenobarbital—avoid concomitant use; combination of voriconazole and posaconazole possibly reduced by phenobarbital

Bosentan: fluconazole possibly increases plasma concentration of bosentan—avoid concomitant use; itraconazole possibly increases plasma concentration of bosentan

Calcium-channel Blockers: negative inotropic effect possibly increased when itraconazole given with calcium-channel blockers; itraconazole inhibits metabolism of felodipine (increased plasma concentration); avoidance of itraconazole advised by manufacturer of lercanidipine; itraconazole possibly inhibits metabolism of dihydropyridines (increased plasma concentration)

Cardiac Glycosides: itraconazole increases plasma concentration of digoxin

Ciclosporin: fluconazole, itraconazole, posaconazole and voriconazole inhibit metabolism of ciclosporin (increased plasma concentration of itraconazole and posaconazole possibly reduced by ciclosporin

Corticosteroids: itraconazole possibly inhibits metabolism of corticosteroids and methylprednisolone; itraconazole increases plasma concentration of inhaled budesonide

Cytotoxics: itraconazole inhibits metabolism of busulfan (increased risk of toxicity); itraconazole possibly increases side-effects of cyclophosphamide; avoid-
Antifungals, Triazole
- Cytotoxics (continued)
  - Increased risk of ventricular arrhythmias when mizolastine given with amiodarone, disopyramide, flecainide 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 antimycarunic and sedative effects when antihistamines given with MAOs or tricyclics; cyproheptadine possibly antagonises antidepressant effect of SSRIs; possible increased antimycarunic 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 midazolam (avoid concomitant use)
- Antimycarunic: increased risk of antimycarunic side-effects when antihistamines given with antimycarunicines
- Antivirals: plasma concentration of loratadine possibly increased by fosamprenavir; plasma concentration of chlorphenamine (chlorpheniramine) possibly increased by lopinavir; plasma concentration of nonsedating 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 betotalo—avoid concomitant use
- Betahistine: antihistamines theoretically antagonise effect of betahistine
- Ucer-healing Drugs: manufacturer of loratadine advises plasma concentration possibly increased by cimetidine
- Antihistamines, Non-sedating see Antihistamines
- Antihistamines, Sedating see Antihistamines
- Antimalarials see Artemether with Lumefantrine, Chloroquine and Hydroxychloroquine, Mefloquine, Primaquine, Proguanil, and Quinine
- Antimetabolites see Cytarabine, Fludarabine, Fluorouracil, Mercaptopurine, Methotrexate, and Tioguaine
- Antimycarunicines
  - Note: Many drugs have antimycarunic 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 antimycarunicines used by inhalation
  - Alcohol: increased sedative effect when hyoscine given with alcohol
- Analgesics: increased risk of antimycarunic side-effects when antihistamines given with nefopam
- Anti-arrhythmics: increased risk of ventricular arrhythmias when mizolastine given with amiodarone, disopyramide, flecainide or propafenone—avoid concomitant use
- Antihistamines (continued)
  - Increased risk of ventricular arrhythmias when mizolastine given with amiodarone, disopyramide, flecainide or propafenone—avoid concomitant use
Antimuscarinics

Antibacterials (continued)
clarithromycin and erythromycin; plasma concentration of clarithromycin possibly increased by erythromycin; plasma concentration of active metabolite of clarithromycin reduced by rifampicin

Antidepressants: plasma concentration of deracin and prydolcin 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 feroterodone advises dose reduction when feroterodone given withitraconazole and ketoconazole—consult feroterodone product literature; plasma concentration of olfactory increased byitraconazole and ketoconazole; manufacturer of tolterodine advises avoid concomitant use withitraconazole and ketoconazole; manufacturer of fesoterodine advises avoid concomitant use withitraconazole

Antihistamines: increased risk of antimuscarinic side-effects when antimuscarinics given with antihistamines

Antipsychotics: antimuscarinics possibly reduce effects of haloperidol; increased risk of antimuscarinic side-effects when antimuscarinics given withclozapine; antimuscarinics reduce plasma concentration ofphenothiazines, but risk of antimuscarinic side-effects increased

Antivirals: manufacturer of darifenacin advises avoid concomitant use with azithromycin; plasma concentration of active metabolite of darifenacin possibly increased by erythromycin and clarithromycin; plasma concentration of actholin possibly increased by clarithromycin or erythromycin; plasma concentration of solifenacin increased byitraconazole and ketoconazole—consult antimuscarinic product literature; manufacturer of tolterodine advises avoid concomitant use; increased risk of ventricular arrhythmias when benperidol given with parenteral

Analgesics: avoid concomitant use of clozapine withazapropazine (increased risk of agranulocytosis); possible severe drowsiness when haloperidol given with indomethacin; increased risk of convulsions when antipsychotics given with tramadol; enhanced hypotensive and sedative effects when antipsychotics given with opioid analgesics

Antipsychotics (continued)
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

Adsorbents: absorption of phenothiazines possibly reduced by kaolin

Alcohol: increased sedative effect when antipsychotics given with alcohol

• Anaesthetics, General: enhanced hypotensive effect when antipsychotics given with general anaesthetics

• Analgesics: avoid concomitant use of clozapine withazapropazine (increased risk of agranulocytosis); possible severe drowsiness when haloperidol given with indomethacin; increased risk of convulsions when antipsychotics given with tramadol; enhanced hypotensive and sedative effects when antipsychotics given with opioid analgesics

Antidepressants: plasma concentration of actholin possibly increased by ciprofloxacin; plasma concentration of olanzapine possibly increased by moxifloxacin; plasma concentration of olanzapine possibly reduced by ritonavir and saquinavir; plasma concentration of solifenacin increased by neflinarv and ritalinov

• Beta-blockers: increased risk of ventricular arrhythmias when feroterodine given with beta-blockers

Calcium-channel Blockers: manufacturer of feroterodine advises avoid concomitant use with verapamil

Cardiac Glycosides: deracin possibly increases plasma concentration of digoxin

Ciclosporin: manufacturer of feroterodine advises avoid concomitant use with ciclosporin

Dopemderine: antimuscarinics antagonise effects of domperidone on gastro-intestinal activity

Dopaminergics: increased risk of antimuscarinic side-effects when antimuscarinics given with amantidine; antimuscarinics possibly reduce absorption of levodopa

Mecamine: effects of antimuscarinics possibly enhanced by mecamamine

Metoclopramide: antimuscarinics antagonise effects of metoclopramide on gastro-intestinal activity

Nitrates: antimuscarinics possibly reduce effects of sublingual tablets of nitrates (failure to dissolve under tongue owing to dry mouth)

Parasympathomimetics: antimuscarinics antagonise effects of parasympathomimetics

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

Antipsychotics (continued)
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 given with aripiprazole possibly reduced by rifampicin; metabolism of haloperidol accelerated by rifampicin (reduced plasma concentration); avoid
Antipsychotics (continued)
- Antimalarials: avoidance of antipsychotics advised by manufacturer of artesunate/mefloquine; increased risk of ventricular arrhythmias when pimozone given with mefloquine 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 risperidone; fluoxetine, haloperidol, pipotazaine, risperidone or zuclopenthixol as cannot be withdrawn quickly if neutropenia occurs; increased risk of ventricular arrhythmias when sulpiride given with haloperidol; increased risk of ventricular arrhythmias when sertindole given with amisulpride—avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with phenoxyazines—avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with sulpiride—avoid concomitant use; increased risk of ventricular arrhythmias when pimozone given with amitriptyline; plasma concentration of pimozone possibly increased by atazanavir—avoid concomitant use; metabolism of aripiprazole possibly inhibited by fluoxetine; plasma concentration of aripiprazole possibly increased by fluoxetine; plasma concentration of aripiprazole possibly increased by paroxetine; plasma concentration of aripiprazole possibly increased by fluoxetine (increased risk of toxicity); metabolism of aripiprazole possibly inhibited by fluoxetine and paroxetine (reduce dose of aripiprazole); plasma concentration of clozapine increased by sertraline and venlafaxine; plasma concentration of haloperidol increased by venlafaxine; clozapine possibly increased CNS effects of MAOIs; plasma concentration of pimozone possibly increased by SSRIs (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of aripiprazole possibly reduced by St John’s wort—increase dose of aripiprazole; 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 pimozone 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—increase dose of aripiprazole; plasma concentration of pimozone and sertindole increased by carbamazepine; antipsychotics antagonise anticonvulsant effect of carbamazepine, valproate, carbamazepine, 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 primidone—increase 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 with ketoconazole or ketoconazole—avoid concomitant use; metabolism of aripiprazole possibly inhibited by ketoconazole (reduce dose of aripiprazole); possible increased risk of ventricular arrhythmias when sertindole given with imidazoles or triazoles—avoid concomitant use; plasma concentration of quetiapine possibly increased by imidazoles and triazoles (reduce dose of quetiapine); increased risk of ventricular arrhythmias when pimozone given with imidazoles or triazoles—avoid concomitant use
Antipsychotics
- 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 fluoxetine; 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 increased by sertraline and venlafaxine; plasma concentration of haloperidol increased by venlafaxine; clozapine possibly increased CNS effects of MAOIs; plasma concentration of pimozone possibly increased by SSRIs (increased risk of ventricular arrhythmias—avoid concomitant use); plasma concentration of aripiprazole possibly reduced by St John’s wort—increase dose of aripiprazole; 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 pimozone 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—increase dose of aripiprazole; plasma concentration of pimozone and sertindole increased by carbamazepine; antipsychotics antagonise anticonvulsant effect of carbamazepine, valproate, carbamazepine, 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 primidone—increase 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 with ketoconazole or ketoconazole—avoid concomitant use; metabolism of aripiprazole possibly inhibited by ketoconazole (reduce dose of aripiprazole); possible increased risk of ventricular arrhythmias when sertindole given with imidazoles or triazoles—avoid concomitant use; plasma concentration of quetiapine possibly increased by imidazoles and triazoles (reduce dose of quetiapine); increased risk of ventricular arrhythmias when pimozone given with imidazoles or triazoles—avoid concomitant use
Appendix 1: Interactions
Antipsychotics

- Beta-blockers (continued)
  - 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 quinapril or sotalol 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 levomepromazine (methotrimeprazine) advises avoid concomitant use with desferrioxamine; avoidance of prochlorperazine advised by manufacturer of desferrioxamine
- Diazoxide: enhanced hypotensive effect when phenothiazines given with diazoxide
- Diuretics: risk of ventricular arrhythmias with amisulpride or sertindole increased by hypokalaemia caused by diuretics; risk of ventricular arrhythmias with pimozide 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 amantadine; antipsychotics antagonise effects of apomorphine, levodopa and pergolide; antipsychotics antagonise hypoprolactinaemic and antiparkinsonian effects of bromocriptine and cabergoline; manufacturer of amisulpride advises avoid concomitant use of levodopa (antagonism of effect); avoidance of antipsychotics advised by manufacturer of pramipexole, ropinirole and rotigotine (antagonism of effect)
- Ivabradine: increased risk of ventricular arrhythmias when pimozide or sertindole given with ivabradine
- Lithium: increased risk of ventricular arrhythmias when sertindole given with lithium—avoid concomitant use; increased risk of extrapyramidal side-effects and possibly neurotoxicity when clozapine, fluoxetine, haloperidol, phenothiazines or quinapril given with lithium; increased risk of extrapyramidal side-effects when sulpiride given with lithium
- Memantine: effects of antipsychotics possibly reduced by memantine
- Methylprednisolone: enhanced hypotensive effect when antipsychotics given with methylprednisolone (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 suxamethonium
- 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

Antipsychotics (continued)

- Sodium Oxycathe: antipsychotics possibly enhance effects of sodium oxycathe
- 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
- Uleri-healing Drugs: effects of antipsychotics, 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 sulpiride reduced by sucralfate
- Vasodilator Antihypertensives: enhanced hypotensive effect when phenothiazines given with hydralazine, minoxidil or sodium nitroprusside

Antivirals


Anaesthetics

- General: increased sedative effect when anaesthetics and hypnotics given with general anaesthetics
- Analgesics: increased sedative effect when anaesthetics and hypnotics given with analgesics
- Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when angiotensin-II receptor antagonists 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 buspirone increased by erythromycin (reduce dose of buspirone); metabolism of zopiclone inhibited by erythromycin and quinupristin/dalfopristin; metabolism of benzodiazepines possibly accelerated by rifampicin (reduced plasma concentration); metabolism of diazepam accelerated by rifampicin (reduced plasma concentration); metabolism of buspirone and zaleplon possibly accelerated by rifampicin; metabolism of zolpidem accelerated by rifampicin (reduced plasma concentration and reduced effect); plasma concentration of zopiclone significantly reduced by rifampicin; metabolism of diazepam inhibited by isoniazid
- Anticoagulants: chloral and triclofos may transiently enhance anticoagulant effect of coumarins
- Antidepressants: plasma concentration of melatonin increased by fluoxetine—avoid concomitant use; plasma concentration of some benzodiazepines increased by fluoxetine; sedative effects possibly increased when zolpidem given with sertraline; manufacturer of buspirone advises avoid concomitant use with MAOIs; plasma concentration of oral midazolam possibly reduced by St John's wort; increased sedative effect when anaesthetics and hypnotics given with mirtazapine, tricyclic-related antidepressants or tricyclics
Anxiolytics and Hypnotics (continued)

Antiepileptics: 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; plasma concentration of clonazepam increased by stiripentol; plasma concentration of diazepam and lorazepam possibly increased by valproate; increased risk of side-effects when clonazepam given with valproate; cllobazam possibly increases plasma concentration of valproate.

- Antifungals: plasma concentration of alprazolam
- Antivirals: plasma concentration of midazolam possibly increased by itraconazole and ketoconazole; plasma concentration of midazolam increased by fluconazole, itraconazole and ketoconazole (risk of prolonged sedation); plasma concentration of buspirone increased by itraconazole (reduce dose of buspirone); 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; buspirone increases plasma concentration of haloperidol; increased risk of hypotension, bradycardia and respiratory depression when parenteral benzodiazepines given with intramuscular clonazepam; clonazepam increases plasma concentration of zotepine.

- Antivirals: plasma concentration of midazolam possibly increased by stavudine—avoid concomitant use of oral midazolam; increased risk of prolonged sedation when midazolam given with edaviren—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 nindavin, nelfinavir and ritonavir (risk of prolonged sedation—avoid concomitant use of oral midazolam); increased risk of prolonged sedation when alprazolam given with nindavin—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 buspirone 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 hypotensive effect when anxiolytics and hypnotics given with beta-blockers.

Calcium-channel Blockers: enhanced hypotensive 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 buspirone increased by diltiazem and verapamil (reduce dose of buspirone).

Cardiac Glycosides: alprazolam increases plasma concentration of digoxin (increased risk of toxicity).

Clonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with clonidine.

Cytotoxics: plasma concentration of midazolam increased by nilotinib.

Anxiolytics and Hypnotics (continued)

Deferasirox: plasma concentration of midazolam possibly reduced by deferasirox.

Diazoxide: enhanced hypotensive 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 hypotensive 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 buspirone increased by grapefruit juice.

Lofexidine: increased sedative effect when anxiolytics and hypnotics given with lofexidine.

Methylodopa: enhanced hypotensive effect when anxiolytics and hypnotics given with methylodopa.

Moxonidine: enhanced hypotensive effect when anxiolytics and hypnotics given with moxonidine; sedative effects possibly increased when benzodiazepines given with moxonidine.

Muscle Relaxants: increased sedative effect when anxiolytics and hypnotics given with baclofen or tizanidine.

Nabulone: increased sedative effect when anxiolytics and hypnotics given with nabulone.

Nitrates: enhanced hypotensive 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.

Ulcerc-Healing Drugs: plasma concentration of melatonin increased by cimetidine; metabolism of benzodiazepines, clomethiazole and zaleplon inhibited by cimetidine (increased plasma concentration); metabolism of diazepam possibly inhibited by esomeprazole and omeprazole (increased plasma concentration).

Vasodilator Antihypertensives: enhanced hypotensive effect when anxiolytics and hypnotics given with hydralazine, minoxidil or sodium nitroprusside.

Amorphine: Antipsychotics: effects of amphetamine antagonised by antipsychotics.

Dopaminergics: effects of amphetamine possibly enhanced by entacapone.

Memitin: effects of dopaminergics possibly enhanced by memantine.

Methylodopa: antiparkinsonian effect of dopaminergics antagonised by methylodopa.

Aprecitant: manufacturer of apraclonidine advises avoid concomitant use with MAOIs, tricyclic-related antidepressants and tricyclics.

Aprepitant

Note: Fosaprepitant is a prodrug of aprepitant.

Antibacterials: plasma concentration of aprepitant possibly increased by clarithromycin and telithromycin; plasma concentration of aprepitant reduced by rifampicin.

Anticoagulants: aprepitant possibly reduces anticoagulant effect of warfarin.

Antidepressants: manufacturer of aprepitant advises avoid concomitant use with St John's wort.
Appendix 1: Interactions

**Progestogens**: aprepitant possibly causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended).

**Antipsychotics**: manufacturer of aprepitant advises concomitant use with pimozide; aprepitant possibly causes contraceptive failure of hormonal contraceptives containing oestrogens (alternative contraception recommended).

**Anti-arrhythmics**: atazanavir possibly increases plasma concentration of dexamethasone and methylprednisolone (reduce dose of dexamethasone and methylprednisolone).

**Antifungals**: plasma concentration of aprepitant possibly reduced by carbamazepine and phenytoin; possibly increased by ritonavir.

**Antidepressants**: increased risk of bleeding when aspirin given with SSRI or venlafaxine; aprepitant possibly reduces plasma concentration of phenytoin and valproate.

**Anticoagulants**: increased risk of bleeding when aspirin given with clopidogrel.

**Antidiabetics**: aspirin reduces plasma concentration of tolbutamide.

**Antibacterials**: manufacturer of artemether/lumefantrine advises concomitant use with atazanavir; atazanavir possibly increases plasma concentration of amiodarone, disopyramide or flecainide (risk of ventricular arrhythmias).

**Antibacterials**: atazanavir possibly increases plasma concentration of amiodarone and lidocaine (lignocaine).

**Antivirals**: manufacturer of artemether/lumefantrine advises concomitant use with ritonavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir.

**Anticoagulants**: plasma concentration of aspirin possibly reduced by ibuprofen; aspirin enhances anticoagulant effect of heparins.

**Antidepressants**: increased risk of bleeding when aspirin given with SSRIs or venlafaxine.

**Antiepileptics**: aspirin enhances effects of phenytoin and valproate.

**Antihypertensives**: increased risk of bleeding when aspirin given with telithromycin.

**Ant Psychiatry**: atazanavir may enhance or reduce anticoagulant effect of warfarin; avoidance of atazanavir advised by manufacturer of rivaroxaban.

**Antitussives**: atazanavir possibly increases plasma concentration of amiodarone and lidocaine (lignocaine).

**Antiluetic Agents**: avoidance of atazanavir advised by manufacturer of fesoterodine—consult fesoterodine product literature.

**Antimigraine**: atazanavir possibly increases plasma concentration of zaniolizine.

**Antimycotics**: atazanavir possibly increases plasma concentration of saquinavir; plasma concentration of atazanavir reduced by nevirapine—avoid concomitant use; atazanavir increases plasma concentration of saquinavir; plasma concentration of atazanavir reduced by
Atazanavir
- Antivirals (continued)
  - 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 
- Calcium-channel Blockers: atazanavir increases plasma concentration of diltiazem (reduce dose of diltiazem); atazanavir possibly increases plasma concentration of verapamil
- Ciclosporin: atazanavir possibly increases plasma concentration of ciclosporin
- Cytotoxics: atazanavir possibly inhibits 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
- Tacrolimus: atazanavir possibly increases plasma concentration of tacrolimus
- Ulcer-healing Drugs: plasma concentration of atovaquone reduced (convulsive threshold lowered); avoid concomitant use of oral midazolam

Antivirals
- Antibacterials: plasma concentration of atovaquone reduced by efavirenz and enfuvirtide (possible therapeutic failure of atovaquone); plasma concentration of atovaquone reduced by tetracycline
- Antibacterials: plasma concentration of atovaquone possibly reduced by metoclopramide
- Atracurium see Muscle Relaxants
- Atropine see Antimuscarinics
- Azapropazone see NSAIDs

Azathioprine
- ACE Inhibitors: increased risk of anaemia or leucopenia when atazanavir given with captopril especially in renal impairment; increased risk of anaemia when atazanavir given with enalapril especially in renal impairment
- Allopurinol: enhanced effects and increased toxicity of azathioprine when given with allopurinol (reduce dose of azathioprine to one quarter of usual dose)
- Aminosalicylates: possible increased risk of leucopenia when atazanavir given with aminosalicylates
- Antihypertensives: increased risk of haematological toxicity when atazanavir given with sulmethoxazole (as co-trimoxazole); increased risk of haematological toxicity when atazanavir given with trimethoprim (also with co-trimoxazole)
- Anticoagulants: atazanavir possibly reduces anticoagulant effect of warfarin
- 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
- Azithromycin see Macrolides

Aztreonam
- Anticoagulants: aztreonam possibly enhances anticoagulant effect of warfarin
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Baclofen see Muscle Relaxants

Balsalazide see Aminosalicylates

Bambuterol see Sympathomimetics, Beta2

Barbiturates
- Alcohol: increased sedative effect when barbiturates given with alcohol
  - Analgesics: barbiturates possibly increase CNS effects of opioid analgesics
- Anti-arrhythmics: 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 warfarin (reduced anticoagulant effect)
- Antidepressants: phenobarbital reduces plasma concentration of paroxetine; phenobarbital accelerates metabolism of amisulpride (reduced plasma concentration); anticonvulsant effect of barbiturates possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of barbiturates antagonised by SSRIs (convulsive threshold lowered); avoid concomitant use of phenobarbital with St John’s wort; anti-
Appendix 1: Interactions

Barbiturates
- Antidepressants (continued)
  convulsant effect of barbiturates antagonised by tricyclics (convulsive threshold lowered), also metabolism of tricyclics possibly accelerated (reduced plasma concentration)
- Antiepileptics: phenobarbital reduces plasma concentration of carbamazepine, lamotrigine, tiagabine and zonisamide; phenobarbital possibly reduces plasma concentration of ethosuximide; plasma concentration of phenobarbital increased by oxcarbazepine, also plasma concentration of an active metabolite of oxcarbazepine reduced; plasma concentration of phenobarbital often increased by phenytoin, plasma concentration of phenytoin often reduced but may be increased; increased sedative effect when barbiturates given with primidone; plasma concentration of phenobarbital increased by nitrazepam; plasma concentration of phenobarbital reduced 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 phenobarbital 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, saquinavir and nelfinavir; phenobarbital possibly reduces plasma concentration of lopinavir; also plasma concentration of phenobarbital possibly increased

Anxiolytics and Hypnotics: phenobarbital often reduces plasma concentration of clonazepam
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 felodipine and isradipine; barbiturates probably reduce effects of dihydropyridines, diltiazem and verapamil

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 irinotecan 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 Receptor Antagonists: phenobarbital reduces plasma concentration of montelukast

Lofexidine: increased sedative effect when barbiturates given with lofexidine

Memantine: effects of barbiturates possibly reduced by memantine

Oestrogens: barbiturates accelerate metabolism of oestrogens (reduced contraceptive effect—see p. 478)

Progestogens: barbiturates accelerate metabolism of progestogens (reduced contraceptive effect—see p. 478)

Sodium Oxybate: barbiturates enhance effects of sodium oxybate (avoid concomitant use)

Symptomomimetics: plasma concentration of phenobarbital possibly increased by methylphenidate

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)

Tibolone: barbiturates accelerate metabolism of tibolone (reduced plasma concentration)

Vitamins: barbiturates possibly increase requirements for vitamin D

Beclometasones see Corticosteroids

Bemiparin see Heparins

Bendrofluazide and bendrofluazide see Diuretics

Benperidol see Antipsychotics

Benzodiazepines see Anxiolytics and Hypnotics

Benzthiazide see Diuretics

Benzylenepicillins see Penicillins

Beta-blockers
Note. Since systemic absorption may follow topical application of beta-blockers to the eye the possibility of interactions, in particular, with drugs such as verapamil should be borne in mind

ACE Inhibitors: enhanced hypertensive effect when beta-blockers given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypertensive effect when beta-blockers given with adrenergic neurone blockers

Alcohol: enhanced hypertensive effect when beta-blockers given with alcohol

Aldesleukin: enhanced hypertensive effect when beta-blockers given with aldesleukin

Alpha-blockers: enhanced hypertensive effect when beta-blockers given with alpha-blockers, also increased risk of first-dose hypotension with post-synaptic alpha-blockers such as prazosin

Anasthetics, General: enhanced hypertensive effect when beta-blockers given with general anaesthetics

Anasthetics, Local: propranolol increases risk of bupivacaine toxicity

Analgesics: hypertensive effect of beta-blockers antagonised by NSAIDs; plasma concentration of esmolol possibly increased by morphine

Angiotensin-II Receptor Antagonists: enhanced hypertensive effect when beta-blockers given with angiotensin-II receptor antagonists

Anti-arrhythmics: increased myocardial depression 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 bradycardia, AV block and myocardial depression when beta-blockers given with amiodarone; increased risk of myocardial depression and bradycardia when beta-blockers given with flecainide; propranolol increases risk of lidocaine (lignocaine) toxicity; plasma concentration of metoprolol and propranolol increased by propafenone

Antibacterials: increased risk of ventricular arrhythmias when sotalol given with efomoxiflacin—avoid con-
**Appendix 1: Interactions**

### Beta-blockers
- **Antibacterials** (continued)
  - comitut; metabolism of bisoprolol 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; enhanced hypotensive effect 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 nizatidine—avoid concomitant use
- **Antimalarials**: avoidance of metoprolol and sotalol advised by manufacturer of arteether/luifenarfine; increased risk of bradycardia when beta-blockers given with mefloquine
- **Antimuscarinics**: increased risk of ventricular arrhythmias when sotalol given with tolterodine
- **Antipsychotics**: plasma concentration of both drugs may increase 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, perphenazine, pipamizide, sertindole or sulpiride; enhanced hypotensive effect when beta-blockers given with phenothiazines
- **Antivirals**: avoidance of metoprolol for heart failure advised by manufacturer of tipranavir
- **Anxiolytics and Hypnotics**: enhanced hypotensive effect when beta-blockers given with anxiolytics and hypnotics
- **Atomoxetine**: increased risk of ventricular arrhythmias when sotalol given with atomoxetine
- **Barbiturates**: plasma concentration of metoprolol and timolol reduced by barbiturates; plasma concentration of propranolol possibly reduced by barbiturates
- **Calcium-channel Blockers**: enhanced hypotensive effect when beta-blockers given with calcium-channel blockers; possible severe hypotension and heart failure when beta-blockers given with nifedipine; increased risk of AV block and bradycardia when beta-blockers given with diltiazem; asystole, severe hypotension and heart failure when beta-blockers given with verapamil (see p. 140)
- **Cardiac Glycosides**: increased risk of AV block and bradycardia when beta-blockers given with cardiac glycosides
- **Ciclosporin**: carvedilol increases plasma concentration of ciclosporin
- **Clonidine**: increased risk of withdrawal hypertension when beta-blockers given with clonidine (withdraw beta-blockers several days before slowly withdrawing clonidine)
- **Corticosteroids**: hypotensive effect of beta-blockers antagonised by corticosteroids
- **Diazoxide**: enhanced hypotensive effect when beta-blockers given with diazoxide
- **Diuretics**: enhanced hypotensive effect when beta-blockers given with diuretics; risk of ventricular arrhythmias with sotalol increased by hypokalaemia caused by loop diuretics or thiazides and related diuretics

### Beta-blockers (continued)
- Dopaminergics: enhanced hypotensive effect when beta-blockers given with levodopa
- Ergot Alkaloids: increased peripheral vasoconstriction when beta-blockers given with ergotamine and methysergide
- 5HT₃ Agonists: increased risk of ventricular arrhythmias when sotalol given with dolasetron—avoid concomitant use
- Ivabradine: increased risk of ventricular arrhythmias when sotalol given with ivabradine
- Methylxypa: enhanced hypotensive effect when beta-blockers given with methylxypa
- Moxisylyte (thymoxamine): possible severe postural hypotension when beta-blockers given with moxisylyte
- Moxonidine: enhanced hypotensive effect when beta-blockers given with moxonidine
- Muscle Relaxants: propranolol enhances effects of muscle relaxants; enhanced hypotensive effect when beta-blockers given with baclofen; possible enhanced hypotensive effect and bradycardia when beta-blockers given with tizanidine
- Nitrates: enhanced hypotensive effect when beta-blockers given 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 given with pilocarpine
- Prostaglandins: enhanced hypotensive effect when beta-blockers given with alprostadil
- **Sympathomimetics**: increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with adrenaline (epinephrine), also reponse to adrenaline (epinephrine) may be reduced; increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with dobutamine; possible increased risk of severe hypertension and bradycardia when non-cardioselective beta-blockers given with noradrenaline (norepinephrine)
- Thyroid Hormones: metabolism of propranolol accelerated by levothyroxine (thyroxine)
- Ucer-healing Drugs: plasma concentration of labetalol, metoprolol and propranolol increased by cimetidine
- Vasodilator Antihypertensives: enhanced hypotensive effect when beta-blockers given with hydralazine, minoxidil or sodium nitroprusside

### Betahistin
- 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 egemfbrzilo—avoid concomitant use
- Bezafrate see Fibrates
- Bicalutamide
- Anticoagulants: bicalutamide possibly enhances anticoagulant effect of coumarins
- Biguanides see Antidiabetics
Appendix 1: Interactions

Bile Acid Sequestrants see Colesevelam, Colestipol, and Colestyramine
Bile Acids see Ursodeoxycholic Acid
Bisoprolol see Beta-blockers
Bisphosphonates
Analgesics: bioavailability of tiludronic acid increased by indomethacin
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 (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Cytotoxics: increased pulmonary toxicity when bleomycin given with cisplatin
Bortezomib
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
Antifungals: plasma concentration of bortezomib increased by ketoconazole
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Bosantan
Antibacterials: plasma concentration of bosantan reduced by efavirenz—avoid concomitant use
Anticoagulants: manufacturer of bosantan recommends monitoring anticoagulant effect of coumarins
Antidiabetics: increased risk of hepatotoxicity when bosantan given with glibenclamide—avoid concomitant use
Antifungals: plasma concentration of bosantan possibly increased by rifampicin—avoid concomitant use
Budesonide see Corticosteroids
Bumetanide see Diuretics
Bupivacaine
Anti-arrhythmics: increased myocardial depression when bupivacaine given with anti-arrhythmics
Beta-blockers: increased risk of bupivacaine toxicity when given with propranolol
Buprenorphine see Opioid Analgesics
Bupropion
Note. Bupropion should be administered with extreme caution to patients receiving other medication known to lower the seizure threshold—see CSM advice BNF section 4.10 and Cautions, Contra-indications and Side-effects of individual drugs
Antidepressants: bupropion possibly increases plasma concentration of citalopram; manufacturer of bupropion advises avoid for 2 weeks after stopping MAOIs; manufacturer of bupropion advises avoid concomitant use with moclobemide
Antiepileptics: plasma concentration of bupropion reduced by carbamazepine and phenytoin; metabolism of bupropion inhibited by valproate
Antivirals: plasma concentration of bupropion increased or decreased by ritonavir
Dopaminergics: increased risk of side-effects when bupropion given with amantadine or levodopa
Buspirone see Anxiolytics and Hypnotics
Busulfan
Analgesics: metabolism of intravenous busulfan possibly inhibited by paracetamol (manufacturer of intravenous busulfan advises caution within 72 hours of paracetamol)
Antibacterials: plasma concentration of busulfan increased by metronidazole (increased risk of toxicity)
Antiepileptics: cytotoxics possibly reduce absorption of phenytoin; plasma concentration of busulfan possibly reduced by phenytoin
Antifungals: metabolism of busulfan inhibited by itraconazole (increased risk of toxicity)
Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets
Cytotoxics: increased risk of hepatotoxicity when busulfan given with tioguanine
Butobarbital see Barbiturates
Butyrophenones see Antipsychotics
Cabergoline
Antibacterials: plasma concentration of cabergoline increased by erythromycin (increased risk of toxicity)
Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of cabergoline antagonised by antipsychotics
Dopemeridine: hypoprolactinaemic effect of cabergoline possibly antagonised by domperidone
Bromocriptine (continued)
Antipsychotics: hypoprolactinaemic and antiparkinsonian effects of bromocriptine antagonised by antipsychotics
Dopemeridine: hypoprolactinaemic effect of bromocriptine possibly antagonised by domperidone
Hormone Antagonists: plasma concentration of bromocriptine increased by octreotide
Memantine: effects of dopaminergics possibly enhanced by memantine
Methyl dopa: antiparkinsonian effect of dopamine antagonised by methyl dopa
Metoclopramide: hypoprolactinaemic effect of bromocriptine antagonised by metoclopramide
Sympathomimetics: risk of toxicity when bromocriptine given with somethethperine
Buclizine see Antihistamines
Bromocriptine
Antipsychotics: avoid concomitant use of cytotoxics
Antidepressants: manufacturer of bromocriptine advises caution within 72 hours of concomitant use
Antibacterials: plasma concentration of bromocriptine possibly increased by ketoconazole—avoid concomitant use
Anticoagulants: manufacturer of bromocriptine recom-
Calcium Salts

Note. see also Antacids

Antibacterials: calcium salts reduce absorption of ciprofloxacin and tetracycline

Bisphosphonates: calcium salts reduce absorption of bisphosphonates

Cardiac Glycosides: large intravenous doses of calcium salts can precipitate arrhythmias when given with cardiac glycosides

Corticosteroids: absorption of calcium salts reduced by corticosteroids

Diuretics: increased risk of hypercalcaemia when calcium salts given with thiazides and related diuretics

Fluorides: calcium salts reduce absorption of fluorides

Iron: calcium salts reduce absorption of oral iron

Thyroid Hormones: calcium salts reduce absorption of levothyroxine (thyroxine)

Calcium-channel Blockers

Note. Dihydropyridine calcium-channel blockers include amlodipine, felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, and nimodipine

ACE Inhibitors: enhanced hypotensive effect when calcium-channel blockers given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypotensive effect when calcium-channel blockers given with adrenergic neurone blockers

Alcohol: enhanced hypotensive effect when calcium-channel blockers given with alcohol; verapamil possibly increases plasma concentration of alcohol

Aldesleukin: enhanced hypotensive effect when calcium-channel blockers given with aldesleukin

• Alpha-blockers: enhanced hypotensive effect when calcium-channel blockers 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 calcium-channel blockers given with general anaesthetics or isoﬂurane; hypotensive effect of verapamil enhanced by general anaesthetics (also AV delay)

Analgesics: hypotensive effect of calcium-channel blockers antagonised by NSAIDs; diltiazem inhibits metabolism of alfentanil (risk of prolonged or delayed respiratory depression)

Angiotensin-II Receptor Antagonists: enhanced hypotensive effect when calcium-channel blockers given with angiotensin-II receptor antagonists

• Anti-arrhythmics: increased risk of bradycardia, AV block and myocardial depression when diltiazem or verapamil given with amiodarone; increased risk of myocardial depression and asystole when verapamil given with disopyramide or flecainide

• Antibacterials: metabolism of verapamil possibly inhibited by erythromycin and rifampicin (increased risk of toxicity); metabolism of felodipine possibly inhibited by erythromycin (increased plasma concentration); manufacturer of lercanidipine and nifedipine advises avoid concomitant use with erythromycin; metabolism of diltiazem increased by midazolam; plasma concentration of nifedipine increased by midazolam

Antifungals: metabolism of dihydropyridines possibly inhibited by itraconazole and ketoconazole (increased plasma concentration); metabolism of felodipine inhibited by 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 micafungin

Antimalarials: possible increased risk of bradycardia when calcium-channel blockers given with mefloquine

Antidepressants: 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; plasma concentration of diltiazem increased by atazanavir (reduce dose of diltiazem); plasma concentration of diltiazem reduced by efavirenz; manufacturer of lercanidipine advises avoid concomitant use with ritonavir; plasma concentration of calcium-channel blockers possibly increased by ritonavir

Antiepileptics: effects of dihydropyridines, nicardipine and nifedipine possibly reduced by phenytoin; effects of felodipine, isradipine and verapamil reduced by phenytoin; diltiazem increases plasma concentration of phenytoin but also effect of diltiazem reduced; effects of felodipine and isradipine reduced by primidone; effects of dihydropyridines, diltiazem and verapamil probably reduced by primidone

Antifungal inotropics: possible increased risk of AV block and myocardial depression when diltiazem given with barbiturates (see p. 140); possible severe hypotension and heart failure when verapamil given with beta-blockers (see p. 140); possible severe hypotension and heart failure when nifedipine given with beta-blockers

Cardiac Glycosides: nifedipine possibly increases plasma concentration of digoxin; diltiazem, lercanidipine and nicardipine increase plasma concentration of digoxin; verapamil increases plasma concentration of digoxin; diltiazem and verapamil increase plasma concentration of imipramine; enhanced hypotensive effect when calcium-channel blockers given with MAOIs; plasma concentration of amiodipine possibly reduced by St John’s wort; diltiazem and verapamil possibly increase plasma concentration of tricyclics

Antidiabetics: glucose tolerance occasionally impaired when nifedipine given with insulin

• Antiepileptics: effects of dihydropyridines, nicardipine and nifedipine probably reduced by carbamazepine; effects of felodipine and isradipine probably reduced by carbamazepine; diltiazem and verapamil enhance effects of carbamazepine; effects of dihydropyridines, nicardipine and nifedipine probably reduced by phenytoin; effects of felodipine, isradipine and verapamil reduced by phenytoin; diltiazem increases plasma concentration of phenytoin but also effect of diltiazem reduced; effects of felodipine and isradipine reduced by primidone; effects of dihydropyridines, diltiazem and verapamil probably reduced by primidone

Antifungal inotropics: possible increased risk of AV block and myocardial depression when diltiazem given with barbiturates (see p. 140); possible severe hypotension and heart failure when verapamil given with beta-blockers (see p. 140); possible severe hypotension and heart failure when nifedipine given with beta-blockers

Calcium-channel Blockers

Antidepressants (continued)
Appendix 1: Interactions

Calcium-channel Blockers

- Cardiac Glycosides (continued)
  - 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
- Clonidine: enhanced hypotensive effect when calcium-channel blockers given with clonidine
- Corticosteroids: hypotensive effect of calcium-channel blockers antagonised by corticosteroids
- Cytotoxics: 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, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil increased by grapefruit juice
- Hormone Antagonists: diltiazem and verapamil increase plasma concentration of dutasteride
- Ivabradine: diltiazem and verapamil increase plasma concentration of ivabradine—avoid concomitant use
- Lipid-regulating Drugs: diltiazem increases plasma concentration of atorvastatin; 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 parenteral magnesium in pre-eclampsia
- Methyldopa: enhanced hypotensive effect when calcium-channel blockers given with methyldopa
- Moxisylyte (thymoxamine): enhanced hypotensive effect when calcium-channel blockers given with moxisylyte
- Moxonidine: enhanced hypotensive effect when calcium-channel blockers given with moxonidine
- Muscle Relaxants: verapamil enhances effects of non-depolarising muscle relaxants and suxamethonium; enhanced hypotensive effect when calcium-channel blockers given with baclofen or tizanidine; hypotension, myocardial depression, and hyperkalaemia when verapamil given with intravenous dantrolene; risk of arrhythmias when diltiazem given with intravenous dantrolene; nifedipine enhances effects of non-depolarising muscle relaxants
- Nitrates: enhanced hypotensive effect when calcium-channel blockers given with nitrates
- Oestrogens: hypotensive effect of calcium-channel blockers antagonised by oestrogens
- Prostaglandins: enhanced hypotensive effect when calcium-channel blockers given with alprostadil
- Sildenafil: enhanced hypotensive effect when amlopidine given with sildenafil
- Sirolimus: diltiazem increases plasma concentration of sirolimus; plasma concentration of both drugs increased when verapamil given with sirolimus

Calcium-channel Blockers (continued)

- 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)
- Ulcer-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
- Carprofen
  - 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
  - Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
  - Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752
- Captoril 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 clarithromycin and erythromycin; plasma concentration of carbamazepine reduced by rifabutin; carbamazepine accelerates metabolism of doxycycline (reduced effect); plasma concentration of carbamazepine increased by isoniazid (also possibly increased isoniazid hepatotoxicity); carbamazepine reduces plasma concentration of telithromycin (avoid during and for 2 weeks after carbamazepine)
  - Anticoagulants: carbamazepine accelerates metabolism of warfarin (reduced anticoagulant effect)
  - Antidepressants: plasma concentration of carbamazepine increased by fluoxetine 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 antidepressants possibly antagonised by MAOIs and tricyclic antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSNRIs and tricyclics (convulsive threshold lowered); avoid concomitant use of anti-epileptics with St John’s wort; carbamazepine accelerates metabolism of tricyclics (reduced plasma concentration and reduced effect)
Carbamazepine (continued)

- 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); plasma concentration of carbamazepine increased by ostitripentol; 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.

- Anti-fungals: plasma concentration of carbamazepine possibly increased by fluconazole, ketoconazole and miconazole; 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 anti-epileptics antagonised by mefloquine.

- Antipsychotics: anticonvulsant effect of carbamazepine antagonised by antipsychotics (convulsive threshold lowered); carbamazepine accelerates metabolism of haloperidol, olanzapine, quetiapine, risperidone and sertindole (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.

- Anti-arrhythmics: plasma concentration of darunavir, fosamprenavir, lopinavir, nelfinavir, saquinavir and tipranavir; plasma concentration of both drugs reduced when carbamazepine given with efavirenz; avoidance of carbamazepine advised by manufacturer of etravirine; carbamazepine possibly reduces plasma concentration of indinavir, also plasma concentration of carbamazepine possibly increased; plasma concentration of carbamazepine possibly increased by ritonavir.

- Anxiolytics and Hypnotics: carbamazepine often reduces plasma concentration of clonazepam; 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 probably reduces effects of dihydropyridines, nicardipine and nifedipine; effects of carbamazepine enhanced by diltiazem and verapamil.

Carbamazepine (continued)

- Cardiac Glycosides: carbamazepine accelerates metabolism of digoxin (reduced effect).

- Ciclosporin: carbamazepine accelerates metabolism of ciclosporin (reduced plasma concentration).

- Corticosteroids: carbamazepine accelerates metabolism of corticosteroids (reduced effect).

- Cytotoxics: carbamazepine reduces plasma concentration of etoposide and ifosfamide—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 eplerenone—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).

- SHT2 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. 478).

- Progestogens: carbamazepine accelerates metabolism of progestogens (reduced contraceptive effect—see p. 478).

- Retinoids: carbamazepine accelerates metabolism of retinoids 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 tobilone (reduced plasma concentration).

- Ulcer-Healing Drugs: metabolism of carbamazepine possibly reduced by cimetidine.

- Vitamin D: increased requirements for vitamin D.

- Carbenepens: see Doripenem, Ertapenem, Imipenem with Clastatin, and Meropenem.

- Carbolic Anhydride Inhibitors: see Diuretics.

- Carboplatin: see Platinum Compounds.

- Carboprost: see Prostaglandins.

- Cardiac Glycosides

- ACE Inhibitors: plasma concentration of digoxin possibly increased by captopril.

- Alpha-blockers: plasma concentration of digoxin increased by prazosin.

- Aminosalicylates: absorption of digoxin possibly reduced by sulfasalazine.

- 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 lidamidose and propafenone (halve dose of digoxin).

- Antibacterials: plasma concentration of digoxin possibly increased by gentamicin, telithromycin and trimethoprim; absorption of digoxin reduced by
Cardiac Glycosides
Antibacterials (continued)

Neomycin: plasma concentration of digoxin possibly reduced by rifampicin; plasma concentration of digoxin increased by macrolides (increased risk of toxicity); metabolism of digoxin 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

anphoter cin: plasma concentration of digoxin increased by etaconazole

Antimalarials: plasma concentration of digoxin possibly increased by chloroquine and hydroxychloroquine; possible increased risk of bradycardia when digoxin given with melfoquine; plasma concentration of digoxin increased by quinine

Antimuscarinics: 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 enalapril; plasma concentration of digoxin increased by 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 cytoxotics

Diuretics: increased cardiac toxicity with cardiac glycosides if hypokalaemia occurs with

acetazolamide, diuretics or dihydropyridines; plasma concentration of digoxin possibly increased by atorvastatin

Muscle Relaxants: risk of ventricular arrhythmias when cardiac glycosides given with aminoglycosides; possible increased risk of bradycardia when cardiac glycosides given with tizanidine

Penicillamine: plasma concentration of digoxin possibly reduced by penicillamine

Sympathomimetics, Beta₂: plasma concentration of digoxin possibly reduced by salbutamol

Cardiac Glycosides (continued)

Ulc er-healing Drugs: plasma concentration of digoxin possibly slightly increased by proton pump inhibitors; absorption of cardiac glycosides possibly reduced by sucralfate

Carisoprodol see Muscle Relaxants

Carmustine

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

Ulc er-healing Drugs: myelosuppressive effects of carmustine possibly enhanced by cimetidine

Catechol see Beta-blockers

Carvedilol see Beta-blockers

Caspofungin

Antibacterials: plasma concentration of caspofungin initially increased and then reduced by rifampicin (consider increasing dose of caspofungin)

Antiepileptics: plasma concentration of caspofungin possibly reduced by carbamazepine and phenytoin—consider increasing dose of caspofungin

Antivirals: plasma concentration of caspofungin possibly reduced by efavirenz and nevirapine—consider increasing dose of caspofungin

Ciclosporin: plasma concentration of caspofungin increased by ciclosporin (manufacturer of caspofungin recommends monitoring liver enzymes)

Corticosteroids: plasma concentration of caspofungin possibly reduced by dexamethasone—consider increasing dose of caspofungin

Tacrolimus: caspofungin reduces plasma concentration of tacrolimus

Cefaclor see Cephalosporins

Cefadroxil see Cephalosporins

Cefalexin see Cephalosporins

Cefixime see Cefalosporins

Cefotaxime see Cephalosporins

Cefuroxime see Cephalosporins

Celecoxib see NSAIDs

Celepitol see Beta-blockers

Cephaparin see Cephalosporins

Antacids: absorption of cefaclor and cefpodoxime reduced by antacids

Antibacterials: possible increased risk of nephrotoxicity when cephalosporins given with aminoglycosides

Anticoagulants: cefaparin reduces coagulation effect of coumarins

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)

Probenecid: excretion of cephalosporins reduced by probenecid (increased plasma concentration)

Ulc er-healing Drugs: absorption of cefpodoxime reduced by histamine H₂-antagonists

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Cetirizine see Antihistamines

Chloral see Anxiolytics and Hypnotics

Chloramphenicol

Antibacterials: metabolism of chloramphenicol accelerated by rifampicin (reduced plasma concentration)

Anticoagulants: chloramphenicol enhances anticoagulant effect of coumarins

Antidiabetics: chloramphenicol enhances effects of sulphonylureas

Antiepileptics: chloramphenicol increases plasma concentration of phenytoin (increased risk of toxicity); metabolism of chloramphenicol accelerated by primidone (reduced plasma concentration)
Analgesics: increased risk of nephrotoxicity when
Antibacterials: increased risk of ventricular arrhythmias
Anti-arrhythmics: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with amiodarone—avoid concomitant use
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p 478)
Tacrolimus: chlorophenicol possibility increases plasma concentration of tacrolimus
Vaccines: antibacterials inactivate oral typhoid vaccine—see p 752
Chlordiazepoxide see Anxiolytics and Hypnotics
Chloroquine and Hydroxychloroquine
Adsorbents: 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
Antibacterials: increased risk of ventricular arrhythmias when chloroquine and hydroxychloroquine given with amiodarone—avoid concomitant use
Antimuscarinics: avoidance of ciclosporin advised by manufacturer of azathioprine/toxicity; absorption of chloroquine possibly increased by clindamycin and nitrofurantoin (increased risk of toxicity)
Cardiac Glycosides: chloroquine and hydroxychloroquine possibly increase plasma concentration of digoxin
Ciclosporin: chloroquine and hydroxychloroquine increase plasma concentration of ciclosporin
Lanthanum: absorption of chloroquine and hydroxychloroquine possibly reduced by lanthanum (give at least 2 hours apart)
Laronidase: avoidance of antimalarials by manufacturer of laronidase advises avoid concomitant use
Parasympathomimetics: chloroquine and hydroxychloroquine have potential to increase symptoms of myasthenia gravis and thus diminish effect of ondansetron and pyridostigmine
Ulcerc-stomach Drugs: metabolism of chloroquine and hydroxychloroquine inhibited by cimetidine (increased plasma concentration)
Vaccines: antimalarials inactivate oral typhoid vaccine—see p 752
Chlorothiazide see Diuretics
Chlorphenamine (chlorpheniramine) see Antihistamines
Chlorpromazine see Antipsychotics
Chlorpropanide see Antidiabetics
Chlorotardione see Diuretics
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
Ciclosporin
Analgesics (continued) increases plasma concentration of diclofenac (half dose of diclofenac)
Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when ciclosporin given with angiotensin-II receptor antagonists
Anti-arrhythmics: 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 sulfadiazine; plasma concentration of ciclosporin possibly increased by chloramphenicol, doxycycline and telithromycin; increased risk of nephrotoxicity when ciclosporin given withaminoglycosides, polymyxins, quinolones, sulphonamides or vancomycin; increased risk of myopathy when ciclosporin given with daptomycin (preferably avoid concomitant use); metabolism of ciclosporin possibly inhibited by macrolides (increased plasma concentration); plasma concentration of ciclosporin increased by saquinavir/daspatrarin; increased risk of nephrotoxicity when ciclosporin given with trimethoprim, 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 hypoglycaemic 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, itracazolae, ketoconazole, posaconazole and voriconazole (increased plasma concentration); metabolism of ciclosporin possibly inhibited by saquinavir/daspatrarin; 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 ciclosporin possibly reduced by griseofulvin and terbinfine; plasma concentration of ciclosporin possibly increased by micafungin
Antimalarials: plasma concentration of ciclosporin increased by chloroquine and hydroxychloroquine (increased risk of toxicity)
Antimuscarnicas: avoidance of ciclosporin advised by manufacturer of darifenacin
Antivirals: increased risk of nephrotoxicity when ciclosporin given with aciclovir; plasma concentration of ciclosporin possibly increased by natazanavir, nelfinavir and ritonavir; plasma concentration of ciclosporin possibly reduced by efavirenz; 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 ursooxycholic acid
Bosentan: ciclosporin increases plasma concentration of bosentan (also plasma concentration of ciclosporin reduced—avoid concomitant use)
Calcium-channel Blockers: combination of ciclosporin with lercanidipine may increase plasma concentra-
Appendix 1: Interactions

Ciclosporin
- Calcium-channel Blockers (continued)
  - tination of either drug (or both)—avoid concomitant use; plasma concentration of ciclosporin increased by 
    - diltiazem, nicardipine and verapamil; ciclosporin possibly increases plasma concentration of nifedipine (increased risk of toxicity including gingival hyperplasia)
- Cardiac Glycosides: ciclosporin increases plasma concentration of digoxin (increased risk of toxicity)
- Colchicine: possible increased risk of nephrotoxicity and myotoxicity when ciclosporin given with colchicine (increased plasma concentration of ciclosporin)
- Corticosteroids: plasma concentration of ciclosporin increased by high-dose methylprednisolone (risk of convulsions); ciclosporin increases plasma concentration of prednisolone
- Cytotoxics: increased risk of nephrotoxicity 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); plasma concentration of ciclosporin reduced by lanreotide and octreotide
- Lipid-regulating Drugs: increased risk of renal impairment when ciclosporin given with bezafibrate or fenofibrate; increased risk of myopathy when ciclosporin given with rosuvastatin (avoid concomitant use); plasma concentration of both drugs may increase when ciclosporin given with ezetimibe; increased risk of myopathy when ciclosporin given with statins
- Mannitol: possible increased risk of nephrotoxicity when ciclosporin given with mannitol
- Metoclopramide: plasma concentration of ciclosporin increased by metoclopramide
- Modafinil: plasma concentration of ciclosporin reduced by modafinil
- Oestrogens: plasma concentration of ciclosporin possibly increased by oestrogens
- Orlistat: absorption of ciclosporin possibly reduced by orlistat
- Potassium Salts: increased risk of hyperkalaemia when ciclosporin given with potassium salts
- Progestogens: metabolism of ciclosporin inhibited by progestogens (increased plasma concentration)
- Sevelamer: plasma concentration of ciclosporin possibly reduced by sevelamer
- Sirolimus: ciclosporin increases plasma concentration of sirolimus
- Sitaxentan: ciclosporin increases plasma concentration of sitaxentan—avoid concomitant use
- Sulfinpyrazone: plasma concentration of ciclosporin reduced by sulfinpyrazone
- Tacrolimus: plasma concentration of ciclosporin increased by tacrolimus (increased risk of nephrotoxicity)—avoid concomitant use
- Ulcer-healing Drugs: plasma concentration of ciclosporin possibly increased by cimetidine; plasma concentration of ciclosporin possibly affected by omeprazole

Ciclosporin
- Ulcer-healing Drugs (continued)
  - concentration of ciclosporin possibly affected by omeprazole

Cidofovir
- Antivirals: combination of cidofovir with tenofovir may increase plasma concentration of either drug (or both)

Cilazapril see ACE Inhibitors

Cilostazol
- Anagrelide: avoidance of cilostazol advised by manufacturer of anagrelide
- Analgesics: manufacturer of cilostazol recommends dose of concomitant aspirin should not exceed 80 mg daily
- Antibacterials: plasma concentration of cilostazol increased by erythromycin (also plasma concentration of erythromycin reduced)—avoid concomitant use
- Antifungals: plasma concentration of cilostazol possibly increased by ketoconazole—avoid concomitant use
- Antivirals: plasma concentration of cilostazol possibly increased by osomprenavir, indinavir, lopinavir, nelfinavir, ritonavir and saquinavir—avoid concomitant use
- Calcium-channel Blockers: plasma concentration of cilostazol increased by diltiazem—avoid concomitant use
- Ulcer-healing Drugs: plasma concentration of cilostazol possibly increased by cimetidine and lansoprazole—avoid concomitant use; plasma concentration of cilostazol increased by omeprazole (risk of toxicity)—avoid concomitant use
- Cimetidine see Histamine H2-antagonists

Cinacalcet
- Antifungals: metabolism of cinacalcet inhibited by ketoconazole (increased plasma concentration)
- Tobacco: metabolism of cinacalcet increased by tobacco smoking (reduced plasma concentration)

Cinnarizine see Antihistamines

Ciprofibrate see Fibrates

Ciprofloxacin see Quinolones

Cisatracurium see Non-depolarising Muscle Relaxants

Citalopram see Antidepressants, SSRI

Clonazepam see Antihistamines

Clindamycin
- Muscle Relaxants: clindamycin 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. 478)

Parasympathomimetics: clindamycin antagonises effects of neostigmine and pyridostigmine

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Clobazam see Anxiolytics and Hypnotics

Clofibric acid see Fibrates

Clofibrate see Fibrates

Ciclosporin
- Ulcer-healing Drugs (continued)
  - concentration of ciclosporin possibly affected by omeprazole
Anticoagulants: manufacturer of clopidogrel advises concomitant use with coumarins or phenindione; increased risk of bleeding when clopidogrel given with dipyridamole.

Ciclosporin: possible increased risk of nephrotoxicity and myotoxicity when ciclosporin given with ciclosporin (increased plasma concentration of ciclosporin).

Lipid-regulating Drugs: possible increased risk of myopathy when ciclosporin given with statins.

Co-anticoagulants: colestyramine may enhance or reduce anticoagulant effect of coumarins and phenindione.

Antidiabetics: colestyramine possibly enhances hypoglycaemic effect of acarbose.

Antiepileptics: colestyramine possibly enhances hypo-glycaemic effect of acarbose.

Antibacterials: colestyramine reduces absorption of mycophenolate.

Diuretics: colestyramine reduces absorption of thiacyclics and related diuretics (give at least 2 hours apart).

Anticoagulants: colestyramine may enhance or reduce anticoagulant effect of coumarins and phenindione.

Antidiabetics: colestyramine possibly enhances hypoglycaemic effect of acarbose.

Antiepileptics: colestyramine possibly enhances hypo-glycaemic effect of acarbose.

Antibacterials: colestyramine reduces absorption of mycophenolate.

Diuretics: colestyramine reduces absorption of thiacyclics and related diuretics (give at least 2 hours apart).

Leftunomide: colestyramine significantly decreases effect of leftunomide (enhanced elimination)—avoid unless drug elimination desired.

Ralofoxene: colestyramine reduces absorption of ralofoxene (manufacturer of ralofoxene advises avoid concurrent administration).

Thyroid Hormones: colestyramine reduces absorption of thyroid hormones.

Colistin see Polymyxins

Contraceptives, oral see Oestrogens and Progestogens

Corticosteroids

Note. Interactions do not generally apply to corticosteroids used for topical action (including inhalation) unless specified.

ACE Inhibitors: corticosteroids antagonise hypotensive effect of ACE inhibitors.

Adrenergic Neurone Blockers: corticosteroids antagonise hypotensive effect of adrenergic neurone blockers.

Alpha-blockers: corticosteroids antagonise hypotensive effect of alpha-blockers.

Codeine see Opioid Analgesics

Co-fluampicil see Penicillins

Colchicine

- Antiinfective: increased risk of colchicine toxicity when given with clarithromycin or erythromycin.
- Ciclosporin: possible increased risk of nephrotoxicity and myotoxicity when ciclosporin given with ciclosporin (increased plasma concentration of ciclosporin).
- Lipid-regulating Drugs: possible increased risk of myopathy when ciclosporin given with statins.

Colestevalem Note. Other drugs should be taken at least 1 hour before or 4 hours after colesveleam to reduce possible interference with absorption.

Colestipol Note. Other drugs should be taken at least 1 hour before or 4-6 hours after colestipol to reduce possible interference with absorption.

Antibacterials: colestipol possibly reduces absorption of bile acids.

Cardiac Glycosides: colestipol possibly reduces absorption of cardiac glycosides.

Diuretics: colestipol reduces absorption of thiacyclics and related diuretics (give at least 2 hours apart).

Thyroid Hormones: colestipol reduces absorption of thyroid hormones.

Colestyrnam Note. Other drugs should be taken at least 1 hour before or 4-6 hours after colestyramine to reduce possible interference with absorption.

Analgesics: colestyramine increases the excretion of meloxicam; colestyramine reduces absorption of paracetamol.

Antibacterials: colestyramine possibly reduces absorption of tetracycline; colestyramine antagonises effects of oral vancomycin.

Anticoagulants: colestyramine may enhance or reduce anticoagulant effect of coumarins and phenindione.

Antidiabetics: colestyramine possibly enhances hypoglycaemic effect of acarbose.

Antiepileptics: colestyramine possibly enhances hypo-glycaemic effect of acarbose.

Antibacterials: colestyramine reduces absorption of mycophenolate.

Diuretics: colestyramine reduces absorption of thiacyclics and related diuretics (give at least 2 hours apart).

Leftunomide: colestyramine significantly decreases effect of leftunomide (enhanced elimination)—avoid unless drug elimination desired.

Ralofoxene: colestyramine reduces absorption of ralofoxene (manufacturer of ralofoxene advises avoid concurrent administration).

Thyroid Hormones: colestyramine reduces absorption of thyroid hormones.

Colistin see Polymyxins

Contraceptives, oral see Oestrogens and Progestogens

Corticosteroids

Note. Interactions do not generally apply to corticosteroids used for topical action (including inhalation) unless specified.
Appendix 1: Interactions

Corticosteroids (continued)

Analgesics: increased risk of gastrointestinal bleeding and ulceration when corticosteroids given with NSAIDs; increased risk of gastrointestinal bleeding and ulceration when corticosteroids given with aspirin, also corticosteroids reduce plasma concentration of salicylate

Angiotensin-II Receptor Antagonists: corticosteroids antagonise hypotensive effect of angiotensin-II receptor antagonists

Antacids: absorption of deflazacort reduced by antacids

- Antibacterials: plasma concentration of methylprednisolone possibly increased by clarithromycin; metabolism of corticosteroids possibly inhibited by erythromycin; metabolism of methylprednisolone inhibited by ketoconazole; corticosteroids possibly reduce plasma concentration of isoniazid; metabolism of corticosteroids accelerated by rifampicin (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

Antifungals: metabolism of corticosteroids possibly 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 itraconazole; metabolism of methylprednisolone possibly inhibited by itraconazole; increased risk of hypokalaemia when corticosteroids given with sodium nitroprusside—consider increasing dose of caspofungin

Antivirals: dexamethasone possibly reduces plasma concentration of caspofungin and sodium nitroprusside; increased risk of hypokalaemia when corticosteroids given with anticoagulants

Antihistamines: metabolism of corticosteroids possibly accelerated by ritonavir; plasma concentration of inhaled and oral budesonide increased by ritonavir; reduced effect of moxonidine after mifepristone

Mifepristone: effect of corticosteroids (including prednisolone) may be reduced for 3–4 days after mifepristone

Antietheptics: metabolism of corticosteroids possibly inhibited by itraconazole; dexamethasone and prednisolone possibly increased by ketoconazole; increased risk of hypokalaemia when corticosteroids given with calcium salicylates

Calcium Salts: corticosteroids reduce absorption of calcium salts

Calcium-channel Blockers: corticosteroids antagonise hypotensive effect of calcium-channel blockers

Cardiac Glycosides: increased risk of hypokalaemia when corticosteroids given with cardiac glycosides

Ciclosporin: high-dose methylprednisolone increases plasma concentration of ciclosporin (risk of convulsions); plasma concentration of prednisolone increased by ciclosporin

Clonidine: corticosteroids antagonise hypotensive effect of clonidine

Cytotoxics: increased risk of haematological toxicity when corticosteroids given with methotrexate

Diazoxide: corticosteroids antagonise hypotensive effect of diazoxide

Diuretics: corticosteroids antagonise diuretic effect of diuretics; increased risk of hypokalaemia when corticosteroids given with anticoagulants

Diuretics (continued)
corticosteroids given with acetazolamide, loop diuretics or thiazides and related diuretics

Methyldopa: corticosteroids antagonise hypotensive effect of methyldopa

Milepristone: effect of corticosteroids (including inhaled corticosteroids) may be reduced for 3–4 days after milepristone

Moxonidine: corticosteroids antagonise hypotensive effect of moxonidine

Muscle Relaxants: corticosteroids possibly antagonise effects of pancuronium and vecuronium

Nitrates: corticosteroids antagonise hypotensive effect of nitrates

Oestrogens: plasma concentration of corticosteroids increased by oral contraceptives containing oestrogen

Sodium Benzoate: corticosteroids possibly reduce effects of sodium benzoate

Sodium Phenytoinate: corticosteroids possibly reduce effects of sodium phenytoinate

Somatropin: corticosteroids may inhibit growth-promoting effect of somatropin

Symptomimetics: metabolism of dexamethasone accelerated by ephedrine

Theophylline: increased risk of hypokalaemia when corticosteroids given with theophylline

Vaccines: high doses of corticosteroids impair immune response to vaccines, avoid concomitant use with live vaccines (see p. 725)

Vasodilator Antihypertensives: corticosteroids antagonise hypotensive effect of hydralazine, minoxidil and sodium nitroprusside

Cortisone see Corticosteroids

Co-trimoxazole see Trimethoprim and Sulfamethoxazole

Coumarins

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 coumarins may be affected by major changes in consumption of alcohol

- Allopurinol: anticoagulant effect of coumarins possibly enhanced by allopurinol

- Anabolic Steroids: anticoagulant effect of coumarins enhanced by anabolic steroids

- Analgesics: anticoagulant effect of coumarins possibly enhanced by NSAIDs; anticoagulant effect of coumarins enhanced by omeprazole (avoid concomitant use); increased risk of haemorrhage when anticoagulants given with intravenous diclofenac (avoid concomitant use, including low-dose heparin); increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant use, including low-dose heparin); anticoagulant effect of coumarins enhanced by tramadol; increased risk of bleeding when coumarins given with aspirin (due to antiplatelet effect); anticoagulant effect of coumarins possibly enhanced by prolonged regular use of paracetamol

- Anti-arrhythmics: metabolism of coumarins inhibited by amiodarone (enhanced anticoagulant effect); anticoagulant effect of coumarins enhanced by propafenone

- Antibacterials: experience in anticoagulant clinics suggests that INR possibly altered when coumarins are given with enoxacin (given for local action on gut); anticoagulant effect of coumarins possibly enhanced by azithromycin, aztreonam,
Antibacterials (continued)

- Cephalosporins, levofloxacin, tetracyclines, tigecycline and trimethoprim: anticoagulant effect of coumarins enhanced by echloramphenicol, ciprofloxacin, clarithromycin, erythromycin, metronidazole, nalidixic acid, norfloxacin, ofloxacin and sulphonamides; studies have failed to demonstrate an interaction with coumarins, but common experience in anticoagulant clinics is that INR can be altered by a course of broad-spectrum penicillins such as ampicillin; metabolism of coumarins accelerated by rifamycins (reduced anticoagulant effect)

- Antidepressants: anticoagulant effect of warfarin possibly enhanced by venlafaxine; anticoagulant effect of coumarins possibly enhanced by SSRIs; anticoagulant effect of coumarins reduced by St John’s wort (avoid concomitant use); anticoagulant effect of warfarin enhanced by mirtazapine; anticoagulant effect of coumarins may be enhanced or reduced by tricyclics

- Antidiabetics: anticoagulant effect of warfarin possibly enhanced by exenatide; coumarins possibly enhance hypoglycaemic effect of sulphonylureas, also possibly change to anticoagulant effect

- Antiepileptics: metabolism of coumarins accelerated by carbamazepine and epimidine (reduced anticoagulant effect); metabolism of coumarins accelerated by phenytoin (possibility of reduced anticoagulant effect, but enhancement also reported); anticoagulant effect of coumarins possibly enhanced by valproate

- Antifungals: anticoagulant effect of coumarins enhanced by fluconazole, itraconazole, ketoconazole and voriconazole; anticoagulant effect of coumarins enhanced by miconazole (miconazole oral gel and possibly vaginal formulations absorbed); anticoagulant effect of coumarins reduced by ergoefolvin

Antimalarials: isolated reports that anticoagulant effect of warfarin may be enhanced by proguanil

- Antivirals: anticoagulant effect of warfarin may be enhanced or reduced by atazanavir, nevirapine and ritonavir; anticoagulant effect of coumarins may be enhanced or reduced by fosamprenavir; anticoagulant effect of coumarins possibly enhanced by ritonavir; anticoagulant effect of warfarin possibly enhanced by saquinavir

Anxiolytics and Hypnotics: anticoagulant effect of coumarins may transiently be enhanced by chloral and triclofos

Aprepitant: anticoagulant effect of warfarin possibly reduced by aprepitant

- Barbiturates: metabolism of coumarins accelerated by barbiturates (reduced anticoagulant effect)

- Bosentan: monitoring anticoagulant effect of coumarins recommended by manufacturer of bosentan

- Clopigogrel: anticoagulant effect of coumarins enhanced due to antiplatelet action of clopidogrel; avoidance of warfarin advised by manufacturer of clopidogrel

- Corticosteroids: anticoagulant effect of coumarins may be enhanced or reduced by corticosteroids (high-dose corticosteroids enhance anticoagulant effect)

- Cranberry Juice: anticoagulant effect of coumarins possibly enhanced by cranberry juice—avoid concomitant use

- Cytotoxics: anticoagulant effect of coumarins possibly enhanced by etoposide, ifosfamide and carfilzomib; anticoagulant effect of coumarins enhanced by fluorouracil; anticoagulant effect of coumarins possibly reduced by azathioprine, mercaptopurine and mitotane; increased risk of bleeding when coumarins given with erlotinib; replacement of warfarin with a heparin advised by
Appendix 1: Interactions

Ciclosporin: danazol inhibits metabolism of ciclosporin.

Anti-arrhythmics: plasma concentration of dabigatran increased by fludarabine.

Analgesics: possible increased risk of bleeding when given with ciclosporin (increased plasma concentration).

Antiepileptics: plasma concentration of darunavir possibly reduced by rifampicin—avoid concomitant use.

Antibacterials: plasma concentration of darunavir reduced by rifampicin (reduced plasma concentration—avoid concomitant use).

Antivirals: plasma concentration of darunavir significantly reduced by ritonavir; 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: possible increased risk of myopathy when danazol given with simvastatin.

Tacrolimus: danazol possibly increases plasma concentration of tacrolimus.

Daptomycin

Antibacterials: plasma concentration of daptomycin 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. 478).

Probenecid: excretion of dapsone reduced by probenecid (increased risk of side-effects).

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.

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. 478).

Probenecid: excretion of dapsone reduced by probenecid (increased risk of side-effects).

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.

Darifenacin

Antimuscarinics

Darunavir

Anti-arrhythmics: darunavir possibly increases plasma concentration of lidocaine (lignocaine)—avoid concomitant use.

Antibacterials: darunavir increases plasma concentration of rifampicin (reduce dose of rifampicin); plasma concentration of darunavir significantly 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 darunavir reduced by St John’s wort—avoid concomitant use.

Antiepileptics: plasma concentration of darunavir possibly reduced by carbamazepine and phenytoin.

Antifungals: plasma concentration of darunavir significantly reduced by antifungals: plasma concentration of darunavir 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: possible increased risk of myopathy when darunavir given with simvastatin.

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.

Dasatinib

Antibacterials: metabolism of dasatinib accelerated by rifampicin (reduced plasma concentration—avoid concomitant use).

Antiepileptics: cytoxotics possibly reduce absorption of phenytoin.

Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis).

Antihistamines: cytoxotics possibly reduce absorption of phenytoin.

Antifungals: cytoxotics possibly reduce absorption of phenytoin.

Cardiac Glycosides: cytoxotics possibly reduce absorption of phenytoin.

Cardiac Glycosides: cytoxotics possibly reduce absorption of phenytoin.

Cardiac Glycosides: cytoxotics possibly reduce absorption of phenytoin.

Coumarins (continued)

Vaccines: anticoagulant effect of warfarin possibly enhanced by influenza vaccine.

Vitamins: anticoagulant effect of coumarins antagonised by vitamin K.
Dextropropoxyphene see Desogestrel
Diazepam see Dextromethorphan
see Dexketoprofen
Dexibuprofen see Dexamethasone
Desmopressin see Deflazacort see Corticosteroids
Desloratadine see Tetracyclines
Desferrioxamine see Demeclocycline
see Deferasirox
Deferasirox
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Diazoxide (continued)
Cardiac Glycosides: 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
Methyldopa: enhanced hypotensive effect when diazoxide given with methyldopa
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
Nitrites: enhanced hypotensive effect when diazoxide given with nitrites
Oestrogens: hypotensive effect of diazoxide antagonised by oestrogens
Prostaglandins: enhanced hypotensive effect when diazoxide given with alprostadil
Vasodilator 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 ganciclovir; increased risk of side-effects when didanosine given with zidovudine; plasma concentration of didanosine increased by tenofovir (increased risk of toxicity)—avoid concomitant use; plasma concentration of didanosine reduced by tipranavir
• Cytotoxics: increased risk of toxicity when didanosine given with hydroxyurea—avoid concomitant use
Digoxin see Cardiac Glycosides
Digoxin see Cardiac Glycosides
Dihydrocodeine see Opioid Analgesics
Diltiazem see Calcium-channel Blockers
Dimercaprol
• Iron: avoid concomitant use of dimercaprol with iron
Dimethyldiuretics
Dimethyldiuretics
• Analgesics: avoid concomitant use of dimethyldiuretics with analgesics

Diphenhydramine see Prostaglandins
Diphenylhydantoin see Opioid Analgesics
Dipipanone see Opioid Analgesics
Dipivine see Sympathomimetics
Diprydamole
Antacids: absorption of diprydamole possibly reduced by antacids
• Anti-arrhythmics: diprydamole enhances and extends the effects of adenosine (important risk of toxicity)
• Anticoagulants: antiplatelet action of diprydamole enhances anticoagulant effect of coumarins and phenindione; diprydamole enhances anticoagulant effect of heparins
• Clopidogrel: increased risk of bleeding when diprydamole given with clopidogrel
• Cytotoxics: diprydamole possibly reduces effects of fludarabine
Disodium Etidronate see Bisphosphonates

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Disodium Pamidronate: see Bisphosphonates

Disopyramide

Anaesthetic: 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 disopyramide given with amiodarone—avoid concomitant use.

- Antibacterials: plasma concentration of disopyramide possibly increased by clarithromycin (increased risk of toxicity); plasma concentration of disopyramide increased by erythromycin (increased risk of toxicity); increased risk of ventricular arrhythmias when disopyramide given with moxifloxacin or quinupristin/dalfopristin—avoid concomitant use; toxicosis when disopyramide accelerated by rifampicins (reduced plasma concentration).

- Antidepressants: increased risk of ventricular arrhythmias when disopyramide given with tricyclics.

- Antidiabetics: disopyramide possibly enhances hypoglycaemic effect of glitazides, insulin and metformin.

- Antiepileptics: plasma concentration of disopyramide reduced by phenytoin; metabolism of disopyramide accelerated by primidone (reduced plasma concentration).

- Antifungals: increased risk of ventricular arrhythmias when disopyramide given with ketoconazole—avoid concomitant use; avoidance of disopyramide advised by manufacturer of itraconazole.

- Antihistamines: increased risk of ventricular arrhythmias when disopyramide given with emozolamine—avoid concomitant use.

- Antimalarials: avoidance of disopyramide advised by manufacturer of quinine/quine/nafenoxamine (risk of ventricular arrhythmias).

- Antimuscarinics: increased risk of antimuscarinic side-effects when disopyramide given with antimuscarinics; increased risk of ventricular arrhythmias when disopyramide 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 ventricular arrhythmias when disopyramide given with amisulpride, pimozide, sertindole or zuclopenthixol—avoid concomitant use; increased risk of ventricular arrhythmias when disopyramide given with phenothiazines or sulpride.

- Antivirals: plasma concentration of disopyramide possibly increased by ritonavir (increased risk of toxicity).

- Atomoxetine: increased risk of ventricular arrhythmias when disopyramide given with atomoxetine.

- 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 sotalol—avoid concomitant use.

- 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 aminoglycosides, loop diuretics or thiazides and related diuretics.

- H2 Antagonists: increased risk of ventricular arrhythmias when disopyramide given with dolasetron—avoid concomitant use.

- Iverapamil: 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

Disulfiram

- Alcohol: disulfiram reaction when disulfiram given with alcohol (see BNF section 4.10).

- Antibacterials: psychotic reaction reported when disulfiram given with metronidazole.

- Anti-cancer drugs: disulfiram can enhance anticoagulant effect of warfarin.

- Antidepressants: increased disulfiram reaction with alcohol reported with concomitant amitriptyline; disulfiram inhibits metabolism of tricyclics (increased plasma concentration).

- Antiepileptics: disulfiram inhibits metabolism of phenytoin (increased risk of toxicity).

- Antidiabetics: disulfiram increases risk of hyperglycaemia when potassium-sparing diuretics and aldosterone antagonists 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).

- Anti-ulcer agents: disulfiram increases risk of hyperkalaemia when potassium-sparing diuretics 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 triamterene given with indometacin—avoid concomitant use; increased risk of toxicity when carbonic anhydrase 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 possibly increased by amiodarone (reduce dose of eplere-
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 rifampicin—avoid concomitant use; avoidance of diuretics advised by manufacturer of fomepizole; increased risk of toxicity when loop diuretics given with aminoalcohols.

Antidepressants: possible increased risk of hypokalaemia where 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 antidiabetics; increased risk of hypoglycaemia when thiazides and related diuretics plus potassium-sparing diuretic given with chlorpropamide; increased risk of hypoglycaemia when potassium-sparing diuretics and aldosterone antagonists plus thiazide given with chlorpropamide.

Antiepileptics: plasma concentration of eplerenone reduced by carbamazepine and phenytoin—avoid concomitant use; increased risk of hyponatraemia when diuretics given with carbamazepine; acetazolamide increases plasma concentration of carbamazepine; effects of furosemide (frusemide) antagonised by phenytoin; increased risk of osteomalia when carbonic anhydrase inhibitors given with phenytoin or primidone; acetazolamide possibly reduces plasma concentration of primidone.

Antifungals: plasma concentration of eplerenone increased by itraconazole 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 ketoconazole (reduce dose of eplerenone).

Antipsychotics: hypokalaemia caused by diuretics increases risk of ventricular arrhythmias with amisulpride or serindole; 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 saquinavir (reduce dose of eplerenone) and ribavirin—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 parental furosemide (frusemide) with chloral or triclofos may displace thyroid hormone from binding sites.

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; spironolactone increases plasma concentration of digoxin, potassium canrenoate 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.

Cytotoxics: avoidance of spironolactone advised by manufacturer of mitotane (agonism of effect); increased risk of nephrotoxicity and otoxicity when diuretics given with platinum compounds.

Diazoxide: enhanced hypotensive and hyperglycaemic effects 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 methaqualone 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 ketoconazole; increased risk of hyperkalaemia when potassium-sparing diuretics and aldosterone antagonists given with triostane.

Lipid-regulating Drugs: absorption of thiazides and related diuretics reduced by colestitol and colestyramine (give at least 2 hours apart).

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.

Methyldopa: enhanced hypotensive effect when diuretics given with methyldopa.

Moxisylyte (thymoxamine): enhanced hypotensive effect when diuretics given with moxisylyte.
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Dopexamine see Dopamine

Doripenem

Antiepileptics: doripenem 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. 478)

Probencid: excretion of doripenem reduced by probenecid (manufacturers of doripenem advise avoid concomitant use)

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Dorzolamide see Diuretics

Dosulepin (dothiepin) see Antidepressants, Tricyclic

Doxapram

Antidepressants: effects of doxapram enhanced by MAOIs

Symptomamimetics: 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: cytotoxics possibly reduce absorption of phenytoin

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)

Antivirals: doxorubicin possibly inhibits effects of stavudine

Cardiac Glycosides: cytotoxics reduce absorption of diuretics given with baclofen or tizanidine

Ciclosporin: increased risk of neurotoxicity when doxorubicin given with ciclosporin

Cytotoxics: plasma concentration of doxorubicin 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 heparin—consult product literature

Duloxetine

Analgesics: possible increased serotonergic 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 serotonergic effects when duloxetine given with SSRIS, St John's wort, amitriptyline, clomipramine, moclobemide, tryptophan or venlafaxine; 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 SSRI-related antidepressants do not start moclobemide for at least 1 week

Antimalarials: avoidance of antidepressants advised by manufacturer of sibutramine when duloxetine given with 5HT1 agonists (manufacturer of sibutramine advises avoid concomitant use)

Dutasteride

Calcium-channel Blockers: plasma concentration of dutasteride increased by diltiazem and verapamil

Hydrogesterone see Progestogens

Edrophonium see Parasympathomimetics

Efalizumab

Vaccines: discontinue efalizumab 8 weeks before and until 2 weeks after vaccination with live or live-attenuated vaccines
Efavirenz

Analgesics: efavirenz reduces plasma concentration of methadone

Antibacterials: 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: plasma concentration of efavirenz reduced by St John’s wort—avoid concomitant use

• Antiinfectives: 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 dose of voriconazole and reduce dose of efavirenz); 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 pimozone (increased risk of ventricular arrhythmias—avoid concomitant use)

• Antivirals: avoidance of efavirenz advised by manufacturer of atazanavir (plasma concentration of atazanavir reduced); efavirenz reduces plasma concentration of darunavir, fosamprenavir and indinavir; efavirenz possibly reduces plasma concentration of estravirine—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

Calcium-channel Blockers: efavirenz reduces plasma concentration of diltiazem

• Ciclosporin: efavirenz possibly reduces plasma concentration of ciclosporin

• Ergot Alkaloids: increased risk of ergotism when efavirenz given with ergot alkaloids—avoid concomitant use

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

• Tacrolimus: efavirenz possibly affects plasma concentration of tacrolimus

Eletriptan see 5HT1 Agonists

Emtricitabine

Antivirals: manufacturer of emtricitabine advises avoid concomitant use with lamivudine

Enalapril see ACE Inhibitors

Enoxaparin see Heparins

Enoximone see Phosphodiesterase Inhibitors

Entacapone

• Anticoagulants: entacapone enhances anticoagulant effect of warfarin

• Antidepressants: manufacturer of entacapone advises caution with moclobemide, paroxetine, tricyclics and venlafaxine; avoid concomitant use of entacapone with non-selective MAOIs

Dopaminergics: entacapone possibly enhances effects of apomorphine; entacapone possibly reduces plasma concentration of rasagiline; manufacturer of

Entacapone

Dopaminergics (continued)

entacapone advises max. dose of 10 mg selegiline if used concomitantly

Iron: absorption of entacapone reduced by oral iron

Methamphetamine: effects of dopaminergics possibly enhanced by memantine

Methylphenidate: entacapone possibly enhances effects of methylphenidate; antiparkinsonian effect of dopaminergics antagonised by methylphenidate

Sympathomimetics: entacapone possibly enhances effects of adrenaline (epinephrine), dobutamine, dopamine and noradrenaline (norepinephrine)

Enteral Foods

• Anticoagulants: the presence of vitamin K in some enteral feeds can antagonise the anticoagulant effect of coumarins and phenindione

Antipieptelics: enteral feeds possibly reduce absorption of phenytol

Ephedrine see Sympathomimetics

Epinephrine (adrenaline) see Sympathomimetics

Epirubicin

Antipieptelics: cytotoxics possibly reduce absorption of phenytol

• 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 omeprazole

Eplerenone see Diuretics

Eprosartan see Angiotensin-1 Receptor Antagonists

Eptifibatide

Iloprost: increased risk of bleeding when eptifibatide given with iloprost

Ergonomide 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

Antidepressants: possible risk of hypotension when ergotamine and methysergide given with reboxetine

• Antifungals: increased risk of ergotism when ergotamine and methysergide given with midazolam or triazoles—avoid concomitant use

• Antivirals: plasma concentration of ergot alkaloids possibly increased by atazanavir—avoid concomitant use; increased risk of ergotism when ergotamine and methysergide given with ritonavir, monitor liver function tests; efavirenz significantly reduces plasma concentration of saquinavir

Beta-blockers: increased peripheral vasodilatation when ergotamine and methysergide given with beta-blockers

• 5HT1 Agonists: increased risk of vasospasm when ergotamine and methysergide given with almotriptan, rizatriptan, sumatriptan or zolmitriptan (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); increased risk of vasospasm when ergotamine and methysergide given with eletriptan or frovatriptan (avoid ergotamine and methysergide for 24 hours after eletriptan or frovatriptan, avoid eletriptan or frovatriptan for 24 hours after ergotamine and methysergide)
Antibacterials: metabolism of ethosuximide inhibited

Ethinylestradiol

Vaccines: avoid concomitant use of etanercept with

Antidepressants: anticonvulsant effect of antiepileptics

Etanercept

see Estropipate

Estradiol

see Estrone

Esmolol

see Erythromycin

Antimalarials: possible increased risk of convulsions

Antipsychotics: anticonvulsant effect of ethosuximide

Ulcer-healing Drugs: increased risk of ergotism when

Anticoagulants: increased risk of bleeding when

Analgesics: increased risk of bleeding when erlotinib

Antiepileptics: ertapenem possibly reduces plasma

Oestrogens: antibacterials that do not induce liver

Antifungals: metabolism of erlotinib inhibited by keto-

Cardiac Glycosides: cytotoxics reduce absorption of
digoxin tablets

Cytotoxics: plasma concentration of erlotinib possibly
increased by capectabine

Tobacco: plasma concentration of erlotinib reduced by
tobacco smoking

Antiepileptics: etravirine possibly reduces plasma
concentration of valproate

Oestrogens: antibacterials that do not induce liver
enzymes possibly reduce contraceptive effect of

Vaccines: antibacterials inactivate oral typhoid
vaccine—see p. 752

Erythromycin see Macrolides

Escitalopram see Antidepressants, SSRI

Esmolol see Beta-blockers

Estradiol see Oestrogens

Estradiol see Oestrogens

Estrone see Oestrogens

Estradiol see Oestrogens

Estradiol see Oestrogens

Antibacterials: metabolism of ethosuximide inhibited by
isoniazid (increased plasma concentration and risk of toxicity)

Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and tricyclcs (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort

Antiepileptics: plasma concentration of ethosuximide possibly reduced by carbamazepine and primidone; plasma concentration of ethosuximide possibly reduced by phenytoin, also plasma concentration of phenytoin possibly increased by valproate

Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine

Antipsychotics: anticonvulsant effect of ethosuximide antagonised by antipsychotics (convulsive threshold lowered)
Antimalarials: avoidance of flecainide advised by
Antihistamines: increased risk of ventricular arrhythmias when flecainide given with
Antidepressants: plasma concentration of flecainide increased by
Antimuscarinics: increased risk of ventricular arrhythmias when flecainide given with
Lipid-regulating Drugs: increased risk of cholelithiasis and gallbladder disease when flecainide given with ezetimibe—discontinue if suspected; increased risk of myopathy when flecainide given with statins; increased risk of myopathy when flecainide given with statins (preferably avoid concomitant use)
Filgrastim: 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
Antihistamines: increased risk of ventricular arrhythmias when flecainide given with trizolastine—avoid concomitant use
Antimalarials: avoidance of flecainide advised by manufacturer of artemether/lumefantrine (risk of ventricular arrhythmias); plasma concentration of flecainide increased by quinine
Antimuscarinics: increased risk of ventricular arrhythmias when flecainide given with oloterdine
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 losapamrevir, indinavir, lopinavir and ritonavir (increased risk of ventricular arrhythmias—avoid concomitant use)
Beta-blockers: increased risk of myocardial depression and bradycardia 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 cetoconazole, ciclosporin, clopidogrel, colchicine and related diuretics
5HT1A Antagonists: increased risk of ventricular arrhythmias when flecainide given with dolasetron—avoid concomitant use
Ulcder-healing Drugs: metabolism of flecainide inhibited by cimetidine (increased plasma concentration)
Flucloxacillin see Penicillins
Fluconazole see Antifungals, Triazole
Flucytosine
Antifungals: renal excretion of flucytosine decreased and cellular uptake increased by amphotericin (toxicity possibly increased)
Cytotoxics: plasma concentration of flucytosine possibly reduced by cytarabine
Fludarabine
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: fludarabine increases intracellular concentration of cytarabine; increased pulmonary toxicity when fludarabine given with pentostatin (unacceptably high incidence of fatalities)
Dipyridamole: effects of fludarabine possibly reduced by dipyridamole
Fludrocortisone see Corticosteroids
Flunisolide see Corticosteroids
Fluorides
Calcium Salts: absorption of fluorides reduced by calcium salts
Fluorouracil
Note. Capecitabine is a prodrug of fluorouracil Note. Tegafur is a prodrug of fluorouracil
Allopurinol: manufacturer of capecitabine advises avoid concomitant use with allopurinol
Antibacterials: metabolism of fluorouracil inhibited by metronidazole (increased toxicity)
Anticoagulants: fluorouracil enhances antiagulant effect of coumarins
Antiepileptics: fluorouracil possibly inhibits metabolism of phenytoin (increased risk of toxicity); 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: capecitabine possibly increases plasma concentration of erlotinib
Filgrastim: neutropenia possibly exacerbated when fluorouracil given with filgrastim
Temoporfin: increased skin photosensitivity when topical fluorouracil used with temoporfin
Ulcder-healing Drugs: metabolism of fluorouracil inhibited by cimetidine (increased plasma concentration)
Fluoxetin see Antidepressants, SSRI
Flupentixol see Antipsychotics
Fluphenazine see Antipsychotics
Flurazepam see Anxiolytics and Hypnotics
Flurbiprofen see NSAIDs
Flutamide
Anticoagulants: fluoxetine enhances antiagulant effect of coumarins
Fluticasone see Corticosteroids
Fluvastatin see Statins
Fluvoxamine see Antidepressants, SSRI
Folates
Aminosaliclates: absorption of folinic acid possibly reduced by sulfasalazine
Antiepileptics: folates possibly reduce plasma concentration of phenytoin and primidone
Barbiturates: folates possibly reduce plasma concentration of phenobarbital
Folic Acid see Folates
Folinic Acid see Folate
Appendix 1: Interactions

Fosamprenavir (continued)

- Antihistamines: fosamprenavir possibly increases plasma concentration of amisuladrone, fexofenadine and propafenone (increased risk of ventricular arrhythmias—avoid concomitant use); fosamprenavir possibly increases plasma concentration of lidocaine (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; avoidance of concomitant fosamprenavir in severe renal and hepatic impairment advised by manufacturer of olithromycin
- Anticoagulants: fosamprenavir may enhance or reduce anticoagulant effect of coumarins; avoidance of fosamprenavir advised by manufacturer of rivaroxaban
- Antidepressants: plasma concentration of fosamprenavir reduced by St John’s wort—avoid concomitant use; fosamprenavir possibly increases side-effects of tricyclics
- Antiepileptics: plasma concentration of fosamprenavir possibly increased by carbamazepine and phenytoin
- Antifungals: fosamprenavir increases plasma concentration of ketoconazole; fosamprenavir possibly increases plasma concentration of itraconazole
- Antihistamines: fosamprenavir possibly increases plasma concentration of loratadine
- Antimalarials: caution with fosamprenavir advised by manufacturer of artemether/lumefantrine
- Antimuscarinics: avoidance of fosamprenavir advised by manufacturer of darifenacin and tolterodine
- Antipsychotics: fosamprenavir possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); fosamprenavir possibly increases plasma concentration of clozapine; fosamprenavir increases plasma concentration of pimozide and sertindole (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antivirals: plasma concentration of fosamprenavir reduced by efavirenz and etravirine; plasma concentration of fosamprenavir increased by etravirine (consider reducing dose of fosamprenavir); 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, diazepam, eszopiclone or midazolam
- Barbiturates: plasma concentration of fosamprenavir possibly reduced by phenobarbital
- Cilostazol: fosamprenavir possibly increases plasma concentration of cilostazol—avoid concomitant use
- Ergot Alkaloids: increased risk of ergotism when fosamprenavir given with ergotamine and methysergide—avoid concomitant use
- Lipid-regulating Drugs: possible increased risk of myopathy when fosamprenavir given with atorvastatin; possible increased risk of myopathy when fosamprenavir given with simvastatin 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 concentra-
Gentamicin see Aminoglycosides
Gestodene see Progestogens

Gestrinone

Antibacterials: metabolism of gestrinone accelerated by rifampicin (reduced plasma concentration)
Antiepileptics: metabolism of gestrinone accelerated by carbamazepine, phenytoin and primidone (reduced plasma concentration)
Barbiturates: metabolism of gestrinone accelerated by barbiturates (reduced plasma concentration)

Glimepiride see Antidiabetics
Glitazide see Antidiabetics
Glipizide see Antidiabetics

Glucosamine

• Anticoagulants: glucosamine enhances anticoagulant effect of warfarin (avoid concomitant use)

Glyceryl Trinitrate see Nitrates
Glycoproteinase see Antimucosaries

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 arteether/lumezantrine

Calcium-channel Blockers: grapefruit juice increases plasma concentration of felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil

Ciclosporin: grapefruit juice increases plasma concentration of ciclosporin (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

Tadalafil: grapefruit juice possibly increases plasma concentration of tadalafil

Vardenafil: grapefruit juice possibly increases plasma concentration of vardenafil—avoid concomitant use

Grisofulvin

Alcohol: griseofulvin possibly enhances effects of alcohol

Anticoagulants: griseofulvin reduces anticoagulant effect of coumarins
Antiepileptics: absorption of griseofulvin reduced by primidone (reduced effect)
Barbiturates: absorption of griseofulvin reduced by phenobarbital (reduced effect)

Ciclosporin: griseofulvin possibly reduces plasma concentration of ciclosporin

Oestrogens: griseofulvin accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 478)

Progestogens: griseofulvin accelerates metabolism of progestogens (reduced contraceptive effect—see p. 478)

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

• Analgesics: possible increased risk of bleeding when heparins given with NSAIDs; increased risk of haemorrhage when anticoagulants given with intravenous dexametomidine (avoid concomitant use, including low-dose heparin); increased risk of haemorrhage when anticoagulants given with ketorolac (avoid concomitant use, including low-dose heparin); anticoagulant effect of heparins enhanced by aspirin

Angiotensin-II Receptor Antagonists: increased risk of hyperkalaemia when heparin given with angiotensin-II receptor antagonists

Dipyradomole: anticoagulant effect of heparins enhanced by dipyradomole

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 glyceryl trinitrate

Sibu tramine: increased risk of bleeding when anticoagulants given with sibutramine

Histamine H2-antagonists

• Alpha-blockers: cimetidine and ranitidine antagonise effects of tolazoline

Analgesics: cimetidine possibly increases plasma concentration of azaprozone; cimetidine inhibits metabolism of opioid analgesics (increased plasma concentration)

Anti-arrhythmics: cimetidine increases plasma concentration of amiodarone and propafenone; cimetidine inhibits metabolism of opioid analgesics (increased plasma concentration)

Antibacterials: histamine H2-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 citalopram, 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

Antiepileptics: cimetidine inhibits metabolism of carbamazepine, phenytoin and valproate (increased plasma concentration)

Antifungals: histamine H2-antagonists reduce absorption of itraconazole and ketoconazole; cimetidine reduces plasma concentration of posaconazole; cimetidine increases plasma concentration of terbinafine
Appendix 1: Interactions

Histamine H2-antagonists (continued)

Antihistamines: manufacturer of loratadine advises cetirizine possibly increases plasma concentration of loratadine

- Antimalarials: avoidance of cetirizine advised by manufacturer of arteether/lumefantrine; cetirizine inhibits metabolism of chloroquine and hydroxychloroquine and quinine (increased plasma concentration of arteether/lumefantrine)

- Antipsychotics: cetirizine possibly enhances effects of antipsychotics, chlorpromazine and clozapine; increased risk of ventricular arrhythmias when cetirizine given with sertindole—avoid concomitant use

Antivirals: histamine H2-antagonists possibly reduce plasma concentration of atazanavir; plasma concentration of cimetidine increased by fosamprenavir; histidine H2-antagonists possibly increase plasma concentration of raltegravir—manufacturer of raltegravir advises avoid concomitant use

Anxiolytics and Hypnotics: cetirizine inhibits metabolism of benzodiazepines, clomethiazole and zaleplon (increased plasma concentration; cetirizine increases plasma concentration of melatonin

Beta-blockers: cetirizine increases plasma concentration of labetalol, metoprolol and propranolol

Calcium-channel Blockers: cetirizine 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

- Cytotoxics: cetirizine possibly enhances myelosuppressive effects of carbustime and lomustine; cetirizine inhibits metabolism of fluorouracil (increased plasma concentration); famotidine possibly increases plasma concentration of raltegravir—manufacturer of raltegravir—manufacturer of raltegravir advises avoid concomitant use

Dopaminergic: cetirizine reduces excretion of pramipexole (increased plasma concentration)

- Ergot Alkaloids: increased risk of ergotism when cetirizine given with ergotamine and methysergide—avoid concomitant use

Hormone Antagonists: absorption of cetirizine possibly delayed by octreotide

5HT1 Agonists

- Antidepressants (continued) risk of CNS toxicity when sumatriptan given with sertraline (manufacturer of sertraline advises avoid concomitant use); possible increased serotonergic effects when 5HT1 agonists 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 serotonergic effects when 5HT1 agonists given with St John’s wort—avoid concomitant use

- Antifungals: plasma concentration of eletriptan increased byitraconazole 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 efavirenz, nelﬁnavir and etonavir (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 eletriptan or frovatriptan given with ergotamine and methysergide (avoid ergotamine and methysergide for 24 hours after eletriptan or frovatriptan, avoid eletriptan or frovatriptan 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)

5HT3 Agonists

Analgesics: ondansetron possibly antagonises effects of tramadol

- Anti-arrhythmics: increased risk of ventricular arrhythmias when doxazosin given with amiodarone, disopyramide, tocainide, 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)

Hydralazine see Vasodilator Antihypertensives

Hydrochlorothiazide see Diuretics

Hydrocortisone see Corticosteroids

Hydroflumethiazide see Diuretics

Hydromorphine see Opioid Analgesics

Hydrotalcite see Antacids

Hydroxybocodamin

Antibacterials: serum hydroxocobalamin reduced by chloramphenicol

Hydroxybreamide

Antiepileptics: serum hydroxocobalamin reduced by phenytoin

Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
Immunoglobulins

Imipramine

Indapamide see Antimuscarinics

Ibandronic Acid see Bisphosphonates

Ibuprofen see NSAIDs

Ilosafamide

- Anticoagulants: ilosafamide possibly enhances anticoagulant effect of coumarins
- Antiepileptics: cytoxotics possibly reduce absorption of phenytoin

Ilprost

Analgesics: increased risk of bleeding when ilprost given with NSAIDs or aspirin

Anticoagulants: ilprost possibly enhances anticoagulant effect of coumarins and heparins; increased risk of bleeding when ilprost given with phenindione

Clopigogrel: increased risk of bleeding when ilprost given with clopibogrel

Epifibatide: increased risk of bleeding when ilprost given with epifibatide

Tirofiban: increased risk of bleeding when ilprost given with tirofiban

Imatinib

- Antibacterials: plasma concentration of imatinib reduced by efavirpicin—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 carbamazepine, oxcarbazepine and 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)

Indinavir

- Anti-arrhythmics: indinavir possibly increases plasma concentration of amiodarone—avoid concomitant use; indinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antibacterials: indinavir increases plasma concentration of rifabutin—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 etelitromycin
- 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 maraviroc and etoconazole (consider reducing dose of indinavir)
- Antimalarials: 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 aripiprazole (reduce dose of aripiprazole), imatinib possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias—avoid concomitant use); indinavir increases plasma concentration of sertrindole (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antivirals: avoid concomitant use of indinavir with atazanavir; plasma concentration of both drugs increased when indinavir given with darunavir; plasma concentration of indinavir reduced by efavirin and nevirapine; plasma concentration of indinavir possibly reduced by etravirine—avoid concomitant use; indinavir increases plasma concentration of maraviroc (consider reducing dose of 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
- Antioxidants 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 ciclesporin
- Cilostazol: indinavir possibly increases plasma concentration of ciclesporin—avoid concomitant use
- Corticosteroids: plasma concentration of indinavir possibly reduced by dexamethasone
- Ergot Alkaloids: increased risk of ergotism when indinavir given with ergotamine and methysergide—avoid concomitant use
Appendix 1: Interactions

Indinavir (continued)
- 5HT1 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; increased risk of myopathy when indinavir given with simvastatin (avoid concomitant use)
- Sildenafil: indinavir increases plasma concentration of sildenafil—reduce initial dose of sildenafil
- Vardenafil: indinavir increases plasma concentration of vardenafil—avoid concomitant use

Ipratropium

Antivirals: increased risk of peripheral neuropathy when indinavir given with adefovir and telbivudine

Alpha-blockers

Antidiabetics

Antimuscarinics

Beta blockers see Angiotensin-II Receptor Antagonists

Isoniazid

Analgesics, Nonsteroidal see NSAIDs

Indomethacin

Barbiturates: plasma concentration of indinavir increased by rifampicin and possibly reduced by corticosteroids

Indicators

Interferons

Note. Peginterferon alfa interactions as for interferon alfa

Antivirals: increased risk of peripheral neuropathy when interferon alfa given with telbivudine

Theophylline: interferon alfa inhibits metabolism of theophylline (increased plasma concentration)

Vaccines: manufacturer of interferon gamma advises avoid concomitant use with vaccines

Ipratropium see Antimuscarinics

Ibexartan see Angiotensin-II Receptor Antagonists

Iron (continued)
- Dimercaprol: avoid concomitant use of iron with dimercaprol

Dopaminergics: oral iron reduces absorption of entacapone; oral iron possibly reduces absorption of levodopa

Methyl dopa: oral iron antagonises hypotensive effect of methyl dopa

Penicillamine: oral iron reduces absorption of penicillamine

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

Isourfane see Anaesthetics, General

Isotretinone see Symptomatometics

Isotretinone

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 increases isoniazid hepatotoxicity); isoniazid inhibits metabolism of ethosuximide (increased plasma concentration and risk of toxicity); isoniazid inhibits metabolism of ethinylestradiol (increased plasma concentration)

Antifungals: isoniazid possibly reduces plasma concentration of ketoconazole

Anxiolytics and 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. 478)

Theophylline: isoniazid possibly increases plasma concentration of theophylline

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

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 clarithromycin and telithromycin—avoid 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 ziprasidone 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 (continued)

- Avoid concomitant use with diltiazem and verapamil—avoid concomitant use
- Grapefruit Juice: plasma concentration of ivabradine increased by grapefruit juice
- Pentamidine isetionate: increased risk of ventricular arrhythmias when ivabradine given with pentamidine i setionate

Kaolin

Analgesics: kaolin possibly reduces absorption of aspirin
Antibacterials: kaolin possibly reduces absorption of tetracyclines
Antimalarials: kaolin reduces absorption of chloroquine and hydroxychloroquine
Antipsychotics: kaolin possibly reduces absorption of phenothiazines

Ketamine see Anaesthetics, General

Ketconazole see Antifungals, Imidazole

Ketoprofen see NSAIDs

Ketorolac see NSAIDs

Ketotifen see Antihistamines

Labelatal 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); 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 memantine

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 concomitant use with foscarinet; manufacturer of lamivudine advises avoid concomitant use of intravenous ganciclovir

Lamotrigine

- Antibacterials: plasma concentration of lamotrigine reduced by rifampicin

- 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 lamotrigine often reduced by carbamazepine, also plasma concentration of an active metabolite of carbamazepine sometimes raised (but evidence is conflicting); plasma concentration of lamotrigine reduced by phenytoin and primidone; 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 memantine

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 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; 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 voriconazole

- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis); manufacturer of lapatinib advises avoid concomitant use with ziprasidone

- Antivirals: manufacturer of lapatinib advises avoid concomitant use with tenofovir and emtricitabine

Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

- Grapefruit Juice: manufacturer of lapatinib advises avoid concomitant use with grapefruit juice

- Ulcer-healing Drugs: absorption of lapatinib possibly reduced by histamine H2-antagonists and proton pump inhibitors

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)

- Antidepressants: laronidase possibly enhanced anticoagulant effect of warfarin

Antidiabetics: laronidase possibly enhances hypoglycaemic effect of tolbutamide

Antiepileptics: laronidase possibly increases plasma concentration of phenytoin

Lipid-regulating Drugs: the effect of laronidase is significantly decreased by colestyramine (enhanced elimination)—avoid unless drug elimination desired

Vaccines: avoid concomitant use of laronidase with live vaccines (see p. 725)

Lenalidomide

Cardiac Glycosides: lenalidomide possibly increases plasma concentration of digoxin

Lercanidipine see Calcium-channel Blockers

Leukotriene Receptor Antagonists

Analgesics: plasma concentration of zafirlukast increased by aspirin
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Levetiracetam

Anaesthetics, General: increased risk of arrhythmias

Barbiturates: plasma concentration of montelukast concentration of theophylline, also plasma concentration of zafirlukast reduced

Levodopa

see Levocetirizine

Antimalarials: possible increased risk of convulsions

Levamisole

see (continued)

Leukotriene Receptor Antagonists (continued)

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

Levarterenol see Beta-blockers

Levobupivacaine

Anti-arrhythmics: increased myocardial depression when levobupivacaine given with anti-arrhythmics

Levocetirizine see Antihistamines

Levodopa

ACE Inhibitors: enhanced hypertensive effect when levodopa given with ACE inhibitors

Adrenergic Neurone Blockers: enhanced hypertensive effect when levodopa given with adrenergic neurone blockers

Alpha-blockers: enhanced hypertensive 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 hypertensive effect when levodopa given with angiotensin-II receptor antagonists

Antidepressants: risk of hypertensive crisis when levodopa given with 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 manufacturer of amisulpride (antagonism of effect)

Anxiolytics and Hypnotics: effects of levodopa antagonised by benzodiazepines

Beta-blockers: enhanced hypertensive effect when levodopa given with beta-blockers

Bupropion: increased risk of side-effects when levodopa given with bupropion

Calcium-channel Blockers: enhanced hypertensive effect when levodopa given with calcium-channel blockers

Clonidine: enhanced hypertensive effect when levodopa given with clonidine

Diazoxide: enhanced hypertensive effect when levodopa given with diazoxide

Diuretics: enhanced hypertensive effect when levodopa given with diuretics

Levodopa (continued)

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

Methamphetamine: enhanced hypertensive effect when levodopa given with methyldopa; antiparkinsonian effect of dopaminergics antagonised by methyldopa

Moxonidine: enhanced hypertensive effect when levodopa given with moxonidine

Muscle Relaxants: possible agitation, confusion and hallucinations when levodopa given with baclofen

Nitrates: enhanced hypertensive effect when levodopa given with nitrates

Oseltamivir: Antidepressives: enhanced hypertensive effect when levodopa given with hydralazine, minoxidil or sodium nitroprusside

Vitamins: effects of levodopa reduced by pyridoxine when given without dopa-decarboxylase inhibitor

Levoloxacin see Quinolones

Levomepromazine (methotrimeprazine) see Antipsychotics

Levonorgestrel see Progestogens

Levotyroxine (thyroxine) see Thyroid Hormones

Lidocaine (lignocaine) Note. Interactions less likely when lidocaine used topically

Anaesthetics, Local: increased myocardial depression when anti-arrhythmics given with bupivacaine, levobupivacaine, prilocaine or ropivacaine

Beta-blockers: increased myocardial depression when anti-arrhythmics given with other anti-arrhythmics

Antibacterials: increased risk of ventricular arrhythmias when lidocaine (lignocaine) given with quinupristin/dalfopristin–avoid concomitant use

Antipsychotics: increased risk of ventricular arrhythmias when anti-arrhythmics that prolong the QT interval given with antipsychotics that prolong the QT interval

Antivirals: plasma concentration of lidocaine (lignocaine) possibly increased by atazanavir and lopinavir, plasma concentration of lidocaine (lignocaine) possibly increased by darunavir and fosamprenavir–avoid concomitant use

Beta-blockers: increased myocardial depression when anti-arrhythmics given with beta-blockers; increased risk of lidocaine (lignocaine) toxicity when given with propranolol

Doxorubicin: Neuronal incoordination of lidocaine (lignocaine) antagonised by hypokalaemia caused by acetzolamide, loop diuretics or ethazidas and related diuretics

SHT3 Antagonists: increased risk of ventricular arrhythmias when lidocaine (lignocaine) given with dolasetron–avoid concomitant use

Muscle Relaxants: neuromuscular blockade enhanced and prolonged when lidocaine (lignocaine) given with metoclopramide

Ulcer-healing Drugs: plasma concentration of lidocaine (lignocaine) increased by cimetidine (increased risk of toxicity)

Linezolid Note. Linezolid is a reversible, non-selective MAO inhibitor—see interactions of MAOIs

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)

Vaccines: antibacterials inactivate oral typhoid vaccine–see p. 752

Liothyronine see Thyroid Hormones

Lipid-regulating Drugs see Colestipol, Colestyramine, 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 reduced by NSAIDs (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 increased plasma concentration of lithium; plasma concentration of lithium possibly affected by topiramate
- Antipsychotics: increased risk of extrapyramidal side-effects when lithium given with clozapine, flupentixol, haloperidol, phenothiazines or zuclopenthixol; increased risk of ventricular arrhythmias when lithium given withsertindole—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 acetazolamide; excretion of lithium reduced by loop diuretics and thiazides and related diuretics (increased plasma concentration and risk of toxicity)—loop diuretics safer than thiazides; excretion of lithium reduced by potassium-sparing diuretics and aldosterone antagonists (increased plasma concentration and risk of toxicity)
- 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
- Parasympathomimetics: lithium antagonises effects of neostigmine and pyridostigmine
- Theophylline: excretion of lithium increased by theophylline (reduced plasma concentration)

Lofepramine see Antidepressants, Tricyclic

Lofexidine
Alcohol: increased sedative effect when lofexidine given with alcohol
Anxiolytics and Hypnotics: increased sedative effect when lofexidine given with anxiolytics and hypnotics
Barbiturates: increased sedative effect when lofexidine given with barbiturates

Lomustine
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
Ulcet-healing Drugs: myelosuppressive effects of lomustine possibly enhanced by cimetidine

Loperamide
Desmopressin: loperamide increases plasma concentration oforal desmopressin

Lopinavir
Note. In combination with ritonavir as Kaletra® (ritonavir is present to inhibit lopinavir metabolism and increase plasma-lopinavir concentration)—see also Ritonavir
- Anti-arrhythmics: lopinavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias—avoid concomitant use); lopinavir possibly increases plasma concentration of lidocaine ( lignocaine)
- Antibacterials: plasma concentration of lopinavir reduced by erifampicin—avoid concomitant use; avoidance of concomitant lopinavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
- Anticoagulants: avoidance of lopinavir advised by manufacturer of rivaroxaban
- Antidepressants: plasma concentration of lopinavir reduced by St. John’s wart—avoid concomitant use
- Antiepileptics: plasma concentration of lopinavir possibly reduced by carbamazepine, phenytoin and primidone
- Antihistamines: lopinavir possibly increases plasma concentration of chlorphenamine (chlorpheniramine)
- Antimalarials: caution with lopinavir advised by manufacturer of arteether/lumefantrine
- Antimuscarinics: avoidance of lopinavir advised by manufacturer of darifenacin and tolterodine
- Antipsychotics: lopinavir possibly inhibits metabolism of piperazine (reduced dose of aripiprazole); lopinavir increases plasma concentration of sertindole (increased risk of ventricular arrhythmias—avoid concomitant use)
- Antivirals: lopinavir reduces plasma concentration of darunavir, also plasma concentration of lopinavir increased (avoid concomitant use); plasma concentration of lopinavir reduced by efavirenz—consider increasing dose of lopinavir; lopinavir reduces plasma concentration of fosamprenavir, effect on lopinavir plasma concentration not predictable—avoid concomitant use; lopinavir increases plasma concentration of maraviroc (consider reducing dose of maraviroc); plasma concentration of lopinavir reduced by nelfinavir, 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 saquinavir and tenofovir; plasma concentration of lopinavir reduced by etipranavir
- Barbiturates: plasma concentration of lopinavir possibly reduced by phenobarbital
- Clotiazol: lopinavir possibly increases plasma concentration of clotiazol—avoid concomitant use
- Corticosteroids: 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

Loprazolam see Anxiolytics and Hypnotics
Loratadine see Antihistamines
Lorazepam see Anxiolytics and Hypnotics
Lormetazepam see Anxiolytics and Hypnotics
Losartan see Angiotensin-II Receptor Antagonists
Lumefantrine see Artemether with Lumefantrine
Lynemcyline see Tetracyclines
Macrolides
Note. See also Telithromycin
Note. Interactions do not apply to small amounts of erythromycin used topically
- Analgesics: erythromycin increases plasma concentration of alfentanil
Appendix 1: Interactions

Antibacterials: increased risk of ventricular arrhythmias when parenteral erythromycin given with amiodarone—avoid concomitant use; erythromycin increases plasma concentration of disopyramide (increased risk of toxicity); clarithromycin possibly increases plasma concentration of disopyramide (increased risk of toxicity)

Antibacterials: increased risk of ventricular arrhythmias when parenteral erythromycin given with moxifloxacin—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 rifamycins

Anticoagulants: azithromycin possibly enhances anticoagulant effect of ecumarins; clarithromycin and erythromycin enhance anticoagulant effect of coumarins

Antidepressants: avoidance of macrolides advised by manufacturer of reboxetine

Antidiabetics: clarithromycin increases effects of metformin

Antiepileptics: clarithromycin and erythromycin increase plasma concentration of carbamazepine; 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

Antimalarials: avoidance of macrolides advised by manufacturer of artether/umefantline

Antimuscarnics: erythromycin possibly increases plasma concentration of disopyramide and tolterodine

Antipsychotics: increased risk of ventricular arrhythmias when parenteral erythromycin given with amisulpride or zuclopenthixol—avoid concomitant use; erythromycin possibly increases plasma concentration of clozapine (possible increased risk of convulsions); increased risk of ventricular arrhythmias when clarithromycin given with pimozone—avoid concomitant use; possible increased risk of ventricular arrhythmias when erythromycin given with pimozone (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 sulpiride

Antivirals: plasma concentration of both drugs increased when clarithromycin given with atazanavir, indinavir and ritonavir (reduced dose of clarithromycin in renal impairment); clarithromycin increases plasma concentration of 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 (concentration of maraviroc is reduced by 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 ritonavir (reduced 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)

Anxiolytics and Hypnotics: clarithromycin and erythromycin inhibit metabolism of midazolam (increased plasma concentration with increased sedative effect); macrolides possibly increase plasma concentration of buspirone (reduce dose of buspirone); erythromycin inhibits the metabolism of zopiclone Aprepitant: clarithromycin possibly increases plasma concentration of aprepitant

Atomoxetine: increased risk of ventricular arrhythmias when parenteral erythromycin given with atomoxetine

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)

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

Cytotoxics: avoidance of clarithromycin advised by manufacturer of nilotinib; 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 eplerenone—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

SHT1: Agonists: clarithromycin and erythromycin increase plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use

Ivabradine: clarithromycin possibly increases plasma concentration of ivabradine—avoid concomitant use; increased risk of ventricular arrhythmias when erythromycin given with ivabradine—avoid concomitant use

Leukotriene Receptor Antagonists: erythromycin reduces plasma concentration of zafirlukast

Lipid-regulating Drugs: clarithromycin increases plasma concentration of atorvastatin and pravas...
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**Appendix 1: Interactions**

**Macrolides**
- Lipid-regulating Drugs (continued)
  - statin; possible increased risk of myopathy when erthyromycin given with atorvastatin; erthyromycin increases plasma concentration of pravastatin; erthyromycin reduces plasma concentration of rosuvastatin; increased risk of myopathy when clarithromycin or erthyromycin 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 478)

**Parasympathomimetics:** erthyromycin increases plasma concentration of galantamine
- Pentamidine Isetionate: increased risk of ventricular arrhythmias when parenteral erthyromycin given with pentamidine isetionate
  - Sildenafil: clarithromycin possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil
  - Sirolimus: clarithromycin increases plasma concentration of sirolimus
  - Tacrolimus: clarithromycin and erthyromycin increase plasma concentration of tacrolimus
  - Theophylline: azithromycin possibly increases plasma concentration of theophylline; clarithromycin inhibits metabolism of theophylline (increased plasma concentration); erthyromycin inhibits metabolism of theophylline (increased plasma concentration), if erthyromycin given by mouth, also decreased plasma-erythrocyte concentration
  - Ulcer-healing Drugs: plasma concentration of erthyromycin increased by cimetidine (increased risk of toxicity, including deafness); plasma concentration of both drugs increased when clarithromycin given with omeprazole

**Magnesium (parenteral)**
- Calcium-channel Blockers: profound hypotension reported with concomitant use of parenteral magnesium and nifedipine in pre-eclampsia
  - Muscle Relaxants: parenteral magnesium enhances effects of non-depolarising muscle relaxants and suxamethonium

**Magnesium Salts (oral) see Antacids**

**Manitol**
- Ciclosporin: possible increased risk of nephrotoxicity when manitol given with ciclosporin

**MAOIs (continued)**
- 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
  - opiate analgesics—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 agonists—avoid concomitant use and for 2 weeks after stopping MAOIs

**Antidepressants:** increased risk of hypertension and CNS excitation when MAOIs given with
- MAOIs should normally be stopped 2 weeks before surgery
  - Antidepressants: increased risk of hypertension and CNS excitation when MAOIs given with
  - Antimicrobials (β-lactams, clavulanic acid) and MAOIs (avoid for at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with venlafaxine (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping 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); after stopping MAOIs do not start moclubemide 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 2 weeks after stopping mirtazapine or sertraline; after stopping MAOIs do not start duloxetine for 2 weeks, also MAOIs should not be started until at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with venlafaxine (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping 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); after stopping MAOIs do not start moclubemide 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
- Antidepressants: increased risk of antidiabetics and sedative effects when MAOIs given with antidiabetics
  - Antimicrobials: avoidance of antidepressants advised by manufacturer of amoxycillin and clavulanic acid
  - Alcohol: MAOIs interact with tyramine found in some beverages containing alcohol and some dealkoholised beverages (hypertensive crisis)—if no tyramine, enhanced hypertensive effect
  - Alpha-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of prazosin and idazoxan
  - Alpha-blockers: avoidance of MAOIs advised by manufacturer of indoramin; enhanced hypertensive effect when MAOIs given with alpha-blockers

**Note**
- For interactions of reversible MAO-A inhibitors (RIMAs) see moclobemide, and for interactions of MAO-B inhibitors see rasagiline 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 hypertensive effect when MAOIs given with adrenergic neurone blockers
- Alcohol: MAOIs interact with tyramine found in some beverages containing alcohol and some dealkoholised beverages (hypertensive crisis)—if no tyramine, enhanced hypertensive effect
  - Alpha-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of prazosin and idazoxan
  - Alpha-blockers: avoidance of MAOIs advised by manufacturer of indoramin; enhanced hypertensive effect when MAOIs given with alpha-blockers

**Antitussives:** MAOIs possibly enhance hypoglycaemic effect of antidiabetics; MAOIs enhance hypoglycaemic effect of insulin, metformin and sulphonylureas
- Antidepressants: increased risk of antidiabetics and sedative effects when MAOIs given with antidiabetics
  - Antimicrobials: avoidance of antidepressants advised by manufacturer of amoxycillin and clavulanic acid
  - Alcohol: MAOIs interact with tyramine found in some beverages containing alcohol and some dealkoholised beverages (hypertensive crisis)—if no tyramine, enhanced hypertensive effect
  - Alpha-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of prazosin and idazoxan
  - Alpha-blockers: avoidance of MAOIs advised by manufacturer of indoramin; enhanced hypertensive effect when MAOIs given with alpha-blockers

**Antidepressants:** increased risk of hypertension and CNS excitation when MAOIs given with
- MAOIs should normally be stopped 2 weeks before surgery
  - Antidepressants: increased risk of hypertension and CNS excitation when MAOIs given with
  - Antimicrobials (β-lactams, clavulanic acid) and MAOIs (avoid for at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with venlafaxine (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping 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); after stopping MAOIs do not start moclubemide 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 2 weeks after stopping mirtazapine or sertraline; after stopping MAOIs do not start duloxetine for 2 weeks, also MAOIs should not be started until at least 5 days after stopping duloxetine; enhanced CNS effects and toxicity when MAOIs given with venlafaxine (venlafaxine should not be started until 2 weeks after stopping MAOIs, avoid MAOIs for 1 week after stopping 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); after stopping MAOIs do not start moclubemide 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
- Antidepressants: increased risk of antidiabetics and sedative effects when MAOIs given with antidiabetics
  - Antimicrobials: avoidance of antidepressants advised by manufacturer of amoxycillin and clavulanic acid
  - Alcohol: MAOIs interact with tyramine found in some beverages containing alcohol and some dealkoholised beverages (hypertensive crisis)—if no tyramine, enhanced hypertensive effect
  - Alpha-adrenoceptor Stimulants: avoidance of MAOIs advised by manufacturer of prazosin and idazoxan
  - Alpha-blockers: avoidance of MAOIs advised by manufacturer of indoramin; enhanced hypertensive effect when MAOIs given with alpha-blockers
Appendix 1: Interactions

MAOIs (continued)
- 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 anticonvulsant 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 elevodopa, avoid levodopa for at least 2 weeks after stopping MAOIs; risk of hypertensive crisis when MAOIs given with rasagiline, avoid MAOIs for at least 2 weeks after stopping rasagiline; enhanced hypotensive effect when MAOIs given with selegiline; avoid concomitant use of MAOIs with tolcapone
- Doxapram: MAOIs enhance effects of doxapram
- 5HT1 Agonists: risk of CNS toxicity when MAOIs given with MAOIs
- Dopamine: avoid concomitant use of non-selective MAOIs with amphetamine; 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
- Diazoxide: enhanced hypotensive effect when MAOIs given with clonidine
- Methyl dopa: avoidance of MAOIs advised by manufacturer of methyl dopa
- Moxonidine: enhanced hypotensive effect when MAOIs given with moxonidine
- Muscle Relaxants: phenelzine enhances effects of suxamethonium
- 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
- Sympathomimetics: risk of hypertensive crisis when MAOIs given with sympathomimetics; risk of hypertensive crisis when MAOIs given with methylphenidate, some manufacturers advise avoid methylphenidate for at least 2 weeks after stopping MAOIs
- Tetrabenazine: risk of CNS excitation and hypertension when MAOIs given with tetrabenazine
- Vasodilator Antihypertensives: enhanced hypotensive effect when MAOIs given with hydralazine, minoxidil or sodium nitroprusside

MAOIs, reversible see Moclobemide

Maraviroc (continued)
- Antifungals: plasma concentration of maraviroc increased by ketoconazole (consider reducing dose of maraviroc)
- Antivirals: plasma concentration of maraviroc increased by atazanavir, darunavir, indinavir, lopinavir and saquinavir (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 nefinavir (consider reducing dose of maraviroc)

Mebendazole
Uler-healing Drugs: metabolism of mebendazole possibly inhibited by cimetidine (increased plasma concentration)

Medroxyprogesterone see Progestogens
Mefenamic Acid see NSAIDs
Mefloquine
- Anti-arrhythmics: increased risk of ventricular arrhythmias when mefloquine given with amiodarone—avoid concomitant use
- Antibacterials: increased risk of ventricular arrhythmias when mefloquine given with moxifloxacin—avoid concomitant use; plasma concentration of mefloquine reduced by efavirenz—avoid concomitant use
- Antiepileptics: mefloquine antagonises anticonvulsant effect of antiepileptics
- Antimalarials: avoidance of antimalarials advised by manufacturer of arteether/lumefantrine; increased risk of convulsions when mefloquine given with chloroquine and hydroxychloroquine; increased risk of convulsions when mefloquine given with quinine (but should not prevent the use of intravenous quinine in severe cases)
- Antipsychotics: increased risk of ventricular arrhythmias when mefloquine given with ziprasidone—avoid concomitant use
- Atomoxetine: increased risk of ventricular arrhythmias when mefloquine given with atomoxetine
- 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
- Ivermectin: increased risk of ventricular arrhythmias when mefloquine given with ivermectin
- Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 752

Megestrol see Progestogens
Melatonin see Anxiolytics and Hypnotics
Meloxicam see NSAIDs
Melphalan
- Antibacterials: increased risk of melphalan toxicity when given with nalidixic acid
- Antiepileptics: cystotoxics possibly reduce absorption of fenothiazine
- Antipsychotics: avoid concomitant use of cytoxotics with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: cytoxotics reduce absorption of digoxin tablets
- Ciclosporin: increased risk of nephrotoxicity when melphalan given with ciclosporin
- Memantine
- Anaesthetics, General: increased risk of CNS toxicity when memantine given with ketamine (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)
Methotrexate (continued)

- Analgesics: excretion of methotrexate probably reduced by NSAIDs (increased risk of toxicity); excretion of methotrexate reduced by azapropazone (avoid concomitant use); excretion of methotrexate reduced by ibuprofen, indometacin, ketoprofen, meloxicam and naproxen (increased risk of toxicity)
- 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 sulframethoxazole (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; cytoxins possibly reduce absorption of phenytoin
- Antimicrobials: antifolate effect of methotrexate increased by trimethoprim
- Antipsychotics: avoid concomitant use of cytotoxics
- Anticoagulants: mercaptopurine possibly reduces anticoagulant effect of coumarins
- Antipsychotics: cytoxins possibly reduce absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytoxins with clozapine (increased risk of agranulocytosis)
- Bacterial: excretion of methotrexate possibly reduced by neomycin; excretion of methotrexate possibly reduced by ciprofloxacin (increased risk of toxicity)
- Cardiac Glycosides: increased risk of haematological toxicitiy when methotrexate given with sulframethoxazole (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; cytoxins possibly reduce absorption of phenytoin
- Antimalarials: antifolate effect of methotrexate increased by trimethoprim (also with co-trimoxazole)
- Antipsychotics: avoid concomitant use of cytotoxics
- Anticoagulants: mercaptopurine possibly reduces anticoagulant effect of coumarins
- Antipsychotics: cytoxins possibly reduce absorption of phenytoin
- Antipsychotics: avoid concomitant use of cytoxins with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: cytoxins reduce absorption of digoxin tablets
- Retinoids: plasma concentration of methotrexate increased by acitretin (also increased risk of hepatotoxicity)—avoid concomitant use
- Theophylline: methotrexate possibly increases plasma concentration of theophylline

Ucer-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

Anasthetics, General: enhanced hypotensive effect when methyldopa given with general anaesthetics

Angiotensin-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
Appendix 1: Interactions

**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 *warfarin.*

**Antiepileptics:** Metronidazole inhibits metabolism of phenytoin (increased plasma concentration); metabolism of metronidazole accelerated by primidone (reduced plasma concentration).

**Barbiturates:** Metabolism of metronidazole accelerated by barbiturates (reduced plasma concentration).

**Cytotoxics:** Metronidazole increases plasma concentration 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. 478).

**Ulcer-healing Drugs:** Metronidazole inhibits metabolism of cimetidine (increased plasma concentration).

**Vaccines:** Antibacterials inactivate oral typhoid vaccine—see p. 752.

**Mianserin** See Antidepressants, Tricyclic (related).

**Mifepristone** Corticosteroids: mifepristone may reduce effect of nifedipine.

**Silodosin** See Antibacterials and Antifungals.

**Mifepristone** Corticosteroids: mifepristone may reduce effect of corticosteroids (including inhaled corticosteroids) for 3–4 days.

**Milrinone** See Phosphodiesterase Inhibitors.

**Minocycline** See Tetracyclines.

**Minoxidil** See Vasodilator Antihypertensives.

**Mitrazapine**

- Alcohol (increased sedative effect when mitrazapine given with alcohol).
- Anticoagulants: mitrazapine enhances anticoagulant effect of *warfarin.*
- Antidepressants: mitrazapine should not be started until 2 weeks after stopping MAOIs, also MAOIs should not be started until at least 2 weeks after stopping mitrazapine; after stopping mitrazapine do not start moclobemide for at least 1 week.
- Antiepileptics: plasma concentration of mitrazapine reduced by carbamazepine and phenytoin.
- Antifungals: plasma concentration of mitrazapine increased by ketoconazole.
- Antimalarials: avoidance of antidepressants advised by manufacturer of *artemether/lumefantrine*.
- Axioptics and Hypnotics: increased sedative effect when mitrazapine given with axioptics.
- Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine.
- Sibutramine: increased risk of CNS toxicity when mitrazapine given with sibutramine (manufacturer of sibutramine advises avoid concomitant use).
- Ulcer-healing Drugs: plasma concentration of mitrazapine increased by cimetidine.

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**Methyldopa** (continued)

**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 antiparkinsonian effect of dopaminergics; increased risk of extrapyramidal side-effects when methyldopa given with amantadine; effects of methyldopa possibly enhanced by entacapone; enhanced hypotensive effect when methyldopa given with levodopa.

**Iiron:** 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.

**Nitrites:** enhanced hypotensive effect when methyldopa given with nitrites.

**Oestrogens:** hypotensive effect of methyldopa antagonised by oestrogens.

**Prostaglandins:** enhanced hypotensive effect when methyldopa given with alprostadil.

- Symptomimetics, Beta-acute hypotension reported when methyldopa given with infusion of *albuterol*.
- Vasodilator Antihypertensives: enhanced hypotensive effect when methyldopa given with hydroalazine, minoxidil or sodium nitroprusside.

**Methyldopa (continued)**

**Analgesics:** metclopromide increases rate of absorption of aspirin (enhanced effect); effects of metclopromide on gastro-intestinal activity antagonised by opioid analgesics; metclopromide increases rate of absorption of paracetamol.

**Antinociceptives:** effects of metclopromide on gastro-intestinal activity antagonised by antinociceptives.

**Antipsychotics:** increased risk of extrapyramidal side-effects when metclopromide given with antipsychotics.

**Atovaquone:** metclopromide reduces plasma concentration of atovaquone.

- Ciclosporin: metclopromide increases plasma concentration of ciclosporin.

**Dopaminergics:** increased risk of extrapyramidal side-effects when metclopromide given with pergolide; avoidance of metclopromide advised by manufacturer of ropinirole and rotigotine (antagonism of effect).

**Muscle Relaxants:** metclopromide enhances effects of suxamethonium.

**Tetrahydrabenzine:** increased risk of extrapyramidal side-effects when metclopromide given with tetrahydrabenzine.

**Metolazone** See Diuretics.

**Metoprolol** See Beta-blockers.

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**Appendix 1: Interactions**

**BNFC 2009**
Mitomycin

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

Mitotane

• Anticoagulants: mitotane 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

Diuretics: manufacturer of mitotane advises avoid concomitant use of spironolactone (antagonism of effect)

Mivacurium see Muscle Relaxants

Mizolastine see Antihistamines

Mobocormide

• Analgesics: possible CNS excitation or depression (hypertension or hypotension) when mobocormide given with dextromethorphan or ephedrine—avoid concomitant use; possible CNS excitation or depression (hypertension or hypotension) when mobocormide given with opioid analgesics

• Antidepressants: mobocormide should not be started for at least 1 week after stopping MAOIs, SSRIs, tricyclic-related antidepressants, ephedrine, mirtazapine, paroxetine, tricyclic-related antidepressants or tricyclics; increased risk of CNS toxicity when mobocormide given with ephedrine, preferably avoid concomitant use; mobocormide should not be started until 5 weeks after stopping fluoxetine; mobocormide should not be started until 2 weeks after stopping paroxetine; possible increased serotonergic effects when mobocormide given with duloxetine

• Antimalarials: avoidance of antidepressants advised by manufacturer of arteether/ lumefantrine

Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine

Bupropion: avoidance of mobocormide advised by manufacturer of bupropion

Dopaminergics: caution with mobocormide advised by manufacturer of entacapone; increased risk of side-effects when mobocormide given with levodopa; avoid concomitant use of mobocormide with selegiline

SHT: Agonists: risk of CNS toxicity when mobocormide given with rizatriptan or sumatriptan (avoid ritatriptan or sumatriptan for 2 weeks after mobocormide); risk of CNS toxicity when mobocormide given with zolmitriptan (reduce dose of zolmitriptan)

Sibutramine: increased CNS toxicity when mobocormide given with sibutramine (manufacturer of sibutramine advises avoid concomitant use), also avoid sibutramine for 2 weeks after stopping mobocormide

Symphotomimetics: risk of hypertensive crisis when mobocormide given with sympathomimetics

Ulcer-healing Drugs: plasma concentration of mobocormide increased by cimetidine (halve dose of mobocormide)

Modafinil

Antiepileptics: modafinil possibly increases plasma concentration of phenytoin

Ciclosporin: modafinil reduces plasma concentration of ciclosporin

Oestrogens: modafinil accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 478)

Moxepril see ACE Inhibitors

Mometasone see Corticosteroids

Monobactams see Aztreonam

Montelukast see Leukotriene Receptor Antagonists

Morphine see Opioid Analgesics

Moxifloxacin 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

Methyldopa: enhanced hypotensive effect when moxisylyte given with methyldopa

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

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
Appendix 1: Interactions

Muscle Relaxants (continued)

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; hypertony, 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 antagonised by corticosteroids

Cytotoxics: effects of suxamethonium enhanced by cyclophosphamide and thiopeta

Diazoide: enhanced hypotensive effect when baclofen or tizanidine given with diazoide

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 (prenatal): effects of non-depolarising muscle relaxants and suxamethonium enhanced by parenteral magnesium

Methamphetamines: 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

Moxonidine: enhanced hypotensive effect when baclofen or tizanidine given with moxonidine

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 suxamethonium possibly enhanced by donepezil; effects of non-depolarising muscle relaxants possibly antagonised by donepezil; effects of suxamethonium enhanced by edrophonium, galantamine, neostigmine, pyridostigmine and rivastigmine; effects of non-depolarising muscle relaxants antagonised by edrophonium, neostigmine, pyridostigmine and rivastigmine

Progesterones: plasma concentration of tizanidine possibly increased by progesterones (increased risk of toxicity)

Sympathomimetics, Beta-2: effects of suxamethonium enhanced by bambuterol

Vasodilator Antihypertensives: enhanced hypotensive effect when baclofen or tizanidine given with hydralazine, minoxidil or sodium nitroprusside

Appendix 1: Interactions

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

Alpha-blockers: enhanced hypotensive effect when baclofen or tizanidine given with alpha-blockers

Anaesthetics, General: effects of atracurium enhanced by ketamine; 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 procaine

Analgesics: excretion of baclofen possibly reduced by NSAIDs (increased risk of toxicity); excretion 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 relaxants and suxamethonium enhanced by aminoglycosides; effects 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
**Mycophenolate** (continued)

- Antibacterials: bioavailability of mycophenolate possibly reduced by metronidazole and norfloxacin; plasma concentration of active metabolite of mycophenolate reduced by rifampicin.
- Antiepileptics: cytoxotics possibly reduce absorption of phenytoin.
- Antipsychotics: avoid concomitant use of cytoxotics 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: cytoxotics reduce absorption of digoxin tablets.
- Iron: absorption of mycophenolate reduced by oral iron.
- Lipid-regulating Drugs: absorption of mycophenolate reduced by colestearamine.
- Sevelamer: plasma concentration of mycophenolate possibly reduced by sevelamer.

**Mycophenolate Mofetil** see Mycophenolate

**Mycophenolate Sodium** see Mycophenolate

**Mycophenolic Acid** see Mycophenolate

**Nabumetone** see NSAIDs

**Nadolol** see Beta-blockers

**Nalidixic Acid** see Quinolones

**Nandrolone** see Anabolic Steroids

**Naproxen** see NSAIDs

**Naratipran** see SHT, Agonists

**Nateglinide** see Antidiabetics

**Nebivolol** see Beta-blockers

**Nefopam**
- Antidepressants: manufacturer of nefopam advises avoid concomitant use with MAOIs; side-effects possibly increased when nefopam given with tricyclics.
- Antimuscarinics: increased risk of antimuscarinic side-effects when nefopam given with antimuscarinics.

**Nelfinavir**

- Analgesics: nelfinavir reduces plasma concentration of methadone.
- Anti-arrhythmics: increased risk of ventricular arrhythmias when nefopam given with amiodarone—avoid concomitant use.
- Antibacterials: nelfinavir increases plasma concentration of rifabutin (halve dose of rifabutin); plasma concentration of nelfinavir significantly reduced by rifampicin—avoid concomitant use; avoidance of concomitant nefopam 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 wort—avoid concomitant use.
- Antiepileptics: plasma concentration of nelfinavir possibly reduced by carbamazepine and epimidine; nelfinavir reduces plasma concentration of phenytoin.
- Antimalarials: caution with nelfinavir advised by manufacturer of arteether/luemfantrine.
- Antimuscarinics: avoidance of nelfinavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when nefopam given with fesoterodine—consult fesoterodine product literature; nefopam increases plasma concentration of solifenacin.

**Nelipivirnav (continued)**

- Antipsychotics: nelfinavir possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); nelfinavir possibly increases plasma concentration of pimozide (increased risk of ventricular arrhythmias—avoid concomitant use); nelfinavir increases plasma concentration of asertindole (increased risk of ventricular arrhythmias—avoid concomitant use).
- Antivirals: plasma concentration of nelfinavir possibly increased by etravirine—avoid concomitant use; combination of nelfinavir with indinavir, ritonavir or saquinavir may increase plasma concentration of either drug (or both); nelfinavir reduces plasma concentration of lopinavir, also plasma concentration of active metabolite of nelfinavir increased; nelfinavir possibly increases plasma concentration of maraviroc (consider reducing dose of maraviroc).
- Anxiolytics and Hypnotics: nelfinavir possibly increases plasma concentration of midazolam (risk of prolonged sedation—avoid concomitant use of oral midazolam).
- Barbiturates: plasma concentration of nelfinavir possibly reduced by barbiturates.
- Ciclorsporin: nelfinavir possibly increases plasma concentration of ciclorsporin.
- Cilostazol: nelfinavir possibly increases plasma concentration of cilostazol—avoid concomitant use.
- Antiepileptics: cytotoxics possibly reduce absorption of digoxin tablets.
- Diuretics: nelfinavir increases plasma concentration of spironolactone—avoid concomitant use.
- Ergot Alkaloids: increased risk of ergotism when nefopam given with ergotamine and methysergide—avoid concomitant use.
- SHT, Agonists: nelfinavir increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use.
- Ibandravine: nelfinavir possibly increases plasma concentration of ibandravine—avoid concomitant use.
- Lipid-regulating Drugs: possible increased risk of myopathy when nefopam given with atorvastatin; possible increased risk of myopathy when nefopam given with rosuvastatin—avoid concomitant use; increased risk of myopathy when nefopam given with simvastatin (avoid concomitant use).
- Oestrogens: nelfinavir accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 478).
- Progestogens: nelfinavir possibly reduces contraceptive effect of progestogens.
- 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 omeprazole—avoid concomitant use.

**Neomycin** see Aminoglycosides

**Neostigmine** see Parasympathomimetics

**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 wort—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 and iraconazole—
Antivirals: nevirapine possibly reduces plasma concentration of efavirenz and indinavir; nevirapine possibly reduces plasma concentration of fosamprenavir; nevirapine possibly reduces plasma concentration of lopinavir—consider increasing dose of lopinavir.

Antipsychotics: nevirapine possibly reduces plasma concentration of aripiprazole—increased dose of aripiprazole.

Antifungals: plasma concentration of nilotinib increased by ketoconazole—avoid concomitant use; nevirapine reduces plasma concentration of itraconazole—increased dose of itraconazole.

Antiepileptics: nilotinib affects concentration of phenytoin; nevirapine possibly reduces plasma concentration of carbamazepine.

Antiemetics: nilotinib possibly increases plasma concentration of ondansetron; nevirapine increases plasma concentration of granisetron.

Progestogens: nevirapine accelerates metabolism of aripiprazole—reduced contraceptive effect—see p. 478.

Nicorandil see Calcium-channel Blockers

Calcium-channel Blockers

Alpha-blockers: enhanced hypotensive effect when nitrates given with alpha-blockers.

Nitrate preparations: enhanced hypotensive effect when nitrates given with nitrate preparations—avoid concomitant use.

Nitrates (continued)

Alpha-blockers: enhanced hypotensive effect when nitrates given with alpha-blockers.

Alpha-blockers: enhanced hypotensive effect when nitrates given with nitrate preparations; effects of sublingual tablets of nitrates possibly reduced by tricyclic-related antidepressants (failure to dissolve under tongue owing to dry mouth)

Anticoagulants: infusion of glyceryl trinitrate reduces anticoagulant effect of heparins.

Antidepressants: enhanced hypotensive effect when nitrates given with MAOIs; effects of sublingual tablets of nitrates possibly 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).

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: enhanced hypotensive effect when nitrates given with 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.

Methylxanthines: enhanced hypotensive effect when nitrates given with methylxanthines.

Moxisylyte: 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 muscle relaxants.

Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers.

Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics.

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens (risk probably small, see p. 478).

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa.

Moxisylyne (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyne.

Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine.

Nitroglycerin (trogitrate): enhanced hypotensive effect when nitrates given with nitroglycerin (trogitrate).

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.

Methylxanthines: enhanced hypotensive effect when nitrates given with methylxanthines.

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 muscle relaxants.

Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers.

Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics.

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens (risk probably small, see p. 478).

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa.

Moxisylyne (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyne.

Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine.

Muscle Relaxants: enhanced hypotensive effect when nitrates given with muscle relaxants.

Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers.

Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics.

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens (risk probably small, see p. 478).

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa.

Moxisylyne (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyne.

Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine.

Muscle Relaxants: enhanced hypotensive effect when nitrates given with muscle relaxants.

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.

Nitrates (continued)

Alpha-blockers: enhanced hypotensive effect when nitrates given with alpha-blockers.

Analgesics, General: enhanced hypotensive effect when nitrates given with general anaesthetics.

Alpha-blockers: enhanced hypotensive effect when nitrates given with alpha-blockers.

Anticoagulants: infusion of glyceryl trinitrate reduces anticoagulant effect of heparins.

Antidepressants: enhanced hypotensive effect when nitrates given with MAOIs; effects of sublingual tablets of nitrates possibly 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).

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: enhanced hypotensive effect when nitrates given with 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.

Methylxanthines: enhanced hypotensive effect when nitrates given with methylxanthines.

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 muscle relaxants.

Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers.

Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics.

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens (risk probably small, see p. 478).

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa.

Moxisylyne (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyne.

Moxonidine: enhanced hypotensive effect when nitrates given with moxonidine.

Muscle Relaxants: enhanced hypotensive effect when nitrates given with muscle relaxants.

Beta-blockers: enhanced hypotensive effect when nitrates given with beta-blockers.

Anxiolytics and Hypnotics: enhanced hypotensive effect when nitrates given with anxiolytics and hypnotics.

Oestrogens: hypotensive effect of nitrates antagonised by oestrogens (risk probably small, see p. 478).

Methyldopa: enhanced hypotensive effect when nitrates given with methyldopa.

Moxisylyne (thymoxamine): enhanced hypotensive effect when nitrates given with moxisylyne.
Nitrofurantoin (continued)
Sulfispyrazone: excretion of nitrofurantoin reduced by sulfispyrazone (increased risk of toxicity)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752
Nitromidazoles see Metronidazole and Tinidazole
Nitrous Oxide see Anaesthetics, General
Nizatidine see Histamine H2–antagonists
Noradrenaline (norepinephrine) see Sympathomimetics
Noregesterone see Progestogens
Noriprophene (noradrenaline) see Sympathomimetics
Northeistone see Progestogens
Noroxacin see Quinolones
Norpregestane see Progestogens
Norrestrol see Progestogens
Nortriptiline 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: avoid concomitant use of NSAIDs with
  • NSAIDs or aspirin (increased side-effects); avoid concomitant use of NSAIDs with ketorolac (increased side-effects and haemorrhage); ibuprofen possibly reduces antplatelet effect of aspirin
  • Angiotensin-II Receptor Antagonists: increased risk of renal impairment when NSAIDs given with angiotensin-II receptor antagonists, also hypotensive effect antagonised
• Antibacterials: indometacin possibly increases plasma concentration of amikacin and gentamicin in neonates; plasma concentration of etoricoxib reduced by rifampicin; possible increased risk of convulsions when NSAIDs given with quinolones
• Anticoagulants: increased risk of haemorrhage when intravenous diclofenac given with anticoagulants (avoid concomitant use, including low-dose heparin); increased risk of haemorrhage when ketorolac given with anticoagulants (avoid concomitant use, including low-dose heparin); aspirin antagonises anticoagulant effect of coumarins (avoid concomitant use); NSAIDs possibly enhance anticoagulant effect of coumarins and phenindione; possible increased risk of bleeding when NSAIDs given with dabigatran etexilate or warfarin
• Antidepressants: increased risk of bleeding when NSAIDs given with SSRIs or venlafaxine
• Antidiabetics: azapropazone enhances effects of tolbutamide (avoid concomitant use); NSAIDs possibly enhance effects of sulphonylureas
• Antiepileptics: azapropazone significantly increases plasma concentration of phenytoin—avoid concomitant use; NSAIDs possibly enhance effects of phenytoin
• Antifungals: plasma concentration of nystatin increased by fluconazole (reduce dose of nystatin); plasma concentration of ceftizoxime increased by fluconazole (halve dose of ceftizoxime); plasma concentration of diclofenac and ibuprofen increased by voriconazole
• Antipsychotics: possible severe drowsiness when indometacin given with haloperidol; avoid concomitant use of azapropazone with clozapine (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

NSAIDs (continued)
Beta-blockers: NSAIDs antagonise hypotensive effect of beta-blockers
Bisphosphonates: indometacin increases bioavailability of thuludronic acid
Calcium-channel Blockers: NSAIDs antagonise hypotensive effect of calcium-channel blockers
Cardiac 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 diclofenac increased by ciclosporin (halve dose of diclofenac)
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); azapropazone reduces excretion of methotrexate (avoid concomitant use); diclofenac, ibuprofen, indometacin, ketoprofen, meloxicam and naproxen reduce excretion of methotrexate (increased risk of toxicity); increased risk of bleeding when NSAIDs given with etoricoxib
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 colestyramine
• Lithium: NSAIDs 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
Moxonidine: NSAIDs antagonise hypotensive effect of moxonidine
Muscle Relaxants: NSAIDs possibly reduce excretion of baclofen (increased risk of toxicity); ibuprofen reduces excretion of baclofen (increased risk of toxicity)
Nitrates: NSAIDs antagonise hypotensive effect of nitrates
Oxestrogen: etoricoxib increases plasma concentration of ethinylestradiol
Penicillamine: possible increased risk of nephrotoxicity when NSAIDs given with penicillamine
• Pentoxyfylline (oxpentifylline): possible increased risk of bleeding when NSAIDs given with pentoxyfylline (oxpentifylline); increased risk of bleeding when ketorolac given with pentoxyfylline (oxpentifylline) (avoid concomitant use)
Appendix 1: Interactions

Antidepressants: contraceptive effect of oestrogens
Antibacterials: contraceptive effect of oestrogens possibly reduced by antibiotics that do not induce hepatic enzymes (risk probably small, see p. 478); oestrogens reduce contraceptive effect—see p. 478; oestrogens reduce contraceptive effect when given with sibutramine
Anticoagulants: oestrogens may enhance or reduce anticoagulant effect of coumarins; oestrogens reduce contraceptive effect when given with warfarin

Aprepitant: possible contraceptive failure of hormonal contraceptives containing oestrogens when given with aprepitant (alternative contraception recommended)
Barbiturates: metabolism of oestrogens accelerated by barbiturates (reduced contraceptive effect—see p. 478)

Beta-blockers: oestrogens antagonise hypotensive effect of beta-blockers
Bile Acids: 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 dopamine

Ethinylestradiol possibly reduced by sugammadex
Estrogen: (reduced contraceptive effect—see p. 478)
Ethinylestradiol possibly reduced by sugammadex
Ethinylestradiol possibly reduced by sugammadex
Estrogen: (reduced contraceptive effect—see p. 478)
Ethinylestradiol possibly reduced by sugammadex
Ethinylestradiol possibly reduced by sugammadex

Phenothiazines: metabolism of oestrogens possibly reduced by phenothiazines
Phenyleptics: metabolism of oestrogens accelerated by phenyleptics
Phenytoin: metabolism of oestrogens possibly reduced by phenytoin

Protease Inhibitors: possible contraceptive failure of protease inhibitors containing oestrogens when given with protease inhibitors (alternative contraception recommended)
Proton Pump Inhibitors: metabolism of oestrogens possibly reduced by proton pump inhibitors
Ritonavir: metabolism of oestrogens possibly reduced by ritonavir
Ritonavir: metabolism of oestrogens possibly reduced by ritonavir
Ritonavir: metabolism of oestrogens possibly reduced by ritonavir
Appendix 1: Interactions

Opioid Analgesics

Alcohol: enhanced hypotensive and sedative effects when opioid analgesics given with alcohol

Antibacterials: plasma concentration of alfentanil 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 anticoagulant effect of coumarins

Antidepressants: plasma concentration of methadone possibly increased by fluvoxamine; possible increased serotonergic effects when pethidine or tramadol given with duloxetine; CNS excitation or depression (hypertension or hypotension) when pethidine given with MAOIs—avoid concomitant use and for 2 weeks after stopping MAOIs; possible CNS excitation or depression (hypertension or hypotension) when opioid analgesics given with MAOIs—avoid concomitant use and for 2 weeks after stopping MAOIs; possible CNS excitation or depression (hypertension or hypotension) when dextromethorphan or pethidine given with moclobemide—avoid concomitant use; increased risk of CNS toxicity when tramadol given with SSRIs or tricyclics; sedative effects possibly increased when opioid analgesics given with tricyclics

Antiepileptics: dextropropoxyphene enhances effects of carbamazepine; effects of tramadol reduced by carbamazepine; plasma concentration of methadone reduced by carbamazepine; metabolism of methadone accelerated by phenytoin (reduced effect and risk of withdrawal effects)

Antifungals: metabolism of buprenorphine inhibited by ketoconazole (reduce dose of buprenorphine); metabolism of alfentanil inhibited by fluconazole (risk of prolonged or delayed respiratory depression); plasma concentration of fentanyl possibly increased by voriconazole (consider reducing dose of voriconazole) when dextromethorphan or pethidine given with moclobemide; possible CNS excitation or depression (hypertension or hypotension) when dextromethorphan or pethidine given with moclobemide—avoid concomitant use; increased risk of CNS toxicity when dextromethorphan or pethidine given with moclobemide—avoid concomitant use; increased risk of CNS toxicity when tramadol given with moclobemide; possible CNS excitation or depression (hypertension or hypotension) when dextromethorphan or pethidine given with moclobemide

Antihistamines: sedative effects possibly increased when opioid analgesics given with sedating antihistamines

Antipsychotics: enhanced hypotensive and sedative effects when opioid analgesics given with antipsychotics; increased risk of convulsions when tramadol given with antipsychotics

Antivirals: plasma concentration of methadone reduced by efavirenz, also plasma concentration of an active metabolite of oxcarbazepine reduced; plasma concentration of fentanyl possibly increased by ritonavir; plasma concentration of carbamazepine (but concentration of an active metabolite of carbamazepine may be increased); also plasma concentration of an active metabolite of oxcarbazepine sometimes reduced by valproate

Antidepressants: anticonvulsant effect of antiepileptics sometimes reduced by valproate

Antihistamines: metabolism of morphine reduced by ritonavir; morphine possibly reduced plasma concentration of zidovudine

Anxiolytics and Hypnotics: increased sedative effect when opioid analgesics given with anxiolytics and hypnotics

Atomoxetine: increased risk of ventricular arrhythmias when methadone given with atomoxetine; possible

Opioid Analgesics

Atomoxetine (continued)

increased risk of convulsions when tramadol given with atomoxetine

Barbiturates: CNS effects of opioid analgesics possibly increased by barbiturates

Beta-blockers: morphine possibly increases plasma concentration of esmolol

Calcium-channel Blockers: metabolism of alfentanil inhibited by diltiazem (risk of prolonged or delayed respiratory depression)

Dopamergic Blockers: metabolism of alfentanil inhibited by diltiazem

Memantine: increased risk of CNS toxicity when dextromethorphan given with memantine (manufacturer of memantine advises avoid concomitant use)

Metoclopramide: opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity

Sodium Oxybate: opioid analgesics enhance effects of sodium oxybate (avoid concomitant use)

Ulcerc-Healing Drugs: metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)

Opioid Analgesics

Barbiturates: CNS effects of opioid analgesics possibly increased by barbiturates

Beta-blockers: morphine possibly increases plasma concentration of esmolol

Calcium-channel Blockers: metabolism of alfentanil inhibited by diltiazem (risk of prolonged or delayed respiratory depression)

Dopamergic Blockers: metabolism of alfentanil inhibited by diltiazem

Memantine: increased risk of CNS toxicity when dextromethorphan given with memantine (manufacturer of memantine advises avoid concomitant use)

Metoclopramide: opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity

Sodium Oxybate: opioid analgesics enhance effects of sodium oxybate (avoid concomitant use)

Ulcerc-Healing Drugs: metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)

Opioid Analgesics

Barbiturates: CNS effects of opioid analgesics possibly increased by barbiturates

Beta-blockers: morphine possibly increases plasma concentration of esmolol

Calcium-channel Blockers: metabolism of alfentanil inhibited by diltiazem (risk of prolonged or delayed respiratory depression)

Dopamergic Blockers: metabolism of alfentanil inhibited by diltiazem

Memantine: increased risk of CNS toxicity when dextromethorphan given with memantine (manufacturer of memantine advises avoid concomitant use)

Metoclopramide: opioid analgesics antagonise effects of metoclopramide on gastro-intestinal activity

Sodium Oxybate: opioid analgesics enhance effects of sodium oxybate (avoid concomitant use)

Ulcerc-Healing Drugs: metabolism of opioid analgesics inhibited by cimetidine (increased plasma concentration)
Appendix 1: Interactions

Oxcarbazepine (continued)

Parasympathomimetics (continued)

Antimalarials: effects of neostigmine and pyrido-
stimine may be diminished because of potential for
chloroquine and hydroxychloroquine to increase
symptoms of myasthenia gravis

Antimuscarinics: effects of parasympathomimetics
organised by antimuscarinics

Beta-blockers: increased risk of arrhythmias when
dilpocarprone given with beta-blockers; effects of
neostigmine and pyridostigmine organised by pro-
pranolol

Lithium: effects of neostigmine and pyridostigmine
organised by lithium

Muscle Relaxants: donepezil possibly enhances effects
of suxamethonium; edrophonium, galantamine,
neostigmine, pyridostigmine and rivastigmine
enhance effects of suxamethonium; donepezil poss-
ibly organises effects of non-depolarising muscle
relaxants; edrophonium, neostigmine,
pyridostigmine and rivastigmine organises effects of
non-depolarising muscle relaxants

Parecoxib see NSAIDs

Paricalcitol see Vitamins

Paroxetine see Antidepressants, SSRI

Pepligrafastin see Filipgrastim

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)

Antivirals: plasma concentration of parlaxilx
increased by nelfinovir and ritonavir

Cardiac Glycosides: cytotoxins reduce absorption of
digoxin tablets

Palperidine see Antipsychotics

Pancreatin

Antidiabetics: pancreatin antagonises hypoglycaemic
effect of acarbose

Pancuronium see Muscle Relaxants

Pantoprazole see Proton Pump Inhibitors

Papaveretum see Opioid Analgesics

Paracetamol

Anticoagulants: prolonged regular use of paracetamol
possibly enhances anticoagulant effect of coumarins

Antiepileptics: metabolism of paracetamol possibly
accelerated by carbamazepine

Cytotoxics: paracetamol possibly inhibits metabolism of
intravenous busulfan (manufacturer of intravenous
busulfan advises caution within 72 hours of para-
cetamol)

Lipid-regulating Drugs: absorption of paracetamol
reduced by colestanime

Metoclopramide: rate of absorption of paracetamol
increased by metoclopramide

Paraldehyde

Alcohol: increased sedative effect when paraldehyde
given with alcohol

Disulfiram: risk of toxicity when paraldehyde given with
disulfiram

Parasympathomimetics

Anti-arrhythmics: effects of neostigmine and pyrido-
stimine possibly organised by propafenone

Antibacterials: plasma concentration of galantamine
increased by erythromycin; effects of
neostigmine and pyridostigmine antagonised by
dimethylguanidine; effects of neostigmine and pyridostigmine antagonised by
dimethylguanidines

Antidepressants: plasma concentration of galantamine
increased by paroxetine

Antifungals: plasma concentration of galantamine
increased by ketoconazole

Paraldehyde

Disulfiram: risk of toxicity when paraldehyde given
with disulfiram

Alcohol: increased sedative effect when paraldehyde
given with alcohol

Parasympathomimetics

Anticoagulants: prolonged regular use of paracetamol
possibly enhances anticoagulant effect of coumarins

Antiepileptics: metabolism of paracetamol possibly
accelerated by carbamazepine

Cytotoxics: paracetamol possibly inhibits metabolism of
intravenous busulfan (manufacturer of intravenous
busulphan advises caution within 72 hours of para-
cetamol)

Lipid-regulating Drugs: absorption of paracetamol
reduced by colestanime

Metoclopramide: rate of absorption of paracetamol
increased by metoclopramide

Paraldehyde

Alcohol: increased sedative effect when paraldehyde
given with alcohol

Disulfiram: risk of toxicity when paraldehyde given with
disulfiram

Parasympathomimetics

Anti-arrhythmics: effects of neostigmine and pyrido-
stimine possibly organised by propafenone

Antibacterials: plasma concentration of galantamine
increased by erythromycin; effects of
neostigmine and pyridostigmine antagonised by
dimethylguanidine; effects of neostigmine and pyridostigmine antagonised by
dimethylguanidines

Antidepressants: plasma concentration of galantamine
increased by paroxetine

Antifungals: plasma concentration of galantamine
increased by ketoconazole

Parasympathomimetics

Anticoagulants: prolonged regular use of paracetamol
possibly enhances anticoagulant effect of coumarins

Antiepileptics: metabolism of paracetamol possibly
accelerated by carbamazepine

Cytotoxics: paracetamol possibly inhibits metabolism of
intravenous busulphan (manufacturer of intravenous
busulphan advises caution within 72 hours of para-
cetamol)

Lipid-regulating Drugs: absorption of paracetamol
reduced by colestanime

Metoclopramide: rate of absorption of paracetamol
increased by metoclopramide

Paraldehyde

Alcohol: increased sedative effect when paraldehyde
given with alcohol

Disulfiram: risk of toxicity when paraldehyde given with
disulfiram

Parasympathomimetics

Anti-arrhythmics: effects of neostigmine and pyrido-
stimine possibly organised by propafenone

Antibacterials: plasma concentration of galantamine
increased by erythromycin; effects of
neostigmine and pyridostigmine antagonised by
dimethylguanidine; effects of neostigmine and pyridostigmine antagonised by
dimethylguanidines

Antidepressants: plasma concentration of galantamine
increased by paroxetine

Antifungals: plasma concentration of galantamine
increased by ketoconazole
Appendix 1: Interactions

Pentamidine Isetionate (continued)
- Antidepressants: increased risk of ventricular arrhythmias when pentamidine isetionate given with tricyclics
- Antifungals: possible increased risk of nephrotoxicity when pentamidine isetionate given with amphotericin
- Antipsychotics: increased risk of ventricular arrhythmias when pentamidine isetionate given with amisulpride—avoid concomitant use; increased risk of ventricular arrhythmias when pentamidine isetionate given with phenothiazines
- Ivabradine: increased risk of ventricular arrhythmias when pentamidine isetionate given with ivabradine

Phentolamine see Opioid Analgesics

Phenobarbital
- Sympathomimetics

Phenytoin
- Antidepressants: effects of phenytoin possibly enhanced by analgesic agents or antihistamines
- Anticoagulants: anticoagulant effect of phenytoin possibly enhanced by aspirin
- Anticoagulants: anticoagulant effect of phenytoin possibly enhanced by oestrogens
- Anticoagulants: anticoagulant effect of phenytoin possibly enhanced by vitamin K

Phenolamine see Antihypertensives
Phenylbutazone see Antipyretics
Phenylbutyric acid see Antipyretics
Phenytoin
- Antidepressants: effects of phenytoin possibly enhanced by tricyclic antidepressants
- Anticoagulants: anticoagulant effect of phenytoin possibly enhanced by aspirin

Phenylalanine see Antipsychotics
Phenylpropanolamine see Antihistamines

Phenylpropionic acid see Antipyretics
Phenylpyruvic acid see Antipyretics
Appendix 1: Interactions

Phenytoin (continued)

- Antidepressants: plasma concentration of phenytoin increased by \textit{fluoxetine} and \textit{fluvoxamine}; phenytoin reduces plasma concentration of \textit{mianserin}, \textit{mirtazapine} and \textit{paroxetine}; anticonvulsant effect of anti-epileptics possibly antagonised by MAOIs and \textit{tricyclic-related antidepressants} (convulsive threshold lowered); anticonvulsant effect of anti-epileptics antagonised by \textit{SSRIs} and \textit{tricyclics} (convulsive threshold lowered); avoid concomitant use of anti-epileptics with \textit{St John's wort}; phenytoin possibly reduces plasma concentration of \textit{tricyclics}

- Antiepileptics: plasma concentration of both drugs often reduced when phenytoin given with \textit{carbamazepine}; also plasma concentration of phenytoin may be increased; plasma concentration of phenytoin possibly increased by \textit{ethosuximide}, also plasma concentration of ethosuximide possibly reduced; phenytoin reduces plasma concentration of \textit{lamotrigine}, \textit{tiagabine} and \textit{zonisamide}; plasma concentration of phenytoin increased by \textit{oxcarbazepine}, also plasma concentration of an active metabolite of oxcarbazepine reduced; phenytoin possibly reduces plasma concentration of \textit{levetiracetam}, also plasma concentration of an active metabolite increased; plasma concentration of phenytoin often reduced but may be increased; plasma concentration of phenytoin possibly increased by \textit{rufinamide}; plasma concentration of phenytoin increased by \textit{estradiol}; plasma concentration of phenytoin increased by \textit{topiramate} (also plasma concentration of topiramate reduced); plasma concentration of phenytoin increased or possibly reduced when given with \textit{valproate}, also plasma concentration of valproate reduced; plasma concentration of phenytoin reduced by \textit{vigabatrin}

- Antifungals: phenytoin reduces plasma concentration of \textit{itraconazole} and \textit{posaconazole}; anticonvulsant effect of phenytoin enhanced by \textit{itraconazole} (consider reducing dose of phenytoin); phenytoin reduces plasma concentration of \textit{itraconazole}—avoid concomitant use; plasma concentration of phenytoin increased by \textit{voriconazole}, also phenytoin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for phenytoin toxicity); phenytoin possibly reduces plasma concentration of \textit{caspofungin}—consider increasing dose of caspofungin

- Antimalarials: possible increased risk of convulsions when anti-epileptics given with \textit{chloroquine} and \textit{hydroxychloroquine}; anticonvulsant effect of anti-epileptics antagonised by \textit{methotrexate}; anticonvulsant effect of phenytoin antagonised by \textit{pyrimethamine}, also increased antifolate effect

- Antipsychotics: anticonvulsant effect of phenytoin antagonised by \textit{risperidone} and \textit{quetiapine}; phenytoin possibly reduced but may be increased plasma concentration of \textit{alcuronium}, \textit{dantrolene} and \textit{diltiazem} reduced; effect of \textit{levodopa} reduced; effect of \textit{diazoxide} reduced; effect of \textit{diltiazem} may be reduced by \textit{levodopa}

- Antivirals (continued): concentration of phenytoin increased or decreased by \textit{zidovudine}

- Anxiolytics and Hypnotics: phenytoin often reduces plasma concentration of \textit{clonazepam}; plasma concentration of phenytoin increased or decreased by \textit{diazepam}; plasma concentration of phenytoin possibly increased or decreased by \textit{benzodiazepines}

- Aprepitant: phenytoin possibly reduces plasma concentration of \textit{aprepitant}

- Barbiturates: phenytoin often increases plasma concentration of \textit{phenobarbital}, plasma concentration of phenytoin often reduced but may be increased \textit{Bupropion}; phenytoin reduces plasma concentration of \textit{bupropion}

- Calcium-channel Blockers: phenytoin reduces effects of \textit{felodipine}, \textit{isradipine} and \textit{verapamil}; phenytoin probably reduces effects of \textit{dihydropyridines}, \textit{nicardipine} and \textit{nifedipine}; plasma concentration of phenytoin increased by \textit{diltiazem} but also effect of \textit{diltiazem} reduced

- Cardio Glycosides: phenytoin accelerates metabolism of \textit{digitalis} (reduced effect); phenytoin possibly reduces plasma concentration of \textit{digoxin}

- Ciclosporin: phenytoin accelerates metabolism of \textit{ciclosporin} (reduced plasma concentration)

- Corticosteroids: phenytoin accelerates metabolism of \textit{corticosteroids} (reduced effect)

- Cytotoxics: phenytoin possibly reduces plasma concentration of \textit{busulfan} and \textit{etoposide}; metabolism of phenytoin possibly inhibited by \textit{fluorouracil} (increased risk of toxicity); phenytoin increases antifolate effect of \textit{methotrexate}; absorption of phenytoin possibly reduced by \textit{cytoxicoids}; phenytoin reduces plasma concentration of \textit{matinid}—avoid concomitant use; avoidance of phenytoin advised by manufacturer of \textit{apatinib}; phenytoin reduces plasma concentration of \textit{irinotecan} and its active metabolite

- Diazoxide: plasma concentration of phenytoin reduced by \textit{diazoxide}, also effect of diazoxide may be reduced

- Disulfiram: metabolism of phenytoin inhibited by \textit{disulfiram} (increased risk of toxicity)

- Diuretics: phenytoin antagonises effects of \textit{frusemide} (frusenide); phenytoin reduces plasma concentration of \textit{eplerenone}—avoid concomitant use; increased risk of osteomalacia when phenytoin given with \textit{carbonic anhydrase inhibitors}

- Dopaminergics: phenytoin possibly reduces effects of lapatinib

- Enteral Foods: absorption of phenytoin possibly reduced by \textit{enteral feeds}

- Folate: plasma concentration of phenytoin possibly reduced by \textit{folate}

- Hormone Antagonists: phenytoin accelerates metabolism of \textit{gestrinone} (reduced plasma concentration); phenytoin possibly accelerates metabolism of \textit{testosterone}

- H2 blockers: phenytoin accelerates metabolism of \textit{omeprazole} (reduced effect)

- Levofloxacin: plasma concentration of phenytoin possibly increased by \textit{levofloxacin}

- Lipid-regulating Drugs: combination of phenytoin with \textit{fluvastatin} may increase plasma concentration of either drug (or both)

- Lithium: neurotoxicity may occur when phenytoin given with lithium without increased plasma concentration of lithium

- Modafinil: plasma concentration of phenytoin possibly increased by \textit{modafinil}

- Muscle Relaxants: phenytoin antagonises muscle relaxant effect of \textit{non-depolaising muscle relaxants} (accelerated recovery from neuromuscular blockade)
**Phenyoitn (continued)**
- Oestrogens: phenytoin accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 478)
- Progestogens: phenytoin accelerates metabolism of progestogens (reduced contraceptive effect—see p. 478)
- Sulfinpyrazone: plasma concentration of phenytoin increased by sulfinpyrazone.
- Sympathomimetics: plasma concentration of phenytoin increased by methylphenidate.
- Tacrolimus: phenytoin reduces plasma concentration of tacrolimus, also plasma concentration of phenytoin possibly increased.
- Theophylline: plasma concentration of both drugs reduced when phenytoin given with theophylline.
- Thyroid Hormones: phenytoin accelerates metabolism of thyroid hormones (may increase requirements in hypothyroidism), also plasma concentration of phenytoin possibly increased.
- Tbolone: phenytoin accelerates metabolism of tibolone.
- UUler-healing Drugs: metabolism of phenytoin inhibited by cimetidine (increased plasma concentration); effects of phenytoin enhanced by omeprazole; absorption of phenytoin reduced by sucralfate.
- Vaccines: effects of phenytoin enhanced by influenza vaccine.
- Vitamins: phenytoin possibly increases requirements for vitamin D.

**Phosphodiesterase Inhibitors**
- Anagrelide: avoidance of enoximone and milrinone advised by manufacturer of anagrelide.

**Physostigmine** see Parasympathomimetics.

**Pilocarpine** see Parasympathomimetics.

**Pirimidine** see Antipsychotics.

**Pindolol** see Beta-blockers.

**Pioglitazone** see Antidiabetics.

**Piperacillin** see Penicillins.

**Pipotiazine** see Antipsychotics.

**Piroxicam** see NSAIDs.

**Pimecrolimus** see Penicillins.

**Pizotifen** Adrenergic Neurone Blockers: pizotifen antagonises hypertensive effect of adrenergic neurone blockers.

**Platinum Compounds**
- Antiabacterials: increased risk of nephrotoxicity and possibly of ototoxicity when platinum compounds given with aminoglycosides or polymyxins; increased risk of nephrotoxicity and ototoxicity when platinum compounds given with capreomycin; increased risk of nephrotoxicity and possibly of ototoxicity when cisplatin given with vancomycin. Antiepileptics: cytoxotics 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.
- Cytotoxics: increased pulmonary toxicity when cisplatin given with leomycin and methotrexate. Diuretics: increased risk of nephrotoxicity and oto-toxicity when platinum compounds given with diur-etics.

**Polymyxin B** see Polymyxins.

**Polymyxins**
- Antiabacterials: increased risk of nephrotoxicity when colistin or polymyxins given with aminoglycosides; increased risk of nephrotoxicity when colistin or polymyxins given with capreomycin; increased risk of nephrotoxicity and ototoxicity when colistin given with teicoplanin or vancomycin; increased risk of nephrotoxicity when polymyxins given with vanco-

**Polymyxins (continued)**
- Antiabacterials: increased risk of nephrotoxicity when polymyxins given with polymyxins; increased risk of nephrotoxicity and possibly of ototoxicity when polymyxins given with teicoplanin or vancomycin.
- Diuretics: increased risk of ototoxicity when polymyxins given with diuretics.
- Muscle Relaxants: polymyxins enhance effects of depolarising muscle relaxants and suxamethonium.
- Oestrogens: antiabacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478).
- Parasympathomimetics: polymyxins antagonise effects of neostigmine and pyridostigmine.
- Vaccines: antiabacterials inactivate oral typhoid vaccine—see p. 752.

**Polystreune Sulphone Resins**
- Thyroid Hormones: polystyrene sulphonate resins reduce absorption of levothyroxine (thyroxine).

**Posaconazole** see Antiabacterials, Triazoles.

**Potassium Canrenoate** see Diuretics.

**Potassium Aminobenzoate**
- Antabacterials: potassium aminobenzoate inhibits effects of sulphamides.

**Potassium Bicarbonate** see Potassium Salts.

**Potassium Chloride** see Potassium Salts.

**Potassium Citrate** see Potassium Salts.

**Potassium Salts**
- Includes salt substitutes.
- ACE Inhibitors: increased risk of hyperkalaemia when potassium salts given with ACE inhibitors. Ailiskiren: increased risk of hyperkalaemia when potassium salts given with ailsiren.
- 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 diuretics.
- Tacrolimus: increased risk of hyperkalaemia when potassium salts given with tacrolimus.

**Prampexole**
- Antipsychotics: manufacturer of prampexole advises avoid concomitant use of antipsychotics (antagonism of effect).
- UUler-healing Drugs: excretion of prampexole reduced by cimetidine (increased plasma concentration).

**Pravastatin** see Statins.

**Prazosin** see Alpha-blockers.

**Prednisolone** see Corticosteroids.

**Prolacine** Anti-arrhythmics: increased myocardial depression when prolacine given with anti-arrhythmics.
- Antibacterials: increased risk of methaemoglobinaemia when prilocaine given with sulphamides.

**Primaquine**
- Antimalarials: avoidance of antimalarials advised by manufacturer of primaquine.

**Mepacrine** Plasma concentration of primaquine increased by mepacrine (increased risk of toxicity).
- Vaccines: antiabacterials inactivate oral typhoid vaccine—see p. 752.
Appendix 1: Interactions

Primidone

Alcohol: increased sedative effect when primidone given with alcohol

Anti-arrhythmics: primidone accelerates metabolism of disopyramide (reduced plasma concentration)

Antibacterials: primidone accelerates metabolism of chloramphenicol, doxycycline and metronidazole (reduced plasma concentration); primidone reduces plasma concentration of ethe thiromycin (avoid during and for 2 weeks after primidone)

Anticoagulants: primidone accelerates metabolism of coumarins (reduced anticoagulant effect)

Antidepressants: primidone reduces plasma concentration of paroxetine; primidone accelerates metabolism of amianserin (reduced plasma concentration); anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and tricyclic-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and etricyclics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort; anticonvulsant effect of primidone antagonised by etricyclics (convulsive threshold lowered), also metabolism of tricyclics possibly accelerated (reduced plasma concentration)

Antiepileptics: primidone often reduces plasma concentration of carbamazepine; also plasma concentration of primidone sometimes reduced (but concentration of an active metabolite of primidone often increased); primidone possibly reduces plasma concentration of ethosuximide; primidone reduces plasma concentration of lamotrigine and tiagabine; plasma concentration of primidone possibly reduced by phenytoin (but concentration of an active metabolite increased); plasma concentration of phenytoin often reduced but may be increased; plasma concentration of primidone possibly increased by valproate (plasma concentration of active metabolite of primidone increased), also plasma concentration of valproate reduced; plasma concentration of primidone possibly reduced by vigabatrin

Antifungals: primidone possibly reduces plasma concentration of posaconazole; primidone possibly reduces plasma concentration of voriconazole—avoid concomitant use; primidone reduces absorption of griseofulvin (reduced effect)

Antimalarias: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of anti-epileptics antagonised by methotrexate

Antipsychotics: anticonvulsant effect of primidone antagonised by antipsychotics (convulsive threshold lowered); primidone accelerates metabolism of haloperidol (reduced plasma concentration); primidone possibly reduces plasma concentration of aripiprazole—increased dose of aripiprazole

Antivirals: primidone possibly reduces plasma concentration of indinavir, saquinavir and ritonavir

Anxiolytics and Hypnotics: primidone reduces plasma concentration of clonazepam

Barbiturates: increased sedative effect when primidone given with barbiturates

Calcium-channel Blockers: primidone reduces effects of felodipine and isradipine; primidone probably reduces effects of dihydropyridines, diltiazem and verapamil

Cardiac Glycosides: primidone accelerates metabolism of digoxin (reduced effect)

Ciclosporin: primidone accelerates metabolism of ciclosporin (reduced effect)

Corticosteroids: primidone accelerates metabolism of corticosteroids (reduced effect)

Diuretics: plasma concentration of primidone possibly reduced by acetazolamide; increased risk of osteo-

Diuretics (continued)

malacia when primidone given with carbonic anhydrase inhibitors

Folates: plasma concentration of primidone possibly reduced by folates

Hormone Antagonists: primidone accelerates metabolism of gestrinone and toremifene (reduced plasma concentration)

Leukotriene Receptor Antagonists: primidone reduces plasma concentration of montelukast

Mexitemine: effects of primidone possibly reduced by memantine

Oestrogens: primidone accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 478)

Progestogens: primidone accelerates metabolism of progesterons (reduced contraceptive effect—see p. 478)

Sympathomimetics: plasma concentration of primidone possibly increased by methylphenidate

Theophylline: primidone accelerates metabolism of theophylline (reduced effect)

Thyroid Hormones: primidone accelerates metabolism of thyroid hormones (may increase requirements for thyroid hormones in hypothyroidism)

Tuberculosis: primidone accelerates metabolism of isoniazide (reduced plasma concentration)

Vitamins: primidone possibly increases requirements for vitamin D

Probenecid

ACE Inhibitors: probenecid reduces excretion of captopril

Anasthetics, General: probenecid possibly enhances effects of thiopental

Antibacterials: probenecid reduces excretion of dextrotofenphosphate, indomethacin, ketoprofen and naphoxon (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 cephalexin and ciprofloxacin (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 famciclovir (increased plasma concentration); probenecid reduces excretion of ganciclovir and zidovudine (increased plasma concentration and risk of toxicity)

Anxiolytics and Hypnotics: probenecid reduces excretion of lorazepam (increased plasma concentration); probenecid reduces excretion of nitrazepam (increased plasma concentration)

Cytotoxics: probenecid reduces excretion of methotrexate (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

Procaine

Lorazidase: procaine possibly inhibits effects of lar onidase (manufacturer of lorazidase advises avoid concomitant use)

Muscle Relaxants: neuromuscular blockade enhanced and prolonged when procaine given with suxamethonium
Progestogens

Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis). Cardiac Glycosides: cytotoxics reduce absorption of digitoxin tablets.

Prochlorperazine see Antipsychotics
\textit{Note:} Interactions of combined oral contraceptives may also apply to combined contraceptive patches and vaginal rings.

Antibacterials: metabolism of progestogens accelerated by rifamycins (reduced contraceptive effect—see p. 478).

Anticoagulants: progestogens may enhance or reduce anticoagulant effect of warfarin; progestogens (used for contraception) given with potassium-sparing diuretics and aldosterone antagonists—avoid concomitant use.

Antidepressants: contraceptive effect of progestogens possibly reduced by nelfinavir; metabolism of fosamprenavir reduced—alternative contraception recommended.

Barbiturates: metabolism of progestogens accelerated by rifampicin (reduced contraceptive effect—see p. 478).

Antifungals: metabolism of progestogens accelerated by itraconazole, ketoconazole, fluconazole (reduced contraceptive effect—see p. 478); progestogens reduce plasma concentration of lamotrigine.

Antivirals: plasma concentration of progestogens possibly reduced by sugammadex; plasma concentration of tizanidine (increased risk of toxicity) given with atorvastatin; plasma concentration of fosamprenavir increased by ritonavir (reduced contraceptive effect—see p. 478); occasional reports of breakthrough bleeding when progestogens (used for contraception) given with cyclosporin; progestogens possibly reduced by nelfinavir; metabolism of fosamprenavir reduced—alternative contraception recommended.

Anticoagulants: isolated reports that proguanil may enhance anticoagulant effect of warfarin; proguanil may enhance anticoagulant effect of warfarin.

Antimalarials: avoidance of antimalarials advised by manufacturer of artemether/lumefantrine; increased antifolate effect when proguanil given with pyrimethamine.

Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 752.

Promazine see Antipsychotics

Propafenone

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 amiodarone.

Antibacterials: metabolism of progestogens accelerated by rifampicin (reduced contraceptive effect).

Anticoagulants: isolated reports that proguanil may enhance anticoagulant effect of warfarin.

Antipsychotics: increased risk of ventricular arrhythmias when mifepristone given with mizolastine—avoid concomitant use.

Antivirals: plasma concentration of progestogens possibly increased by sitaxsentan; plasma concentration of propafenone increased by verapamil.

Anti-arrhythmics: increased risk of ventricular arrhythmias when mifepristone given with mizolastine—avoid concomitant use.

Beta-blockers: increased myocardial depression when anti-arrhythmics given with beta-blockers; propafenone increases plasma concentration of metoprolol and propranolol.

Cardiac Glycosides: propafenone increases plasma concentration of digoxin (halve dose of digoxin).

Ciclosporin: propafenone possibly increases plasma concentration of ciclosporin.

5HT3 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.

Panprotheline see Antimuscarinics

Propiverine see Antimuscarinics

Propofol see Anaesthetics, General

Propranolol see Beta-blockers

Prostaglandins

ACE Inhibitors: enhanced hypertensive effect when alprostadil given with ACE inhibitors.

Adrenergic Neurone Blockers: enhanced hypertensive effect when alprostadil given with adrenergic neurone blockers.

Alpha-blockers: enhanced hypertensive effect when alprostadil given with alpha-blockers.

Angiotensin-II Receptor Antagonists: enhanced hypertensive effect when alprostadil given with angiotensin-II receptor antagonists.

Beta-blockers: enhanced hypertensive effect when alprostadil given with beta-blockers.
Appendix 1: Interactions

Anticoagulants: esomeprazole, omeprazole and pantoprazole possibly enhance anticoagulant effect of coumarins.

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: prostaglandins potentiate uterotoxic effect of oxytocin.

Ciclosporin: omeprazole possibly affects plasma concentration.

Cardiac Glycosides: quinine increases plasma concentration of digoxin.

Protein Kinase Inhibitors

Prostaglandins

Calcium-channel Blockers: enhanced hypotensive effect when alprostadil given with calcium-channel blockers.

Clonidine: enhanced hypotensive effect when alprostadil given with clonidine.

Diazoxide: enhanced hypotensive effect when alprostadil given with diazoxide.

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: prostaglandins potentiate uterotoxic effect of oxytocin.

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.

Antiepileptics: omeprazole possibly enhances effects of phenytoin; omeprazole 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 atazanavir; omeprazole reduces plasma concentration of atazanavir—avoid concomitant use; omeprazole increases plasma concentration of ritonavir—avoid concomitant use; proton pump inhibitors possibly increase plasma concentration of ritonavir—manufacturer of ritonavir advises avoid concomitant use; omeprazole increases plasma concentration of saquinavir; plasma concentration of esomeprazole and omeprazole reduced by ritonavir.

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.

Clonazepam: omeprazole increases plasma concentration of clonazepam (risk of toxicity)—avoid concomitant use; lansoprazole possibly increases plasma concentration of clonazepam—avoid concomitant use.

Cloprednol: proton pump inhibitors possibly reduce antiallergic effect of cloprednol.

Cytotoxic: omeprazole possibly reduces excretion of methotrexate (increased risk of toxicity); proton pump inhibitors possibly reduce absorption of lopatinib.

Proton Pump Inhibitors

Tacrolimus: omeprazole possibly increases plasma concentration of tacrolimus.

Ulcere-healing Drugs: absorption of lansoprazole possibly reduced by sucralfate.

Pseudoephedrine see Sympathomimetics.

Pyrazinamide

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small; see p. 478).

Probenecid: pyrazinamide antagonises effects of probenecid.

Sulfonpyrazone: pyrazinamide antagonises effects of sulfonpyrazone.

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.

Quetiapine see Antipsychotics.

Quinagolide

Mannitol: effects of dopaminergics possibly enhanced by mannitol.

Methyldopa: antiparkinsonian effect of dopaminergics antagonised by methyldopa.

Quinapril see ACE Inhibitors.

Quinidine

Anti-arrhythmics: increased risk of ventricular arrhythmias when quinine given with amiodarone—avoid concomitant use; quinine increases plasma concentration of flecainide.

Antibacterials: increased risk of ventricular arrhythmias when quinine given with moxifloxacin—avoid concomitant use.

Antimalarials: avoidance of antimalarials advised by manufacturer of arteether/lumefantrine; increased antifolate effect when pyrimethamine given with proguanil.

Antivirals: increased antifolate effect when pyrimethamine given with zidovudine.

Cytotoxic: pyrimethamine antagonises anticonvulsant effect of phenytoin, also increased antifolate effect.

Antiarrhythmics: increased risk of ventricular arrhythmias when quinine given with amiodarone—avoid concomitant use; quinine increases plasma concentration of flecainide.

Antibacterials: increased risk of ventricular arrhythmias when quinine given with moxifloxacin—avoid concomitant use.

Antimalarials: avoidance of antimalarials advised by manufacturer of arteether/lumefantrine; increased risk of convulsions when quinine given with mefloquine (but should not prevent the use of intravenous quinine in severe cases).

Antipsychotics: increased risk of ventricular arrhythmias when quinine given with ziprasidone—avoid concomitant use.

Cardiac Glycosides: quinine increases plasma concentration of digoxin.

Muscle Relaxants: quinine possibly enhances effects of suxamethonium.

Ulcere-healing Drugs: metabolism of quinine inhibited by cimetidine (increased plasma concentration).

Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 752.

Quinolones

Analgesics: possible increased risk of convulsions when quinolones given with NSAIDs; manufacturer of ciprofloxacin advises avoid premedication with opioid analgesics (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis.

Proton Pump Inhibitors (continued)

TACROLIMUS: omeprazole possibly increases plasma concentration of tacrolimus.

Ulcere-healing Drugs: absorption of lansoprazole possibly reduced by sucralfate.

Pseudoephedrine see Sympathomimetics.

Pyrazinamide

Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small; see p. 478).

Probenecid: pyrazinamide antagonises effects of probenecid.

Sulfonpyrazone: pyrazinamide antagonises effects of sulfonpyrazone.

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.

Quinagolide see Antipsychotics.

Quinidine

Anti-arrhythmics: increased risk of ventricular arrhythmias when quinine given with amiodarone—avoid concomitant use; quinine increases plasma concentration of flecainide.

Antibacterials: increased risk of ventricular arrhythmias when quinine given with moxifloxacin—avoid concomitant use.

Antimalarials: avoidance of antimalarials advised by manufacturer of arteether/lumefantrine; increased risk of convulsions when quinine given with mefloquine (but should not prevent the use of intravenous quinine in severe cases).

Antipsychotics: increased risk of ventricular arrhythmias when quinine given with ziprasidone—avoid concomitant use.

Cardiac Glycosides: quinine increases plasma concentration of digoxin.

Muscle Relaxants: quinine possibly enhances effects of suxamethonium.

Ulcere-healing Drugs: metabolism of quinine inhibited by cimetidine (increased plasma concentration).

Vaccines: antimalarials inactivate oral typhoid vaccine—see p. 752.

Quinolones

Analgesics: possible increased risk of convulsions when quinolones given with NSAIDs; manufacturer of ciprofloxacin advises avoid premedication with opioid analgesics (reduced plasma concentration of ciprofloxacin) when ciprofloxacin used for surgical prophylaxis.
Quinolones (continued)
Antacids: absorption of ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin reduced by antacids

- Anti-arrhythmics: increased risk of ventricular arrhythmias when levofloxacin or moxifloxacin given with
  amiodarone—avoid concomitant use; increased risk of ventricular arrhythmias when moxifloxacin given with
disopyramide—avoid concomitant use

- Antibacterials: increased risk of ventricular arrhythmias when moxifloxacin given with parenteral
  erythromycin—avoid concomitant use

- Anticoagulants: levofloxacin possibly enhances anti-
  coagulant effect of coumarins and phenindione; ciprofloxacin, nalidixic acid, norfloxacin and ofloxacin
  enhance anti-coagulant effect of coumarins

- Antidepressants: ciprofloxacin inhibits metabolism of
duloxetine—avoid concomitant use; increased risk of
  ventricular arrhythmias when moxifloxacin given with
tricyclics—avoid concomitant use

- Antidiabetics: ciprofloxacin and norfloxacin possibly
  enhance effects of glibenclamide

- Anti-arrhythmics: increased risk of ventricular arrhythmias when moxifloxacin given with
  disopyramide—avoid concomitant use; increased risk of
  ventricular arrhythmias when moxifloxacin given with
calcium salts—avoid concomitant use; increased risk of
  ventricular arrhythmias when moxifloxacin given with
theophylline; ciprofloxacin, levofloxacin, moxifloxacin and ofloxacin reduced by sucralfate

- Antiepileptics: ciprofloxacin increases or decreases
  plasma concentration of phenytoin

- Antihistamines: increased risk of ventricular arrhythmias
  when moxifloxacin given with mizolastine—avoid concomitant use

- Animalarials: avoidance of quinolones advised by
  manufacturer of arteether/umefantrine; increased risk of ventricular arrhythmias when
  moxifloxacin given with chloroquine and hydroxy-
  chloroquine, methoquine or quinine—avoid concomitant use

- Antipsychotics: increased risk of ventricular arrhythmias
  when moxifloxacin given with benperidol—avoid concomitant use; increased risk of ventricular arrhythmias
  when moxifloxacin given with haloperidol, phenothiazines, ziproide, sertindole or
  zuclopenthixol—avoid concomitant use; ciprofloxacin increases plasma concentration of clozapine; ciprofloxacin
  possibly increases plasma concentration of olanzapine

- Atomoxetine: increased risk of ventricular arrhythmias
  when moxifloxacin given with atomoxetine

- Beta-blockers: increased risk of ventricular arrhythmias
  when moxifloxacin given with sotalol—avoid concomitant use

Calcium Salts: absorption of ciprofloxacin reduced by
calcium salts

- Ciclosporin: increased risk of nephrotoxicity when
  quinolones given with ciclosporin

- Cytotoxics: nalidixic acid increases risk of melphalan
toxicity; ciprofloxacin possibly reduces excretion of
methotrexate (increased risk of toxicity); norfloxacin possibly reduces bioavailability of mycophenolate; avoidance of
moxifloxacin advised by manufacturer of
nilotinib

Dairy Products: absorption of ciprofloxacin and nor-
floxacin reduced by dairy products

Dopaminergic: ciprofloxacin inhibits metabolism of
ropinirole (increased plasma concentration)

5HT1A Agonists: quinolones possibly inhibit metabolism of
zolmitriptan (reduce dose of zolmitriptan)

Iron: absorption of ciprofloxacin, levofloxacin, moxi-
floxacin, norfloxacin and ofloxacin reduced by oral
iron

- Muscle Relaxants: ciprofloxacin increases plasma
  concentration of diazoxide (increased risk of toxicity)—avoid concomitant use

Oestrogens: antibacterials that do not induce liver
enzymes possibly reduce contraceptive effect of
oestrogens (risk probably small, see p. 478)

- Pentamidine Isetionate: increased risk of ventricular
  arrhythmias when moxifloxacin given with pent-
  amidine isetionate—avoid concomitant use

Quinolones (continued)

Antidepressants: ciprofloxacin inhibits metabolism of
duloxetine—avoid concomitant use; increased risk of
ventricular arrhythmias when moxifloxacin given with
tricyclics—avoid concomitant use

Anticoagulants: levofloxacin possibly enhances anti-
cogulant effect of coumarins and phenindione; ciprofloxacin, nalidixic acid, norfloxacin and ofloxacin
enhance anti-coagulant effect of coumarins

Antidepressants: increased risk of ventricular arrhythmias when moxifloxacin given with
theophylline; ciprofloxacin and norfloxacin increase plasma concentration of
theophylline

Ulcer-healing Drugs: absorption of ciprofloxacin, levofloxacin, moxifloxacin and ofloxin
ac reduced by sucralfate

Vaccines: antibacterials inactivate oral typhoid
vaccine—see p. 752

Zinc: absorption of ciprofloxacin, levofloxacin, moxi-
floxacin, norfloxacin and ofloxacin reduced by zinc

Quinupristin with Dalfopristin

- Anti-arrhythmics: increased risk of ventricular arrhythmias when quinupristin/dalfopristin given with
disopyramide or lidocaine (lignocaine)—avoid concomitant use

Antibacterials: manufacturer of quinupristin/dalfopristin
recommends monitoring liver function when
given with rifampicin

Antivirals: quinupristin/dalfopristin possibly increases
plasma concentration of saquinavir

Anxiolytics and Hypnotics: quinupristin/dalfopristin
inhibits metabolism of midazolam (increased plasma concentration with increased sedation); quinupristin/dalfopristin inhibits the metabolism of
zolpidem

Calcium-channel Blockers: quinupristin/dalfopristin
increases plasma concentration of nifedipine

Ciclosporin: quinupristin/dalfopristin increases plasma concentration of
ciclosporin

Ergot Alkaloids: manufacturer of quinupristin/dalfopristin
advises avoid concomitant use with
ergotamine and methysergide

Oestrogens: antibacterials that do not induce liver
enzymes possibly reduce contraceptive effect of
oestrogens (risk probably small, see p. 478)

Tacrolimus: quinupristin/dalfopristin increases plasma
concentration of tacrolimus

Vaccines: antibacterials inactivate oral typhoid
vaccine—see p. 752

Rabeprazole see Proton Pump Inhibitors

Ranolazine see Raloxifene

Anticoagulants: ranolazine antagonises anticoagulant
effects of coumarins

Lipid-regulating Drugs: absorption of ranolazine
reduced by colestyramine (manufacturer of
ranolazine advises avoid concomitant administration)

Raltegravir

Antibacterials: plasma concentration of raltegravir
reduced by rifampicin—consider increasing dose of
raltegravir

Ulcer-healing Drugs: plasma concentration of ralte-
gravir increased by emtricitabine—avoid concomi-
tant use; plasma concentration of raltegravir possibly increased by histamine H2-antagonists and proton
pump inhibitors—manufacturer of raltegravir advises
avoid concomitant use

Ramipril see ACE Inhibitors

Ranitidine see Histamine H2-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 pethidine (avoid pethidine for
2 weeks after rasagiline)

- Antidepressants: after stopping rasagiline do not start
fluoxetine for 2 weeks, also rasagiline should not be
Appendix 1: Interactions

Rifamycins (continued)

Analgesics: rifampicin reduces plasma concentration of etoricoxib; rifampicin accelerates metabolism of methadone (reduced effect)

Antacids: absorption of rifampicin reduced by antacids

Anti-arrhythmics: rifamycins accelerate metabolism of disopyramide (reduced plasma concentration); rifampicin accelerates metabolism of propafenone (reduced effect)

Antibacterials: rifampicin reduces plasma concentration of clarithromycin and dapsone; plasma concentration of rifabutin increased by clarithromycin (increased risk of uveitis—reduce rifabutin dose); rifampicin accelerates metabolism of chloramphenicol (reduced plasma concentration); plasma concentration of rifabutin possibly increased by macrolides (increased risk of uveitis—reduce rifabutin dose); monitoring of liver function with rifampicin recommended by manufacturer of quinupristin/dalfopristin; rifampicin reduces plasma concentration of etelitromycin (avoid during and for 2 weeks after rifampicin); rifampicin possibly reduces plasma concentration of trimethoprim

Anticoagulants: rifamycins accelerate metabolism of coumarins (reduced anticoagulant effect); rifampicin reduces plasma concentration of rivaroxaban

Antidepressants: rifampicin possibly reduces plasma concentration of tricyclics

Antidiabetics: rifamycins accelerate metabolism of chlorpropamide and tolbutamide (reduced effect); rifampicin reduces plasma concentration of rosiglitazone—consider increasing dose of rosiglitazone; rifampicin reduces plasma concentration of nateglinide; rifampicin possibly antagonises hypoglycaemic effect of repaglinide; rifamycins possibly accelerate metabolism of sulphonylureas (reduced effect)

Antiepileptics: rifabutin reduces plasma concentration of carbamazepine; rifampicin reduces plasma concentration of lamotrigine; rifamycins accelerate metabolism of phenytoin (reduced plasma concentration)

Antifungals: rifamycins accelerate metabolism of ketoconazole (reduced plasma concentration), also plasma concentration of rifampicin may be reduced by ketoconazole; plasma concentration of rifabutin increased by rifunoxazole (increased risk of uveitis—reduce rifabutin dose); rifampicin accelerates metabolism of efloconazole and eterconazole (reduced plasma concentration); rifabutin reduces plasma concentration of eterconazole—avoid concomitant use; plasma concentration of rifabutin increased by posaconazole (also plasma concentration of posaconazole reduced); rifampicin reduces plasma concentration of posaconazole and itraconazole; plasma concentration of rifabutin increased by voriconazole, also rifabutin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for rifabutin toxicity); rifampicin reduces plasma concentration of voriconazole—avoid concomitant use; rifampicin initially increases and then reduces plasma concentration of caspofungin (consider increasing dose of caspofungin); plasma concentration of rifabutin possibly increased by posaconazole (increased risk of uveitis—reduce rifabutin dose)

Antimalarials: rifampicin reduces plasma concentration of mefloquine—avoid concomitant use Antimuscarinics: rifampicin reduces plasma concentration of active metabolite of fesoterodine

Antipsychotics: rifampicin accelerates metabolism of haloperidol (reduced plasma concentration); rifabutin and rifampicin possibly reduce plasma concentration of aripiprazole—increase dose of

Rasagiline

- Antidepressants (continued)
  - started until at least 5 weeks after stopping fluoxetine; after stopping rasagiline do not start
  - fluvoxamine for 2 weeks; risk of hypertensive crisis when rasagiline given with MAOIs, avoid MAOIs for at least 2 weeks after stopping rasagiline; increased risk of CNS toxicity when rasagiline given with SSRIs or SNRIs

Dopaminergics: plasma concentration of rasagiline possibly reduced by entacapone

Methyldopa: antiparkinsonian effect of dopaminergics antagonised by methyldopa

Sympathomimetics: avoid concomitant use of rasagiline with sympathomimetics

Reboxetine

- Antibacterials: manufacturer of reboxetine advises avoid concomitant use with macrolides

- Antidepressants: manufacturer of reboxetine advises avoid concomitant use with fluvoxamine; increased risk of hypertension and CNS excitation when reboxetine given with MAOIs (MAOIs should not be started until 1 week after stopping reboxetine, avoid reboxetine for 2 weeks after stopping MAOIs)

- Antifungals: manufacturer of reboxetine advises avoid concomitant use with midazoles and triazoles

- Antimeta
trols: avoidance of antidepressants advised by manufacturer of artemether/lumefantrine

Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine

Diuretics: possible increased risk of hypokalaemia when reboxetine given with loop diuretics or thiazides and related diuretics

Ergot Alkaloids: possible risk of hypertension when reboxetine given with ergotamine and methysergide

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

Rapaglinide see Anti-diabetics

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 anticoagulant effect of coumarins

Antiepileptics: lamotrigine; rifamycins accelerate metabolism of phenytoin (reduced plasma concentration)

Antifungals: rifampicin reduces plasma concentration of fesoterodine (reduced plasma concentration); rifabutin reduces plasma concentration of eterconazole; plasma concentration of rifabutin possibly increased by macrolides (increased risk of uveitis—reduce rifabutin dose); monitoring of liver function with rifabutin recommended by manufacturer of quinupristin/dalfopristin; rifampicin reduces plasma concentration of etelitromycin (avoid during and for 2 weeks after rifampicin); rifampicin possibly reduces plasma concentration of trimethoprim

Anticoagulants: rifamycins accelerate metabolism of coumarins (reduced anticoagulant effect); rifampicin reduces plasma concentration of rivaroxaban

Antidepressants: rifampicin possibly reduces plasma concentration of tricyclics

Antidiabetics: rifamycins accelerate metabolism of chlorpropanamide and tolbutamide (reduced effect); rifampicin reduces plasma concentration of rosiglitazone—consider increasing dose of rosiglitazone; rifampicin reduces plasma concentration of nateglinide; rifampicin possibly antagonises hypoglycaemic effect of repaglinide; rifamycins possibly accelerate metabolism of sulphonylureas (reduced effect)

Antiepileptics: rifabutin reduces plasma concentration of carbamazepine; rifampicin reduces plasma concentration of lamotrigine; rifamycins accelerate metabolism of phenytoin (reduced plasma concentration)

Antifungals: rifampicin accelerates metabolism of ketoconazole (reduced plasma concentration), also plasma concentration of rifampicin may be reduced by ketoconazole; plasma concentration of rifabutin increased by rifunoxazole (increased risk of uveitis—reduce rifabutin dose); rifampicin accelerates metabolism of efloconazole and eterconazole (reduced plasma concentration); rifabutin reduces plasma concentration of eterconazole—avoid concomitant use; plasma concentration of rifabutin increased by posaconazole (also plasma concentration of posaconazole reduced); rifampicin reduces plasma concentration of posaconazole and itraconazole; plasma concentration of rifabutin increased by voriconazole, also rifabutin reduces plasma concentration of voriconazole (increase dose of voriconazole and also monitor for rifabutin toxicity); rifampicin reduces plasma concentration of voriconazole—avoid concomitant use; rifampicin initially increases and then reduces plasma concentration of caspofungin (consider increasing dose of caspofungin); plasma concentration of rifabutin possibly increased by posaconazole (increased risk of uveitis—reduce rifabutin dose)

Antimalarials: rifampicin reduces plasma concentration of mefloquine—avoid concomitant use Antimuscarinics: rifampicin reduces plasma concentration of active metabolite of fesoterodine

Antipsychotics: rifampicin accelerates metabolism of haloperidol (reduced plasma concentration); rifabutin and rifampicin possibly reduce plasma concentration of aripiprazole—increase dose of

Rifamycins

ACE Inhibitors: rifampicin reduces plasma concentration of active metabolite of imidapril (reduced antihypertensive effect)
Rifamycins
- Antipsychotics (continued)
  - Aripiprazole; rifampicin possibly reduces plasma concentration of clozapine
- Antivirals: rifampicin possibly reduces plasma concentration of abacavir and ritonavir; plasma concentration of ritabafin increased by atazanavir, darunavir, fosamprenavir and lopinavir; rifampicin reduces plasma concentration of etravirine, tipranavir and nevirapine—avoid concomitant use; rifampicin significantly reduces plasma concentration of efavirenz; increases—decrease of efavirenz; plasma concentration of rifabutin reduced by efavirenz; increase of rifabutin; avoidance of rifampicin advised by manufacturer of etravirine and zidovudine; plasma concentration of both drugs reduced when rifabutin given with etravirine; rifampicin accelerates metabolism of indinavir; plasma concentration of ritabafin increased by ritonavir; rifampicin reduces plasma concentration of maraviroc and raltegravir; consider increasing dosing of maraviroc and raltegravir; plasma concentration of ritabafin increased by nelfinavir (halve dose of rifabutin); plasma concentration of rifabutin possibly increased by nevirapine; plasma concentration of ritabafin increased by ritonavir (increased risk of toxicity); rifampicin significantly reduces plasma concentration of saquinavir; lopinavir, ritonavir and saquinavir; rifampicin possibly reduces plasma concentration of tipranavir—avoid concomitant use
- Anxiolytics and Hypnotics: rifampicin accelerates metabolism of diazepam (reduced plasma concentration); rifampicin possibly accelerates metabolism of benzodiazepines (reduced plasma concentration); rifampicin possibly accelerates metabolism of midazolam and nitrazepam; rifampicin accelerates metabolism of zolpidem (reduced plasma concentration and reduced effect); rifampicin significantly reduces plasma concentration of zopiclone
- Aprepitant: rifampicin reduces plasma concentration of aprepitant
- Atovaquone: rifabutin and rifampicin reduce plasma concentration of atovaquone (possible therapeutic failure of atovaquone).
- Barbiturates: plasma concentration of rifampicin possibly reduced by phenobarbital.
- Beta-blockers: rifampicin accelerates metabolism of bisoprolol and propranolol (plasma concentration significantly reduced); rifampicin reduces plasma concentration of carvedilol, celiprolol and metoprolol.
- Bosentan: rifampicin reduces plasma concentration of bosentan—avoid concomitant use.
- Calcium-channel Blockers: rifampicin possibly accelerates metabolism of isradipine and nicardipine (possible significantly reduced plasma concentration); rifampicin accelerates metabolism of amlodipine, fludipine, nimodipine and verapamil (plasma concentration significantly reduced).
- Cardiac Glycosides: rifamycins accelerate metabolism of digoxin (reduced effect); rifampicin reduces plasma concentration of digoxin.
- Ciclosporin: rifampicin accelerates metabolism of ciclosporin (reduced plasma concentration).
- Corticosteroids: rifamycins accelerate metabolism of corticosteroids (reduced effect).
- Cytotoxics: rifampicin reduces plasma concentration of active metabolite of mycophenolate; rifampicin accelerates metabolism of dasatinib (reduced effect).
- Cytotoxics (continued)
  - Plasma concentration—avoid concomitant use; rifampicin accelerates metabolism of erlotinib and sunitinib (reduced plasma concentration); rifampicin reduces plasma concentration of matinib—avoid concomitant use; avoidance of ritabafutin and rifampicin advised by manufacturer of lapatinib; rifampicin reduces plasma concentration of sorafene; rifampicin reduces plasma concentration of active metabolite of temsirolimus—avoid concomitant use.
- Deferasirox: rifampicin reduces plasma concentration of deferasirox.
- Diuretics: rifampicin reduces plasma concentration of spironolactone—avoid concomitant use.
- Hormone Antagonists: rifampicin possibly reduces plasma concentration of exemestane; rifampicin accelerates metabolism of gestrinone (reduced plasma concentration).
- 5HT3 Antagonists: rifampicin accelerates metabolism of ondansetron (reduced effect).
- Lipid-regulating Drugs: rifampicin possibly reduces plasma concentration of atorvastatin and simvastatin; rifampicin accelerates metabolism of fluvastatin (reduced effect).
- Oestrogens: rifamycins accelerate metabolism of oestrogens (reduced contraceptive effect—see p. 478); antibacterials that do not induce liver enzymes possibly reduce contraceptive effects of oestrogens (risk probably small, see p. 478).
- Progestogens: rifamycins accelerate metabolism of progestogens (reduced contraceptive effect—see p. 478).
- Sirolimus: rifabutin and rifampicin reduce plasma concentration of sirolimus—avoid concomitant use.
- Tacrolimus: rifampicin reduces plasma concentration of tacrolimus.
- Tadalafil: rifampicin reduces plasma concentration of tadalafil.
- Theophylline: rifampicin accelerates metabolism of theophylline (reduced plasma concentration).
- Thyroid Hormones: rifamycins accelerate metabolism of levothyroxine (thyroxine) (may increase requirements for levothyroxine (thyroxine) in hypothyroidism).
- Tobilone: rifampicin accelerates metabolism of tobilone (reduced plasma concentration).
- Ucer-healing Drugs: rifampicin accelerates metabolism of cimetidine (reduced plasma concentration).
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.
- Rimonabant
  - Antifungals: plasma concentration of rimonabant increased by ketoconazole.
  - Risedronate Sodium see Bisphosphonates.
  - Risperidone see Antipsychotics.
  - Ritodrine see Sympathomimetics, Beta2.
- Ritonavir
  - Alpha-blockers: ritonavir possibly increases plasma concentration of alfuzosin—avoid concomitant use.
  - Analgesics: ritonavir possibly increases plasma concentration of NSAIDs and buprenorphine; ritonavir increases plasma concentration of dextropropoxyphene and pirroxicam (risk of toxicity)—avoid concomitant use; ritonavir increases plasma concentration of fentanyl and fentanyl; ritonavir reduces plasma concentration of metapone; ritonavir possibly reduces plasma concentration of morphone; ritonavir reduces plasma concentration of pethidine, but increases plasma concentration of toxic metabolite of pethidine (avoid concomitant use).
Appendix 1: Interactions

**Ritonavir (continued)**

- Anti-arrhythmics: ritonavir increases plasma concentration of amiodarone and epropanefen (increased risk of ventricular arrhythmias—avoid concomitant use); ritonavir possibly increases plasma concentration of disopyramide (increased risk of toxicity); ritonavir possibly increases plasma concentration of flecainide (increased risk of ventricular arrhythmias—avoid concomitant use).
- Antibacterials: ritonavir possibly increases plasma concentration of azithromycin and erythromycin; ritonavir increases plasma concentration of clarithromycin (reduce dose of clarithromycin in renal impairment); ritonavir increases plasma concentration of rifabutin (increased risk of toxicity); plasma concentration of ritonavir possibly reduced by rifampicin; plasma concentration of both drugs increased when ritonavir given with fusidic acid—avoid concomitant use; avoidance of concomitant ritonavir in severe renal and hepatic impairment advised by manufacturer of telithromycin.
- Anticoagulants: ritonavir may enhance or reduce anticoagulant effect of warfarin; ritonavir possibly enhances anticoagulant effect of coumarins and phenindione; ritonavir increases plasma concentration of rivaroxaban—manufacturer of rivaroxaban advises avoid concomitant use.
- Antidepressants: ritonavir possibly reduces plasma concentration of paroxetine; side-effects possibly increased when ritonavir given with trazodone; ritonavir possibly increases plasma concentration of SSRIs and tricyclics; plasma concentration of ritonavir reduced by St. John’s wort—avoid concomitant use.
- Antidiabetics: ritonavir possibly increases plasma concentration of tolbutamide.
- Antiepileptics: ritonavir possibly increases plasma concentration of carbamazepine; plasma concentration of ritonavir possibly reduced by phenytoin, also plasma concentration of phenytoin possibly affected.
- Antifungals: combination of ritonavir withitraconazole 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.
- Antimalarials: caution with ritonavir advised by manufacturer of arteether/lumefantrine.
- Antimuscarotics: avoidance of ritonavir advised by manufacturer of darifenacin and tolterodine; manufacturer of fesoterodine advises dose reduction when 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 doxapram (increased risk of toxicity)—avoid concomitant use; ritonavir reduces plasma concentration of olanzapine—consider increasing dose of olanzapine; ritonavir increases plasma concentration of omeprazole and esetindole (increased risk of ventricular arrhythmias—avoid concomitant use).
- Antivirals: ritonavir increases toxicity of efavirenz, monitor liver 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,

**Ritonavir**

- Anxiolytics and Hypnotics (continued): 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 buprenorphine (increased risk of toxicity—use)
- 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.
- Cytotoxics: avoidance of ritonavir advised by manufacturer of lapatinib and letrozol; ritonavir increases plasma concentration of palitaxel.
- Diuretics: ritonavir increases plasma concentration of spironolactone—avoid concomitant use.
- Ergot Alkaloids: increased risk of ergotism when ritonavir given with ergotamine and methysergide—avoid concomitant use.
- HST, Agonists: ritonavir increases plasma concentration of eletriptan (risk of toxicity)—avoid concomitant use.
- Ibravadin: ritonavir possibly increases plasma concentration of ibravadin—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. 478).
- Sildenafil: ritonavir significantly increases plasma concentration of sildenafil—avoid concomitant use.
- Sympathomimetics: ritonavir possibly increases plasma concentration of dexamfetamine.
- Tacrolimus: ritonavir possibly increases plasma concentration of tacrolimus.
- Tadalafil: ritonavir increases plasma concentration of tadalafil.
- Telithromycin—avoid concomitant use.
- Theophylline: ritonavir accelerates metabolism of theophylline (reduced plasma concentration).
- Vardenafil: ritonavir possibly increases plasma concentration of vardenafil—avoid concomitant use.
- Telithromycin—avoid concomitant use.

**Rivaroxaban**

- Analgesics: increased risk of haemorrhage when anti-coagulants given with intravenous edelofenac (avoid concomitant use, including low-dose heparin); increased risk of haemorrhage when anti-coagulants given with esetibolac (avoid concomitant use, including low-dose heparin).
- Antibacterials: plasma concentration of rivaroxaban reduced by rifampicin.
- Antifungals: plasma concentration of rivaroxaban increased by ketokonazole—avoid concomitant use; manufacturer of rivaroxaban advises avoid
Rivaroxaban
- Antifungals: 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 anti-coagulants given with sibutramine.

Rosuvastatin see Parasympathomimetics

Rizatriptan see 5HT1 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
- Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by methyl dopa
- Metoclopramide: manufacturer of ropinirole advises avoid concomitant use of metoclopramide (antagonism of effect)
- Oestrogens: plasma concentration of ropinirole increased by oestrogens

Rufinamide
- Anti-arrhythmics: increased myocardial depression when rufinamide given with anti-arrhythmics
- Antidepressants: metabolism of rufinamide inhibited by fluvoxamine—avoid prolonged administration of fluvoxamine

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
- Methyl dopa: antiparkinsonian effect of dopaminergics antagonised by methyl dopa
- 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 anti-epileptics with St John’s Wort
- Antiepileptics: rufinamide possibly increases plasma concentration of phenytoin; plasma concentration of rufinamide possibly increased by valproate (reduce dose of rufinamide)
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of anti-epileptics antagonised by mefloquine
- Oestrogens: rufinamide accelerates metabolism of oestradiol (reduced contraceptive effect—see p. 478)
- Progestogens: rufinamide accelerates metabolism of progestogens (reduced contraceptive effect—see p. 478)

St John’s Wort
- Antibacterials: St John’s Wort reduces plasma concentration of telithromycin (avoid during and for 2 weeks after St John’s Wort)
- Anticoagulants: St John’s Wort reduces anticoagulant effect of coumarins (avoid concomitant use)
- Antidepressants: possible increased serotonergic effects when St John’s Wort with duloxetine; St John’s Wort reduces plasma concentration of amitriptyline; increased serotonergic effects when St John’s Wort with SSRI—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 antidepressants advised by manufacturer of etravirine/lambdaferine
- Antipsychotics: St John’s Wort possibly reduces plasma concentration of aripiprazole—increased dose of aripiprazole
- Antivirals: St John’s Wort reduces plasma concentration of atazanavir, darunavir, efavirenz, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir and saquinavir—avoid concomitant use; avoidance of St John’s Wort advised by manufacturer of etravirine; St John’s Wort possibly reduces plasma concentration of maraviroc and tipranavir—avoid concomitant use
- Anxiolytics 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: St John’s Wort possibly reduces plasma concentration 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
- Cytotoxics: St John’s Wort reduces plasma concentration of imatinib—avoid concomitant use; avoidance of St John’s Wort advised by manufacturer of lapatinib; St John’s Wort accelerates metabolism of irinotecan (reduced plasma concentration—avoid concomitant use)
- Diuretics: St John’s Wort reduces plasma concentration of eplerenone—avoid concomitant use
- 5HT1 Agonists: increased serotonergic effects when St John’s Wort given with 5HT1 agonists—avoid concomitant use
- Ivermectin: St John’s Wort reduces plasma concentration of ivermectin—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, Beta2

Salmeterol see Sympathomimetics, Beta2

Saquinavir
- Antibacterials: plasma concentration of saquinavir reduced by efafarinib; plasma concentration of saquinavir significantly reduced by rifampicin, 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
Appendix 1: Interactions

Tacrolimus: saquinavir increases plasma concentration.

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/lumeferantrine.

Antipsychotics: saquinavir possibly inhibits metabolism of aripiprazole (reduce dose of aripiprazole); saquinavir possibly increases plasma concentration of ziprasidone (increased risk of ventricular arrhythmias—avoid concomitant use); saquinavir increases plasma concentration of tiapride (increased risk of ventricular arrhythmias—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 efavirenz; 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 etravirine.

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 (increased risk of ventricular arrhythmias—avoid concomitant use).

Corticosteroids: plasma concentration of saquinavir increased by ketoconazole; plasma concentration of saquinavir possibly increased by rifampin; saquinavir possibly reduced by dexamethasone.

CYTOTOXICS: Avoidance of saquinavir advised by manufacturer of lapatinib.

Diuretics: saquinavir increases plasma concentration of eplerenone (reduce dose of eplerenone).

Ergot Alkaloids: increased risk of ergotism when saquinavir given with ergotamine and methysergide—avoid concomitant use.

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 (avoid 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.

Vardenafil: saquinavir possibly increases plasma concentration of vardenafil—reduce initial dose of vardenafil.

Ergot Alkaloids: increased risk of ergotism when saquinavir given with ergotamine and methysergide—avoid concomitant use.

Corticosteroids: plasma concentration of saquinavir increased by ketoconazole; plasma concentration of saquinavir possibly increased by rifampin; saquinavir possibly reduced by dexamethasone.

Ciprofloxacin: saquinavir possibly increases plasma concentration of ciprofloxacin.

Ciclosporin: saquinavir possibly increases plasma concentration of ciclosporin.

Cytotoxic: saquinavir possibly reduces plasma concentration of mycophenolate.

Tacrolimus: saquinavir possibly reduces plasma concentration of tacrolimus.

Sildenafil: saquinavir possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil.

Ergot Alkaloids: increased risk of ergotism when saquinavir given with ergotamine and methysergide—avoid concomitant use.

Corticosteroids: plasma concentration of saquinavir increased by ketoconazole; plasma concentration of saquinavir possibly increased by rifampin; saquinavir possibly reduced by dexamethasone.

Ciprofloxacin: saquinavir possibly increases plasma concentration of ciprofloxacin.

Ciclosporin: saquinavir possibly increases plasma concentration of ciclosporin.

Cytotoxic: saquinavir possibly reduces plasma concentration of mycophenolate.

Tacrolimus: saquinavir possibly reduces plasma concentration of tacrolimus.

Sildenafil: saquinavir possibly increases plasma concentration of sildenafil—reduce initial dose of sildenafil.

Ergot Alkaloids: increased risk of ergotism when saquinavir given with ergotamine and methysergide—avoid concomitant use.

Corticosteroids: plasma concentration of saquinavir increased by ketoconazole; plasma concentration of saquinavir possibly increased by rifampin; saquinavir possibly reduced by dexamethasone.

Ciprofloxacin: saquinavir possibly increases plasma concentration of ciprofloxacin.

Ciclosporin: saquinavir possibly increases plasma concentration of ciclosporin.

Cytotoxic: saquinavir possibly reduces plasma concentration of mycophenolate.

Tacrolimus: saquinavir possibly reduces plasma concentration of tacrolimus.
Sildenafil

**Alpha-blockers:** enhanced hypotensive effect when sildenafil given with α-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.

**Calcium-channel Blockers:** plasma concentration of sildenafil increased significantly increased by verapamil; plasma concentration of sildenafil increased by diltiazem; plasma concentration of both drugs increased when given with oestrogens (when used as oral replacement therapy)

**Ciclosporin:** plasma concentration of sitaxentan increased by ciclosporin, auranofin, azathioprine, intravenous immunoglobulin (IVIg) and rituximab

**Diuretics:** increased dose of sitaxentan increased by allopurinol (for long-term use) and probenecid

**Antiepileptics:** effects of sitaxentan possibly increased by antiepileptics (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** effects of sitaxentan possibly increased by antipsychotics (avoid concomitant use)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Antipsychotics:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)

**Anticoagulants:** sitaxentan enhances anticoagulant effect of vitamin K antagonists

**Antifungals:** plasma concentration of sildenafil possibly increased by antifungals (avoid concomitant use)

**Antivirals:** plasma concentration of sildenafil possibly increased by antivirals (avoid concomitant use)

**Antidepressants:** increased risk of side-effects when simvastatin given with oestrogens (when used as oral replacement therapy)
Appendix 1: Interactions

Statins
- Antibacterials: atorvastatin and simvastatin possibly reduced by rifampicin; metabolism of fluvastatin accelerated by rifampicin (reduced effect); increased risk of myopathy when statins given with adadaprim (preferably avoid concomitant use); increased risk of myopathy when simvastatin given with folic acid; increased risk of myopathy when atorvastatin given with simvastatin (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
- Antiinfectives: fluvox帕ramine possibly increases plasma concentration of glibenclamide
- Antiepileptics: combination of fluvox帕ramine with phenytoin may increase plasma concentration of either drug (or both)
- Antifungals: increased risk of myopathy when simvastatin given with itraconazole, ketoconazole or posaconazole (avoid concomitant use); possible increased risk of myopathy when simvastatin given with miconazole—avoid concomitant use; plasma concentration of fluvastatin increased by itraconazole; increased risk of myopathy when atorvastatin given with atorvastatin 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 itraconazole
- Antimycotics: 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 increased by darunavir; plasma concentration of atorvastatin, pravastatin and simvastatin reduced by efavirenz; 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 averapamil
- 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 daasatinib; plasma concentration of simvastatin increased by imatinib
- 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 abacavir; effects of stavudine possibly inhibited by abacavir; effects of stavudine possibly inhibited by didovudine (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

Stiripentol
- Antiepileptics: stiripentol enhances plasma concentration of carbamazepine and phenytoin
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by mefloquine
- Antioxidants and Hypnotics: stiripentol increases plasma concentration of clobazam
- Barbiturates: stiripentol increases plasma concentration of phenobarbital

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 cardiac glycosides
- Theophylline: sucralfate possibly reduces absorption of theophylline (give at least 2 hours apart)
- Thyroid Hormones: sucralfate reduces absorption of levothyroxine (thyroxine)
- Urease-Harming Drugs: sucralfate possibly reduces absorption of Lansoprazole

Sugammadex
- Antibacterials: response to sugammadex possibly reduced by flucloxacinil and fucidic acid
- Hormone Antagonists: response to sugammadex possibly reduced by toremifene
- Oestrogens: sugammadex possibly reduces plasma concentration of oestrogens
- Progestogens: sugammadex possibly reduces plasma concentration of progestogens
Appendix 1: Interactions

**Sulfa drugs**

- Adrenergic Neurone Blockers: ephedrine, isometheptene, metaraminol, methylphenidate, noradrenaline (norepinephrine), oxymetazoline, phenylephrine, pseudoephedrine and xylometazoline antagonise sympathetic action on cardiovascular system possibly enhanced by ritonavir
- Beta-blockers: increased risk of hypotension when used concomitantly with phenytoin; methylphenidate possibly increases plasma concentration of primidone
- Antipsychotics: hypertensive effect of sympathomimetics antagonised by antipsychotics
- Antidepressants: risk of hypertensive crisis when sympathomimetics given with MAOIs or moclobemide; risk of hypertensive crisis when sympathomimetics given with MAOIs, some manufacturers advise avoid methylphenidate for at least 2 weeks after stopping MAOIs; methylphenidate possibly inhibits metabolism of SSRIs and tricyclics; increased risk of hypertension and arrhythmias when adrenaline (epinephrine) given with tricyclics (but local anaesthetics with adrenaline appear to be safe); increased risk of hypertension and arrhythmias when noradrenaline (norepinephrine) given with tricyclics
- Antipsychotics: methylphenidate increases plasma concentration of phenytoin; methylphenidate possibly increases plasma concentration of primidone
- Antivirals: plasma concentration of dexamfetamine possibly increased by ritonavir; Barbiturates: methylphenidate possibly increases plasma concentration of phenobarbital

**Anaesthetics**

- Increased risk of myocardial ischaemia when benzodiazepines given with opioids
- Anticoagulants: increased risk of thromboembolism when used concomitantly with aspirin
- Anticoagulants: increased risk of thromboembolism when used concomitantly with clopidogrel
- Anticoagulants: increased risk of thromboembolism when used concomitantly with ticagrelor
- Anticoagulants: increased risk of thromboembolism when used concomitantly with prasugrel
- Anticoagulants: increased risk of thromboembolism when used concomitantly with rivaroxaban
- Anticoagulants: increased risk of thromboembolism when used concomitantly with apixaban
- Anticoagulants: increased risk of thromboembolism when used concomitantly with edoxaban
- Anticoagulants: increased risk of thromboembolism when used concomitantly with dabigatran
- Anticoagulants: increased risk of thromboembolism when used concomitantly with fondaparinux
- Anticoagulants: increased risk of thromboembolism when used concomitantly with lepirudin
- Anticoagulants: increased risk of thromboembolism when used concomitantly with hirudin
- Anticoagulants: increased risk of thromboembolism when used concomitantly with argatroban
- Anticoagulants: increased risk of thromboembolism when used concomitantly with betamethasone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with methylprednisolone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with dexamethasone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with prednisolone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with dexamethasone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with prednisolone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with dexamethasone
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- Anticoagulants: increased risk of thromboembolism when used concomitantly with prednisolone
- Anticoagulants: increased risk of thromboembolism when used concomitantly with dexamethasone
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- Anticoagulants: increased risk of thromboembolism when used concomitantly with predn...
Tacrolimus

- Diuretics: increased risk of hyperkalaemia when tacrolimus given with potassium-sparing diuretics and aldosterone antagonists
- Grapefruit Juice: plasma concentration of tacrolimus increased by grapefruit juice
- Potassium Salts: increased risk of hyperkalaemia when tacrolimus given with potassium salts
- Antiepileptics: plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Oestrogens: tacrolimus possibly inhibits metabolism of oestrogens; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Progestogens: tacrolimus significantly inhibits metabolism of progestogens
- Sevelamer: plasma concentration of tacrolimus possibly reduced by sevelamer
- Uric-healing Drugs: plasma concentration of tacrolimus possibly increased by omeprazole

Tadalafil

- 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 increased by ritonavir
- Nitrate: tadalafil significantly enhances hypotensive effect of enicorandil
- Sildenafil: plasma concentration of tadalafil possibly increased by ethinylestradiol
- Oestrogens; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Aminoglycosides; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Ketoconazole; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Nevirapine; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Rifampicin; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Ritonavir; plasma concentration of tacrolimus possibly increased by ethinylestradiol
- Anticoagulants: tadalafil significantly enhances hypotensive effect of ecarin

Tamsulosin see Alpha-blockers

- Antiplatelets: plasma concentration of tadalafil possibly increased by amiloride and spironolactone
- Antivirals: plasma concentration of tadalafil possibly increased by amiloride and spironolactone
- Oncology Drugs: increased risk of nephrotoxicity and ototoxicity when telitromycin given with aminoglycosides or colistin
- Oestrogens: antibiotics that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
- Vaccines: antibiotics inactivate oral tephid vaccine—see p. 752

Televirdine

- Interferons: increased risk of peripheral neuropathy when telitromycin given with interferon alfa

Teletromycin

- Antibacterials: plasma concentration of telitromycin reduced by rifampicin (avoid during and for 2 weeks after rifampicin)
- Antidepressants: plasma concentration of telitromycin decreased by St. John’s Wort (avoid during and for 2 weeks after St. John’s Wort)
- Antiepileptics: plasma concentration of telitromycin reduced by primidone (avoid during and for 2 weeks after carbamazepine, phenytoin and primidone)
- Antifungals: manufacturer of telitromycin advises avoid concomitant use with ketoconazole in severe renal and hepatic impairment

Antimucorotics: manufacturer of fosoterodine advises dose reduction when telitromycin given with
Telithromycin

<table>
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<tr>
<th>Antimuscarinics (continued)</th>
<th>consult fesoterodine product literature</th>
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<tr>
<td>Telithromycin</td>
<td>fesoterodine—consult fesoterodine product literature</td>
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Antipsychotics: increased risk of ventricular arrhythmias when telithromycin given with pimozide—avoid concomitant use

Antivirals: manufacturer of telithromycin advises avoid concomitant use with atazanavir, fosamprenavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir and tipranavir in severe renal and hepatic impairment; telithromycin possibly increases plasma concentration of maraviro (consider reducing dose of maraviro)

Anxiolytics and Hypnotics: telithromycin inhibits metabolism of emidazolam (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)

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 eplerenone—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. 478)

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

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Telmisartan see Angiotensin-II Receptor Antagonists

Temazepam see Anxiolytics and Hypnotics

Temocillin see Penicillins

Tenoxicam see NSAIDs

Tenofovir

Antivirals: manufacturer of tenofovir advises avoid concomitant use with adeovir; 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 atazanavir increased by lopinavir

Tetraclin see Alpha-blockers

Terbinafine

Antibacterials: plasma concentration of terbinafine reduced by rifampicin

Antidepressants: terbinafine possibly increases plasma concentration of imipramine and nortryptiline

Ciclosporin: terbinafine possibly reduces plasma concentration of ciclosporin

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)

Ulcerc-Healing Drugs: plasma concentration of terbinafine increased by cimetidine

Tetralanic see Sympathomimetics, Beta2

Terpene Mixture see Rowachol®

Testolactone

Anticoagulants: testolactone enhances anticoagulant effect of ecomarins and phenindione

Testosterone

Anticoagulants: testosterone enhances anticoagulant effect of ecomarins and phenindione

Antidiabetics: testosterone possibly enhances hypoglycaemic effect of antidiabetics

Tetranabenzine

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 metoclopromide

Tetracosalcide see Corticosteroids

Tetracyclines see Tetracyclines

Tetracyclines

ACE Inhibitors: absorption of tetracyclines reduced by quinapril tablets (quinapril tablets contain magnesium carbonate)

Adsortbents: absorption of tetracyclines possibly reduced by kaolin

Antacids: absorption of tetracyclines reduced by antacids

Anticoagulants: tetracyclines possibly enhance anticoagulant effect of ecomarins and phenindione

Antiepileptics: metabolism of doxycycline accelerated by carbamazepine (reduced effect); metabolism of doxycycline accelerated by phenytoin and primindone (reduced plasma concentration)

Atovaquone: tetracycline reduces plasma concentration of atovaquone

Barbiturates: metabolism of doxycycline accelerated by barbiturates (reduced plasma concentration)
Appendix 1: Interactions

Tetracyclines (continued)
Calcium Salts: absorption of tetracycline reduced by calcium salts.
- Ciclosporin: doxycycline possibly increases plasma concentration of ciclosporin.
- Cytotoxins: 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. 478).
- 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 dicitrato-bismuthate.
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752.
- Zinc: absorption of tetracyclines reduced by zinc, also absorption of zinc reduced by tetracyclines.

Theophylline
Alloquolin: plasma concentration of theophylline possibly increased by alloquolin.
- Anaesthetics, General: increased risk of convulsions when theophylline given with ketamine; increased risk of arrhythmias when theophylline given with halothane.
- Anti-arrhythmics: theophylline antagonises anti-arrhythmic effect of adenosine; plasma concentration of theophylline increased by propafenone.
- Antibacterials: plasma concentration of theophylline possibly increased by azithromycin and isoriazid; 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 concentration of tetracycin; 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 ketoconazole.
- Antivirals: metabolism of theophylline possibly accelerated by ritonavir (reduced plasma concentration).
- Anxiolytics and Hypnotics: theophylline possibly reduces effects of benzodiazepines.

Theophylline (continued)
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 thiazides and related diuretics.
- Doxapram: increased CNS stimulation when theophylline given with doxapram.
- Interferons: metabolism of theophylline inhibited by interferon alfa (increased plasma concentration).
- Leukotriene Receptor 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 (expentifylline): plasma concentration of theophylline increased by pentoxifylline (expentifylline).
- Sulfonpyrazone: plasma concentration of theophylline reduced by sulfonpyrazone.
- Sympathomimetics: manufacturer of theophylline advises avoid concomitant use with ephedrine in children.
- Sympathomimetics, Beta2: increased risk of hypokalaemia when theophylline given with high doses of beta2 sympathomimetics—for CSM advice (hypokalaemia) see p. 173.
- Tobacco: metabolism of theophylline increased by tobacco smoking (reduced plasma concentration).
- Ulcer-healing Drugs: metabolism of theophylline inhibited by cimetidine (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.

Thiazolidinediones see Antidiabetics
Thiopental see Anaesthetics, General
Thiotepa
Antiepileptics: cytotoxins possibly reduce absorption of phenytoin.
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis).
- Cardiac Glycosides: cytotoxins reduce absorption of digoxin tablets.
- Muscle Relaxants: thiopeta enhances effects of aminosteroids.

Thioxanthenes see Antipsychotics
Thyroid Hormones
Antacids: absorption of levothyroxine (thyroxine) possibly reduced by antacids.
- Anti-arrhythmics: for concomitant use of thyroid hormones and amiodarone see p. 109.
- Antibacterials: metabolism of levothyroxine (thyroxine) accelerated by rifampicin (may increase requirements for levothyroxine (thyroxine) in hypothyroidism).
- Anticoagulants: thyroid hormones enhance anticoagulant effect of coumarins and phenindione.
- Antidepressants: thyroid hormones enhance effects of amitriptyline and imipramine; thyroid hormones possibly enhance effects of tricyclics.
Appendix 1: Interactions 873

Thyroid Hormones (continued)
Antiepileptics: metabolism of thyroid hormones accelerated by carbamazepine and primidone (may increase requirements for thyroid hormones in hypothyroidism); metabolism of thyroid hormones accelerated by phenytoin (may increase requirements 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: requirements for thyroid hormones in hypothyroidism may be increased by oestrogens
Poly styrene Sulphonate Resins: absorption of levothyroxine (thyroxine) reduced by polystyrene sulphonate resins
Ulc er-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 SS RIs 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
• Antimalarials: 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
Tiaprofenic Acid see NSAIDs
Tibolone
Antibacterials: metabolism of tibolone accelerated by rifampicin (reduced plasma concentration)
Antiepileptics: metabolism of tibolone accelerated by carbamazepine and primidone (reduced plasma concentration); metabolism of tibolone accelerated by phenytoin
Barbiturates: metabolism of tibolone accelerated by barbiturates (reduced plasma concentration)
Ticarcillin see Penicillins
Tigecycline
Anticoagulants: tigecycline possibly enhances anticoagulant effect of coumarins
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752
Tilmicosin see Bacteriostatics
Tinidazole
Alcohol: possibility of disulfiram-like reaction when tinidazole given with alcohol
Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752
Tinzaparin see Heparins

Tioguanine
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: increased risk of hepatotoxicity when tioguanine given with busulfan
Tiopronin see Antimuscarnics
Tipranavir
Antacids: absorption of tipranavir reduced by antacids
• Antibacterials: tipranavir increases plasma concentration of clarithromycin (reduce dose of clarithromycin in renal impairment), also plasma concentration of tipranavir increased by clarithromycin, tipranavir increases plasma concentration of ritabutin (reduce dose of ritabutin); plasma concentration of tipranavir possibly reduced by rifampicin—avoid concomitant use; avoidance of concomitant tipranavir in severe renal and hepatic impairment advised by manufacturer of telithromycin
Anticoagulants:avoidance of tipranavir advised by manufacturer of rivaroxaban
• Antidepressants: plasma concentration of tipranavir possibly reduced by St John’s wort—avoid concomitant use
Antiepileptics: plasma concentration of tipranavir possibly reduced by carbamazepine
Antifungals: plasma concentration of tipranavir increased by fluconazole
Antimalarials: caution with tipranavir advised by manufacturer of artemether/lumefantrine
Antimuscarinics: avoidance of tipranavir advised by manufacturer of darifenacin
• Antivirals: tipranavir reduces plasma concentration of abacavir, didanosine,fosamprenavir, elopainvar, saquinavir and zidovudine; plasma concentration of tipranavir increased by atazanavir (also plasma concentration of atazanavir reduced); tipranavir reduces plasma concentration of etravirine, also plasma concentration of tipranavir increased (avoid concomitant use)
• Beta-blockers: manufacturer of tipranavir advises avoid concomitant use with metoprolol for heart failure
• Lipid-regulating Drugs: possible increased risk of myopathy when tipranavir given with rosvastatin—avoid concomitant use
• Ulcer-healing Drugs: tipranavir reduces plasma concentration ofesomeprazole and omeprazole
Vitamins: increased risk of bleeding when tipranavir given with high doses of vitamin E
Tirofiban
Iloprost: increased risk of bleeding when tirofiban given with iloprost
Tizanidine see Muscle Relaxants
Tobacco
Cinacalcet: tobacco smoking increases cinacalcet metabolism (reduced plasma concentration)
Cytotoxics: tobacco smoking reduces plasma concentration of erlotinib
Theophylline: tobacco smoking increases theophylline metabolism (reduced plasma concentration)
Tobramycin see Aminoglycosides
 Tolazoline see Alpha-blockers
Tolbutamide see Antidiabetics
Tolcapone
Antidepressants: avoid concomitant use of tolcapone with MAOIs
Methyldopa: effects of tolcapone possibly increased by methyldopa
Methylprednisolone: antiparkinsonian effect of dopaminergics possibly antagonised by methylprednisolone
Tolfenamic Acid see NSAIDs
Tolterodine see Antimuscarinics
Topiramate
- 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
- Antidiabetics: topiramate possibly reduces plasma concentration of glipizide
- Antiepileptics: plasma concentration of topiramate often reduced by carbamazepine; topiramate increases plasma concentration of phenytoin (also plasma concentration of topiramate reduced)
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxychloroquine; anticonvulsant effect of antiepileptics antagonised by antifolate
- Lithium: topiramate possibly affects plasma concentration of lithium
- Oestrogens: topiramate accelerates metabolism of oestrogens (reduced contraceptive effect—see p. 478)
- Progestogens: topiramate accelerates metabolism of progestogens (reduced contraceptive effect—see p. 478)

Torasemide see Diuretics
Toremifene
- Anticoagulants: toremifene possibly enhances anticoagulant effect of coumarins
- Antidepressants: toremifene possibly enhances hypoglycaemic effect of repaglinide—manufacturer advises avoid concomitant use; trimethoprim rarely enhances the effects of sulphonylureas
- Antiepileptics: trimethoprim increases plasma concentration of phenytoin (also increased antifolate effect)
- Antimalarials: increased antifolate effect when trimethoprim given with pyrimethamine
- Antivirals: trimethoprim possibly increases plasma concentration of aciclovir

Trimethoprim
Antibacterials (continued)
tion of both drugs may increase when trimethoprim given with dapsone
Anticoagulants: trimethoprim possibly enhances anticoagulant effect of coumarins
Antidiabetics: trimethoprim possibly enhances hypoglycaemic effect of repaglinide—manufacturer advises avoid concomitant use; trimethoprim rarely enhances the effects of sulphonylureas
- Antiepileptics: trimethoprim increases plasma concentration of phenytoin (also increased antifolate effect)
- Antimalarials: increased antifolate effect when trimethoprim given with pyrimethamine
- Antivirals: trimethoprim (as co-trimoxazole) increases plasma concentration of lamivudine—avoid concomitant use of high-dose co-trimoxazole
Cardiac Glycosides: trimethoprim possibly increases plasma concentration of digoxin
- Ciclosporin: increased risk of nephrotoxicity when trimethoprim given with ciclosporin, also plasma concentration of ciclosporin reduced by intravenous trimethoprim
- Cytotoxics: increased risk of haematological toxicity when trimethoprim (also with co-trimoxazole) given with azathioprine, mercaptopurine or methotrexate
- Diuretics: increased risk of hyperkalaemia when trimethoprim given with eplerenone
- Oestrogens: antibacterials that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
- Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Trimipramine see Antidepressants, Tricyclic
Tripotassium Dicitratobismuthate
Antibacterials: tripotassium dicitratobismuthate reduces absorption of tetracyclines
Tropicamid see Antimuscarinics
Trospium see Antimuscarinics
Tryptophan
- Antidepressants: possible increased serotonergic effects when tryptophan given with duloxetine; CNS excitation and confusion when tryptophan given with MAOIs (reduce dose of tryptophan); agitation and nausea may occur when tryptophan given with SSRIs
- Antimalarials: avoidance of antidepressants advised by manufacturer of artemether/lumefantrine
- Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine
- Sibutramine: increased risk of CNS toxicity when tryptophan given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)
- Typhoid Vaccine (oral) see Vaccines
- Typhoid Vaccine (parenteral) see Vaccines

Ubidecarenone
Anticoagulants: ubidecarenone may enhance or reduce anticoagulant effect of warfarin
Ulcen-healing Drugs see Histamine H2-antagonists, Proton Pump Inhibitors, Sucralfate, and Tripotassium Dicitratobismuthate
Ursodeoxycholic Acid
Antacids: absorption of bile acids possibly reduced by antacids
- Ciclosporin: ursodeoxycholic acid increases absorption of ciclosporin
- Lipid-regulating Drugs: absorption of bile acids possibly reduced by colestipol and colestyramine
- Oestrogens: elimination of cholesterol in bile increased when bile acids given with oestrogens
Valproate
- Antipsychotics (continued)
  - old 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

Antioedematous Drugs: metabolism of vancomycin inhibited by cimetidine (increased plasma concentration)

Vancomycin
Anaesthetics, General: hypersensitivity-like reactions can occur when intravenous vancomycin given with general anaesthetics
Antibacterials: increased risk of nephrotoxicity and ototoxicity when vancomycin given with aminoglycosides, capreomycin or colistin; increased risk of nephrotoxicity when vancomycin given with polymyxins
Antifungals: possible increased risk of nephrotoxicity when vancomycin given with amphotericin

Cyclosporin: increased risk of nephrotoxicity and possibly of ototoxicity when vancomycin given with cisplatin

Diuretics: increased risk of ototoxicity when vancomycin given with loop diuretics

Lipid-regulating Drugs: effects of oral vancomycin antagonised by colestyramine

Muscle Relaxants: vancomycin enhances effects of suxamethonium

Oestrogens: antagonists that do not induce liver enzymes possibly reduce contraceptive effect of oestrogens (risk probably small, see p. 478)
Tacrolimus: possible increased risk of nephrotoxicity when vancomycin given with tacrolimus

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Vardenafil
- 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 fosamprenavir; plasma concentration of vardenafil increased by ritonavir—avoid concomitant use;

Antifungals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by indinavir—avoid concomitant use;

Antivirals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by ritonavir—avoid concomitant use;

Sodium Benzoate: valproate possibly reduces effects of sodium benzoate
Sodium Phenylbutyrate: valproate possibly reduces effects of sodium phenylbutyrate

Anticoagulants: valproate possibly enhances anticoagulant effect of warfarin

Antipsychotics: anticonvulsant effect of valproate possibly inhibited by erythromycin (increased plasma concentration)

Diuretics: increased risk of ototoxicity when vancomycin given with amphotericin

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Vardenafil
- 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 fosamprenavir; plasma concentration of vardenafil increased by ritonavir—avoid concomitant use;

Antifungals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by indinavir—avoid concomitant use;

Antivirals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by ritonavir—avoid concomitant use;

Sodium Benzoate: valproate possibly reduces effects of sodium benzoate
Sodium Phenylbutyrate: valproate possibly reduces effects of sodium phenylbutyrate

Anticoagulants: valproate possibly enhances anticoagulant effect of warfarin

Antipsychotics: anticonvulsant effect of valproate possibly inhibited by erythromycin (increased plasma concentration)

Diuretics: increased risk of ototoxicity when vancomycin given with amphotericin

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752

Vardenafil
- 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 fosamprenavir; plasma concentration of vardenafil increased by ritonavir—avoid concomitant use;

Antifungals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by indinavir—avoid concomitant use;

Antivirals: plasma concentration of vardenafil possibly increased by fosamprenavir; plasma concentration of vardenafil increased by ritonavir—avoid concomitant use;

Sodium Benzoate: valproate possibly reduces effects of sodium benzoate
Sodium Phenylbutyrate: valproate possibly reduces effects of sodium phenylbutyrate

Anticoagulants: valproate possibly enhances anticoagulant effect of warfarin

Antipsychotics: anticonvulsant effect of valproate possibly inhibited by erythromycin (increased plasma concentration)

Diuretics: increased risk of ototoxicity when vancomycin given with amphotericin

Vaccines: antibacterials inactivate oral typhoid vaccine—see p. 752
Vardenafil (continued)

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 (continued)

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 with 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
Anaesthetics, 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
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
Dopaminergics: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with levodopa
Methyldopa: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with methyldopa
Moxisylyte (thyromoxamine): enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with moxisylyte

Vasodilator Antihypertensives (continued)

Minoxidine: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with minoxidine
Muscle Relaxants: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with baclofen
Nicorandil: possible increased hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with nicorandil
Nitrates: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with nitrates
Oestrogens: hypotensive effect of hydralazine, minoxidil and sodium nitroprusside antagonised by oestrogens
Prostaglandins: enhanced hypotensive effect when hydralazine, minoxidil or sodium nitroprusside given with alprostadil
Vasodilator Antihypertensives: enhanced hypotensive effect when hydralazine given with minoxidil or sodium nitroprusside; enhanced hypotensive effect when minoxidil given with sodium nitroprusside

Vecuronium see Muscle Relaxants

Venlafaxine
- Analgesics: increased risk of bleeding when venlafaxine given with NSAIDs or aspirin
- Anticoagulants: venlafaxine possibly enhances anticoagulant effect of warfarin
- Antidepressants: possible increased serotonergic effect 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
- Antimalarials: avoidance of antidepressants advised by manufacturer of arteether/lumefantrine
- Antipsyhotics: venlafaxine increases plasma concentration of clozapine and haloperidol
- Atomoxetine: possible increased risk of convulsions when antidepressants given with atomoxetine
- Dopaminergics: caution with venlafaxine advised by manufacturer of entacapone; increased risk of hypertension and CNS excitation when venlafaxine given with MAOIs (venlafaxine should not be started until 1 week after stopping MAOIs, 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 SSRI-related antidepressants given with sibutramine (manufacturer of sibutramine advises avoid concomitant use)

Veralapamil see Calcium-channel Blockers

Vigabatrin
- Antidepressants: anticonvulsant effect of antiepileptics possibly antagonised by MAOIs and etricletics-related antidepressants (convulsive threshold lowered); anticonvulsant effect of antiepileptics antagonised by SSRIs and etricletics (convulsive threshold lowered); avoid concomitant use of antiepileptics with St John’s wort
- Antiepileptics: vigabatrin reduces plasma concentration of phenytoin; vigabatrin possibly reduces plasma concentration of primidone
- Antimalarials: possible increased risk of convulsions when antiepileptics given with chloroquine and hydroxyzine; anticonvulsant effect of antiepileptics antagonised by fenofibrate
- Barbiturates: vigabatrin possibly reduces plasma concentration of phenobarbital

Vildagliptin see Antidiabetics
Vibrastine
- Antibacterials: toxicity of vibrastine increased by:
  - erythromycin—avoid concomitant use
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
- Antifungals: metabolism of vibrastine possibly inhibited by posaconazole (increased risk of neurotoxicity)
- Antipsychotics: avoid concomitant use of cytotoxics with clozapine (increased risk of agranulocytosis)
- Cardiac Glycosides: cytotoxics reduce absorption of digoxin tablets

Vinblastine
- Antiepileptics: cytotoxics possibly reduce absorption of phenytoin
- Antifungals: metabolism of vinblastine possibly inhibited by posaconazole 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 coumarins and phenindione
- Antiepileptics: vitamin D requirements possibly increased when given with carbamazepine, phenytoin or primidone
- Antifungals: plasma concentration of paricalcitol possibly increased by ketoconazole
- Antivirals: increased risk of bleeding when high doses of vitamin E given with tipranavir
- Barbiturates: vitamin D requirements possibly increased when given with barbiturates
- Diuretics: increased risk of hypercalcaemia when vitamin D given with thiazides and related diuretics
- Dopaminergics: pyridoxine reduces effects of levodopa when given without dopa-decarboxylase inhibitor
- Retinoids: risk of hypervitaminosis A when vitamin A given with retinoids
- Selenium: ascorbic acid possibly reduces absorption of selenium (give at least 4 hours apart)

Zalcitabine see Antifungals; Triazole

Warfarin see Coumarins

Xipamide see Diuretics

Xylometazoline see Sympathomimetics

Zafirlukast see Leukotriene Receptor Antagonists

Zaleplon see Anxiolytics and Hypnotics

Zidovudine
- Analgesics (continued) centration 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 itraconazole (increased risk of toxicity)

Antimalarials: increased antifolate effect when zidovudine given with pyrimethamine

Antivirals: profound myelosuppression when zidovudine given with efniclovir (if possible avoid concomitant administration, particularly during initial ganciclovir therapy); increased risk of anaemia when zidovudine given with zidovudine—avoid concomitant use; zidovudine possibly inhibits effects of stavudine (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 5HT1 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 anti-epileptics 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 anti-epileptics antagonised by mefloquine
- Barbiturates: plasma concentration of zonisamide reduced by phenobarbital

Zopiclone see Anxiolytics and Hypnotics

Zotepine see Antipsychotics

Zuclopenthixol see Antipsychotics
A2 Borderline substances

A2.1 Enteral feeds (non-disease specific) ......................................................... 879
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A2.7 Nutritional supplements for metabolic diseases ..................................... 912

In certain conditions some foods (and toilet preparations) have characteristics of drugs and the Advisory Committee on Borderline Substances (ACBS) 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: All the food products listed in this appendix have ACBS approval. The clinical condition for which the product has been approved is included with each entry.

Foods included in this Appendix may contain cariogenic sugars and appropriate oral hygiene measures should be taken.

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 For most enteral feeds and nutritional supplements, the main source of carbohydrate is either maltodextrin or glucose syrup; other carbohydrate sources are listed in the relevant table, below. Feeds containing residual lactose (less than 1 g lactose/100 mL formula) are described as ‘clinically lactose-free’ or ‘lactose-free’ by some manufacturers. The presence of lactose (including residual lactose) in feeds is indicated in the relevant table, below. The primary sources of protein or amino acids are included with each product entry. The fat or oil content is derived from a variety of sources such as vegetables, soya bean, corn, palm nuts, and seeds; where the fat content is derived from animal or fish sources, this information is included in the relevant table, below. The presence of medium chain triglycerides (MCT) is also noted where the quantity exceeds 30% of the fat content.

Enteral feeds and nutritional supplements can contain varying amounts of vitamins, minerals, and trace elements—the manufacturer’s product literature should be consulted for more detailed information. For further information on enteral nutrition, see section 9.4.2. Feeds containing vitamin K may affect the INR in children receiving warfarin; see interactions: Appendix 1 (vitamins).

The suitability of food products for patients requiring a vegan, kosher, halal, or other compliant diet should be confirmed with individual manufacturers.

Standard ACBS indications:
Disease-related malnutrition, intractable malabsorption, pre-operative preparation of malnourished patients, dysphagia, proven inflammatory bowel disease, following total gastrectomy, short-bowel syndrome, bowel fistula

Paediatric ACBS indications:
Disease-related malnutrition, intractable malabsorption, growth failure, pre-operative preparation of malnourished patients, dysphagia, short-bowel syndrome, bowel fistula
### A2.1 Enteral feeds (non-disease specific)

#### A2.1.1 Enteral feeds (non-disease specific): less than 5 g protein/100 mL

For further information on composition of feeds, see p. 878

#### A2.1.1.1 Enteral feeds: 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in a child under 1 year; not recommended for child 1–6 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® Original (Fresenius Kabi)</td>
<td>Liquid (sip or tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>3.8 g cows' milk soya</td>
<td>13.8 g (sugars 3.5 g)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish gelatin Feed in flexible pack contains fish oil and fish gelatin</td>
<td>Standard, p. 878</td>
<td>Bottle: 200 mL = £1.66 Black currant, chocolate, mocha, nut, peach, vanilla Flexible pack: 500 mL = £3.21 1000 mL = £6.33 1500 mL = £9.51</td>
</tr>
<tr>
<td>Fresubin® Original Fibre (Fresenius Kabi)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>3.8 g cows' milk soya</td>
<td>13.8 g (sugars 1 g)</td>
<td>3.4 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 878 except bowel fistula. Not suitable for child under 2 years</td>
<td>Flexible pack: 500 mL = £3.63 1000 mL = £7.24 1500 mL = £10.20</td>
</tr>
<tr>
<td>Isosource® Fibre (Nestlé)</td>
<td>Liquid (tube feed)</td>
<td>422 kJ (100 kcal) per 100 mL</td>
<td>3.8 g cows' milk</td>
<td>13.6 g</td>
<td>3.4 g</td>
<td>1.4 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 Not suitable for child under 2 years</td>
<td>Flexible pack: 500 mL = £3.39 1000 mL = £6.77</td>
</tr>
<tr>
<td>Isosource® Standard (Nestlé)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>4 g cows' milk</td>
<td>13.6 g</td>
<td>3.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £2.98 1000 mL = £5.95</td>
</tr>
<tr>
<td>Jevity® (Abbott)</td>
<td>Liquid (tube feed)</td>
<td>441 kJ (106 kcal) per 100 mL</td>
<td>4 g caseinates</td>
<td>14.1 g (sugars 470 mg)</td>
<td>3.47 g</td>
<td>1.76 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 except bowel fistula. Not suitable for child under 2 years</td>
<td>Flexible pack: 500 mL = £3.85 1000 mL = £7.23 1500 mL = £10.86</td>
</tr>
<tr>
<td>Modulen IBD® (Nestlé)</td>
<td>Standard dilution (20%) of powder (sip or tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>3.6 g casein</td>
<td>11 g (sugars 3.98 g)</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Crohn's disease active phase, and in remission if malnourished Can: 400 g = £13.60 Unflavoured(^2) (8.3-g measuring scoop provided)</td>
<td></td>
</tr>
</tbody>
</table>

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1. Sugar content varies with flavour
2. Flavouring: see Flavour Mix, p. 909
### A2.1.1 Enteral feeds: 1 kcal/mL and less than 5 g protein/100 mL

*(product list continued)*

Not suitable for use in child under 1 year; not recommended for child 1–6 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Novasource® Gl Control (Nestlé)</td>
<td>Liquid (tube feed) 444 kJ (106 kcal) per 100 mL</td>
<td>4.1 g cows’ milk</td>
<td>14.4 g (sugars 500 mg)</td>
<td>3.5 g (MCT 40%)</td>
<td>2.2 g</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £4.52</td>
</tr>
<tr>
<td>Nutrison® (Nutricia Clinical)</td>
<td>Liquid (tube feed) 420 kJ (100 kcal) per 100 mL</td>
<td>4 g cows’ milk</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Bottle: 500 mL = £3.65 Flexible pack: 500 mL = £4.05 1000 mL = £7.11 1500 mL = £10.65</td>
</tr>
<tr>
<td>Formerly Nutrison® Standard</td>
<td>Nutrison® Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (tube feed) 420 kJ (100 kcal) per 100 mL</td>
<td>4 g cows’ milk</td>
<td>12.3 g (sugars 1 g)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878 except bowel fistula</td>
</tr>
<tr>
<td>Osmolite® (Abbott)</td>
<td>Liquid (tube feed) 424 kJ (100 kcal) per 100 mL</td>
<td>4 g caseinates soy isolate</td>
<td>13.6 g (sugars 630 mg)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Can: 250 mL = £1.79 Bottle: 500 mL = £3.39 1000 mL = £6.46 1500 mL = £9.69</td>
</tr>
</tbody>
</table>

#### Soya protein formula (see also section A2.3.1)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrison® Soya (Nutricia Clinical)</td>
<td>Liquid (tube feed) 420 kJ (100 kcal) per 100 mL</td>
<td>4 g soy isolate</td>
<td>12.3 g (sugars 700 mg)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose Milk protein-free</td>
<td>Standard, p. 878; also cows’ milk and protein and lactose intolerance</td>
<td>Bottle: 500 mL = £4.12 Flexible pack: 1000 mL = £8.24</td>
</tr>
<tr>
<td>Nutrison® Soya Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (tube feed) 420 kJ (100 kcal) per 100 mL</td>
<td>4 g soy isolate</td>
<td>12.3 g (sugars 700 mg)</td>
<td>3.9 g</td>
<td>1.5 g</td>
<td>Gluten-free</td>
<td>Residual lactose Milk protein-free</td>
<td>Standard, p. 878 except bowel fistula; also cows’ milk protein and lactose intolerance</td>
<td>Flexible pack: 1500 mL = £13.25</td>
</tr>
</tbody>
</table>
### Peptide-based formula

<table>
<thead>
<tr>
<th>Formula</th>
<th>Type (sip or tube feed)</th>
<th>Energy per 100 mL</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>Indications</th>
<th>ACBS</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptamen® (Nestlé)</td>
<td>Liquid (sip or tube feed)</td>
<td>420 kJ (100 kcal)</td>
<td>4 g whey peptides</td>
<td>12.7 g (sugars 480 mg)</td>
<td>3.7 g (MCT 70%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Cup (vanilla flavour): 200 mL = £2.68 Can (unflavoured): 375 mL = £4.84 Flexible pack: 500 mL = £5.38 1000 mL = £10.10</td>
<td></td>
</tr>
<tr>
<td>Peptisorb® (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>425 kJ (100 kcal)</td>
<td>4 g whey protein hydrolysate</td>
<td>17.6 g (sugars 1.7 g)</td>
<td>1.7 g (MCT 47%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Bottle: 500 mL = £5.50 Flexible pack: 500 mL = £6.04 1000 mL = £10.92</td>
<td></td>
</tr>
<tr>
<td>Survimed® OPD (Fresenius Kabi)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal)</td>
<td>4.5 g lactalbumin hydrolysate</td>
<td>15 g (sugars 300 mg)</td>
<td>2.4 g (MCT 54%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 878; also growth failure</td>
<td>Flexible pack: 500 mL = £5.34</td>
<td></td>
</tr>
</tbody>
</table>

1. Sugar content varies with flavour
2. Flavouring: see Flavour Mix, p. 909

---

### A2.1.1.2 Enteral feeds: Less than 1 kcal/mL and less than 5 g protein/100 mL

Not suitable for use in child under 1 year; not recommended for child 1–6 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy per 100 mL</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elemental 028® Extra (SHS)</td>
<td>Liquid (sip or tube feed)</td>
<td>360 kJ (86 kcal)</td>
<td>2.5 g (protein equivalent)</td>
<td>11 g (sugars 4.7 g)</td>
<td>3.5 g (MCT 35%)</td>
<td>Nil</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula</td>
<td>Carton: 250 mL = £2.88 Grapefruit, orange and pineapple, summer fruits</td>
<td>Sachet: 100 g = £5.60 Banana, citrus, orange, unflavoured</td>
</tr>
<tr>
<td>Standard dilution (20%) of powder (sip or tube feed)</td>
<td>Liquid (sip or tube feed)</td>
<td>374 kJ (89 kcal)</td>
<td>2.5 g (protein equivalent)</td>
<td>11.8 g (sugars 1.8 g)</td>
<td>3.5 g (MCT 35%)</td>
<td>Nil</td>
<td></td>
<td>Sachet: 100 g = £5.60 Banana, citrus, orange, unflavoured</td>
<td></td>
</tr>
<tr>
<td>Powder provides protein equivalent 12.5 g, carbohydrate 59 g, fat 17.45 g, energy 1871 kJ (443 kcal)/100 g</td>
<td></td>
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</tbody>
</table>

1. Nutritional values may vary with flavour—consult product literature
2. Flavouring: see Modju® Flavour System, p. 909
### A2.1.2 Enteral feeds (non-disease specific): 5 g (or more) protein/100 mL

For further information on the composition of feeds, see p. 878

### A2.1.2.1 Enteral feeds: 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; not recommended for child 1–6 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinutren® 1.5</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.6 g cows’ milk</td>
<td>21 g (sugars 5.2 g&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>5 g</td>
<td>less than 500 mg</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 Not suitable for use in child under 3 years</td>
<td>Plastic cup: 4 × 200 mL = £6.59 Apricot, banana, chocolate, coffee, strawberry-raspberry, vanilla</td>
</tr>
<tr>
<td>(Nestlé)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Clinutren® 1.5 Fibre</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.7 g cows’ milk</td>
<td>19 g (sugars 6.1 g)</td>
<td>5.9 g</td>
<td>2.6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 except bowel fistula Not suitable for use in child under 3 years</td>
<td>Plastic cup: 4 × 200 mL = £6.59 Plum or vanilla</td>
</tr>
<tr>
<td>(Nestlé)</td>
<td></td>
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</tr>
<tr>
<td>Fresubin® 2250</td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.6 g cows’ milk</td>
<td>18.8 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 1500 mL = £11.39</td>
</tr>
<tr>
<td>Complete</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>(Fresenius Kabi)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(Formerly Fresubin® Energy Fibre)</td>
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<td></td>
</tr>
<tr>
<td>Fresubin® Energy</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.6 g cows’ milk</td>
<td>18.8 g (sugars&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free&lt;sup&gt;2&lt;/sup&gt; Residual lactose Contains fish gelatin</td>
<td>Standard, p. 878</td>
<td>Bottle: 200 mL = £1.66 Banana, black currant, cappuccino, chocolate, lemon, neutral, strawberry, tropical fruits, vanilla</td>
</tr>
<tr>
<td>(Fresenius Kabi)</td>
<td></td>
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<tr>
<td></td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.6 g cows’ milk</td>
<td>18.8 g (sugars 1.4 g)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £3.91 1000 mL = £7.70 1500 mL = £10.32</td>
</tr>
<tr>
<td>Fresubin® Energy</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.6 g cows’ milk</td>
<td>18.8 g (sugars&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish gelatin</td>
<td>Standard, p. 878</td>
<td>Bottle: 200 mL = £1.74 Banana, caramel, cherry, chocolate, strawberry, vanilla</td>
</tr>
<tr>
<td>Fibre</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Fresenius Kabi)</td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>5.6 g cows’ milk</td>
<td>18.8 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £4.30 1000 mL = £8.20</td>
</tr>
</tbody>
</table>

1. Sugar content varies with flavour
2. Strawberry flavour may contain traces of wheat starch and egg
<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>Energy (kcal)</th>
<th>Carbohydrates</th>
<th>Fats</th>
<th>Lactose</th>
<th>Gluten</th>
<th>Lactose</th>
<th>Residual lactose</th>
<th>Protein</th>
<th>Vitamins</th>
<th>Micronutrients</th>
<th>Summary</th>
<th>Pack Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® HP Energy</td>
<td>Liquid (tube feed)</td>
<td>630 (150 kcall)</td>
<td>7.5 g cows’ milk</td>
<td>17 g (sugars 1 g)</td>
<td>5.8 g (MCT 57%)</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Contains fish oil and fish gelatin</td>
<td>Standard, also CAPD and haemodialysis</td>
<td>Flexible pack: 500 mL = £3.99, 1000 mL = £8.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isosource® Energy Fibre</td>
<td>Liquid (tube feed)</td>
<td>670 (160 kcall)</td>
<td>5.7 g cows’ milk</td>
<td>20 g</td>
<td>6.2 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £3.66, 1000 mL = £7.31</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Jevity® 1.5 kcal</td>
<td>Liquid (tube feed)</td>
<td>640 (152 kcall)</td>
<td>4.9 g cows’ milk</td>
<td>20.2 g</td>
<td>5.5 g</td>
<td>1.5 g</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878 except bowel fistula</td>
<td>Flexible pack: 500 mL = £4.69, 1000 mL = £8.70, 1500 mL = £13.58</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Novasource® Gl Forte</td>
<td>Liquid (tube feed)</td>
<td>631 (150 kcall)</td>
<td>6 g cows’ milk</td>
<td>18.3 g (sugars 1.8 g)</td>
<td>5.9 g</td>
<td>2.2 g</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £4.49, 1000 mL = £8.98</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Nutrison® Energy Multi Fibre</td>
<td>Liquid (tube feed)</td>
<td>630 (150 kcall)</td>
<td>6 g cows’ milk</td>
<td>18.5 g (sugars 1.5 g)</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Bottle: 500 mL = £4.25, Flexible pack: 500 mL = £4.72, 1000 mL = £8.55, 1500 mL = £12.80</td>
<td></td>
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</tr>
<tr>
<td>Osmolite® 1.5 kcal</td>
<td>Liquid (tube feed)</td>
<td>632 (150 kcall)</td>
<td>6.25 g cows’ milk soy protein isolate</td>
<td>20 g (sugars 4.9 g)</td>
<td>5 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 500 mL = £4.35, 1000 mL = £8.10, 1500 mL = £12.13</td>
<td></td>
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</tr>
</tbody>
</table>
## A2.1.2.2 Enteral feeds: Less than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; not recommended for child 1–6 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy (per 100 mL)</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresubin® 1000</td>
<td>Liquid (tube feed)</td>
<td>420 kJ</td>
<td>5.5 g cows’ milk</td>
<td>12.5 g (sugars 1.1 g)</td>
<td>3.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 1000 mL = £8.20</td>
</tr>
<tr>
<td>Complete (Fresenius Kabi)</td>
<td></td>
<td>(100 kcal)</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td></td>
<td>per 100 mL</td>
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<td></td>
</tr>
<tr>
<td>Fresubin® 1200</td>
<td>Liquid (tube feed)</td>
<td>500 kJ</td>
<td>6 g cows’ milk</td>
<td>15 g (sugars 1.22 g)</td>
<td>4.1 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 1000 mL = £10.61</td>
</tr>
<tr>
<td>Complete (Fresenius Kabi)</td>
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<td>(120 kcal)</td>
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<td></td>
<td>per 100 mL</td>
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</tr>
<tr>
<td>Jevity® Plus</td>
<td>Liquid (tube feed)</td>
<td>504 kJ</td>
<td>5.5 g caseinates soy isolates</td>
<td>15.1 g (sugars 890 mg)</td>
<td>3.93 g</td>
<td>2.2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 Not suitable for child under 2 years; not recommended for child 2–10 years</td>
<td>Flexible pack: 1000 mL = £8.49</td>
</tr>
<tr>
<td>(Abbott)</td>
<td>per 100 mL</td>
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<td></td>
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</tr>
<tr>
<td>Jevity® Promote</td>
<td>Liquid (tube feed)</td>
<td>427 kJ</td>
<td>5.55 g caseinates soy isolates</td>
<td>12 g (sugars 670 mg)</td>
<td>3.32 g</td>
<td>1.7 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 Not suitable for child under 2 years; not recommended for child 2–10 years</td>
<td>Flexible pack: 1000 mL = £8.49</td>
</tr>
<tr>
<td>(Abbott)</td>
<td>per 100 mL</td>
<td></td>
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</tr>
<tr>
<td>Nutrison® MCT</td>
<td>Liquid (tube feed)</td>
<td>420 kJ</td>
<td>5 g cows’ milk</td>
<td>12.6 g (sugars 1 g)</td>
<td>3.3 g (MCT 61%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 1000 mL = £7.73</td>
</tr>
<tr>
<td>(Nutricia Clinical)</td>
<td>per 100 mL</td>
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</tr>
<tr>
<td>Nutrison® Protein</td>
<td>Liquid (tube feed)</td>
<td>525 kJ</td>
<td>6.3 g cows’ milk</td>
<td>14.2 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td>Flexible pack: 1000 mL = £7.95</td>
</tr>
<tr>
<td>Plus (Nutricia Clinical)</td>
<td></td>
<td>(125 kcal)</td>
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<td>per 100 mL</td>
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</tr>
<tr>
<td>Nutrison® Protein</td>
<td>Liquid (tube feed)</td>
<td>525 kJ</td>
<td>6.3 g cows’ milk</td>
<td>14.1 g (sugars 1.1 g)</td>
<td>4.9 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Disease related malnutrition</td>
<td>Flexible pack: 1000 mL = £8.85</td>
</tr>
<tr>
<td>Plus Multi Fibre     (Nutricia Clinical)</td>
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<td>(125 kcal)</td>
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<td>per 100 mL</td>
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</tr>
<tr>
<td>Nutrison® 1000</td>
<td>Liquid (tube feed)</td>
<td>420 kJ</td>
<td>5.5 g cows’ milk</td>
<td>11.3 g (sugars 700 mg)</td>
<td>3.7 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Disease related malnutrition in patients with low energy and/or low fluid requirements</td>
<td>Flexible pack: 1000 mL = £8.59</td>
</tr>
<tr>
<td>Complete Multi Fibre (Nutricia Clinical)</td>
<td></td>
<td>(100 kcal)</td>
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<td></td>
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<tr>
<td></td>
<td>per 100 mL</td>
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<td></td>
</tr>
<tr>
<td>Nutrison® 1200</td>
<td>Liquid (tube feed)</td>
<td>505 kJ</td>
<td>5.5 g cows’ milk</td>
<td>15 g (sugars 1.2 g)</td>
<td>4.3 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 except bowel fistula</td>
<td>Bottle: 500 mL = £4.55 Flexible pack: 1000 mL = £9.10 1500 mL = £13.66</td>
</tr>
<tr>
<td>Complete Multi Fibre (Nutricia Clinical)</td>
<td></td>
<td>(120 kcal)</td>
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<td></td>
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<td></td>
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<tr>
<td></td>
<td>per 100 mL</td>
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</tr>
</tbody>
</table>
### A2.1.2.3 Enteral feeds: More than 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; not recommended for child 1–6 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ensure® Twocal</strong> (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>838 kJ (200 kcal) per 100 mL</td>
<td>8.4 g cows’ milk</td>
<td>21 g (sugars 4.5 g)</td>
<td>8.9 g</td>
<td>1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also haemodialysis and CAPD</td>
<td>Carton: 200 mL = £2.03 Banana, neutral, strawberry, vanilla</td>
</tr>
</tbody>
</table>

### A2.1.3 Enteral feeds (non-disease specific): Child under 12 years

For further information on composition of feeds, see p. 878.

### A2.1.3.1 Enteral feeds, Child: Less than 1 kcal/mL and less than 4 g protein/100 mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nutri® Low Energy Multi Fibre</strong> (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>315 kJ (75 kcal) per 100 mL</td>
<td>2.1 g whey protein and caseinate</td>
<td>9.3 g (sugars 600 mg)</td>
<td>3.3 g</td>
<td>800 mg</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Paediatric, p. 878 except bowel fistula, in child 1–6 years, body-weight 8–20 kg</td>
<td>Bottle: 200 mL = £2.05 Flexible pack: 500 mL = £5.18</td>
</tr>
<tr>
<td><strong>Nutriprem® 1</strong> (Cow &amp; Gate)</td>
<td>Liquid (sip feed)</td>
<td>335 kJ (80 kcal) per 100 mL</td>
<td>2.5 g whey protein and casein</td>
<td>7.6 g (lactose 6.3 g)</td>
<td>4.4 g</td>
<td>800 mg</td>
<td>Contains soya, fish oil and egg lipid</td>
<td>Low birth-weight formula</td>
<td>Bottle: 60 mL Hospital supply only</td>
</tr>
</tbody>
</table>
### A2.1.3.1 Enteral feeds, Child: Less than 1 kcal/mL and less than 4 g protein/100 mL (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nutriprem</strong> 2 (Cow &amp; Gate)</td>
<td>Liquid (sip feed)</td>
<td>310 kJ (75 kcal) per 100 mL</td>
<td>2 g whey protein and casein</td>
<td>7.4 g (lactose 5.8 g)</td>
<td>4.1 g</td>
<td>800 mg</td>
<td>Contains soya, fish oil and egg lipid</td>
<td>Catch-up growth in pre-term infants (less than 35 weeks at birth) and small for gestational-age infants up to 6 months corrected age</td>
<td>Carton: 200 mL = £1.54 (Bottle: 100 mL Hospital supply only) Can: 900 g = £10.28 (5.1-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>SMA</strong> High Energy (SMA Nutrition)</td>
<td>Liquid (sip feed)</td>
<td>382 kJ (91 kcal) per 100 mL</td>
<td>2 g whey protein and casein</td>
<td>9.8 g lactose</td>
<td>4.9 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Disease related malnutrition and malabsorption, and growth failure in child from birth to 18 months</td>
<td>Carton: 250 mL = £2.07</td>
</tr>
<tr>
<td><strong>Emsogen</strong> (SHS)</td>
<td>Standard dilution (20%) of powder (sip or tube feed)</td>
<td>368 kJ (88 kcal) per 100 mL</td>
<td>2.5 g protein equivalent (essential and non-essential amino acids)</td>
<td>12 g (sugars 1.6 g)</td>
<td>3.3 g (MCT 83%)</td>
<td>Nil</td>
<td>Lactose-free</td>
<td>Short-bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula Not suitable for child under 1 year or as sole source of nutrition in child 1–5 years</td>
<td>Sachet: 100 g = £5.54 Orange Unflavoured†</td>
</tr>
</tbody>
</table>

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### A2.1.3.2 Enteral feeds, Child: 1 kcal/mL and less than 4 g protein/100 mL

Not suitable for child under 1 year unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinutren Junior</strong> (Nestlé)</td>
<td>Standard dilution (22%) of powder (sip or tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.97 g whey protein and caseinate</td>
<td>13.3 g</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also growth failure in child 1–10 years</td>
<td>Can: 400 g = £9.72 Vanilla (7.85-g measuring scoop provided)</td>
</tr>
</tbody>
</table>

Powder provides: protein 13.9 g, carbohydrate 62.2 g, fat 18.3 g, energy 1950 kJ (467 kcal)/100 g

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1. Nutritional values may vary with flavour—consult product literature
2. Additional source of alpha linolenic acid needed if used as sole source of nutrition
3. Flavouring: see Modjul® Flavour System, p. 909

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Appendix 2: Borderline substances
<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>Nutritional Information</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frebini Original (Fresenius Kabi)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.5 g cows’ milk, 12.5 g (sugars 700 mg), 4.4 g Nil, Gluten-free, Residual lactose contains fish oils and fish gelatin. Standard, p. 878; also growth failure in child 1–10 years, body-weight 8–30 kg. Flexible pack: 500 mL = £4.73</td>
</tr>
<tr>
<td>Frebini Original Fibre (Fresenius Kabi)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.5 g cows’ milk, 12.5 g (sugars 700 mg), 4.4 g 750 mg, Gluten-free, Residual lactose contains fish oils and fish gelatin. Standard, p. 878; also growth failure in child 1–10 years, body-weight 8–30 kg. Flexible pack: 500 mL = £5.25</td>
</tr>
<tr>
<td>Infatrini* (Nutricia Clinical)</td>
<td>Liquid (sip or tube feed)</td>
<td>415 kJ (100 kcal) per 100 mL</td>
<td>2.6 g cows’ milk, 10.3 g (lactose 5.2 g), 5.4 g 800 mg, Gluten-free, Contains fish oil. Failure to thrive, disease-related malnutrition and malabsorption, in child from birth up to body-weight 8 kg. Bottle: 100 mL = £1.05, 200 mL = £2.01, Flexible pack: 500 mL = £5.25</td>
</tr>
<tr>
<td>Nutrini* (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.8 g cows’ milk, 12.3 g (sugars 1 g), 4.4 g Nil, Gluten-free, Residual lactose. Standard, p. 878; also growth failure in child 1–6 years, body-weight 8–20 kg. Bottle: 200 mL = £2.11, Flexible pack: 500 mL = £5.28</td>
</tr>
<tr>
<td>Nutrini Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.8 g whey protein and caseinate, 12.3 g (sugars 800 mg), 4.4 g 800 mg, Gluten-free, Residual lactose contains fish oil. Standard, p. 878; also growth failure in child 1–6 years, body-weight 8–20 kg. Bottle: 200 mL = £2.35, Flexible pack: 500 mL = £5.87</td>
</tr>
<tr>
<td>Paediasure* Fibre (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>422 kJ (100 kcal) per 100 mL</td>
<td>2.8 g cows’ milk, 11.2 g (sugars 3.92 g), 4.98 g Nil, Gluten-free, Residual lactose. Paediatric, p. 878 in child 1–10 years, body-weight 8–30 kg. Can: 250 mL = £2.54, Vanilla, Carton: 200 mL = £2.04, Banana, chocolate, strawberry, vanilla (bottle). Flexible pack: 500 mL = £5.09, Vanilla</td>
</tr>
<tr>
<td>Paediasure Fibre (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.8 g caseinates and whey protein, 10.9 g (sugars 3.84 g), 4.98 g 730 mg, Gluten-free, Residual lactose. Paediatric, p. 878 in child 1–10 years, body-weight 8–30 kg. Carton: 200 mL = £2.19, Banana, strawberry, vanilla. Flexible pack: 500 mL = £5.52, Vanilla</td>
</tr>
<tr>
<td>Tentrini* (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>3.3 g whey protein and caseinate, 12.3 g (sugars 800 mg), 4.2 g Nil, Gluten-free, Residual lactose contains fish oil. Standard, p. 878; also growth failure in child 7–12 years, body-weight 21–45 kg. Bottle or Flexible pack: 500 mL = £4.66</td>
</tr>
</tbody>
</table>

1. Nutritional values may vary with flavour—consult product literature.

Appendix 2: Borderline substances.
### A2.1.3.2 Enteral feeds, Child: 1 kcal/mL and less than 4 g protein/100 mL

Not suitable for child under 1 year unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tentrini® Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>3.3 g whey protein and caseinate</td>
<td>12.3 g (sugars 800 mg)</td>
<td>4.2 g</td>
<td>1.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 878 except bowel fistula; also growth failure in child 7–12 years body-weight 21–45 kg</td>
<td>Bottle or Flexible pack: 500 mL = £5.12</td>
</tr>
<tr>
<td>Hydrolysate Formula</td>
<td>See also Infant Formula (Hydrolysate), section 2.3.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nutrini® Peptisorb (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.8 g whey protein hydrolysate</td>
<td>13.7 g (sugars 800 mg)</td>
<td>3.9 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also growth failure in child 1–6 years, body-weight 8–20 kg</td>
<td>Flexible pack: 500 mL = £8.15</td>
</tr>
<tr>
<td>Formerly Nutrin® Pepti</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Peptamen® Junior (Nestlé)</td>
<td>Liquid (tube feed)</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>3 g whey protein hydrolysate</td>
<td>13.2 g</td>
<td>4 g (MCT 60%)</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Hydrolysed with pork trypsin</td>
<td>Short bowel syndrome, intractable malabsorption, proven inflammatory bowel disease, bowel fistula, in child 1–10 years</td>
<td>Flexible pack: 500 mL = £5.54</td>
</tr>
</tbody>
</table>

Powder provides: protein 13.7 g, carbohydrate 62.9 g, fat 17.5 g, energy 1910 kJ (457 kcal)/100 g

### A2.1.3.3 Enteral feeds, Child: More than 1 kcal/mL and less than 4 g protein/100 mL

Not suitable for child under 1 year unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isosource® Junior (Nestlé)</td>
<td>Liquid (tube feed)</td>
<td>512 kJ (122 kcal) per 100 mL</td>
<td>2.7 g cows’ milk</td>
<td>17 g</td>
<td>4.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also growth failure in child 1–6 years, body-weight 8–20 kg</td>
<td>Flexible pack: 500 mL = £4.84</td>
</tr>
<tr>
<td>Fortini® (Nutricia Clinical)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>3.4 g cows’ milk</td>
<td>18.8 g (sugars 7.4 g)</td>
<td>6.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Disease-related malnutrition and growth failure in child 1–6 years, body-weight 8–20 kg</td>
<td>Bottle: 200 mL = £2.52 Strawberry, vanilla</td>
</tr>
<tr>
<td>Fortini® Multifibre (Nutricia Clinical)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>3.4 g cows’ milk</td>
<td>18.8 g (sugars 7.4 g)</td>
<td>6.8 g</td>
<td>1.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Disease-related malnutrition and growth failure in child 1–6 years, body-weight 8–20 kg</td>
<td>Bottle: 200 mL = £2.65 Banana, chocolate, strawberry, vanilla</td>
</tr>
<tr>
<td>Product</td>
<td>Formulation</td>
<td>Energy</td>
<td>Protein</td>
<td>Carbohydrate</td>
<td>Fat</td>
<td>Fibre</td>
<td>Special Characteristics</td>
<td>ACBS Indications</td>
<td>Presentation &amp; Flavour</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>-------------------------------------------------------</td>
</tr>
<tr>
<td>Nutrini® Energy (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal)</td>
<td>4.1 g caseinate whey protein</td>
<td>18.5 g (sugars 1.1 g)</td>
<td>6.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Fish oil and fish gelatin</td>
<td>Standard, p. 878; also growth failure in child 1–6 years, body-weight 8–20 kg</td>
<td>Bottle: 200 mL = £2.59 Flexible pack: 500 mL £6.62</td>
</tr>
<tr>
<td>Nutrini® Energy Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal)</td>
<td>4.1 g caseinate whey protein</td>
<td>18.5 g (sugars 1.1 g)</td>
<td>6.7 g</td>
<td>800 mg</td>
<td>Gluten-free Residual lactose Fish oil</td>
<td>Paediatric, p. 878 except bowel fistula; also total gastrectomy, in child 1–6 years, body-weight 8–20 kg</td>
<td>Bottle: 200 mL = £2.74 Flexible pack: 500 mL £6.82</td>
</tr>
<tr>
<td>Paediasure® Plus (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>632 kJ (151 kcal)</td>
<td>4.2 g caseinates whey protein</td>
<td>16.7 g (sugars 1.1 g)</td>
<td>7.47 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Paediatric, p. 878 in child 1–10 years, body-weight 8–30 kg</td>
<td>Carton: 200 mL = £1.43 Flexible pack: 500 mL £6.23</td>
</tr>
</tbody>
</table>

1. Sugar content varies with presentation

A2.1.3.4 Enteral feeds, Child: 1.5 kcal/mL and more than 4 g protein/100 mL

Not suitable for child under 1 year unless otherwise stated

---

1. Sugar content varies with presentation

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutrini® Energy Fibre Drink (Fresenius Kabi)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal)</td>
<td>3.8 g cows’ milk</td>
<td>18.7 g (sugars 4.5 g)</td>
<td>6.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Disease-related malnutrition and growth failure in child 1–10 years, body-weight 8–30 kg</td>
<td>Bottle: 200 mL = £2.25 Flexible pack: 500 mL £5.93</td>
</tr>
<tr>
<td>Nutrini® Energy Fibre (Fresenius Kabi)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal)</td>
<td>3.75 g cows’ milk</td>
<td>18.75 g (sugars 830 mg)</td>
<td>6.7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil and fish gelatin</td>
<td>Standard, p. 878; also growth failure in child 1–10 years, body-weight 8–30 kg</td>
<td>Bottle: 200 mL = £2.30 Flexible pack: 500 mL £6.34</td>
</tr>
<tr>
<td>Resource® Junior (Nestlé)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal)</td>
<td>3 g cows’ milk</td>
<td>20.6 g (sugars 4.9 g)</td>
<td>6.2 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 in child 1–10 years</td>
<td>Carton: 200 mL = £1.69 Flexible pack: 500 mL £6.63</td>
</tr>
</tbody>
</table>

---

1. Sugar content varies with flavour
2. Nutritional values may vary with flavour—consult product literature

1. Sugar content varies with presentation
### A2.1.3.4 Enteral feeds, Child: 1.5 kcal/mL and more than 4 g protein/100 mL

Not suitable for child under 1 year unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paediasure® Plus Fibre (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>626 kJ (150 kcal) per 100 mL</td>
<td>4.2 g caseinates whey protein</td>
<td>16.4 g&lt;sup&gt;1&lt;/sup&gt;</td>
<td>7.47 g</td>
<td>1.1 g</td>
<td>Gluten-free Residual lactose</td>
<td>Paediatric, p. 878 in child 1–10 years, body-weight 8–30 kg</td>
<td>Carton: 200 mL = £2.64 Vanilla Flexible pack: 500 mL = £6.63 Vanilla</td>
</tr>
<tr>
<td>Tentrini® Energy (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>4.9 g whey protein and caseinate</td>
<td>18.5 g (sugars 1.1 g)</td>
<td>6.3 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Standard, p. 878; also growth failure, in child 7–12 years, body-weight 21–45 kg</td>
<td>Bottle or Flexible pack: 500 mL = £5.76</td>
</tr>
<tr>
<td>Tentrini® Energy Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (tube feed)</td>
<td>630 kJ (150 kcal) per 100 mL</td>
<td>4.9 g whey protein and caseinate</td>
<td>18.5 g (sugars 1.1 g)</td>
<td>6.3 g</td>
<td>1.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Paediatric, p. 878; also proven inflammatory bowel disease, in child 7–12 years, body-weight 21–45 kg</td>
<td>Bottle or Flexible pack: 500 mL = £6.35</td>
</tr>
</tbody>
</table>

1. Sugar content varies with presentation

### A2.2 Nutritional supplements (non-disease specific)

#### A2.2.1 Nutritional supplements: less than 5g protein/100mL

For further information on composition of feeds, see p. 878

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrich® (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>431 kJ (103 kcal) per 100 mL</td>
<td>3.76 g caseinates soy isolate</td>
<td>14 g (sugars 4.96 g)</td>
<td>3.52 g</td>
<td>1.36 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 except bowel fistula</td>
<td>Can: 350 mL = £2.24 Vanilla</td>
</tr>
<tr>
<td>Ensure® (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>423 kJ (100 kcal)&lt;sup&gt;1&lt;/sup&gt; per 100 mL</td>
<td>4 g caseinates soy isolate</td>
<td>13.6 g (sugars 3.93 g)</td>
<td>3.36 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td>Can: 250 mL = £1.96 Chocolate, vanilla</td>
</tr>
</tbody>
</table>

1. Nutritional values may vary with flavour—consult product literature
### A2.2.1.2 Nutritional supplements: More than 1 kcal/mL and less than 5 g protein/100mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinutren</strong>&lt;sup&gt;c&lt;/sup&gt; Fruit (Nestlē)</td>
<td>Liquid (sip feed)</td>
<td>520 kJ</td>
<td>4 g whey protein hydrolysate</td>
<td>27 g (sugars 9.5 g&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>less than 200 mg</td>
<td>less than 200 mg</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 878 Not suitable for child under 3 years</td>
<td>Carton: 4 x 200 mL = £6.63 Apple, grapefruit, orange, pear-cherry, raspberry-black currant</td>
</tr>
<tr>
<td><strong>Ensure</strong> Plus Juce&lt;sup&gt;c&lt;/sup&gt; (Abbott)</td>
<td>Liquid (sip feed)</td>
<td>638 kJ</td>
<td>4.8 g whey protein isolate</td>
<td>32.7 g (sugars 9.4 g&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 878</td>
<td>Bottle: 220 mL = £1.75 Apple, fruit punch, grapefruit, lemon-lime, orange, peach, pineapple, strawberry</td>
</tr>
<tr>
<td><strong>Fortijuce</strong>&lt;sup&gt;c&lt;/sup&gt; (Nutricia Clinical)</td>
<td>Liquid (sip feed)</td>
<td>640 kJ</td>
<td>4.0 g cows’ milk</td>
<td>33.5 g (sugars 13.1 g&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 878 Not suitable for child under 3 years</td>
<td>Bottle: 200 mL = £1.80 Starter pack: 4 x 200 mL = £7.00 Apple, black currant, forest fruits, lemon, orange, strawberry, tropical Starter pack (mixed) 4 x 200 mL = £7.00</td>
</tr>
<tr>
<td><strong>Provide</strong> Xtra Juice Drink (Fresenius Kabi)</td>
<td>Liquid (sip feed)</td>
<td>525 kJ</td>
<td>3.75 g pea and soya protein hydrolysates</td>
<td>27.5 g&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Nil</td>
<td>Nil&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Gluten-free Lactose-free Non-milk taste Sweet-flavoured products contain fish gelatin</td>
<td>Standard, p. 878</td>
<td>Carton: 200 mL = £1.63 Apple, black currant, carrot-apple, cherry, citrus-cola, lemon-lime, melon, orange-pineapple, tomato</td>
</tr>
<tr>
<td><strong>Resource</strong>&lt;sup&gt;c&lt;/sup&gt; Dessert Energy (Nestlē)</td>
<td>Semi-solid</td>
<td>671 kJ</td>
<td>4.8 g cows’ milk</td>
<td>21.2 g (sugars 9.9 g&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>6.2 g</td>
<td>Nil</td>
<td>Gluten-free Contains lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis</td>
<td>Cup: 125 g = £1.35 Caramel, chocolate, vanilla</td>
</tr>
<tr>
<td><strong>Resource</strong>&lt;sup&gt;c&lt;/sup&gt; Fruit Flavour Drink (Nestlē)</td>
<td>Liquid (sip feed)</td>
<td>638 kJ</td>
<td>4.0 g cows’ milk</td>
<td>33.5 g (sugars 8 g&lt;sup&gt;1&lt;/sup&gt;)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Residual lactose Non-milk taste</td>
<td>Standard, p. 878 Not suitable for child under 3 years</td>
<td>Carton: 200 mL = £1.53 Apple, orange, pineapple</td>
</tr>
</tbody>
</table>

1. Sugar content varies with flavour
2. Fibre content varies with flavour
### A2.2 Nutritional supplements: 5g (or more) protein/100mL

For further information on composition of feeds, see p. 878

#### A2.2.2 Nutritional supplements: 1.5 kcal/mL and 5 g (or more) protein/100 mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ensure® Plus Fibre (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>642 kJ (153 kcal) † per 100 mL</td>
<td>6.25 g cows’ milk soya protein isolate</td>
<td>20.2 g (sugars 5.5 g)</td>
<td>4.92 g</td>
<td>2.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis</td>
<td>Bottle: 200 mL = £1.74 Banana, chocolate, fruits of the forest, raspberry, strawberry, vanilla</td>
</tr>
<tr>
<td>Ensure® Plus Milkshake style (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>632 kJ (150 kcal) † per 100 mL</td>
<td>6.25 g cows’ milk soya protein isolate</td>
<td>20.2 g (sugars 5.6 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis</td>
<td>Can: 250 mL = £2.22 (vanilla) 250 mL = £2.16 (chicken or mushroom) Bottle: 220 mL = £1.73 Banana, black currant, caramel, chocolate, coffee, fruits of the forest, orange, peach, raspberry, strawberry, vanilla, neutral</td>
</tr>
<tr>
<td>Ensure® Plus Yoghurt style (Abbott)</td>
<td>Liquid (sip feed)</td>
<td>632 kJ (150 kcal) † per 100 mL</td>
<td>6.25 g cows’ milk</td>
<td>20.2 g (sugars 11.7 g)</td>
<td>4.92 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis</td>
<td>Bottle: 220 mL = £1.73 Orange, peach, pineapple, strawberry</td>
</tr>
<tr>
<td>Ensure® Plus Commence (Abbott)</td>
<td>Starter pack (5–10 day’s supply), contains: Ensure® Plus Milkshake Style (various flavours), 1 pack (10 × 220-mL) = £18.00.</td>
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<tr>
<td>Enmix® Plus Commence (Abbott)</td>
<td>Starter pack (5–10 day’s supply), contains: Ensure® Plus (Milkshake, Yoghurt, &amp; Juice style; various flavours), 1 pack (10 × 220-mL) = £17.80.</td>
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<tr>
<td>Fortisip® Bottle (Nutricia Clinical)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) † per 100 mL</td>
<td>6 g cows’ milk</td>
<td>18.4 g ‡</td>
<td>5.8 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 Not suitable for child under 3 years</td>
<td>Bottle: 200 mL = £1.80 Banana, chocolate, neutral, orange, strawberry, toffee, tropical fruits, vanilla</td>
</tr>
<tr>
<td>Fortisip® Multi Fibre (Nutricia Clinical)</td>
<td>Liquid (sip feed)</td>
<td>630 kJ (150 kcal) † per 100 mL</td>
<td>6 g cows’ milk</td>
<td>18.4 g (sugars 7.0 g)</td>
<td>5.8 g</td>
<td>2.3 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 Not suitable for child under 3 years</td>
<td>Bottle: 200 mL = £1.85 Banana, chocolate, orange, strawberry, tomato, vanilla</td>
</tr>
</tbody>
</table>

1. Minor nutritional variations between flavours—consult product literature
2. Sugar content varies with flavour
### A2.2.2 Nutritional supplements: Less than 1.5kcal/mL and 5g (or more) protein/100mL

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinutren® Dessert</td>
<td>Semi-solid</td>
<td>520 kJ</td>
<td>9.5 g cows’ milk</td>
<td>15.5 g (sugars 14.5 g)</td>
<td>2.6 g</td>
<td>500 mg</td>
<td>Gluten-free, Contains lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis, Not suitable for child under 3 years</td>
<td>Pot: 4 x 125 g = £5.40 Caramel, chocolate, peach, vanilla</td>
</tr>
<tr>
<td>Ensure® Plus Cêrème</td>
<td>Semi-solid</td>
<td>574 kJ</td>
<td>5.68 g milk protein isolate</td>
<td>18.4 g (sugars 12.4 g)</td>
<td>4.47 g</td>
<td>Nil</td>
<td>Gluten-free, Residual lactose, Contains soya</td>
<td>Standard, p. 878; also CAPD, haemodialysis, Not suitable for child under 3 years</td>
<td>Pot: 125 g = £1.63 Banana, chocolate, neutral, vanilla</td>
</tr>
<tr>
<td>Fortimel® Regular</td>
<td>Liquid (sip feed)</td>
<td>420 kJ</td>
<td>10 g cows’ milk</td>
<td>10.3 g (sugars 8.1 g)</td>
<td>2.1 g</td>
<td>Nil</td>
<td>Gluten-free, Contains lactose</td>
<td>Standard, p. 878; Not suitable for child under 3 years</td>
<td>Bottle: 200 mL = £1.52 Chocolate, forest fruits, strawberry, vanilla</td>
</tr>
<tr>
<td>Fortisip® Fruit Dessert</td>
<td>Semi-solid</td>
<td>560 kJ</td>
<td>7 g whey isolate</td>
<td>16.7 g (sugars 11.3 g)</td>
<td>4 g</td>
<td>2.6 g</td>
<td>Residual lactose</td>
<td>Standard, p. 878; except bowel fistula; also CAPD, haemodialysis, Not suitable for child under 3 years</td>
<td>Pot: 3 x 150 g = £6.09 Apple</td>
</tr>
<tr>
<td>Resource® Protein</td>
<td>Liquid (sip feed)</td>
<td>530 kJ</td>
<td>9.4 g cows’ milk</td>
<td>14 g (sugars 4.5 g)</td>
<td>3.5 g</td>
<td>Nil</td>
<td>Gluten-free, Contains lactose</td>
<td>Standard, p. 878; Not suitable for child under 3 years</td>
<td>Bottle: 200 mL = £1.33 Apricot, chocolate, forest fruits, strawberry, vanilla</td>
</tr>
</tbody>
</table>

1. Sugar content varies with flavour
2. Fibre content varies with flavour
3. Minor nutritional variations between flavours—consult product literature
4. Nutritional values may vary with flavour—consult product literature
### A2.2.3 Nutritional supplements: More than 1.5kcal/mL and 5g (or more) protein/100mL

Not suitable for use in child under 1 year; use with caution in child 1–5 years unless otherwise stated.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complan® Shake</td>
<td>Powder</td>
<td>1057 kJ &lt;sup&gt;1&lt;/sup&gt; (251 kcal) per 57 g</td>
<td>8.8 g cows’ milk</td>
<td>35.2 g (sugars 22.7 g)</td>
<td>8.4 g</td>
<td>Trace</td>
<td>Gluten-free Contains lactose</td>
<td>Standard, p. 878</td>
<td>Sachet: 4 × 57 g = £3.26 Banana, chocolate, milk, strawberry, vanilla</td>
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<tr>
<td>Foodlink®</td>
<td>Powder</td>
<td>1838 kJ &lt;sup&gt;1&lt;/sup&gt; (437 kcal) per 100 g</td>
<td>21.9 g cows’ milk</td>
<td>57.3 g</td>
<td>13.3 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Standard, p. 878</td>
<td>Carton: 450 g = £3.29 Banana, chocolate, neutral, strawberry</td>
</tr>
<tr>
<td>Recommended serving = 3 heaped tablespoonfuls in 250 mL water provides: protein 12.5 g, carbohydrate 32.7 g, fat 7.6 g, energy 1048 kJ (249 kcal) &lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
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</tr>
<tr>
<td>Foodlink®</td>
<td>Powder</td>
<td>1804 kJ (428 kcal) per 100 g</td>
<td>19.5 g cows’ milk</td>
<td>57.1 g (sugars 36.8 g)</td>
<td>12.3 g</td>
<td>8 g</td>
<td>Contains lactose</td>
<td>Standard, p. 878</td>
<td>Sachet: 10 × 63 g = £6.67 Vanilla + fibre</td>
</tr>
<tr>
<td>Recommended serving = 4 heaped tablespoonfuls in 250 mL water provides: protein 12.3 g, carbohydrate 38 g, fat 7.5 g, fibre 5 g, energy 1137 kJ (270 kcal) &lt;sup&gt;1&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Forticreme®</td>
<td>Semi-solid</td>
<td>675 kJ (160 kcal) per 100 g</td>
<td>9.5 g cows’ milk</td>
<td>19.2 g (sugars 10.6 g)</td>
<td>5 g</td>
<td>100 mg&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis Not suitable for child under 3 years</td>
<td>Pot: 4 × 125 g = £6.99 Banana, chocolate, forest fruits, vanilla</td>
</tr>
<tr>
<td>Fortisip® Extra</td>
<td>Liquid (sip feed)</td>
<td>675 kJ (160 kcal) per 100 mL</td>
<td>10 g cows’ milk</td>
<td>18.1 g (sugars 9 g)</td>
<td>5.3 g</td>
<td>Nil&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Contains lactose</td>
<td>Standard, p. 878; Standard for child under 3 years</td>
<td>Bottle: 200 mL = £1.80 Chocolate, forest fruits, mocha, strawberry, vanilla</td>
</tr>
<tr>
<td>Fresubin® 2kcal Fibre</td>
<td>Liquid (sip feed)</td>
<td>840 kJ (200 kcal) per 100 mL</td>
<td>10 g cows’ milk</td>
<td>22.5 g (sugars 5.8 g)</td>
<td>7.8 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis Not suitable for child under 3 years</td>
<td>Bottle: 200 mL = £1.69 Fruits of the forest, cappuccino, vanilla</td>
</tr>
<tr>
<td>Fresubin® Cre`me</td>
<td>Semi-solid</td>
<td>756 kJ (180 kcal) per 100 g</td>
<td>10 g cows’ milk</td>
<td>19 g (sugars 14.4 g)</td>
<td>7.2 g</td>
<td>2 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis Not suitable for child under 3 years</td>
<td>Pot: 4 × 125 g = £6.92 Cappuccino, strawberry, vanilla</td>
</tr>
<tr>
<td>Renilon® 7.5</td>
<td>Liquid (sip feed)</td>
<td>840 kJ (200 kcal) per 100 mL</td>
<td>7.5 g cows’ milk</td>
<td>20 g (sugars 4.8 g)</td>
<td>10 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; Not suitable for child under 3 years</td>
<td>Carton: 125 mL = £1.79 Apricot, caramel</td>
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</tr>
</tbody>
</table>

<sup>1</sup> Nutritional values may vary with flavour—consult product literature

<sup>2</sup> Fibre content varies with flavour
<table>
<thead>
<tr>
<th>Resource</th>
<th>Type</th>
<th>Serving Size</th>
<th>Energy (kJ/100 kcal)</th>
<th>Milk (g)</th>
<th>Sugar (g)</th>
<th>Protein (g)</th>
<th>Carbohydrate (g)</th>
<th>Gluten-free</th>
<th>Residual Lactose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Resource 2.0</strong>&lt;br&gt;Fibre (Nestlé)</td>
<td>Liquid (sip feed)</td>
<td>836 kJ (200 kcal)</td>
<td>9 g cows' milk</td>
<td>21.4 g (sugars 5.5 g)</td>
<td>8.7 g</td>
<td>2.5 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td>Not suitable for child under 6 years; caution in child 6–10 years</td>
<td>Carton: 200 mL = £1.65 Apricot, coffee, neutral, strawberry, summer fruits, vanilla</td>
</tr>
<tr>
<td><strong>Resource</strong>&lt;br&gt;Dessert Fruit (Nestlé)</td>
<td>Semi-solid</td>
<td>678 kJ (160 kcal)</td>
<td>5 g cows' milk</td>
<td>24 g (sugars 16.4 g)</td>
<td>5 g</td>
<td>1.4 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878; also CAPD, haemodialysis</td>
<td>Cup: 3 × 125 g = £4.05 Apple, apple-peach, apple-strawberry</td>
<td></td>
</tr>
<tr>
<td><strong>Resource</strong>&lt;br&gt;Shake (Nestlé)</td>
<td>Liquid (sip feed)</td>
<td>730 kJ (174 kcal)</td>
<td>5.1 g cows' milk</td>
<td>22.6 g (sugars 6.4 g)</td>
<td>7 g</td>
<td>Nil</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td></td>
<td>Carton: 175 mL = £1.50 Banana, chocolate, lemon, strawberry, summer fruits, toffee, vanilla</td>
</tr>
<tr>
<td><strong>Vegenat-med</strong>&lt;br&gt;Balanced Protein (Vegenat)</td>
<td>Powder</td>
<td>1924 kJ (458 kcal) per 110 g serving</td>
<td>18 g cows' milk</td>
<td>62 g</td>
<td>15.35 g</td>
<td>5.8 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878</td>
<td>Not suitable for child under 14 years</td>
<td>Sachet: 12 × 110 g = £33.89 Apple, chocolate, honey, orange</td>
</tr>
<tr>
<td><strong>Vegenat-med</strong>&lt;br&gt;High Protein (Vegenat)</td>
<td>Powder</td>
<td>1940 kJ (463 kcal) per 110 g serving</td>
<td>23.3 g cows' milk</td>
<td>57.2 g</td>
<td>15.6 g</td>
<td>6 g</td>
<td>Gluten-free Residual lactose</td>
<td>Standard, p. 878 except bowel fistula</td>
<td>Not suitable for child under 14 years</td>
<td>Sachet: 12 × 110 g = £47.44 Chicken, chickpea, fish, fish-vegetable, ham, lentil, veal, vegetable, winter vegetable 12 × 110 g = £45.75 Curry chicken 12 × 110 g = £45.07 Lemon, rice with lemon 24 × 55 g = £43.46 Rice with apple</td>
</tr>
</tbody>
</table>

1. Nutritional values may vary with flavour—consult product literature
2. Flavour not suitable for child under 3 years
### A2.3 Specialised formulas

For further information on composition of feeds, see p. 878

#### A2.3.1 Specialised formulas: Infant and child

Specialised formulas are suitable for infants from birth unless otherwise indicated (see also A2.1.3.1 Enteral feeds (non-disease specific); Child under 12 years).

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS</th>
<th>Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACBS</td>
<td></td>
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<td><strong>Indications</strong></td>
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<tr>
<td><strong>Presentation &amp; Flavour</strong></td>
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<tr>
<td>Neocate Active (SHS)</td>
<td>Standard dilution (21%) of powder</td>
<td>1255 kJ (300 kcal) per 300 mL serving (63 g sachet made up to 300 mL with water)</td>
<td>8.3 g protein equivalent (essential and non-essential amino acids)</td>
<td>34 g (sugars 3.1 g)</td>
<td>14.5 g Nil</td>
<td>Milk protein-free</td>
<td>See above</td>
<td>Nutritional supplement only</td>
<td>Sachet: 14 x 63 g = £49.14 Black currant, unflavoured^2</td>
<td></td>
</tr>
<tr>
<td>Powder provides: protein equivalent 13.1 g, carbohydrate 54 g, fat 23 g, energy 1992 kJ (475 kcal)/100 g</td>
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<tr>
<td>Neocate Advance (SHS)</td>
<td>Standard dilution (25%) of powder</td>
<td>420 kJ (100 kcal) per 100 mL</td>
<td>2.5 g protein equivalent (essential and non-essential amino acids)</td>
<td>14.6 g (sugars 1.3 g)</td>
<td>3.5 g (MCT 35%)</td>
<td>Milk protein-free</td>
<td>See above</td>
<td>Not suitable for child under 1 year</td>
<td>Sachet: 100 g = £4.82 Unflavoured^2 15 x 50 g = £38.43 Banana-vanilla</td>
<td></td>
</tr>
<tr>
<td>Powder provides: protein equivalent 10 g, carbohydrate 58.5 g, fat 14 g, energy 1683 kJ (400 kcal)/100 g</td>
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</tr>
<tr>
<td>Neocate LCP (SHS)</td>
<td>Standard dilution (14.7%) of powder</td>
<td>293 kJ (70 kcal) per 100 mL</td>
<td>1.9 g protein equivalent (essential and non-essential amino acids)</td>
<td>7.9 g (sugars 720 mg)</td>
<td>3.4 g Nil</td>
<td>Milk protein-free</td>
<td>Cows’ milk allergy, multiple food protein intolerance, and conditions requiring an elemental diet</td>
<td>Can: 400 g = £22.91 (4.9 g measuring scoop provided)</td>
<td></td>
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</tr>
<tr>
<td>Powder provides: protein equivalent 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g</td>
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</tr>
</tbody>
</table>

1. Sugar content varies with flavour
2. Flavouring: see Modul® Flavour System, p. 909
<table>
<thead>
<tr>
<th>Formula</th>
<th>Manufacturer</th>
<th>Standard dilution</th>
<th>Energy (kJ)</th>
<th>Essential Amino Acids</th>
<th>Non-Essential Amino Acids</th>
<th>Gluten-Free</th>
<th>Lactose-Free</th>
<th>Indicated Conditions</th>
<th>Cost (Can: 400 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutramigen® AA</td>
<td>Mead Johnson</td>
<td>(13.6%) of powder</td>
<td>286</td>
<td>1.89 g</td>
<td>7 g</td>
<td>Nil</td>
<td>Gluten-Free</td>
<td>Severe cows’ milk protein intolerance, and other gastro-intestinal disorders where an elemental diet is specifically indicated</td>
<td>£21.22</td>
</tr>
<tr>
<td>Nutramigen® 1</td>
<td>Mead Johnson</td>
<td>(13.5%) of powder</td>
<td>280</td>
<td>1.9 g</td>
<td>7.5 g</td>
<td>Nil</td>
<td>Gluten-Free</td>
<td>Disaccharide and/or whole protein intolerance where additional medium chain triglycerides are not included</td>
<td>£8.61</td>
</tr>
<tr>
<td>Nutramigen® 2</td>
<td>Mead Johnson</td>
<td>(14.6%) of powder</td>
<td>285</td>
<td>1.7 g</td>
<td>8.6 g</td>
<td>Nil</td>
<td>Gluten-Free</td>
<td>Established disaccharide and/or whole protein intolerance (where additional chain triglycerides are not indicated) Not suitable for child under 6 months</td>
<td>£8.61</td>
</tr>
<tr>
<td>Pepdite®</td>
<td>SHS</td>
<td>(15%) of powder</td>
<td>297</td>
<td>2.1 g</td>
<td>7.8 g</td>
<td>Nil</td>
<td>Lactose-Free</td>
<td>Disaccharide and/or whole protein intolerance</td>
<td>£14.70</td>
</tr>
</tbody>
</table>

**Specialised formulas: Infant and child: Hydrolysate formula**

<table>
<thead>
<tr>
<th>Formula</th>
<th>Manufacturer</th>
<th>Standard dilution</th>
<th>Energy (kJ)</th>
<th>Essential Amino Acids</th>
<th>Non-Essential Amino Acids</th>
<th>Contains</th>
<th>Contains Lactose and Fish Oil</th>
<th>Indicated Conditions</th>
<th>Cost (Can: 400 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow &amp; Gate Pepti®</td>
<td>Cow &amp; Gate</td>
<td>(13.6%) of powder</td>
<td>275</td>
<td>1.6 g</td>
<td>7.1 g</td>
<td>800 mg</td>
<td>Whey hydrolysed (sugars 6.4 g)</td>
<td>Established cows’ milk protein intolerance, with or without secondary lactose intolerance</td>
<td>£19.39</td>
</tr>
<tr>
<td>Cow &amp; Gate Pepti-Junior®</td>
<td>Cow &amp; Gate</td>
<td>(12.8%) of powder</td>
<td>275</td>
<td>1.8 g</td>
<td>6.8 g</td>
<td>Nil</td>
<td>Whey hydrolysed (sugars 1.1 g)</td>
<td>Residual lactose</td>
<td>£10.68</td>
</tr>
<tr>
<td>Nutramigen® 1</td>
<td>Mead Johnson</td>
<td>(13.5%) of powder</td>
<td>280</td>
<td>1.9 g</td>
<td>7.5 g</td>
<td>Nil</td>
<td>Casein hydrolysed</td>
<td>Disaccharide and/or whole protein intolerance where additional medium chain triglycerides are not included</td>
<td>£8.61</td>
</tr>
<tr>
<td>Nutramigen® 2</td>
<td>Mead Johnson</td>
<td>(14.6%) of powder</td>
<td>285</td>
<td>1.7 g</td>
<td>8.6 g</td>
<td>Nil</td>
<td>Casein hydrolysed</td>
<td>Established disaccharide and/or whole protein intolerance (where additional chain triglycerides are not indicated) Not suitable for child under 6 months</td>
<td>£8.61</td>
</tr>
<tr>
<td>Pepdite®</td>
<td>SHS</td>
<td>(15%) of powder</td>
<td>297</td>
<td>2.1 g</td>
<td>7.8 g</td>
<td>Nil</td>
<td>Protein equivalent (non-milk hydrolysate)</td>
<td>Contains meat (pork) and soya derivatives</td>
<td>£14.70</td>
</tr>
</tbody>
</table>

**Powder provides:** protein 13.9 g, carbohydrate 51 g, fat 26 g, energy 2092 kJ (498 kcal)/100 g
### A2.3.1 Specialised formulas: Infant and child: Hydrolysate formula

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pepdite® 1+ (SHS)</strong></td>
<td>Standard dilution (22.8%) of powder</td>
<td>423 kJ (100 kcal)</td>
<td>3.1 g protein equivalent (non-milk hydrolysate, essential amino acids)</td>
<td>13 g (sugars 1.2 g)</td>
<td>3.9 g (MCT 35%)</td>
<td>Nil</td>
<td>Lactose-free, Contains meat (pork) and soya derivatives</td>
<td>Disaccharide and/or whole protein intolerance, or where amino acids or peptides are indicated in conjunction with medium chain triglycerides Not suitable for child under 1 year</td>
<td>Can: 400 g = £15.44 Unflavoured</td>
</tr>
<tr>
<td><strong>Pregestimil® (Mead Johnson)</strong></td>
<td>Standard dilution (13.5%) of powder</td>
<td>280 kJ (68 kcal)</td>
<td>1.89 g casein hydrolysed</td>
<td>6.9 g</td>
<td>3.8 g (MCT 54%)</td>
<td>Nil</td>
<td>Gluten-free, Lactose-free, Residual lactose</td>
<td>Disaccharide and/or whole protein intolerance, or where amino acids or peptides are indicated in conjunction with medium chain triglycerides</td>
<td>Can: 400 g = £9.44 (4.5-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>Prejomin® (Milupa)</strong></td>
<td>Standard dilution (15%) of powder</td>
<td>315 kJ (75 kcal)</td>
<td>2 g soya, collagen (porcine) hydrolysate</td>
<td>8.6 g (sugars 400 mg)</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Gluten-free, Lactose-free, Contains meat (pork) derivatives</td>
<td>Disaccharide and/or whole protein intolerance, where additional medium chain triglycerides are not indicated</td>
<td>Can: 400 g = £10.12 (5-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>Enfamil® O-Lac (Mead Johnson)</strong></td>
<td>Standard dilution (13%) of powder</td>
<td>280 kJ (68 kcal)</td>
<td>1.42 g cows’ milk</td>
<td>7.2 g</td>
<td>3.7 g Nil</td>
<td>Glutent-free, Residual lactose</td>
<td>Proven lactose intolerance</td>
<td>Can: 400 g = £3.86 (4.3-g measuring scoop provided)</td>
<td></td>
</tr>
<tr>
<td><strong>Galactomin 17® (SHS)</strong></td>
<td>Standard dilution (13.6%) of powder</td>
<td>295 kJ (70 kcal)</td>
<td>1.7 g protein equivalent (cows’ milk)</td>
<td>7.5 g (sugars 1.4 g)</td>
<td>3.7 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Proven lactose intolerance in pre-school children, galactosaemia, and galaktokinase deficiency</td>
<td>Can: 400 g = £13.16 Unflavoured (4.3-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>SMA® LF (SMA Nutrition)</strong></td>
<td>Standard dilution (13%) of powder</td>
<td>281 kJ (67 kcal)</td>
<td>1.5 g casein, whey</td>
<td>7.2 g (sugars 2.6 g)</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Proven lactose intolerance</td>
<td>Can: 430 g = £4.57</td>
</tr>
</tbody>
</table>

1. Flavouring: see **Modjul® Flavour System**, p. 909
### Specialised formulas: Infant and child: MCT-enhanced formula

<table>
<thead>
<tr>
<th>Formula</th>
<th>Standard dilution</th>
<th>Powder provides:</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Energy (kJ)</th>
<th>Can:</th>
<th>Flavoured?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caprilon®</strong> (SHS)</td>
<td>12.7% of powder</td>
<td>protein 11.8g, carbohydrate 55.1g, fat 28.3g, energy 2184kJ (522kcal)/100g</td>
<td>1.5g cows’ milk 7g (sugars 1.3g) 3.6g (MCT 75%)</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>Disorders in which a high intake of MCT is beneficial</td>
<td>420g = £14.28 (4.2g measuring scoop provided)</td>
<td></td>
</tr>
<tr>
<td><strong>MCT Pepdite®</strong> (SHS)</td>
<td>15% of powder</td>
<td>protein equivalent (non-milk peptides, essential amino acids)</td>
<td>2g protein equivalent (non-milk peptides, essential amino acids) 8.8g (sugars 1.2g) 5g (MCT 75%)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free Contains meat (pork) and soya derivatives</td>
<td>Disorders in which a high intake of MCT is beneficial</td>
<td>400g = £16.01 (5g measuring scoop provided)</td>
<td></td>
</tr>
<tr>
<td><strong>MCT Pepdite® +1</strong> (SHS)</td>
<td>20% of powder</td>
<td>protein equivalent (whey)</td>
<td>2.8g protein equivalent (whey) 11.8g (sugars 1.6g) 3.6g (MCT 75%)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free Contains meat (pork) and soya derivatives</td>
<td>Disorders in which a high intake of MCT is beneficial</td>
<td>400g = £16.01 Unflavoured¹</td>
<td></td>
</tr>
<tr>
<td><strong>Monogen®</strong> (SHS)</td>
<td>17.5% of powder</td>
<td>protein equivalent (whey)</td>
<td>2g protein equivalent (whey) 12g (sugars 1.2g) 2.1g (MCT 90%)</td>
<td>Nil</td>
<td>Residual lactose Supplementation with essential fatty acids may be needed</td>
<td>Long-chain acyl-CoA dehydrogenase deficiency (LCAD), carnitine palmitoyl transferase deficiency (CPTD), primary and secondary lipoprotein lipase deficiency</td>
<td>400g = £15.91 Unflavoured¹</td>
<td></td>
</tr>
<tr>
<td><strong>InfaSoy®</strong> (Cow &amp; Gate)</td>
<td>12.7% of powder</td>
<td>protein 14.2g, carbohydrate 52g, fat 28.3g, energy 2170kJ (519kcal)/100g</td>
<td>1.8g soya 6.6g (sugars 1g) 3.6g (MCT 75%)</td>
<td>Nil</td>
<td>Lactose-free</td>
<td>Proven lactose and associated sucrose intolerance in pre-school children, galactokinase deficiency, galactosaemia, and proven whole cows’ milk sensitivity</td>
<td>900g = £7.47 (4.2g measuring scoop provided)</td>
<td></td>
</tr>
<tr>
<td><strong>Isomil®</strong> (Abbott)</td>
<td>13.2% of powder</td>
<td>protein 13.7g, carbohydrate 52.4g, fat 28.1g, energy 2163kJ (517kcal)/100g</td>
<td>1.8g soya protein isolate 6.9g (sugars 2.4g) 3.7g (MCT 75%)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Proven lactose intolerance in pre-school children, galactokinase deficiency, galactosaemia, and proven whole cows’ milk sensitivity</td>
<td>400g = £3.38 Unflavoured¹</td>
<td></td>
</tr>
</tbody>
</table>

¹ Flavoured; see **Modjul® Flavour System**, p. 909
<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wysoy®</td>
<td>Standard dilution (13.2%) of powder</td>
<td>280 kJ (67 kcal) per 100 mL</td>
<td>1.8 g soya protein isolate</td>
<td>6.9 g (sugars 2.5 g)</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Lactose-free</td>
<td>Proven lactose and associated sucrose intolerance in pre-school children, galactokinase deficiency, galactosaemia, and proven whole cows’ milk sensitivity</td>
<td>Can: 430 g = £4.44 860 g = £8.41</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 14 g, carbohydrate 54 g, fat 27 g, energy 2155 J (515 kcal)/100 g</td>
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</tr>
<tr>
<td>▪ Specialised formulas: Infant and child: Low calcium formula</td>
<td></td>
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<tr>
<td>Locasol® (SHS)</td>
<td>Standard dilution (13.1%) of powder</td>
<td>278 kJ (66 kcal) per 100 mL</td>
<td>1.9 g cows’ milk</td>
<td>7 g (sugars 6.9 g)</td>
<td>3.4 g</td>
<td>Nil</td>
<td>Contains lactose Calcium less than 7 mg/100 mL No added vitamin D</td>
<td>Conditions of calcium intolerance requiring restriction of calcium and vitamin D intake</td>
<td>Can: 400 g = £18.29 (4.4-g measuring scoop provided)</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 14.6 g, carbohydrate 53.7 g, fat 26.1 g, energy 2125 kJ (508 kcal)/100 g</td>
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</tr>
<tr>
<td>▪ Specialised formulas: Infant and child: Fructose-based formula</td>
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<td></td>
</tr>
<tr>
<td>Galactomin 19® (SHS)</td>
<td>Standard dilution (12.9%) of powder</td>
<td>288 kJ (69 kcal) per 100 mL</td>
<td>1.9 g protein equivalent (cows’ milk)</td>
<td>6.4 g (fructose 6.3 g)</td>
<td>4 g</td>
<td>Nil</td>
<td>Residual lactose, galactose and glucose</td>
<td>Conditions of glucose plus galactose intolerance</td>
<td>Can: 400 g = £34.65</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein equivalent 14.6 g, carbohydrate 49.7 g, fat 30.8 g, energy 2233 kJ (534 kcal)/100 g</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>▪ Specialised formulas: Infant and child: Pre-thickened infant feeds</td>
<td></td>
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<tr>
<td>Not to be used for a period of more than 6 months; not to be used in conjunction with any other feed thickener or antacid products</td>
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<td></td>
</tr>
<tr>
<td>Enfamil® AR (Mead Johnson)</td>
<td>Standard dilution (13.5%) of powder</td>
<td>285 kJ (68 kcal) per 100 mL</td>
<td>1.7 g cows’ milk</td>
<td>7.6 g (lactose 4.6 g)</td>
<td>3.5 g</td>
<td>Nil</td>
<td>Contains lactose, pregelatinised rice starch</td>
<td>Significant gastro-oesophageal reflux</td>
<td>Can: 400 g = £2.90 (4.5-g measuring scoop provided)</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 12.5 g, carbohydrate 56 g, fat 26 g, energy 2093 kJ (500 kcal)/100 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SMA® Staydown (SMA Nutrition)</td>
<td>Standard dilution (12.9%) of powder</td>
<td>279 kJ (67 kcal) per 100 mL</td>
<td>1.6 g casein, whey</td>
<td>7 g (lactose 5 g)</td>
<td>3.6 g</td>
<td>Nil</td>
<td>Contains lactose, pre-cooked corn starch</td>
<td>Significant gastro-oesophageal reflux</td>
<td>Can: 900 g = £6.49</td>
</tr>
<tr>
<td></td>
<td>Powder provides: protein 12.4 g, carbohydrate 54.3 g, fat 28 g, energy 2166 kJ (518 kcal)/100 g</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>
### A2.3.2 Modular feeds for specific clinical conditions

For further information on composition of feeds, see p. 878

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alicalm</strong>&lt;sup&gt;c&lt;/sup&gt; (SHS)</td>
<td>Standard dilution (30%) of powder &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>567 kJ (135 kcal) 17.4 g caseinate &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>166 kJ (40 kcal) 4.5 g caseinate &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>11.2 g (sugars 3.2 g) 1 g</td>
<td>5.3 g</td>
<td>Nil</td>
<td>Residual lactose</td>
<td>Crohn's disease &lt;br&gt; Not suitable for child under 1 year; use as nutritional supplement only in children 1–6 years</td>
<td>Powder: 400 g = £16.20 &lt;br&gt; Vanilla</td>
</tr>
<tr>
<td><strong>Casilan 90</strong>&lt;sup&gt;c&lt;/sup&gt; (Heinz)</td>
<td>Powder &lt;br&gt; <strong>Per 100 g</strong></td>
<td>1572 kJ (370 kcal) 90 g cows' milk &lt;br&gt; <strong>Per 100 g</strong></td>
<td>300 mg 1 g</td>
<td>4.5 g caseinate &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>17.4 g (sugars 3.2 g) 1 g</td>
<td>Nil</td>
<td>Gluten-free Electrolytes/100 g: Na&lt;sup&gt;+&lt;/sup&gt; 1.3 mmol K&lt;sup&gt;+&lt;/sup&gt; 8.7 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 35 mmol P&lt;sup&gt;+&lt;/sup&gt; 22.6 mmol</td>
<td>Nutritional supplement for use in biochemically proven hypoproteinaemia</td>
<td>Can: 250 g = £6.90</td>
</tr>
<tr>
<td><strong>Forticare</strong>&lt;sup&gt;c&lt;/sup&gt; (Nutricia Clinical)</td>
<td>Liquid (sip feed) &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>675 kJ (160 kcal) 9 g cows' milk &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>19.1 g (sugars 13.6 g) 1 g</td>
<td>5.3 g</td>
<td>2.1 g</td>
<td>Gluten-free Residual lactose Contains fish oil</td>
<td>Nutritional supplement in patients with lung cancer undergoing chemotherapy, or with pancreatic cancer Not suitable for child under 3 years</td>
<td>Carton: 125 mL = £1.92 &lt;br&gt; Cappuccino, orange-lemon, peach-ginger</td>
<td></td>
</tr>
<tr>
<td><strong>Generaid</strong>&lt;sup&gt;c&lt;/sup&gt; (SHS)</td>
<td>Powder &lt;br&gt; <strong>Per 100 g</strong></td>
<td>1586 kJ (374 kcal) 76 g protein equivalent (whey protein, plus branched chain amino acids) &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>5 g (sugars 5 g)</td>
<td>5.5 g</td>
<td>Nil</td>
<td>Electrolytes/100 g: Na&lt;sup&gt;+&lt;/sup&gt; 6.1 mmol K&lt;sup&gt;+&lt;/sup&gt; 10.8 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 6.5 mmol P&lt;sup&gt;+&lt;/sup&gt; 6.45 mmol</td>
<td>Nutritional supplement for use in chronic liver disease and/or portohepatic encephalopathy</td>
<td>Tub: 200 g = £23.97 Unflavoured&lt;sup&gt;1&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td><strong>Generaid Plus</strong>&lt;sup&gt;c&lt;/sup&gt; (SHS)</td>
<td>Standard dilution (22%) of powder &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>428 kJ (102 kcal) 2.4 g protein equivalent (whey protein, branched chain amino acids) &lt;br&gt; <strong>Per 100 mL</strong></td>
<td>13.6 g (sugars 1.4 g) 1.4 g</td>
<td>4.2 g (MCT 32%)</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na&lt;sup&gt;+&lt;/sup&gt; 0.7 mmol K&lt;sup&gt;+&lt;/sup&gt; 2.7 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 1.72 mmol P&lt;sup&gt;+&lt;/sup&gt; 1.67 mmol</td>
<td>A sole source of nutrition or nutritional supplement in children over 1 year with hepatic disorders</td>
<td>Can: 400 g = £17.15 Unflavoured&lt;sup&gt;1&lt;/sup&gt; (5-g measuring scoop provided)</td>
<td></td>
</tr>
</tbody>
</table>

1. Flavouring: see Modjul® Flavour System, p. 909
### Appendix 2: Borderline substances

#### A2.3.2 Modular feeds for specific clinical conditions (product list continued)

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KetoCal</strong>&lt;sup&gt;*&lt;/sup&gt; (SHS)</td>
<td>Standard dilution (20%) of powder</td>
<td>602 kJ (146 kcal) per 100 mL</td>
<td>3.1 g cows’ milk with additional amino acids</td>
<td>600 mg (sugars 120 mg)</td>
<td>14.6 g (LCT 100%)</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na&lt;sup&gt;+&lt;/sup&gt; 4.3 mmol K&lt;sup&gt;+&lt;/sup&gt; 4.1 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 2.15 mmol P&lt;sup&gt;+&lt;/sup&gt; 2.77 mmol</td>
<td>Sole source of nutrition or nutritional supplement as part of ketogenic diet in management of epilepsy resistant to drug therapy, in children over 1 year, only on the advice of secondary care physician with experience of ketogenic diet</td>
<td>Can: 300 g = £23.87 Vanilla, Unflavoured</td>
</tr>
<tr>
<td><strong>Kindergarten</strong>&lt;sup&gt;*&lt;/sup&gt; (SHS)</td>
<td>Standard dilution (20%) of powder</td>
<td>421 kJ (101 kcal) per 100 mL</td>
<td>1.5 g whey protein</td>
<td>11.8 mg (sugars 1.2 g)</td>
<td>5.3 g (LCT 93%)</td>
<td>Nil</td>
<td>Electrolytes/100 mL: Na&lt;sup&gt;+&lt;/sup&gt; 2 mmol K&lt;sup&gt;+&lt;/sup&gt; 0.6 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 2.8 mmol P&lt;sup&gt;+&lt;/sup&gt; 3 mmol Low Vitamin A</td>
<td>Sole source of nutrition or nutritional supplement for infants and children with chronic renal failure receiving peritoneal rapid overnight dialysis</td>
<td>Tub: 400 g = £15.18 (5-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>Medium-chain Tri-glyceride (MCT) Oil (SHS)</strong></td>
<td>Liquid</td>
<td>3515 kJ (855 kcal) per 100 mL</td>
<td>Nil</td>
<td>Nil</td>
<td>MCT 100%</td>
<td>Nil</td>
<td>Nutritional supplement for steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangectasia, intestinal surgery, chronic liver disease and liver cirrhosis, other proven malabsorption syndromes, ketogenic diet in management of epilepsy, type 1 hyperlipoproteinaemia</td>
<td>Bottle: 500 mL = £11.50</td>
<td></td>
</tr>
<tr>
<td><strong>Nepro</strong>&lt;sup&gt;*&lt;/sup&gt; (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>838 kJ (200 kcal) per 100 mL</td>
<td>7 g cows’ milk</td>
<td>20.6 g (sugars 3.26 g)</td>
<td>9.6 g</td>
<td>1.56 g</td>
<td>Gluten-free Residual lactose Electrolytes/100 mL: Na&lt;sup&gt;+&lt;/sup&gt; 3.67 mmol K&lt;sup&gt;+&lt;/sup&gt; 2.72 mmol Ca&lt;sup&gt;2+&lt;/sup&gt; 3.43 mmol P&lt;sup&gt;+&lt;/sup&gt; 2.23 mmol</td>
<td>Sole source of nutrition or nutritional supplement in patients with chronic renal failure who are on haemodialysis or CAPD, or with cirrhosis, or other conditions requiring a high energy, low fluid, low electrolyte diet. Not suitable for child under 1 year; use with caution in child 1–5 years</td>
<td>Carton: 200 mL = £2.28 Strawberry, vanilla&lt;sup&gt;1&lt;/sup&gt; Flexible pack: 500 mL = £4.95 Vanilla</td>
</tr>
</tbody>
</table>

1. Minor nutritional variations between flavours—consult product literature
<table>
<thead>
<tr>
<th>Product</th>
<th>Type</th>
<th>Energy/kcal/100 mL</th>
<th>Protein/g</th>
<th>Fat/g</th>
<th>Carbohydrate/g</th>
<th>Gluten-free</th>
<th>Lactose</th>
<th>Nutritional Uses</th>
<th>Packaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>ProSure® (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>529 kJ (125 kcal)</td>
<td>6.65</td>
<td>18.3</td>
<td>2.56</td>
<td>Residual</td>
<td>Caution</td>
<td>Nutritional supplement for patients with pancreatic cancer. Not suitable for child under 1 year; use with caution in child 1–4 years.</td>
<td>Carton: 240 mL = £2.70 Banana, vanilla¹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per 100 mL</td>
<td>cows' milk</td>
<td>sugars 2.95</td>
<td>g</td>
<td>contains</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>fish oil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protifar® (Nutricia Clinical)</td>
<td>Powder</td>
<td>1580 kJ (373 kcal)</td>
<td>88.5</td>
<td>less than 1.5</td>
<td>1.6</td>
<td>Gluten-free</td>
<td>Residual lactose</td>
<td>Nutritional supplement for use in biochemically proven hypoproteinaemia.</td>
<td>Can: 225 g = £7.22 Unflavoured (2.5-g measuring scoop provided)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per 100 g</td>
<td>cows' milk</td>
<td></td>
<td></td>
<td>lactose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Renamil® (KoRa)</td>
<td>Powder (sip or tube feed when reconstituted)</td>
<td>2003 kJ (477 kcal)</td>
<td>4.6</td>
<td>70.8</td>
<td>19.3</td>
<td>Nil</td>
<td></td>
<td>Sole source of nutrition or nutritional supplement for adults and children over 1 year with chronic renal failure</td>
<td>Sachet: 10 x 100 g = £25.40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per 100 g</td>
<td>cows' milk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renapro® (KoRa)</td>
<td>Powder</td>
<td>1580 kJ (372 kcal)</td>
<td>90</td>
<td>800</td>
<td>1</td>
<td>Nil</td>
<td></td>
<td>Nutritional supplement for biochemically proven hypoproteinaemia and patients undergoing dialysis. Not suitable for child under 1 year.</td>
<td>Sachet: 30 x 20 g = £69.60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per 100 g</td>
<td>whey protein</td>
<td>mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suplena® (Abbott)</td>
<td>Liquid (sip or tube feed)</td>
<td>840 kJ (200 kcal)</td>
<td>3</td>
<td>25.5</td>
<td>9.6</td>
<td>Nil</td>
<td></td>
<td>A sole source of nutrition or nutritional supplement in patients with chronic or acute renal failure who are not undergoing dialysis, or with chronic or acute liver disease with fluid restriction; other conditions requiring high energy, low protein, low electrolyte, low volume enteral feed. Not suitable for child under 1 year; use with caution in child 1–5 years.</td>
<td>Can: 237 mL = £2.34 Vanilla</td>
</tr>
<tr>
<td></td>
<td></td>
<td>per 100 mL</td>
<td>caseinates</td>
<td>sugars 2.7</td>
<td>g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Minor nutritional variations between flavours—consult product literature

Appendix 2: Borderline substances
### A2.4 Feed supplements

#### A2.4.1 High-energy supplements

For further information on composition of feeds, see p. 878

#### A2.4.1.1 High-energy supplements: carbohydrate

Flavoured carbohydrate supplements are not suitable for child under 1 year; liquid supplements should be diluted before use in child under 5 years.

**ACBS Indications**: disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high or readily available carbohydrate supplement.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caloreen® (Nestlé)</td>
<td>Powder</td>
<td>1640 kJ</td>
<td>Nil</td>
<td>96 g Maltodextrin</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>See above Not suitable for child under 3 years</td>
<td>Powder: 500 g = £3.42 Unflavoured (10-g measuring scoop provided)</td>
</tr>
<tr>
<td></td>
<td>(per 100 g)</td>
<td>(390 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>1615 kJ</td>
<td>Nil</td>
<td>95 g Glucose polymer (sugars 8.6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>See above</td>
<td>Sachets: 4 × 132 g = £5.04 Can: 200 g = £1.96 2.5 kg = £17.94 25 kg = £121.85 Unflavoured</td>
</tr>
<tr>
<td></td>
<td>(per 100 g)</td>
<td>(380 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>1630 kJ</td>
<td>Nil</td>
<td>96 g Maltodextrin (sugars 6 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>See above</td>
<td>Can: 400 g = £3.55 Neutral (5-g measuring scoop provided)</td>
</tr>
<tr>
<td></td>
<td>(per 100 g)</td>
<td>(384 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Bottle: 200 mL = £1.42 Neutral, orange</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>1050 kJ</td>
<td>Nil</td>
<td>61.9 g Maltodextrin (sugars 12.2 g)</td>
<td>Nil</td>
<td>Nil</td>
<td>Liquid not suitable for child under 3 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(per 100 mL)</td>
<td>(247 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Powder</td>
<td>1610 kJ</td>
<td>Nil</td>
<td>96 g Dried glucose syrup</td>
<td>Nil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>See above</td>
<td>Can: 500 g = £3.48 2.5 kg = £17.14 25 kg = £101.97 (10-g measuring scoop provided)</td>
</tr>
<tr>
<td></td>
<td>(per 100 g)</td>
<td>(380 kcal)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Sugar content varies with flavour
### A2.4.1.2 High-energy supplements: fat

Liquid supplements should be diluted before use in child under 5 years.

**ACBS indications:** disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat (or fat and carbohydrate) supplement.

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Calogen</strong>&lt;sup&gt;a&lt;/sup&gt; (Nutricia Clinical)</td>
<td>Liquid (emulsion)</td>
<td>1850 kJ (450 kcal)&lt;sup&gt;1&lt;/sup&gt; per 100 mL</td>
<td>Nil</td>
<td>100 mg</td>
<td>50 g (LCT 100%)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>See above.</td>
<td>Bottle: 200 mL = £3.80, 500 mL = £9.32 Banana&lt;sup&gt;2&lt;/sup&gt;, neutral, strawberry&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Liquigen</strong>&lt;sup&gt;a&lt;/sup&gt; (SHS)</td>
<td>Liquid (emulsion)</td>
<td>1850 kJ (450 kcal) per 100 mL</td>
<td>Nil</td>
<td>Nil</td>
<td>50 g (MCT 97%) Fractio-nated coconut oil</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>Steatorrhoea associated with cystic fibrosis of the pancreas, intestinal lymphangiectasia, intestinal surgery, chronic liver disease, liver cirrhosis, other proven malabsorp-tion syndromes, ketogenic diet in epilepsy, and in type 1 lipoprotei-naemia</td>
<td>Bottle: 250 mL = £7.26</td>
</tr>
<tr>
<td><strong>Duobar</strong>&lt;sup&gt;a&lt;/sup&gt; (SHS)</td>
<td>Bar</td>
<td>1211 kJ (292 kcal) per 45 g</td>
<td>Less than 20 mg</td>
<td>22.5 g (sucrose)</td>
<td>22.5 g Nil</td>
<td>Contains phenylalanine 180 micrograms/45-g bar Gluten-free Lactose-free</td>
<td>See above</td>
<td>Bar: 45 g = £1.54 Neutral, strawberry, toffee</td>
<td></td>
</tr>
<tr>
<td><strong>Duocal</strong>&lt;sup&gt;a&lt;/sup&gt; (SHS)</td>
<td>Liquid</td>
<td>695 kJ (166 kcal) per 100 mL</td>
<td>Nil</td>
<td>23.7 g (sugars 2.1 g)</td>
<td>7.9 g (MCT 30%)</td>
<td>Nil</td>
<td>Contains vitamin E</td>
<td>See above</td>
<td>Bottle: 250 mL = £3.14</td>
</tr>
<tr>
<td><strong>Duocal</strong>&lt;sup&gt;a&lt;/sup&gt; Super Soluble (SHS)</td>
<td>Powder</td>
<td>2061 kJ (492 kcal) per 100 g</td>
<td>Nil</td>
<td>72.7 g (sugars 6.5 g)</td>
<td>22.3 g (MCT 35%)</td>
<td>Nil</td>
<td>Gluten-free Lactose-free</td>
<td>See above</td>
<td>Can: 400 g = £14.16 (5-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>Energivit</strong>&lt;sup&gt;a&lt;/sup&gt; (SHS)</td>
<td>Standard dilution (15%) of powder</td>
<td>309 kJ (74 kcal) per 100 mL</td>
<td>Nil</td>
<td>10 g (sugars 900 mg)</td>
<td>3.75 g</td>
<td>Nil</td>
<td>Lactose-free With vitamins, minerals, and trace elements</td>
<td>For children requiring additional energy, vitamins, minerals, and trace elements following a protein-restricted diet</td>
<td>Can: 400 g = £17.23 (5-g measuring scoop provided)</td>
</tr>
<tr>
<td><strong>MCT Duocal</strong>&lt;sup&gt;a&lt;/sup&gt; (SHS)</td>
<td>Powder</td>
<td>2082 kJ (497 kcal) per 100 g</td>
<td>Nil</td>
<td>72 g (sugars 10.1 g)</td>
<td>23.2 g (MCT 83%)</td>
<td>Nil</td>
<td>See above</td>
<td>Can: 400 g = £16.84</td>
<td></td>
</tr>
</tbody>
</table>

---

1. Nutritional values may vary with flavour—consult product literature
2. Flavour not suitable for child under 3 years
### A2.4.1.3 High-energy supplements: protein

#### ACBS indications:
disease-related malnutrition, malabsorption states, or other conditions requiring fortification with a high fat or carbohydrate (with protein) supplement

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACBS indications:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biochemically proven hypoproteinaemia</td>
<td></td>
</tr>
<tr>
<td><strong>Product Formulation Energy Protein Carbohydrate Fat Fibre Special Characteristics</strong></td>
<td><strong>Vitapro®</strong>&lt;sup&gt;®&lt;/sup&gt; (Vitaflo) Powder 1506 kJ (360 kcal) per 100 g 75 g whey protein isolate 9 g 6 g Nil Contains lactose</td>
<td><strong>Dialamine</strong>&lt;sup&gt;®&lt;/sup&gt; (SHS) Standard dilution (20%) of powder 264 kJ (62 kcal) per 100 mL 4.3 g protein equivalent (essential and non-essential amino acids) 11.2 g (sugars 10.2 g) Nil Nil Contains vitamin C</td>
<td><strong>Protein and carbohydrate</strong></td>
<td><strong>Calshake®</strong>&lt;sup&gt;®&lt;/sup&gt; (Fresenius Kabi) Powder 1841 kJ (439 kcal) per 87 g 4.1 g cows’ milk 56.4 g (sugars 20 g) 22 g Nil Contains lactose Gluten-free</td>
<td><strong>Enshake®</strong>&lt;sup&gt;®&lt;/sup&gt; (Abbott) Powder 1893 kJ (450 kcal) per 100 g 8.4 g cows’ milk, soy protein isolate 69 g (sugars 14.5 g) 15.6 g Nil Residual lactose With vitamins and minerals</td>
<td><strong>Pro-Cal®</strong>&lt;sup&gt;®&lt;/sup&gt; (Vitaflo) Powder 2788 kJ (667 kcal) per 100 g 13.5 g cows’ milk 27 g 56 g Nil Contains lactose</td>
<td><strong>Tub:</strong> 250 g = £7.10 2kg = £55.73 (5-g measuring scoop provided)</td>
<td><strong>Can:</strong> 400 g = £57.53 Orange</td>
<td></td>
</tr>
<tr>
<td><strong>Presentation &amp; Flavour</strong></td>
<td>Tub: 250 g = £7.10 2kg = £55.73 (5-g measuring scoop provided)</td>
<td>Hypoproteinaemia, chronic renal failure, wound fistula leakage with excessive protein loss, conditions requiring a controlled nitrogen intake, and haemodialysis Not suitable for child under 6 months</td>
<td>Not suitable for child under 1 year Not suitable for child under 1 year; use with caution in child 1–6 years</td>
<td>See above</td>
<td>See above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Powder provides:</strong></td>
<td>Powder provides: protein equivalent 25 g, carbohydrate 65 g, vitamin C 125 mg, energy 1530 kJ (360 kcal)/100 g</td>
<td>Hypoproteinaemia, chronic renal failure, wound fistula leakage with excessive protein loss, conditions requiring a controlled nitrogen intake, and haemodialysis Not suitable for child under 6 months</td>
<td>Not suitable for child under 1 year</td>
<td>See above</td>
<td>See above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Powder provides:</strong></td>
<td>Powder: one sachet reconstituted with 240 mL whole milk provides approx. 2 kcal/mL and protein 12 g</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Sachet: 87 g = £1.87 Banana, neutral, strawberry, vanilla 90 g = £1.87 Chocolate</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Powder</strong></td>
<td>Powder: 96.5 g reconstituted with 240 mL whole milk provides approx. 2 kcal/mL and protein 16 g</td>
<td></td>
<td></td>
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<td></td>
<td>Sachet: 96.5 g = £1.87 Banana, chocolate, strawberry, vanilla</td>
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<tr>
<td><strong>Powder</strong></td>
<td>Powder: 15 g provides: protein 2 g, carbohydrate 4 g, fat 8.4 g, energy 418 kJ (100 kcal)</td>
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<td>Sachets: 25 × 15 g = £12.83 Tub: 510 g = £11.88 1.5 kg = £24.21 12.5 kg = £172.13 25 kg = £265.25 (15-g measuring scoop provided)</td>
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</table>

1. Nutritional values may vary with flavour—consult product literature

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**Appendix 2: Borderline substances**
| Pro-Cal® Shot (Vitaflo) | Liquid | 1393 kJ (334 kcal) per 100 mL | 6.7 g cows’ milk | 13.4 g | 28.2 g | Nil | Contains lactose | See above | Not suitable for child under 1 year | Bottle: 6 x 250 mL = £25.80
Banana, neutral, strawberry¹ |
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<tbody>
<tr>
<td>QuickCal® (Vitaflo)</td>
<td>Powder</td>
<td>3263 kJ (780 kcal) per 100 g</td>
<td>4.6 g cows’ milk</td>
<td>17 g</td>
<td>77 g</td>
<td>Nil</td>
<td>Contains lactose</td>
<td>See above</td>
<td>Not suitable for child under 1 year</td>
<td>Sachets: 25 x 13 g = £11.54</td>
</tr>
<tr>
<td>Scandishake® Mix (Nutricia Clinical)</td>
<td>Powder</td>
<td>2099 kJ (500 kcal) per 100 g</td>
<td>4.7 g cows’ milk</td>
<td>65 g (sugars 14.3 g)</td>
<td>24.7 g</td>
<td>Nil</td>
<td>Gluten-free</td>
<td>Contains lactose</td>
<td>See above</td>
<td>Not suitable for child under 3 years</td>
</tr>
<tr>
<td>Vitasavoury® (Vitaflo)</td>
<td>Powder</td>
<td>2590 kJ (619 kcal) per 100 g</td>
<td>12.7 g cows’ milk</td>
<td>23.5 g (sugars 1.5 g)</td>
<td>52.3 g</td>
<td>6.2 g</td>
<td>Contains lactose</td>
<td>See above</td>
<td>Not suitable for child under 3 years</td>
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</tr>
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</table>

1. Flavour not suitable for child under 3 years
2. Nutritional values may vary with flavour—consult product literature

### A2.4.2 Fibre, vitamin, and mineral supplements

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High-fibre supplements</strong></td>
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<tr>
<td>Resource® Bene-fiber® (Nestlé)</td>
<td>Powder</td>
<td>323 kJ (76 kcal) per 100 g</td>
<td>Nil</td>
<td>19 g guar gum, partially hydrolysed</td>
<td>Nil</td>
<td>78 g</td>
<td>Gluten-free</td>
<td>Lactose-free</td>
<td>Standard, p. 878 except dysphagia</td>
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<td></td>
<td>Not suitable for child under 5 years</td>
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</table>
| | | | | | | | | | Sachets: 16 x 8 g = £5.72
Can: 250 g = £8.76 (5-g measuring scoop provided) |

¹ Nutritional values may vary with flavour—consult product literature.
### Vitamin and Mineral supplements

<table>
<thead>
<tr>
<th>Product</th>
<th>Formulation</th>
<th>Energy</th>
<th>Protein</th>
<th>Carbohydrate</th>
<th>Fat</th>
<th>Fibre</th>
<th>Special Characteristics</th>
<th>ACBS Indications</th>
<th>Presentation &amp; Flavour</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic Mineral Mixture® (SHS)</strong></td>
<td>Powder</td>
<td>729 kJ (175 kcal) per 100 g</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Nil</td>
<td>Contains trace elements Electrolytes/100 g: Na+ 172 mmol K+ 212 mmol Ca2+ 205 mmol P+ 192 mmol</td>
<td>Mineral supplement for synthetic diets Suitable for infants (but may require further dilution)</td>
<td>Tub: 100 g = £9.94</td>
</tr>
</tbody>
</table>

| **Paediatric Seravit® (SHS)**        | Powder      | 1275 kJ (300 kcal) per 100 g | Nil     | 75 g¹        | Nil | Nil   | Vitamin and mineral supplement in infants and children with restrictive therapeutic diets | Tub: 200 g = £14.03 Unflavoured¹ 200 g = £14.94 Pineapple² (5-g measuring scoop provided) | 200 g = £14.94         |

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1. Sugar content varies with flavour
2. Flavouring: see Modjul® Flavour System, p. 909
3. Flavour not suitable for child under 6 months
A2.5 Feed additives

A2.5.1 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 concentration of the corresponding disaccharide enzyme on intestinal biopsy or by breath hydrogen test or lactose intolerance test. For dosage and administration details, consult product literature

Fructose (Laevulose)
For proven glucose/galactose intolerance

A2.5.2 Feed thickeners and pre-thickened foods

Carobel, Instant® (Cow & Gate)
Powder, carob seed flour. Net price 135 g = £2.81.
For thickening feeds in the treatment of vomiting

Nutilis® (Nutricia Clinical)
Powder, modified maize starch, gluten- and lactose-free, net price 20 × 9-g sachet = £5.71, 225 g = £4.38.
For thickening of foods in dysphagia. Not to be prescribed for children under 3 years

Resource® Thickened Drink (Nestlé)
Liquid, carbohydrate 22 g, energy: orange 375 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, modified maize starch. Gluten- and lactose-free, net price 227 g = £15.75; 6.4-g sachet = £15.75.
For thickening of foods in dysphagia. Not to be prescribed for children under 1 year

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 × 115 mL = £7.50
Nutritional supplement for patient hydration in the dietary management of dysphagia. Not to be used in children under 3 years

Thick and Easy® (Fresenius Kabi)
Powder, modified maize starch, net price 225-g can = £4.15; 100 × 9-g sachets = £26.35; 4.54 kg = £70.53.

Thickened Juices, liquid, modified food starch. Flavours: apple, orange, net price 118-mL pot = 54p; apple, black currant, cranberry, kiwi-strawberry, and orange, 1.42-litre bottle = £3.81.
For thickening of foods in dysphagia. Not suitable for children under 1 year except in cases of failure to thrive

Thixo-D® (Sutherland)
Powder, modified maize starch, gluten-free. Net price 375-g tub = £6.75.
For thickening of foods in dysphagia. Not to be prescribed for children under 1 year except in cases of failure to thrive

Vitaquick® (Vitaflo)
Powder, modified maize starch. Net price 300 g = £6.40; 2 kg = £32.59; 6 kg = £93.40.
For thickening of foods in dysphagia. Not to be prescribed for children under 1 year except in cases of failure to thrive

A2.5.3 Flavouring preparations

Flavour Mix® (Nestlé)
Powder. Flavours: banana, chocolate, coffee, lemon-lime, strawberry. Net price 60 g = £5.62

FlavourPac® (Vitaflo)
Powder, flavours: black currant, lemon, orange, tropical or raspberry, net price 30 × 4-g sachets = £11.29
For use with Vitaflo’s range of unflavoured protein substitutes for metabolic diseases

Modjul® Flavour System (SHS)
Powder, carbohydrate-based flavours, black currant, 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; not suitable for child under 6 months
Appendix 2: Borderline substances

A2.6 Foods for special diets

A2.6.1 Gluten-free foods

ACBS indications: gluten-sensitive enteropathies including steatorrhoea due to gluten sensitivity, coeliac disease, and dermatitis herpetiformis.

Aproten® (Ultrapharm)

Barkat® (Gluten Free Foods Ltd)
Gluten-free. Baguettes (par-baked), net price 200 g = £2.99. Bread (white, par-baked, sliced), 500 g = £3.40; country loaf (par-baked, sliced), 250 g = £2.99; rolls (par-baked), 300 g = £2.99. Bread mix, 500 g = £5.10. Multi grain bread, 500 g = £5.95. Rice bread (sliced), brown or white, 450 g = £5.95. Crackers (matzo), 200 g = £2.24. Biscuits (coffee) 200 g = £1.49. Pasta (animal shapes, macaroni, spaghetti, spelt, potato, tagliatelle), 500 g = £4.46. Buckwheat (penne or spirals) 250 g = £1.79. Rice pizza crust, brown or white, 500 g = £3.40. Flour mix, 750 g = £4.75.

Bi-Aglut® (Ultrapharm)
Gluten-free. Bread flour mix or plain flour, net price 500 g = £4.75. Bread rolls, 150 g = £1.77. Bread sticks, 150 g = £1.95. Biscuits, 180 g = £2.89. Crackers, 150 g = £2.36. Cracker toast, 240 g = £4.18. Pasta (fusilli, macaroni, penne, spaghetti), 500 g = £5.23.

Dietary Specials (Nutrition Point)
Gluten-free. Bread, loaf, sliced (brown, white or multi-grain), net price 400 g = £2.80; bread rolls, long (white) 3 = £1.75. Bread mix, 500 g = £4.95; cracker bread, 150 g = £1.80; cake mix (white), 750 g = £4.95; white mix, 500 g = £4.95. Tea biscuits, 220 g = £2.00. Pasta (spaghetti, penne, fusilli), 500 g = £3.20. Pizza base 2 × 150 g = £4.90.

Ener-G® (General Dietary)
Gluten-free. Cookies (vanilla flavour), net price 435 g = £5.00. Rolls, dinner, 6 = £2.97, long, white 220 g = £2.39, round, white 220 g = £2.39; Rice bread (sliced), brown, 474 g = £4.39; white, 456 g = £4.39. Rice loaf (sliced), 612 g = £4.39. Seattle brown loaf, 600 g = £5.05. Tapioca bread (sliced), 480 g = £4.39. Rice pasta (macaroni, small shells, and lasagne), 454 g = £4.08; spaghetti, 447 g = £3.98; tagliatelle, 400 g = £3.98; vermicelli, 300 g = £4.08; cannelloni, 335 g = £3.98. Brown rice pasta: lasagne, 454 g = £3.98; macaroni, 454 g = £3.98; spaghetti, 447 g = £3.98. Xanthan gum, 170 g = £6.93.

Freebake® (Freebake)
Gluten-free. Bread mix, net price 2.4 kg = £12.15, cake mix, 2.4 kg = £11.90, pizza base 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. Bread, white (sliced or unsliced), 400 g = £2.50. Bread rolls, white, 4 × 75 g = £2.00.

Glutafin® (Nutricia Dietary)
Gluten-free. Bread loaf, fibre or white (sliced), 400 g = £3.25; rolls, fibre or white, 4 = £3.25. Biscuits, savoury, 125 g = £1.80, savoury shorts 150 g = £2.47. Biscuits, digestive, sweet or tea, 150 g = £1.80. Biscuits, 200 g = £3.51. Biscuits, shortbread, 100 g = £1.49. Mixes, bread, fibre or white, 500 g = £5.63. Cake, 500 g = £5.63. 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. Bread, fibre loaf (sliced), 400 g = £2.89; part-baked, 400 g = £3.25; fresh, white or brown (sliced), 400 g = £3.02. Seeded loaf, 400 g = £3.13. White loaf (sliced), 400 g = £2.89; part-baked, 400 g = £3.25. Fibre rolls, 4 = £3.25, White rolls, 4 = £3.25; part-baked, 4 = £3.25; long, part-baked, 2 = £3.25. Mixes (bread, fibre, fibre bread, pastry, and white), 500 g = £5.63.

Heron Foods® (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, pizza base mix, 500 g = £5.25.

Juevela® (SHS)
Gluten-free. Harvest mix, fibre mix, and flour mix, net price 500 g = £6.06. Bread (whole or sliced), 400 g-loaf = £2.92; part-baked loaf (with or without fibre), 400 g = £3.13; fresh sliced loaf (white) 400 g = £3.17, (fibre) 400 g = £2.92. Fibre bread (sliced and unsliced), 400 g = £2.92. Bread rolls, white, 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 = £2.86. Pizza 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, 160 g = £2.51.

Lifestyle® (Ultrapharm)
Gluten-free. Brown bread (sliced and unsliced), net price 400 g = £2.82. High fibre bread (sliced or unsliced), 400 g = £2.82. Bread rolls (brown, white, or high-fibre) 400 g = £2.82.

Livwell® (Livwell)
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.

Orgran® (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 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 = £2.80. Crispbread (corn or rice), 200 g = £2.56. Pasta and pizza mix, 375 g = £3.33. Flour, self-raising, 500 g = £2.89. Bread mix, 450 g = £3.10.

Proceli® (Germapharm)
Gluten-free. Bread, white (sliced), net price 165 g = £2.24; sandwich bread, 155 g = £2.18; baguettes (part-baked), 2 × 125 g = £2.96. Bread buns, 4 × 50 g = £3.25. 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, puntini, short spaghetti, spirals), 250 g = £2.99. Pizza bases, 3 × 12 g = £5.99. Rice bread (sandwich loaf), 200 g = £2.32, rice bread (brown), 220 g = £2.32.

Pure® (Innovative)
Gluten-free. Blended flour, net price 1 kg = £3.75; potato starch flour, 500 g = £1.49; rice flour, (brown), 500 g = £1.40, (white), 500 g = £1.50; tapioca starch flour, 500 g = £1.99; teff flour, (brown or white), 1 kg = £4.20; xanthan gum, 100 g = £5.75.

Rite-Diet® (Nutricia Dietary)
Gluten-free. Flour mix (white or fibre), 500 g = £5.22.
**A2.6.1.1 Gluten- and wheat-free foods**

**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. Five flour bread loaf, 576 g = £3.60. Seattle brown rolls (round or long), 4 x 119 g = £3.00

**Glutafin® (Nutricia Dietary)**
Gluten-free, wheat-free. Crisp bread, 2 x 125 g = £3.82. Mixes (flour bread, bread), 500 g = £5.63; cake or pastry mix, 500 g = £5.63

**Sunnyvale® (Everfresh)**
Gluten-free, Mixed grain bread (sourdough), net price 400 g = £1.91

**A2.6.2 Low-protein foods**

**ACBS indications:** inherited metabolic disorders, renal or liver failure, requiring a low-protein diet

**Aproten® (Ultrapharm)**
Low protein. Low Na+ and K+. Biscuits, net price 180 g (36) = £2.88. Bread mix, 250 g = £2.17. Crisp bread, 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, net price 454 g = £4.05. Rice bread, 600 g = £4.39

**Fate® (Fate)**
Low protein. Mix (all-purpose), net price 500 g = £6.35. Cake mix, 2 x 250 g = £6.35, (chocolate-flavour), 2 x 250 g = £6.35.

**Harifen® (Ultrapharm)**
Low protein. Cracker toast, net price 200 g = £2.75. Cookies, white chip, 200 g = £2.25

**Juvella® (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 = £6.51; chocolate chip, 130 g = £6.51. Pizza base, 2 x = £2.73

**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 = £11.08; wafers (orange, vanilla, or chocolate), 100 g = £2.02. Breakfast cereal, (loops) 375 g = £6.23. Egg replacer, 500 g = £12.14. Egg-white replacer, 100 g = £7.81. (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. Crackers, 150 g = £2.84. Herb crackers, 150 g = £2.84. Pasta (fusilli, penne, spaghetti), 500 g = £6.91, (macaroni, puntoni, tagliatelle), 250 g = £3.32, (conchiglie, gnocchetti sardi), 500 g = £6.66, (lasagne), 250 g = £3.36, (animal shapes), 500 g = £6.64, (vermicelli), 250 g = £3.44. Snack Pot (curry, or tomato and basil), 47 g = £3.67. Rice, 500 g = £6.71

**Low protein drink (Milupa)**
Powder, protein (whey) 450 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 childhood
**Note** Termed Milupa® lp-drink by manufacturer

**PK Foods (Gluten Free Foods Ltd)**
Low protein. Bread, white (sliced), 550 g = £4.00. Crisp bread, 75 g = £2.00. Pasta (spiral) 250 g = £2.00. Aminex® biscuits, 200 g = £3.75, cookies, 150 g = £3.75, rusks, 200 g = £4.25

For phenylketonuria and similar amino acid abnormalities
Cookies (chocolate chip, orange, or cinnamon), 150 g = £3.75. Egg replacer, 350 g = £3.75. Mix flour, 750 g = £6.99. Jelly (orange or cherry flavour), 4 x 80 g = £5.76. For phenylketonuria only

**Promin® (Firstplay Dietary)**
Low protein. Burger mix, 2 x 62 g = £5.60. Lamb (and mint), 4 x 72g = £5.60. 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, spiral) and pasta tricolour (alphabets, shells, spirals), 500 g = £6.35. Lasagne sheets, 200 g = £6.35
**Appendix 2: Borderline substances**

**2. Maxamaid products** are generally intended for use in children 1–8 years old.

**Analog products** are generally intended for use in children up to 1 year.

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**A2.7 Nutritional supplements for metabolic diseases**

**Glutaric aciduria (type 1)**

**GA Gel** (Vitaflo)
- Gel, protein equivalent (essential and non-essential amino acids except lysine, and low tryptophan) 8.4 g, carbohydrate 8.6 g, fat 3.8 g, energy 280 kJ (67 kcal)/100 mL.
- Nutritional supplement for dietary management of type 1 glutaric aciduria in children 6 months–10 years old.

**XLYS, Low TRY, Maxamaid** (SHS)
- Powder, protein equivalent (essential and non-essential amino acids except lysine and tryptophan) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements.
- Unflavoured (flavouring: see FlavourPac®, p. 909), net price 30 × 20-g sachets = £141.51.
- Nutritional supplement for dietary management of type 1 glutaric aciduria.

**Glucogenesis**

**Corn flour and corn starch**
- For hypoglycaemia associated with glucogen-storage disease.

**Glucose**
- (Dextrose monohydrate)
- Net price 100 g = 39p.
- For glucogen storage disease and sucrose/isomaltose intolerance.

**Homocystinuria or hypermethionimiaemia**

**HCU cooler** (Vitaflo)
- 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 children over 3 years with homocystinuria.

**HCU Express** (Vitaflo)
- Powder, 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 (flavouring: see FlavourPac®, p. 909), net price 30 × 25-g sachets = £253.24.
- A methionine-free protein substitute for use as a nutritional supplement in children over 8 years with homocystinuria.

**Taranis** (Firstplay Dietary)
- Low protein.
- Cake bars (lemon), net price 6 × 40 g = £5.25.

**Ultra** (Ultrapharm)
- Low protein.
- PKU bread, 400 g = £2.25. PKU flour, 500 g = £3.07. PKU biscuits, 200 g = £2.21. PKU pizza base, 400 g = £2.35. PKU savoy biscuits, 150 g = £2.06.

**Valpiform** (Ultrapharm)
- Low protein.
- Biscuits, shortbread, net price 120 g = £4.06.

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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.
trace elements. Unflavoured, (flavouring: see Flavour Pack®, p. 909), net price 30 × 20-g sachets = £141.51.
A methionine-free protein substitute for use as a nutritional supplement for the dietary management of children 1–10 years with homocystinuria

**HCU LV® (SHS)**
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 (flavouring: see Modjul® Flavour System, p. 909), or tropical flavour (flavouring varies slightly), net price 30 × 27.8-g sachets = £386.17.
A nutritional supplement for the dietary management of hypermethioninaemia or vitamin B6 non-responsive homocystinuria in children over 8 years

**XLEU Faladon (SHS)**
Powder, protein equivalent (essential and non-essential amino acids, except leucine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Unflavoured, net price 400 g = £28.22 (5-g measuring scoop provided).
Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children 1–10 years with homocystinuria

**XMET Homidon (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, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see Modjul® Flavour System, p. 909), net price 500 g = £145.76.
Nutritional supplement for the dietary management of hypermethioninaemia or homocystinuria in children

**Hyperlysinaemia**

**XLYS Analog (SHS)**
Powder, protein equivalent (essential and non-essential amino acids except lysine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Unflavoured, net price 400 g = £28.22 (5-g measuring scoop provided).
Nutritional supplement for the dietary management of hyperlysinaemia

**XLYS Maxamoid (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, (flavouring: see Modjul® Flavour System, p. 909), net price 500 g = £76.94.
Nutritional supplement for the dietary management of hyperlysinaemia

**Isovaleric acidaemia**

**XLEU Analog (SHS)**
Powder, protein equivalent (essential and non-essential amino acids except leucine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Unflavoured, net price 400 g = £28.22 (5-g measuring scoop provided).
Nutritional supplement for the dietary management of isovaleric acidaemia

**XLEU Maxamoid (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, (flavouring: see Modjul® Flavour System, p. 909), net price 500 g = £76.94.
Nutritional supplement for the dietary management of isovaleric acidaemia

**Maple syrup urine disease**

**Isoleucine Amino Acid Supplement (Vitaflo)**
Powder, isoleucine 50 mg, carbohydrate 4 g, fat nil, energy 64 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £42.23.
Nutritional supplement for use in the dietary management of maple syrup urine disease and other inborn errors of amino acid metabolism in children over 1 year and adults

**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 sachet, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see Modjul® Flavour System, p. 909), net price 30 × 29-g sachets = £162.82.
Nutritional supplement for the dietary management of 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, fat nil, energy 1386 kJ (326 kcal)/
Appendix 2: 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
3. Maxamum products are generally intended for use in children over 8 years

### 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, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Unflavoured, net price 400 g = £28.22 (5-g measuring scoop provided). Nutritional supplement for the dietary management of maple syrup urine disease children in over 8 years and adults.

### 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, (flavouring: see Flavour Pac®, p. 909), net price 30 × 25-g sachets = £253.24. Nutritional supplement for the dietary management of maple syrup urine disease in children over 8 years and adults.

### MSUD express cooler® (Vitaflo)

**Liquid**, protein equivalent (essential and non-essential amino acids except isoleucine, leucine, and valine) 15 g, carbohydrate 7.8 g, fat trace, energy 386 kJ (92 kcal)/130-mL pouch, with vitamins, minerals, and trace elements. Orange flavour, net price 30 × 130-mL pouch = £258.30. Nutritional supplement for the dietary management of maple syrup urine disease in children over 3 years and adults.

### Methylmalonic propionic acidaemia

1. **XMTVI Analog (SHS)**
   - **Powder**, protein equivalent (essential and non-essential amino acids except methionine, threonine, and valine, and low isoleucine) 13 g, carbohydrate 54 g, fat 23 g, energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Unflavoured, net price 400 g = £28.22 (5-g measuring scoop provided). Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia in children and adults.

2. **XMTVI 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, fat nil, energy 1386 kJ (326 kcal)/100 g, with vitamins, minerals, and trace elements. Unflavoured, (flavouring: see Modjul® Flavour System, p. 909), net price 200 g = £58.28. Nutritional supplement for the dietary management of methylmalonic acidaemia or propionic acidaemia in children and adults.

3. **Cystine Amino Acid Supplement (Vitaflo)**
   - **Powder**, cystine 500 mg, carbohydrate 5.4 g, fat nil, energy 63 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £42.23. Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in children over 1 year.

4. **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 vitamins, minerals, and trace elements. Tropical flavour, net price 50 × 12.5-g sachets = £165.67. Nutritional supplement for the dietary management of disorders of protein metabolism including urea cycle disorders in children over 3 years.

### Other inborn errors of metabolism

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
3. Maxamum products are generally intended for use in children over 8 years
Key Omega® (Vitaflor)
Powder, protein (cows’ milk, soya) 170 mg, carbohydrate 2.8 g, fat 800 mg (of which arachidonic acid 200 mg, docosahexaenoic acid 100 mg), energy 80 kJ (19 kcal)/4 g, net price 30 × 4-g sachets = £32.30
Nutritional supplement for the dietary management of inborn errors of metabolism

Leucine Amino Acid Supplement (Vitaflor)
Powder, leucine 100 mg, carbohydrate 4 g, fat nil, energy 64 kJ (15 kcal)/4 g, net price 30 × 4-g sachets = £42.23
Nutritional supplement for the dietary management of inborn errors of amino acid metabolism in children over 1 year

Phenylketonuria

Add-Ins® (SHS)
Powder, protein equivalent (containing essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate nil, fat 5.1 g, energy 359 kJ (86 kcal)/18.2-g sachet, with vitamins, minerals, and trace elements. Unflavoured, net price 60 × 18.2-g sachets = £294.00.
Nutritional supplement for the dietary management of proven phenylketonuria in children over 4 years

Easiphen® (SHS)
Liquid, 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)/100 mL, with vitamins, minerals, and trace elements. Forest berries, orange, or tropical flavour, net price 250-mL carton = £7.56.
Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years

Lophlex® (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 2.5 g, fat 60 mg, fibre 220 mg, energy 385 kJ (91 kcal)/27.8-g sachet, with vitamins, minerals, and trace elements. Flavours: berry, orange, or unflavoured, net price 30 × 27.8-g sachets = £226.87.
Nutritional supplement for the dietary management of proven phenylketonuria in children over 8 years and adults including pregnant women

Lophlex LQ® (SHS)
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 20 g, carbohydrate 8.8 g, fibre 340 mg, energy 490 kJ (115 kcal)/125 mL, with vitamins, minerals, and trace elements. Flavours: berry, citrus, or orange, net price 3 × 125 mL = £24.27.
Nutritional supplement for the dietary management of phenylketonuria in children over 8 years and adults including pregnant women

Lophlex LQ 10 (SHS)
Liquid, protein equivalent (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 × 62.5 mL = £243.00.
Nutritional supplement for the dietary management of phenylketonuria in children over 4 years and adults including pregnant women

Loprofin® PKU Drink (SHS)
Liquid, protein (cows’ milk) 400 mg (phenylalanine 10 mg), lactose 9.4 g, fat 2 g, energy 165 kJ (40 kcal)/100 mL. Net price 200-mL carton = 60p.
Nutritional supplement for the dietary management of phenylketonuria in children over 1 year

Milupa PKU 2-prima® (Milupa)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 10 g, fat nil, energy 1100 kJ (280 kcal)/100 g, with vitamins, minerals, and trace elements. Vanilla flavour, net price 500 g = £112.70.
Nutritional supplement for the dietary management of phenylketonuria in children 1–8 years

Milupa PKU 2-secunda® (Milupa)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 70 g, carbohydrate 6.8 g, fat nil, energy 1306 kJ (307 kcal)/100 g, with vitamins, minerals, and trace elements. Vanilla flavour, net price 500 g = £143.15
Nutritional supplement for the dietary management of phenylketonuria in children 9–15 years

Milupa PKU 3-advanta® (Milupa)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 70 g, carbohydrate 4.7 g, fat nil, energy 1270 kJ (299 kcal)/100 g, with vitamins, minerals, and trace elements. Vanilla flavour, net price 500 g = £143.15
Nutritional supplement for the dietary management of phenylketonuria in children over 15 years

Minaphlex® (SHS)
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.4 g, carbohydrate 9.9 g, fat 3.9 g, energy 455 kJ (108 kcal)/29-g sachet, with vitamins, minerals, and trace elements. Chocolate, pineapple-vanilla. Unflavoured (carbohydrate 11 g, energy 474 kJ (113 kcal)/29-g sachet), net price 30 × 29-g sachets = £98.92.
Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years

Phlexy-10® Exchange System (SHS)
Bar, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.33 g, carbohydrate 20.5 g, fat 5.7 g, fibre 1.7 g/42-g bar. Citrus fruit flavour. Net price per bar = £4.76
Capsules, protein equivalent (essential and non-essential amino acids except phenylalanine) 416.5 mg/capsule. Net price 200-cap pack = £33.33
Tablets, protein equivalent (essential and non-essential amino acids except phenylalanine) 833 mg tablet. Net price 75-tab pack = £21.59
Drink Mix, powder, (essential and non-essential amino acids except phenylalanine) 8.33 g, carbohydrate 8.8 g/20-g sachet. Apple-black currant, citrus, or tropical flavour. Net price 30 × 20-g sachet = £100.51
Nutritional supplement for the dietary management of phenylketonuria

Phlexy-Vits® (SHS)
Powder, vitamins, minerals, and trace elements, net price 30 × 7-g sachets = £56.08.
Tablets, vitamins, minerals, and trace elements, net price 180-tab pack = £268.69.
For use as a vitamin and mineral component of restricted therapeutic diets in children over 11 years and adults with phenylketonuria and similar amino acid abnormalities

PK Aid 4® (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 79 g, carbohydrate 4.5 g, fat nil, energy 1420 kJ (334 kcal)/100 g. Unflavoured, (flavouring: see Modjul® Flavour System, p. 909). Net price 500 g = £112.04 (5-g measuring scoop provided).
Nutritional supplement for the dietary management of phenylketonuria and adults

PKU Anamix Junior LQ® (SHS)
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 8.8 g, fat 4.8 g, fibre 310 mg, energy 497 kJ (118 kcal)/125 mL, with vitamins, minerals, and trace elements. Lactose-free. Flavours: Berry or orange, net price 125-mL
Appendix 2: Borderline substances

PKU cooler10® (Vitaflor)
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 5.1 g, energy 258 kJ (62 kcal)/87-mL pouch, with vitamins, minerals, and trace elements. Orange or purple option, net price 30 x 87-mL = £105.00. Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU cooler15® (Vitaflor)
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 7.8 g, energy 386 kJ (92 kcal)/150-mL pouch, with vitamins, minerals, and trace elements. Orange or purple option, net price 30 x 150-mL = £156.60. Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU cooler20® (Vitaflor)
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. Nutritional supplement for the dietary management of phenylketonuria in children over 3 years

PKU express® (Vitaflor)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 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. Orange, orange, tropical, or unflavoured, net price 30 x 25-g sachets = £153.53. Nutritional supplement for the dietary management of phenylketonuria in children over 8 years

PKU gel® (Vitaflor)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 8.4 g, carbohydrate 3.8 g, energy 315 kJ (76 kcal)/25 g, with vitamins, minerals, and trace elements. Lemon, orange, tropical, or unflavoured, net price 30 x 25-g sachets = £89.51. For use as part of the low-protein dietary management of phenylketonuria in children 1–10 years

PKU Start® (Vitaflor)
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 15 g, carbohydrate 8.3 g, fat 2.9 g, energy 286 kJ (68 kcal)/100 mL with vitamins, minerals, and trace elements. Contains lactose and fish oil. Net price 500-mL bottle = £5.30. For the dietary management of phenylketonuria in children under 12 months

TYR cooler
Liquid, protein equivalent (essential and non-essential amino acids except phenylalanine) 10 g, carbohydrate 5.1 g, energy 258 kJ (62 kcal)/87-mL pouch, with vitamins, minerals, and trace elements. Orange or purple option, net price 30 x 87-mL = £105.00. Nutritional supplement for the dietary management of phenylketonuria in children 1–10 years

L-Tyrosine (SHS)
Powder, net price 100 g = £12.53. For use as a supplement in maternal phenylketonurics who have low plasma tyrosine concentrations

XP Analog (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 13 g, carbohydrate 54 g, fat 23 g (of which LCT 95%), energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Net price 400 g = £22.54 (5-g measuring scoop provided).
Nutritional supplement for the dietary management of phenylketonuria in children under 1 year

XP Analog LCP (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 13 g, carbohydrate 54 g, fat 23 g (of which LCT 98.7%), energy 1990 kJ (475 kcal)/100 g, with vitamins, minerals, and trace elements; standard dilution (15%) provides protein equivalent 1.95 g, carbohydrate 8.1 g, fat 3.5 g, energy 300 kJ (72 kcal)/100 mL. Net price 400 g = £25.64 (5-g measuring scoop provided).
Nutritional supplement for the dietary management of phenylketonuria in children under 1 year

XP Maxamum® (SHS)
Powder, protein equivalent (essential and non-essential amino acids except phenylalanine) 25 g, carbohydrate 51 g, fat less than 500 mg, energy 1311 kJ (309 kcal)/100 g, with vitamins, minerals, and trace elements. Orange flavour, or unflavoured, net price 500 g = £45.52. Nutritional supplement for the dietary management of phenylketonuria in children 1–8 years

Tyrosinaemia

TYR cooler® (Vitaflor)
Liquid, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 15 g, carbohydrate 7.8 g, fat nil, energy 386 kJ (92 kcal)/100 g, with vitamins, minerals, and trace elements. Orange or unflavoured (flavouring; see Flavour Pac®, p. 909), net price 30 x 20-g sachets = £88.51. For use as part of the low-protein dietary management of tyrosinaemia in children 1–10 years

TYR express® (Vitaflor)
Powder, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 15 g, carbohydrate 3.8 g, fat less than 100 mg, energy 315 kJ (76 kcal)/25 g, with vitamins, minerals, and trace elements. Unflavoured (flavouring; see Flavour Pac®, p. 909), net price 30 x 25-g sachets = £253.24. Nutritional supplement for the dietary management of tyrosinaemia in children over 8 years

TYR Gel® (Vitaflor)
Gel, protein equivalent (essential and non-essential amino acids except tyrosine and phenylalanine) 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 (flavouring; see Flavour Pac®, p. 909), net price 30 x 20-g sachets = £141.51. Nutritional supplement for the dietary management of tyrosinaemia in children 1–10 years

Tyrosine Amino Acid Supplement (Vitaflor)
Powder, tyrosine 1.9 g, carbohydrate 2.9 g, energy 62 kJ (15 kcal)/4-g sachet, net price 30 x 4-g sachets = £37.80. Nutritional supplement for the dietary management of tyrosinaemia and other inborn errors of amino acid metabolism
**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, citrullaemia, arginosuccinic aciduria, and deficiency of N-acetyl glutamate synthetase

**Conditions for which ACBS products can be prescribed**
*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; E45 Emollient Bath Oil; E45 Emollient Wash Cream; E45 Lotion

**Dermatitis herpetiformis**
See also Gluten-sensitive enteropathies, p. 910

**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 hygienic purposes.

**Eczema**
See Dermatitis, above

**Photodermatoses (skin protection in)**
Delph Sun Lotion SPF 50; E45 Sun SPF 50; Spectraban Ultra; Sunsense Ultra; Uvistat Lipscreen SPF 50, Uvistat Suncream SPF 30 and 50.

**Pruritus**
See Dermatitis, above

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
Cautionary and advisory labels for dispensed medicines

Preparations in the *BNF for Children* include code numbers of the cautionary labels that pharmacists are recommended to add when dispensing. It is also expected that, when necessary, pharmacists will counsel children or their carers.

Counselling needs to be related to the age, experience, background, and understanding of the child or carer. The pharmacist should ensure understanding of how to take or use the medicine and how to follow the correct dosage schedule. Any effects of the medicine on co-ordination, performance of skilled tasks, 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, or discoloration of urine or stools 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 should be mentioned where necessary.

Original packs Most preparations are now dispensed in unbroken original packs (see Patient Packs, p. xii) that include further advice for the patient in the form of patient information leaflets. The advice in patient information leaflets may be less appropriate when the medicine is for a child, particularly for unlicensed medicines or indications. Pharmacists should explain discrepancies to carers, if necessary. The patient information leaflet should only be withheld in exceptional circumstances because it contains other information that should be provided. 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 are provided for injections on the assumption that they will be administered by a healthcare professional or a well-instructed child or carer. 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 child. 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 for Children* 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 for Children apply to medicines dispensed against a prescription. Children and carers should be made 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 for Children 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 BNF 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 coordination and 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. It should be remembered that children and adolescents do, on occasion, consume alcohol and should be made aware of potential problems.
   - 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 ketozonazole 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 ofloxacin 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 2-3 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 2-3 hours apart. Doxycycline, lymecycline and minocycline are less likely to form chelates and therefore only require label 6 (see above).

8. **Do not take 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-tuberculose 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.
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.

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 explanations given. This label may also be used on other preparations to remind the patient of the instructions that have been given.

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 (e.g. phenothiazines and sulphonamides) may, on rare occasions, cause reactions in susceptible patients. Exposure to high intensity ultraviolet radiation from sunray lamps and sunbeds is particularly likely to cause reactions.

Do not take anything containing aspirin while taking this medicine
To be used on preparations containing probenecid and sulfipyrazone whose activity is reduced by aspirin. Label 12 should not be used for anticoagulants since label 10 is more appropriate.

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.

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 reddish), and rifampicin (red).

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.

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 to transfer the tablets to plastic or less suitable containers.

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.

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 suppositories.

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'.

. . . with or after food
To be used on preparations that are liable to cause gastric irritation, or those that are better absorbed with food.

. . . 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).

. . . 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.

. . . 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.

. . . 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.

. . . 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.

. . . 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.

To be spread thinly . . .
To be used on external preparations that should be applied sparingly (e.g. corticosteroids, dithranol).

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 overdosage with paracetamol.

Do not take with any other paracetamol products
To be used on all containers of dispensed preparations containing paracetamol.

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.

Contains aspirin
To be used on all containers of dispensed preparations containing aspirin when the name on the label does not include the word "aspirin".

Contains an aspirin-like medicine
To be used on containers of dispensed preparations containing aspirin derivatives.
A local policy on the dilution of drugs with intravenous fluids should be drawn up by a multi-disciplinary team 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 diluted with infusion fluid 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 mixed with an infusion fluid in a syringe 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 syringe should be labelled with the neonate’s name and hospital number, the name and quantity of drug, the infusion fluid, and the expiry date and time. If a problem occurs during administration, containers should be retained for a period after use in case they are needed for investigation.

6. Administration using a suitable motorised syringe driver is advocated for preparations where strict control over administration is required.

7. 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 parenteral nutrition). 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.

**Blood** Because of the large number of incompatibilities, drugs should not 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.

**Method**

Ready-prepared infusions should be used whenever available. 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, further dilution with 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* injection requires dilution in infusions of pH greater than 5.5).

When drug dilutions 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 drug may form owing to differences in density. *Potassium chloride* is particularly prone to this ‘layering’ effect when added without adequate mixing to infusions; if such a mixture is administered it may have a serious effect on the heart.

A time limit between dilution 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 and sodium nitroprusside.
### Table of drugs given by continuous intravenous infusion to neonates

The table lists key drugs given by continuous intravenous infusion to neonates.

**Covers addition to Glucose intravenous infusion 5% and 10% and Sodium chloride intravenous infusion 0.9%. 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.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Amount/Dilution/Solution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adrenaline/Epinephrine</strong></td>
<td>(p. 146) Dilute 3 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 100 nanograms/kg/minute; infuse through a central venous catheter. Incompatible with bicarbonate and alkaline solutions. <strong>Note</strong> Usually made up with adrenaline 1 in 1000 (1 mg/mL) solution; this concentration of adrenaline is not licensed for intravenous administration.</td>
</tr>
<tr>
<td><strong>Alprostadil</strong> (Prostin VR®)</td>
<td>(p. 166) Dilute 150 micrograms/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 nanograms/kg/minute. Undiluted solution must not come into contact with the barrel of the plastic syringe; add the required volume of alprostadil to a volume of infusion fluid in the syringe, and then make up to final volume</td>
</tr>
<tr>
<td><strong>Atracurium besilate</strong></td>
<td>(p. 780) Dilute 60 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 120 micrograms/kg/hour; minimum concentration of 500 micrograms/mL, max. concentration of 5 mg/mL</td>
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<tr>
<td><strong>Dobutamine (as hydrochloride)</strong></td>
<td>(p. 143) Dilute 30 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 micrograms/kg/minute; max. concentration of 5 mg/mL; infuse higher concentration solutions through central venous catheter only. Incompatible with bicarbonate and other strong alkaline solutions</td>
</tr>
<tr>
<td><strong>Dopamine hydrochloride</strong></td>
<td>(p. 143) Dilute 30 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.3 mL/hour provides a dose of 3 micrograms/kg/minute; max. concentration of 3.2 mg/mL; infuse higher concentration solutions through central venous catheter. Incompatible with bicarbonate and other alkaline solutions</td>
</tr>
<tr>
<td><strong>Glyceril trinitrate</strong></td>
<td>(p. 135) Dilute 3 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 1 mL/hour provides a dose of 1 microgram/kg/minute; max. concentration of 400 micrograms/mL (but concentration of 1 mg/mL has been used via a central venous catheter). <strong>Note</strong> Glass or polyethylene apparatus is preferable; loss of potency will occur if PVC is used</td>
</tr>
<tr>
<td><strong>Heparin (as sodium)</strong></td>
<td>(p. 148) Maintenance of umbilical arterial catheter, dilute 50 units to a final volume of 50 mL with Sodium Chloride 0.45% or use ready-made bag containing 500 units in 500 mL Sodium Chloride 0.9%; infuse at 0.5 mL/hour</td>
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<td></td>
<td>Treatment of thrombosis, dilute 1250 units/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 1 mL/hour provides a dose of 25 units/kg/hour</td>
</tr>
<tr>
<td><strong>Insulin (soluble)</strong></td>
<td>(p. 423) Dilute 5 units to a final volume of 50 mL with Sodium Chloride 0.9% and mix thoroughly; an intravenous infusion rate of 0.1 mL/kg/hour provides a dose of 0.01 units/kg/hour <strong>Note</strong> Insulin may be absorbed by plastics, flush giving set with 5 mL of infusion fluid containing insulin</td>
</tr>
<tr>
<td><strong>Midazolam</strong></td>
<td>(p. 774) Neonate body-weight under 3.3 kg, dilute 15 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 30 micrograms/kg/hour</td>
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<tr>
<td></td>
<td>Neonate body-weight over 3.3 kg, dilute 50 mg to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.05–0.1 mL/kg/hour provides a dose of 50–100 micrograms/kg/hour</td>
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<tr>
<td><strong>Morphine sulphate</strong></td>
<td>(p. 255) Dilute 2.5 mg/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride 0.9%; an intravenous infusion rate of 0.1 mL/hour provides a dose of 5 micrograms/kg/hour</td>
</tr>
<tr>
<td><strong>Noradrenaline/Norepinephrine</strong></td>
<td>(p. 145) Dilute 600 micrograms (base)/kg body-weight to a final volume of 50 mL with Glucose 5% or Sodium Chloride and Glucose; an intravenous infusion rate of 0.1 mL/hour provides a dose of 20 nanograms (base)/kg/minute; infuse through central venous catheter; max. concentration of noradrenaline (base) 40 micrograms/mL (higher concentrations can be used if fluid restricted). Discard if discoloured. Incompatible with bicarbonate or alkaline solutions <strong>Note</strong> 1 mg of noradrenaline acid tartrate is equivalent to 500 micrograms of the base. Dose expressed as the base</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Preparation</th>
<th>Formulation Details</th>
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</thead>
<tbody>
<tr>
<td>Aciclovir Cream, BP</td>
<td></td>
</tr>
<tr>
<td>Aciclovir Oral Suspension, BP, 200 mg</td>
<td></td>
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<tr>
<td>Aciclovir Tablets, BP, 800 mg</td>
<td></td>
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<tr>
<td>Amoxicillin Capsules, BP</td>
<td></td>
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<tr>
<td>Amoxicillin Oral Powder, DPF</td>
<td></td>
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<tr>
<td>Amoxicillin Oral Suspension, BP</td>
<td></td>
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<tr>
<td>Amphotericin Lozenges, BP</td>
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<tr>
<td>Ampicillin Capsules, BP</td>
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<tr>
<td>Ampicillin Oral Suspension, BP</td>
<td></td>
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<tr>
<td>Artificial Saliva, DPF</td>
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<tr>
<td>Artificial Saliva Substitutes</td>
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<tr>
<td>AS Saliva Orthana®</td>
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<tr>
<td>Glandosane®</td>
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<tr>
<td>BioXtra®</td>
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<tr>
<td>Saliveze®</td>
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<tr>
<td>Salivix®</td>
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<tr>
<td>Aspirin Tablets, Dispersible, BP</td>
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<tr>
<td>Azithromycin Oral Suspension, 200 mg</td>
<td></td>
</tr>
<tr>
<td>Beclomethasone Pressurised Inhalation, BP, 50 micrograms/metered inhalation, CFC-free, as:</td>
<td></td>
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<tr>
<td>Clenil Modulite®</td>
<td></td>
</tr>
<tr>
<td>Benzylamine Mouthwash, BP 0.15%</td>
<td></td>
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<tr>
<td>Benzylamine Oromucosal Spray, BP 0.15%</td>
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<tr>
<td>Betamethasone Soluble Tablets, 500 micrograms, DPF</td>
<td></td>
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<tr>
<td>Carbamazepine Tablets, BP</td>
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<tr>
<td>Carmellose Gelatin Paste, DPF</td>
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<tr>
<td>Cefalexin Capsules, BP</td>
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<tr>
<td>Cefalexin Oral Suspension, BP</td>
<td></td>
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<tr>
<td>Cefalexin Tablets, BP</td>
<td></td>
</tr>
<tr>
<td>Cefradine Capsules, BP</td>
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<tr>
<td>Cefradine Oral Solution, DPF</td>
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<tr>
<td>Cetirizine Hydrochloride Tablets, 10 mg, DPF</td>
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<tr>
<td>Chlorhexidine Gluconate 1% Gel, DPF</td>
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<tr>
<td>Chlorhexidine Mouthwash, BP</td>
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<tr>
<td>Chlorhexidine Oral Spray, DPF</td>
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<tr>
<td>Chlorphenamine Oral Suspension, BP</td>
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<tr>
<td>Chlorphenamine Tablets, BP</td>
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<tr>
<td>Choline Salicylate Dental Gel, BP</td>
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<tr>
<td>Clindamycin Capsules, BP</td>
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<tr>
<td>Co-amoxiclav Tablets, BP, 250/125 (amoxicillin 250 mg as trihydrate, clavulanic acid 125 mg as potassium salt)</td>
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<tr>
<td>Diazepam Oral Solution, BP, 2 mg/5 mL</td>
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<tr>
<td>Diazepam Tablets, BP</td>
<td></td>
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<tr>
<td>Diclofenac Sodium Tablets, BP</td>
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<tr>
<td>Dihydrocodeine Tablets, BP, 30 mg</td>
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<tr>
<td>Doxycycline Capsules, BP, 100 mg</td>
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<tr>
<td>Doxycycline Tablets, 20 mg, DPF</td>
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<tr>
<td>Ephedrine Nasal Drops, BP</td>
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<tr>
<td>Erythromycin Ethyl Succinate Oral Suspension, BP</td>
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<tr>
<td>Erythromycin Ethyl Succinate Tablets, BP</td>
<td></td>
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<tr>
<td>Erythromycin Tablets, BP</td>
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<tr>
<td>Fluconazole Capsules, 50 mg, DPF</td>
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<tr>
<td>Fluconazole Oral Suspension, 50 mg/5 mL, DPF</td>
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<tr>
<td>Hydrocortisone Cream, BP, 1%</td>
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<tr>
<td>Hydrocortisone Oromucosal Tablets, BP</td>
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<tr>
<td>Hydrogen Peroxide Mouthwash, BP</td>
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<tr>
<td>Ibuprofen Oral Suspension, BP, sugar-free</td>
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<tr>
<td>Ibuprofen Tablets, BP</td>
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<tr>
<td>Lansoprazole Capsules, DPF</td>
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<tr>
<td>Lidocaine 5% Ointment, DPF</td>
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<tr>
<td>Lidocaine Spray 10%, DPF</td>
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<tr>
<td>Loratadine Tablets, 10 mg, DPF</td>
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<tr>
<td>Menthol and Eucalyptus Inhalation, BP</td>
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<tr>
<td>Metronidazole Oral Suspension, BP</td>
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<tr>
<td>Metronidazole Tablets, BP</td>
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<tr>
<td>Miconazole Cream, BP</td>
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<tr>
<td>Miconazole Oromucosal Gel, BP</td>
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<tr>
<td>Miconazole and Hydrocortisone Cream, BP</td>
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<tr>
<td>Miconazole and Hydrocortisone Ointment, BP</td>
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<tr>
<td>Mouthwash Solution-tablets, DPF</td>
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<tr>
<td>Nitrazepam Tablets, BP</td>
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<tr>
<td>Nystatin Oral Suspension, BP</td>
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<tr>
<td>Gastro-resistant Omeprazole Capsules, BP</td>
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<tr>
<td>Oxytetracycline Tablets, BP</td>
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<tr>
<td>Paracetamol Oral Suspension, BP</td>
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<td>Paracetamol Tablets, BP</td>
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<tr>
<td>Paracetamol Tablets, Soluble, BP</td>
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<tr>
<td>Pencloclov Cream, DPF</td>
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<tr>
<td>Phenoxybenzylpenicillin Oral Solution, BP</td>
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<tr>
<td>Phenoxybenzylpenicillin Tablets, BP</td>
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<tr>
<td>Promethazine Hydrochloride Tablets, BP</td>
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<tr>
<td>Promethazine Oral Solution, BP</td>
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<tr>
<td>Saliva Stimulating Tablets, DPF</td>
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<tr>
<td>Sodium Chloride Mouthwash, Compound, BP</td>
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<tr>
<td>Sodium Fluoride Mouthwash, BP</td>
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<td>Sodium Fluoride Oral Drops, BP</td>
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<tr>
<td>Sodium Fluoride Tablets, BP</td>
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<tr>
<td>Sodium Fluoride Toothpaste 0.619%, DPF</td>
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<tr>
<td>Sodium Fluoride Toothpaste 1.1%, DPF</td>
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<tr>
<td>Sodium Fusidate Ointment, BP</td>
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<td>Temazepam Oral Solution, BP</td>
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<td>Temazepam Tablets, BP</td>
<td></td>
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<tr>
<td>Tetracycline Tablets, BP</td>
<td></td>
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<tr>
<td>Triamcinolone Dental Paste, BP</td>
<td></td>
</tr>
</tbody>
</table>
Nurse Prescribers’ Formulary

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**

<table>
<thead>
<tr>
<th>Medicinal Preparations</th>
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</thead>
<tbody>
<tr>
<td>Almond Oil Ear Drops, BP</td>
</tr>
<tr>
<td>Arachis Oil Enema, NPF</td>
</tr>
<tr>
<td>Aspirin Tablets, Dispersible, 300 mg, BP</td>
</tr>
<tr>
<td>Bisacodyl Suppositories, BP (includes 5-mg and 10-mg strengths)</td>
</tr>
<tr>
<td>Bisacodyl Tablets, BP</td>
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<tr>
<td>Catheter Maintenance Solution, Chlorhexidine, NPF</td>
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<tr>
<td>Catheter Maintenance Solution, Sodium Chloride, NPF</td>
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<tr>
<td>Catheter Maintenance Solution, ‘Solution G’, NPF</td>
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<tr>
<td>Catheter Maintenance Solution, ‘Solution R’, NPF</td>
</tr>
<tr>
<td>Chlorhexidine Gluconate Alcoholic Solutions containing at least 0.05%</td>
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<tr>
<td>Chlorhexidine Gluconate Aqueous Solutions containing at least 0.05%</td>
</tr>
<tr>
<td>Choline Salicylate Dental Gel, BP</td>
</tr>
<tr>
<td>Chlortrimazole Cream 1%, BP</td>
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<tr>
<td>Co-danthramer Capsules, NPF</td>
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<tr>
<td>Co-danthramer Capsules, Strong, NPF</td>
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<tr>
<td>Co-danthramer Oral Suspension, NPF</td>
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<tr>
<td>Co-danthrusate Capsules, BP</td>
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<tr>
<td>Co-danthrusate Oral Suspension, NPF</td>
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<tr>
<td>Crotamiton Cream, BP</td>
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<tr>
<td>Crotamiton Lotion, BP</td>
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<tr>
<td>Dimeticone barrier creams containing at least 10%</td>
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<tr>
<td>Dimeticone Lotion, NPF</td>
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<tr>
<td>Docusate Capsules, BP</td>
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<tr>
<td>Docusate Enema, NPF</td>
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<tr>
<td>Docusate Oral Solution, BP</td>
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<tr>
<td>Docusate Oral Solution, Paediatric, BP</td>
</tr>
<tr>
<td>Econazole Cream 1%, BP</td>
</tr>
<tr>
<td>Emollients as listed below: Aqueous Cream, BP</td>
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<tr>
<td>Arachis Oil, BP</td>
</tr>
<tr>
<td>Cetraben® Emollient Cream</td>
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<tr>
<td>Decubal® Clinic</td>
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<tr>
<td>Dermamist®</td>
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<tr>
<td>Diprobase® Cream</td>
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<tr>
<td>Diprobase® Ointment</td>
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<tr>
<td>Doublebase®</td>
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<tr>
<td>E45® Cream</td>
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<tr>
<td>Emulsifying Ointment, BP</td>
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<tr>
<td>Epaderm®</td>
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<tr>
<td>Hydromol® Cream</td>
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<tr>
<td>Hydromol® Ointment</td>
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<tr>
<td>Hydrous Ointment, BP</td>
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<tr>
<td>Linola® Gamma Cream</td>
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<tr>
<td>Lipobase®</td>
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<tr>
<td>Liquid and White Soft Paraffin Ointment, NPF</td>
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<tr>
<td>Neutrogena® Dermatological Cream</td>
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<tr>
<td>Oilaum® Cream</td>
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<tr>
<td>Oilaum® Junior Cream</td>
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<tr>
<td>Paraffin, White Soft, BP</td>
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<tr>
<td>Paraffin, Yellow Soft, BP</td>
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<tr>
<td>QV® Cream</td>
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<tr>
<td>QV® Lotion</td>
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<tr>
<td>QV® Wash</td>
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<tr>
<td>Ultrabase®</td>
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<tr>
<td>Unguentum M®</td>
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<tr>
<td>Zerobase® Cream</td>
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<tr>
<td>Emollient Bath Additives as listed below: Alpha Keri® Bath Oil</td>
</tr>
<tr>
<td>Balneum®</td>
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<tr>
<td>Cetraben® Emollient Bath Additive</td>
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<tr>
<td>Dermalo® Bath Emollient</td>
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<tr>
<td>Diproboth®</td>
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<tr>
<td>Doublebase® Emollient Bath Additive</td>
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<tr>
<td>Doublebase® Emollient Shower Gel</td>
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<tr>
<td>Hydromol® Emollient</td>
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<tr>
<td>Imuder® Bath Oil</td>
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<tr>
<td>Oilaum® Emollient</td>
</tr>
<tr>
<td>Oilaum® Junior Emollient Bath Additive</td>
</tr>
<tr>
<td>Oilaum® Gel</td>
</tr>
<tr>
<td>QV® Bath Oil</td>
</tr>
</tbody>
</table>

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)
Folic Acid 400 micrograms/5 mL Oral Solution, NPF
Folic Acid Tablets 400 micrograms, BP
Ibuprofen Oral Suspension, BP
Ibuprofen Tablets, BP
Ispaghula Husk Granules, BP
Ispaghula Husk Granules, Effervescent, BP
Ispaghula Husk Oral Powder, BP
Lactulose Solution, BP
Lidocaine Ointment, BP
Lidocaine and Chlorhexidine Gel, BP
Macrogol Oral Powder, NPF
Macrogol Oral Powder, Compound, NPF
Macrogol Oral Powder, Compound, Half-strength, NPF
Magnesium Hydroxide Mixture, BP
Magnesium Sulphate Paste, BP
Malathion alcoholic lotions containing at least 0.5%
Malathion aqueous lotions containing at least 0.5%
Mebendazole Oral Suspension, NPF
Mebendazole Tablets, NPF
Methylcellulose Tablets, BP
Miconazole Cream 2%, BP
Miconazole Oromucosal Gel, BP
Mouthwash Solution-tablets, NPF
Nicotine Inhalation Cartridge for Oromucosal Use, NPF
Nicotine Lozenge, NPF
Nicotine Medicated Chewing Gum, NPF
Nicotine Nasal Spray, NPF
Nicotine Sublingual Tablets, NPF
Nicotine Transdermal Patches, NPF
Nystatin 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)
Paracetamol Tablets, BP
Paracetamol Tablets, Soluble, BP (includes 120-mg and 500-mg tablets)
Permethrin Cream, NPF
Phenothrin Alcoholic Lotion, NPF
Phenothrin Aqueous Lotion, NPF
Phosphates Enema, BP
Phosphate suppositories, NPF
Piperazine and Senna Powder, NPF
Povidone—Iodine Solution, BP
Senna Granules, Standardised, BP
Senna Oral Solution, NPF
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 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 I XA 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)

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 BNF).

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.

Up-to-date information and guidance on nurse independent prescribing is available on the Department of Health website at www.dh.gov.uk/nonmedicalprescribing
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. 927.

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.
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Special-order Manufacturers

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 all medicines manufactured in the NHS; access is restricted to NHS pharmacy staff. The characteristics of unlicensed formulations may vary, see also Unlicensed Medicines (p. 7) and Extemporaneous Preparations (p. 8).

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.

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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 BNFC (page 21) 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>
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**Age (at time of reaction):**

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<th>Identification (Your Practice / Hospital Ref.)*:</th>
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**SUSPECTED DRUG(S)**

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<th>Give brand name of drug and batch number if known</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
<th>Date stopped</th>
<th>Prescribed for</th>
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**SUSPECTED REACTION(S)**

Please describe the reaction(s) and any treatment given:

Date reaction(s) started: ____________________ Date reaction(s) stopped: ____________________

Do you consider the reaction to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

- Patient died due to reaction
- Life threatening
- Congenital abnormality
- Involved or prolonged inpatient hospitalisation
- Involved persistent or significant disability or incapacity
- Medically significant; please give details:

---

* 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>
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<tr>
<th>Drug (Brand, if known)</th>
<th>Route</th>
<th>Dosage</th>
<th>Date started</th>
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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: ____________________________

__________________________  Tel No: ________________________
Post code: ________________  Speciality: __________________
Speciality: __________________ Speciality: __________________
Signature: ________________  Date: ________________________

Send to Medicines and Healthcare products Regulatory Agency, CHM FREEPOST, LONDON SW8 5BR
NEWBORN LIFE SUPPORT

**BIRTH**

Term gestation? Amniotic fluid clear? Breathing or crying? Good muscle tone?

Yes

Term gestation? Amniotic fluid clear? Breathing or crying? Good muscle tone?

No

Provide warmth Position; clear airway if necessary* Dry, stimulate, reposition

Evaluate breathing, heart rate, colour† and tone

Apnoeic or HR <100 min⁻¹

Give positive pressure ventilation†*

HR <60 min⁻¹

Ensure effective lung inflation,†† then add chest compression

HR <60 min⁻¹

Consider adrenaline etc.

**ROUTINE CARE**

Provide warmth Dry Clear airway if necessary Assess colour†

---

*Tracheal intubation may be considered at several steps Consider supplemental oxygen at any stage if cyanosis persists

---

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STILL UNRESPONSIVE?
(no signs of a circulation)

15 chest compressions
2 rescue breaths

After 1 minute call resuscitation team then continue CPR

NOT BREATHING NORMALLY?

5 rescue breaths

UNRESPONSIVE?

Shout for help

Open airway

PAEDIATRIC BASIC LIFE SUPPORT
(Healthcare professionals with a duty to respond)
Unresponsive?

Commence BLS
Oxygenate/ventilate

Call Resuscitation Team

CPR 15:2
Until defibrillator/monitor attached

Immediately resume CPR 15:2 for 2 min

Assess rhythm

Shockable (VF/pulseless VT)
Non-shockable (PEA/Asystole)

1 Shock 4 J/kg or AED
(attenuated as appropriate)

During CPR
- Correct reversible causes*
- Check electrode position and contact
- Attempt/verify: IV/IO access, airway and oxygen
- Give uninterrupted compressions when trachea intubated
- Give adrenaline every 3-5 min
  - Consider: amiodarone, atropine, magnesium

Immediately resume CPR 15:2 for 2 min

*Reversible causes
- Hypoxia
- Hypovolaemia
- Hypo/hyperkalaemia/metabolic
- Hypothermia
- Tension pneumothorax
- Tamponade, cardiac
- Toxins
- Thromboembolism

Hypoxia
Hypovolaemia
Hypo/hyperkalaemia/metabolic
Hypothermia

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**BODY SURFACE AREA IN CHILDREN**

Body-weight under 40kg

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<thead>
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<th>Surface area (m²)</th>
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Values are calculated using the Boyd equation

*Note*  Height is not required to estimate body surface area using these tables

**BODY SURFACE AREA IN CHILDREN**

**Body-weight over 40kg**

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<thead>
<tr>
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<th>Surface area (m²)</th>
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Values are calculated using the Boyd equation

**Note** Height is not required to estimate body surface area using these tables

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 child’s condition requires investigation and further treatment, the child 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; 300 micrograms (0.3 mL) should be given if child is small or prepubertal

Chlorphenamine injection 10 mg/mL

- By intravenous injection over 1 minute or by intramuscular injection
  Child under 6 months 250 micrograms/kg (max. 2.5 mg), repeated if required up to 4 times in 24 hours
  Child 6 months–6 years 2.5 mg, repeated if required up to 4 times in 24 hours
  Child 6–12 years 5 mg, repeated if required up to 4 times in 24 hours
  Child 12–18 years 10 mg, repeated if required up to 4 times in 24 hours

High-flow oxygen (section 3.6) and intravenous fluids should be given if required.

Hydrocortisone (preferably as sodium succinate) by intravenous injection (section 6.3.2) has delayed action but it should be given to severely affected children to prevent further deterioration.

Asthma: acute

(section 3.1)

Regard each emergency consultation as being for severe acute 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 a close-fitting face mask if child under 3 years)
  Child under 18 years 4–10 puffs each inhaled separately, repeated at 10–20 minute intervals or as necessary

or salbutamol nebuliser solution 1 mg/mL, 2 mg/mL

- By inhalation of nebulised solution (via oxygen-driven nebuliser if available)
  Child under 5 years 2.5 mg every 10–20 minutes or as necessary
  Child 5–12 years 2.5–5 mg every 10–20 minutes or as necessary
  Child 12–18 years 5 mg every 10–20 minutes or as necessary

or terbutaline nebulised solution 2.5 mg/mL

- By inhalation of nebulised solution (via oxygen-driven nebuliser if available)
  Child under 5 years 5 mg every 10–20 minutes or as necessary
  Child 5–12 years 5–10 mg every 10–20 minutes or as necessary
  Child 12–18 years 10 mg every 10–20 minutes or as necessary

If response to beta₂ agonist is poor (while awaiting transfer to hospital) ipratropium nebuliser solution 250 micrograms/mL

- By inhalation of nebulised solution (via oxygen-driven nebuliser if available)
  Child under 12 years 250 micrograms every 20–30 minutes if necessary
  Child 12–18 years 500 micrograms every 20–30 minutes if necessary

Plus (in all cases)

Either prednisolone soluble tablets 5 mg

- By mouth
  Child under 12 years 1–2 mg/kg (max. 40 mg) daily for 3–5 days; if the child is already taking oral corticosteroids, give prednisolone 2 mg/kg (max. 60 mg)
  Child 12–18 years 40–50 mg daily for at least 5 days

or hydrocortisone (preferably as sodium succinate)

- By intravenous injection
  Child under 2 years 4 mg/kg (max. 25 mg)
  3–4 times daily, until conversion to oral prednisolone is possible
  Child 2–5 years 4 mg/kg (max. 50 mg) 3–4 times daily, until conversion to oral prednisolone is possible
  Child 5–18 years 4 mg/kg (max. 100 mg) 3–4 times daily, until conversion to oral prednisolone is possible

High-flow oxygen (section 3.6) should be given if available

Croup

(section 3.1)

Dexamethasone oral solution 2 mg/5mL

- By mouth
  Child 1 month–2 years 150 micrograms/kg as a single dose
Convulsions
(section 4.8.2)

Either midazolam buccal solution 10 mg/mL or injection solution given by buccal route
- By buccal administration, repeated once after 10 minutes if necessary
  - Neonate: 300 micrograms/kg
  - Child 1–6 months: 300 micrograms/kg (max. 2.5 mg)
  - Child 6 months–1 year: 2.5 mg
  - Child 1–5 years: 5 mg
  - Child 5–10 years: 7.5 mg
  - Child 10–18 years: 10 mg

or diazepam rectal solution 2 mg/mL, 4 mg/mL
- By rectum, repeated once after 10 minutes if necessary
  - Neonate: 1.25–2.5 mg
  - Child 1 month–2 years: 5 mg
  - Child 2–12 years: 5–10 mg
  - Child 12–18 years: 10 mg

Meningococcal disease
(Table 1, section 5.1)

Benzylicpenicillin 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

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

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

Note: Give single dose and transfer urgently to hospital

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

or if allergic to penicillin or atypical organism suspected

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: 500 mg 4 times daily

Prescribing for children
Weight, height, and gender

The table below shows the mean values for weight, height and gender by age; these values have been derived from the UK-WHO growth charts 2009 and UK1990 standard centile charts, by extrapolating the 50th centile, and may be used to calculate doses in the absence of actual measurements. However, the child's

Diabetic hypoglycaemia
(section 6.1.4)

Glucose or sucrose
- By mouth
  - Child 2–18 years: approx. 10–20 g (2–4 teaspoonsfuls of sugar or 3–6 sugar lumps or 55–110 mL Lucozade® Energy Original or 100–200 mL Coca-Cola®—both non-diet versions or Glucogel® 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)

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)
actual weight and height might vary considerably from the values in the table and it is important to see the child to ensure that the value chosen is appropriate. In most cases the child’s actual measurement should be obtained as soon as possible and the dose re-calculated.

<table>
<thead>
<tr>
<th>Age</th>
<th>Weight kg</th>
<th>Height cm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full term neonate</td>
<td>3.5</td>
<td>51</td>
</tr>
<tr>
<td>1 month</td>
<td>4.3</td>
<td>55</td>
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<tr>
<td>2 months</td>
<td>5.4</td>
<td>58</td>
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<tr>
<td>3 months</td>
<td>6.1</td>
<td>61</td>
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<td>4 months</td>
<td>6.7</td>
<td>63</td>
</tr>
<tr>
<td>6 months</td>
<td>7.6</td>
<td>67</td>
</tr>
<tr>
<td>1 year</td>
<td>9</td>
<td>75</td>
</tr>
<tr>
<td>3 years</td>
<td>14</td>
<td>96</td>
</tr>
<tr>
<td>5 years</td>
<td>18</td>
<td>109</td>
</tr>
<tr>
<td>7 years</td>
<td>23</td>
<td>122</td>
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<tr>
<td>10 years</td>
<td>32</td>
<td>138</td>
</tr>
<tr>
<td>12 years</td>
<td>39</td>
<td>149</td>
</tr>
<tr>
<td>14 year-old boy</td>
<td>49</td>
<td>163</td>
</tr>
<tr>
<td>14 year-old girl</td>
<td>50</td>
<td>159</td>
</tr>
<tr>
<td>Adult male</td>
<td>68</td>
<td>176</td>
</tr>
<tr>
<td>Adult female</td>
<td>58</td>
<td>164</td>
</tr>
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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>
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<tr>
<td>1</td>
<td>0.45</td>
<td>1</td>
<td>6.35</td>
<td>50</td>
<td>1.8</td>
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<tr>
<td>2</td>
<td>0.91</td>
<td>2</td>
<td>12.70</td>
<td>100</td>
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<td>3</td>
<td>1.36</td>
<td>3</td>
<td>19.05</td>
<td>150</td>
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<tr>
<td>4</td>
<td>1.81</td>
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<td>200</td>
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<tr>
<td>5</td>
<td>2.27</td>
<td>5</td>
<td>31.75</td>
<td>500</td>
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<tr>
<td>6</td>
<td>2.72</td>
<td>6</td>
<td>38.10</td>
<td>1000</td>
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<tr>
<td>7</td>
<td>3.18</td>
<td>7</td>
<td>44.45</td>
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<tr>
<td>8</td>
<td>3.63</td>
<td>8</td>
<td>50.80</td>
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<tr>
<td>9</td>
<td>4.08</td>
<td>9</td>
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<td>10</td>
<td>4.54</td>
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<td>11</td>
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<td>69.85</td>
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<td>12</td>
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<tr>
<td>13</td>
<td>5.90</td>
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<td>15</td>
<td>6.81</td>
<td>15</td>
<td>95.25</td>
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</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) = 4.186 megajoules (MJ)
- 1 megajoule (MJ) = 238.8 kilocalories (kcal)
- 1 millimetre of mercury = 133.3 pascals (Pa)
- (mmHg)
- 1 kilopascal (kPa) = 7.5 mmHg (pressure)

Plasma-drug concentrations in BNF for Children 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.

Recommended wording of cautionary and advisory labels
For details see Appendix 3

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
20 ... with or after food
21 ... half to one hour before food
22 ... an hour before food or on an empty stomach
23 ... sucked or chewed
24 ... swallowed whole, not chewed
25 ... dissolved under the tongue
26 ... with plenty of water
27 To be spread thinly ...
28 Do not take more than 2 at any one time. Do not take more than 8 in 24 hours
29 Do not take with any other paracetamol products
30 Contains aspirin and paracetamol. Do not take with any other paracetamol products
31 Contains aspirin
32 Contains an aspirin-like medicine
Abbreviations and symbols

Internationally recognised units and symbols are used in the BNF for Children where possible.

ACBS Advisory Committee on Borderline Substances, see Appendix 2
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
CAPD Continuous ambulatory peritoneal dialysis
CHM Commission on Human Medicines
CHMP Committee for Medicinal Products for Human Use
CNS central nervous system
CPMP Committee on Proprietary Medicinal Products
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 inhibitors
max. maximum
m/r modified-release
NCL no cautionary labels, see Appendix 3
NHS National Health Service
not prescribable under National Health Service (NHS)
NICE National Institute for Health and Clinical Excellence
NPF Nurse Prescribers’ Formulary
NSAID non-steroidal anti-inflammatory drug
PGD patient group direction
trade mark
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 inhibitors
UK United Kingdom
Units for SI units see Prescription Writing
USP United States Pharmacopeia 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>
<th>Metabisulphite</th>
</tr>
</thead>
<tbody>
<tr>
<td>E104</td>
<td>Quinoline Yellow</td>
<td>E320</td>
<td>Butylated</td>
<td>Hydroxyanisole</td>
</tr>
<tr>
<td>E110</td>
<td>Sunset Yellow FCF</td>
<td>E123</td>
<td>Amaranth</td>
<td>Hydroxytyocele</td>
</tr>
<tr>
<td>E124</td>
<td>Ponceau 4R</td>
<td>E321</td>
<td>Butylated</td>
<td>Lecithins</td>
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<td>Erythrosine BS</td>
<td>E132</td>
<td>Indigo Carmine</td>
<td>Lecithins</td>
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<td>E420</td>
<td>Sorbitol</td>
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<td>E171</td>
<td>Titanium Dioxide</td>
<td>E421</td>
<td>Mannitol</td>
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<tr>
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<td>Glycerol</td>
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<td>E200</td>
<td>Sorbic Acid</td>
<td>E901</td>
<td>Beeswax</td>
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<tr>
<td>E211</td>
<td>Sodium Benzoate</td>
<td>E1520</td>
<td>Propylene Glycol</td>
<td>(white and yellow)</td>
</tr>
</tbody>
</table>