WHO Model Formulary for Children

Based on the
Second Model List of
Essential Medicines for
Children 2009

make medicines child size

2010

World Health Organization

WHO Library Cataloguing-in-Publication Data:

WHO model formulary for children 2010.

Based on the second model list of essential medicines for children 2009.

1.Essential drugs. 2.Formularies. 3.Pharmaceutical preparations. 4.Child. 5.Drug utilization. I.World Health Organization.

ISBN 978 92 4 159932 0 (NLM classification: QV 55)

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SELECTED WHO PUBLICATIONS OF RELATED INTEREST

The selection and use of essential medicines.

Report of the WHO Expert Committee
(including the WHO Model List of Essential Medicines and the 2nd WHO Model List of Essential Medicines for Children)
WHO Technical Report Series, No. 958, 2010 (in print)

Pocket book of hospital care for children.

2005 (378 pages)

The international pharmacopoeia, fourth edition.

Volume 1: general notices; monographs for pharmaceutical substances (A–O)
Volume 2: monographs for pharmaceutical substances (P–Z); monographs for dosage forms and radiopharmaceutical preparations; methods of analysis; reagents.
2006 (1500 pages), also available in CD-ROM version

Basic tests for drugs: pharmaceutical substances, medicinal plant materials and dosage forms.

1998 (94 pages)

Quality assurance of pharmaceuticals: a compendium of guidelines and related materials.

Volume 1: 1997 (244 pages)
Volume 2: Good manufacturing practices and inspection.
2nd updated edition, 2007 (in print)

WHO Expert Committee on Specifications for Pharmaceutical Preparations.

Forty-third report.
WHO Technical Report Series, No. 953, 2009 (172 pages)

International nonproprietary names (INN) for pharmaceutical substances.

Cumulative List no. 13
2010 (available in CD-ROM format only)

Further information on these and other WHO publications can be obtained from
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e-mail: bookorders@who.int; order on line: http://www.who.int/bookorders)

Contents

Abbreviations

ACE	angiotensin-converting enzyme
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
APTT	activated partial thromboplastin time
ART	antiretroviral
ATC	anatomical therapeutic chemical
AUC	area under the curve
AV	atrioventricular
BCG	Bacillus Calmette–Guérin (vaccine)
BNFC	British National Formulary for Children
BP	British Pharmacopoeia
BSA	body surface area
CNS	central nervous system
CrCl	creatinine clearance
CSF	cerebrospinal fluid
ECG	electrocardiogram
EEG	electroencephalogram
EMLc	Essential Medicines List for Children
G6PD	glucose 6-phosphate dehydrogenase
GFR	glomerular filtration rate
GI	gastrointestinal
GORD	gastro-oesophageal reflux disease
GVHD	graft-versus-host disease
HIV	human immunodeficiency virus
Ht	height
IM	intramuscular
INR	international normalized ratio
IV	intravenous
MB	multibacillary leprosy
MDI	metered dose inhaler
MDR-TB	multidrug-resistant tuberculosis
MMR	measles, mumps, rubella
MRI	magnetic resonance imaging
MSSA	methicillin-sensitive *Staphylococcus aureus*
MTCT	mother-to-child transmission
NSAIM	non-steroidal anti-inflammatory medicine
ORS	oral rehydration solution
PB	paucibacillary leprosy
PCP	*Pneumocystis carinii (Pneumocystis jiroveci)* pneumonia
PDA	patent ductus arteriosus
PR	per rectum
PTB	pulmonary tuberculosis
PVC	polyvinyl chloride
SC	subcutaneous
SIADH	syndrome of inappropriate antidiuretic hormone secretion
spp.	species
SSRI	selective serotonin reuptake inhibitor
TB	tuberculosis
TSH	thyroid stimulating hormone
USP	United States Pharmacopeia
WHO	World Health Organization
Wt	weight

Introduction

In 2007, the World Health Assembly passed a Resolution titled 'Better Medicines for Children'. This resolution recognized the need for research and development into medicines for children, including better dosage forms, better evidence and better information about how to ensure that medicines for treating the common childhood diseases are given at the right dose for children of all ages. The World Health Organization has therefore developed a program of work on medicines for children, including the development of a Model List of Essential Medicines for children (EMLc). As an extra resource for health-care workers and national programmes that supply medicines for children, this new edition of the WHO Model Formulary has been prepared, based on the 2nd edition of the EMLc, to provide prescribers with the best information about how to use the medicines included on the List.

In developing the WHO Model Formulary for Children, the editors have based decisions on treatment regimens on the best available evidence from clinical studies in children, that have been assessed and evaluated by the WHO Expert Committee on Selection and Use of Essential Medicines. However, as has been found by all authorities in relation to medicines for children, in many cases the recommendations on dose and duration of treatment in children have to be extrapolated from studies in adults and adjusted based on our understanding of the effect of age and development on the absorption, distribution and metabolism and excretion of different medicines in children of different ages. One of the aims of this publication is therefore not only to describe what is known about treatments, but to highlight where more research is needed.

An electronic version of the WHO Formulary for Children is also available, intended as a starting point for developing institutional or national formularies. The text of the Formulary can be used by groups who wish to develop their own version, by adapting the text or by adding or deleting entries to align the formulary to their own list of essential medicines.

This edition of the WHO Model Formulary is fully compatible with the 2nd List of Essential Medicines for Children, as recommended by the WHO Expert Committee on the Selection and Use of Essential Medicines in March 2009. Comments and suggestions are welcome and should be sent to:

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Factors influencing paediatric drug therapy

Medicines in children

> It was once said that the moral test of government is how that government treats those who are in the dawn of life, the children; those who are in the twilight of life, the elderly; and those who are in the shadows of life—the sick, the needy and the handicapped.[1]

Children are among the most vulnerable individuals in any society. Nowhere is this more true than in their access to appropriate health care. As part of the treatment of children, health-care workers need access to drug dosage information. This formulary aims to provide that information universally, to assist in the management of children.

The use of medicines in infants and children presents a unique set of challenges to the prescriber. Physiological variances between children and adults, including the ontogeny of organ maturity and body composition, significantly influence the actions, effectiveness and safety of medicines. However, most pharmacokinetic and pharmacodynamic studies provide little, if any, information on drug action in infants and children, because they are usually conducted in adults.

Paediatric pharmacology developed initially from the extrapolation of therapeutic practice and experience in adults and the use of "scaled down" adult doses. This practice is clinically successful for the majority of drugs which are relatively non-toxic and have a wide margin between therapeutic and toxic doses. Drugs with a narrow therapeutic margin, such as the aminoglycoside antibiotics and digoxin, require more sophisticated knowledge and individualized dosage regimens. Doses of such agents are scaled by weight or allometrically ($wt^{3/4}$), then modified according to the results of serum drug concentration measurements, if these are available. Over the last two decades, there has been an increased recognition of the necessity to perform studies specifically in children and adolescents. Major national and international approaches, such as those of the European Union and the United States, have resulted in some new information to improve the use of medicines in children.

This formulary is the result of the establishment of the *WHO Model List of Essential Medicines for Children* (EMLc). The list can be accessed at http://www.who.int/selection_medicines/en/.

Absorption

Oral absorption

The gastrointestinal tract, particularly the stomach, undergoes significant changes from birth until around 3 years of age. Before then, the stomach has low levels of acid, and acid-labile drugs, such as the penicillins, show enhanced absorption. On the other hand, this depressed level of acidity may result in reduced absorption of weak acids such as phenobarbitone, phenytoin and rifampicin. The incomplete absorption experienced with these anticonvulsants may necessitate their continued parenteral administration.

The delayed gastric emptying seen in neonates and young infants is probably not as important as previously believed. In the first few weeks of life this may be significant, but most sick neonates receive their drugs parenterally.

Of considerable importance, particularly to the general public, is the question of drug administration and absorption relative to meals. Current evidence suggests that, with the exception of isoniazid, captopril, rifampicin, phenoxymethylpenicillin and tetracyclines (except doxycycline and minocycline), all medications should be administered with meals to avoid gastrointestinal irritation and to aid compliance.

Topical absorption

Topical absorption of drugs is enhanced in children and especially in infants. This is a direct result of the relative thinness of the stratum corneum. Absorption may be further enhanced in the presence of burnt or excoriated areas and with occlusive dressings. This has been well documented with the use of corticosteroid creams for eczema and nappy rash in infants, especially when the area treated has been occluded with plastic pants.

Rectal absorption

Rectal administration may be useful in patients who are vomiting and in infants and young children who are reluctant to take oral medication.

The rectal route is not ideal for all drugs. Considerable individual variation in rectal venous drainage, and hence in the extent of drug absorption, can produce either sub-therapeutic or toxic drug levels. Drugs with narrow therapeutic margins should not be administered rectally. One drug which is recommended for rectal administration in children is diazepam for the treatment of seizures. Paracetamol may also be administered rectally; however, the absorption may be erratic and therapeutic levels cannot be guaranteed.

Distribution

Numerous factors, including body composition, plasma–protein binding and the blood–brain barrier influence drug distribution in the various paediatric age groups.

Body composition

Total body water and fat composition alter significantly during the transition from birth to adult life. Total body water as a percentage of body weight is approximately 80% at birth, 65% at 12 months and 60% for a young adult male.

On the other hand, fat content as a percentage of body weight varies with age, being about 3% in premature infants, 12% in full-term neonates, 30% at 1 year of age and about 18% in the average adult.

Therefore, larger mg/kg body weight doses of water-soluble drugs need to be given to neonates and infants to achieve plasma concentrations similar to those seen in adults. However, this has to be balanced against diminished hepatic function and renal elimination before arriving at a final dosage recommendation.

Plasma protein binding

Drug–protein binding is diminished in neonates due to a lower concentration of plasma proteins, particularly albumin, and the lower drug-binding capacity of fetal albumin. This may lead to an increase in the fraction of unbound, pharmacologically active drug in the plasma. There may also be competition between endogenous substances, especially free fatty acids and bilirubin, and drugs for albumin-binding sites.

However, when drugs administered to neonates are examined in detail, very few highly protein-bound drugs are used. From a practical point of view, highly protein-bound drugs such as phenytoin, sulfonamides, salicylates and diazepam should be given with caution in the presence of hyperbilirubinaemia.

In older children, there are several disease states which may affect drug–protein binding, including hepatic disease, nephrotic syndrome, chronic renal failure, cardiac failure and malnutrition.

Blood–brain barrier

The blood–brain barrier is a permeability barrier between the circulation and the brain cells bathed in cerebrospinal fluid (CSF). The blood–brain barrier is functionally incomplete in the neonate, and certain substances show increased penetration into the brain. One of the most important factors which determine the rate of transport of drugs across the blood–brain barrier is their lipid solubility. This gives rise to increased brain uptake of barbiturates and morphine in infants.

As meningitis is a relatively common problem in paediatric practice, the extent to which antimicrobial agents penetrate the CSF is an important consideration. Although some agents penetrate poorly under normal circumstances, in the presence of meningeal inflammation, penetration may be considerably enhanced, so that adequate CSF drug concentrations are attained. Drugs in this category include penicillins, cefalosporins, rifampicin and vancomycin. Drugs which penetrate well even in the absence of meningeal inflammation include chloramphenicol and the combination sulfamethoxazole and trimethoprim.

Although the aminoglycosides continue to be used for meningitis caused by Gram-negative organisms, the CSF concentrations achieved are generally low and inconsistent. Higher concentrations can be obtained by direct intrathecal or intraventricular injections, but controversy exists over the efficacy of such routes of administration. The newer cefalosporins, such as cefotaxime, appear to be more appropriate agents in most cases.

Metabolism

The various metabolic reactions that occur in the mature liver are not fully developed at birth. Cardiac insufficiency and respiratory distress may also contribute to decreased metabolic activity. Lidocaine, phenobarbital, phenytoin and diazepam show decreased metabolism in the neonate, resulting in increased drug half-lives.

During the first 15 days of life in premature and full-term babies, decreased metabolism is evident, but this is followed by a dramatic increase. Between 1 and 10 years of age, hepatic microsomal

oxidation is more rapid than in adults. Therefore phenobarbital, phenytoin and theophylline have shorter half-lives in children than in adults. This more rapid metabolism is almost certainly due to the fact that, during childhood, the liver is larger relative to body weight than in adult life. Allometric scaling may give a better prediction of the metabolic activity of the liver.

Excretion

Renal function is significantly less developed in premature and full-term neonates than it is in children and adults. Adult values for glomerular filtration rate are reached after about 3 to 6 months of age, while tubular function does not mature fully until after this.

Renal function is of particular importance to drug disposition in the neonatal period. Most sick neonates receive antibiotics for suspected or proven infection, and most of these agents are water soluble. In general, the lower the gestational age of the infant, the more prolonged the half-life will be in this period. The rate of elimination increases rapidly during the ensuing weeks, so that half-lives similar to those seen in adults are usually achieved by the end of the first month.

The *WHO Model Formulary for Children*

The hope is that this Formulary improves therapies in children by offering the best dosing information for those medicines currently listed on the EMLc. The Formulary is not, however, a substitute for the appropriate use of treatment guidelines, and should be used in conjunction with guidelines such as the *WHO Pocket Book of Hospital Care for Children.*

1. Humphrey, Hubert H. Speech at the dedication of the Hubert H Humphrey building, Washington, DC, 4 November 1977. http://www.vernalproject.org/IcDQuotes/IcDQuoteA.shtml (accessed 30 March 2008).

How to use the WHO Model Formulary for Children

Medication monographs are listed by section according to the WHO Model List of Essential Medicines for Children March 2009. Omission of a particular medication does not necessarily indicate that it is not available or recommended in children; merely that it is not considered an essential medicine for children by WHO. Medicines and dosage forms are listed in alphabetical order within each section and there is no implication of preference for one form over another. Standard treatment guidelines should be consulted for information on appropriate dosage forms.

The WHO Model Formulary for Children classifies children by age and doses medicines accordingly, most often in mg/kg. The Formulary is intended for use for children up to 12 years of age.

Definition of age ranges

Neonate: 0–28 days
Infant 1–12 months
Child 1–12 years

If a maximum dose is listed this provides an indication of the upper dose limit when dosing paediatrics per kilogram.

Allowances must be made when using weight as a basis for dosing in oedematous or obese children. In such children the ideal weight for height and age should be used. In many cases, progressive dose adjustments may be required according to the patient's response.

Doses based on surface area are quoted for some drugs. Surface area is calculated by the following equation:

Body surface area

$$(m^2) = \sqrt{\frac{Ht\ (cm) \times Wt\ (kg)}{3600}}$$

Mosteller RD. Simplified calculation of body surface area.
New England Journal of Medicine, 1987, 317(17):1098 (letter).

Explanatory notes for drug monographs:

Section and section number

This indicates the section and any subsection that the medicine is classified under as per the WHO Model List of Essential Medicines for Children March 2009. A single medication may appear multiple times on the list in different sections for differing indications.

Drug Name

The generic (non-proprietary) name.

Dose Forms

The dose form is listed as per the WHO Model List of Essential Medicines for Children March 2009. Some countries may have access to preparations which differ in terms of concentration or dose form. When a medicine is in solution or a mixture the concentration in the medication monograph is expressed as mg/ml to avoid confusion, this may differ from the WHO Model List of Essential Medicines for Children March 2009.

ATC Code
The Anatomical Therapeutic Chemical (ATC) classification system code designated by WHO to classify drugs.

Special Notes
Indicate if the medicine is also known by another name, different spelling or abbreviation.
Also, notes if there is a WHO age/weight restriction or representative status.

Warnings
Where there is a significant warning, risk or adverse effect associated with using the medication.

Indications
Indications for use from the WHO Model List of Essential Medicines for Children March 2009.

Contraindications
Details of any contraindications to use of the drug.

Precautions
Details of any precautions or monitoring required.

Dose
Indication.
Route:
Age dose and frequency.
Alternative route:
Age dose and frequency.

Renal impairment
Advice for use of this drug in these circumstances.
Renal impairment is usually divided into three grades:

Mild: GFR 20–50 ml/minute or approximate serum creatinine 150–300 micromol/litre
Moderate: GFR 10–20 ml/minute or serum creatinine 300–700 micromol/litre
Severe: GFR < 10 ml/minute or serum creatinine > 700 micromol/litre

Consult specialist texts for further information on use of drugs in renal impairment.

Hepatic Impairment
Advice for use of this drug in these circumstances.

Consult specialist texts for further information on use of drugs in hepatic impairment.

Adverse effects
Details of adverse effects associated with this medication.

Adverse effects have been classified by incidence where possible:
Common: > 1% (> 1 in 100 people)
Uncommon: 0.1%–1% (> 1 in 1,000 people and < 1 in 100 people)
Rare: < 0.1% (< 1 in 1,000 people)

Interactions with other medications

Details any drug interactions. Potentially hazardous drug interactions are indicated by the symbol * meaning the combined administration of the drugs involved should be avoided, or only taken with caution and appropriate monitoring. Interactions with no symbol do not usually have serious consequences.

Notes

Includes ancillary information where applicable such as administration instructions, patient advice and storage instructions.

References

Includes a list of references used to compile this drug monograph. Consult individual references for more information.

The presence of an entry on the Essential Medicines List and/or WHO Children's Formulary carries no assurance as to pharmaceutical quality. It is the responsibility of the relevant national or regional drug regulatory authority to ensure that each product is of appropriate pharmaceutical quality (including stability) and that when relevant, different products are interchangeable.

For recommendations and advice concerning all aspects of the quality assurance of medicines see the WHO Medicines web site http://www.who.int/medicines/areas/quality_assurance/en/index.html

Changes to the WHO Model List of Essential Medicines for Children

Changes made to the 1st List (October 2007) to produce the 2nd List (March 2009) are listed below.

Changes to the List

Additions

Section 4.2	Acetylcysteine, oral liquid: 10% and 20%.
Section 5	Lorazepam, parenteral formulation: 2 mg/ml in 1 ml ampoule; 4 mg/ml in 1 ml ampoule.
Section 6.2.1	Cefalexin, powder for reconstitution with water: 125 mg/5 ml; 250 mg/5 ml and solid oral dosage form: 250 mg. Cefotaxime, powder for injection: 250 mg per vial. Ceftazidime, powder for injection: 1 g (as pentahydrate) in vial.
Section 6.2.2	Ciprofloxacin, oral liquid: 250 mg/5 ml and solution for IV infusion: 2 mg/ml. Doxycycline, oral liquid: 25 mg/5 ml and 50 mg/5 ml.
Section 6.2.4	Amikacin, powder for injection: 100 mg; 500 mg in vial.
Section 6.4.2.3	Atazanavir, solid oral dosage form: 100 mg; 150 mg; 300 mg. Lopinavir + ritonavir (LPV/r), tablet (heat stable): 100 mg + 25 mg ; 200 mg + 50 mg. Ritonavir, tablet (heat stable): 25 mg; 100 mg. Lamivudine + nevirapine + stavudine, tablet (dispersible): 30 mg + 50 mg + 6 mg; 60 mg + 100 mg + 12 mg. Lamivudine + nevirapine + zidovudine, tablet: 30 mg + 50 mg + 60 mg. Lamivudine + zidovudine, tablet: 30 mg + 60 mg.
Section 6.5.3.1	Artemether + lumefantrine, tablet (dispersible): 20 mg + 120 mg.
Section 6.5.4	Sulfadiazine, tablet: 500 mg.
Section 8.2	Carboplatin, injection: 50 mg/5 ml; 150 mg/15 ml; 450 mg/45 ml; 600 mg/60 ml.
Section 8.4	Amitriptyline, tablet: 10 mg; 25 mg. Cyclizine, injection: 50 mg/ml and tablet: 50 mg. Dexamethasone, injection: 4 mg/ml and tablet: 2 mg. Diazepam, injection: 5 mg/ml and oral liquid: 2 mg/5 ml and rectal solution: 2.5 mg; 5 mg; 10 mg and tablet: 5 mg; 10 mg. Docusate sodium, capsule: 100 mg and oral liquid: 50 mg/5 ml. Hyoscine hydrobromide, injection: 400 micrograms/ml; 600 micrograms/ml and transdermal patches: 1 mg/72 hours. Ibuprofen, oral liquid: 100 mg/5 ml and tablet: 200 mg; 400 mg and 600 mg. Midazolam, injection: 1 mg/ml and 5 mg/ml. Morphine, granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg and injection: 10 mg/ml and oral liquid: 10 mg/5 ml and tablet (controlled release): 10 mg; 30 mg; 60 mg and tablet (immediate release): 10 mg. Senna, oral liquid: 7.5 mg/5 ml.

Section 12.3	Enalapril, tablet: 2.5 mg; 5 mg.
Section 15.1	Chlorhexidine, solution: 20% (digluconate).
Section 17	Pancreatic enzymes, age-appropriate formulations and doses including lipase, protease and amylase.
Section 17.1	Omeprazole, powder for oral liquid: 20 mg; 40 mg sachets and solid oral dosage form: 10 mg; 20 mg; 40 mg.
Section 17.2	Dexamethasone, injection: 4 mg/ml in 1 ml ampoule and oral liquid: 0.5 mg/5 ml; 2 mg/5 ml and solid oral dosage form: 0.5 mg; 0.75 mg; 1.5 mg; 4 mg. Ondansetron, injection: 2 mg base/ml in 2 ml ampoule (as hydrochloride) and oral liquid: 4 mg base/5 ml and solid oral dosage form: Eq 4 mg base; Eq 8 mg base.
Section 18.1	Fludrocortisone, tablet: 100 micrograms. Hydrocortisone, tablet: 5 mg; 10 mg; 20 mg.
Section 28	**Ear, nose and throat conditions in children (new section):** Acetic acid, topical: 2%, in alcohol. Budesonide, nasal spray: 100 micrograms per dose. Ciprofloxacin, topical: 0.3% drops. Xylometazoline, nasal spray: 0.05%.
Section 29	**Specific medicines for neonatal care (new section):** Caffeine citrate, injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml) and oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml). Surfactant, suspension for intratracheal instillation: 25 mg/ml or 80 mg/ml. Prostaglandin E, solution for injection: Prostaglandin E: 0.5 mg/ml in alcohol and Prostaglandin E2: 1 mg/ml. Ibuprofen, solution for injection: 5 mg/ml.

Amendments to dosage strength and form

Section 5	Diazepam, injection: 5 mg/ml in 2 ml ampoule (intravenous or rectal) changed to rectal solution or gel: 5 mg/ml in 0.5 ml; 2 ml and 4 ml tubes.
Section 10.2	Heparin sodium, injection: 1000 IU/ml; 5000 IU/ml; 20 000 IU/ml in 1 ml ampoule changed to injection: 1000 IU/ml; 5000 IU/ml in 1 ml ampoule.
Section 16	Spironolactone, oral liquid: 1 to 20 mg/ml and tablet: 25 mg changed to oral liquid: 5 mg/5 ml; 10 mg/5 ml; 25 mg/5 ml and tablet: 25 mg.
Section 25.1	Budesonide, 50 micrograms per dose (dipropionate); 250 micrograms (dipropionate) per dose changed to inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose.
Section 26.2	Potassium chloride, solution: 11.2% in 20 ml ampoule changed to solution for dilution: 7.5% (equivalent to K^+ 1 mmol/ml and Cl^- 1 mmol/ml); 15% (equivalent to K^+ 2 mmol/ml and Cl^- 2 mmol/ml).

Deletions

Section 6.2.2	Erythromycin, powder for injection: 500 mg (as lactobionate) in vial. Sulfadiazine, injection: 250 mg (sodium salt) in 4 ml ampoule and tablet: 500 mg.
Section 6.2.4	Rifampicin + isoniazid, tablet: 60 mg + 30 mg; 60 mg + 60 mg (for intermittent use three times weekly). Rifampicin + isoniazid + pyrazinamide, tablet: 60 mg + 30 mg + 150 mg.
Section 6.4.2.3	Nelfinavir (NFV), oral powder: 50 mg/g and tablet: 250 mg (as mesilate).
Section 8.2	Cisplatin, powder for injection: 10 mg; 50 mg in vial.
Section 13.5	Dithranol, ointment: 0.1% to 2.0%.
Section 17.2	Promethazine, injection: 25 mg (hydrochloride)/ml in 2 ml ampoule and oral liquid: 5 mg (hydrochloride)/5 ml and tablet: 10 mg; 25 mg (hydrochloride).
Section 18.5	Insulin injection (soluble), injection: 40 IU/ml in 10 ml vial. Intermediate-acting insulin, injection: 40 IU/ml in 10 ml vial (as compound insulin zinc suspension or isophane insulin).
Section 25.2	Caffeine citrate, injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml) and oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml).
Section 26.2	Glucose with sodium chloride, 4% glucose, 0.18% sodium chloride (equivalent to Na^+ 30 mmol/l, Cl^- 30 mmol/l). Potassium chloride, solution: 11.2% in 20 ml ampoule.

Moved from complementary to core

Section 6.5.2	Amphotericin B, powder for injection: 50 mg in vial. As deoxycholate or liposomal.

SECTION 1:
Anaesthetics

1 Anaesthetics

1.1 General anaesthetics and oxygen

To produce a state of prolonged full surgical anaesthesia reliably and safely, careful administration of a variety of drugs and close monitoring of the patient are required. Anaesthesia should be undertaken by non-specialist personnel only as a last resort, because anaesthetic drugs may be fatal if inappropriately used. Irrespective of the type of anaesthesia used (i.e. general or regional), it is essential that facilities for intubation and mechanically assisted ventilation are available.

Anaesthesia may be induced and maintained with intravenous medications and/or inhalation of a volatile agent (section 1.1). A range of other drugs including local anaesthetics (section 1.2), preoperative medications (section 1.3), opioid analgesics (section 2.2), muscle relaxants and reversal agents (e.g. cholinesterase inhibitors; section 20) may also be required.

Oxygen should be added routinely during anaesthesia with inhalation agents, even when air is used as the carrier, to protect against hypoxia.

Halothane

ATC code: N01AB01

Inhalation

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Induction and maintenance of anaesthesia.

Contraindications: History of unexplained jaundice or fever following previous exposure to halothane; family history of malignant hyperthermia; raised cerebrospinal fluid pressure; porphyria.

Precautions: Anaesthetic history should be carefully taken to determine previous exposure and previous reactions to halothane (fulminant hepatic failure is a rare complication of re-exposure to halothane); avoid use if adequate resuscitation facilities are not available.

Dose:

Induction of anaesthesia.
Inhalation through specifically calibrated vaporizer:
Infant or **Child** initially 0.5% then gradually increase inspired gas concentration to 1.5–2% in oxygen or nitrous oxide-oxygen.

Maintenance of anaesthesia.
Inhalation through specifically calibrated vaporizer:
Infant or **Child** 0.5–2% in oxygen or nitrous oxide-oxygen.

Hepatic impairment: Avoid if history of unexplained pyrexia or jaundice following previous exposure to halothane.

Adverse effects: Common Bradycardia, respiratory depression.

Uncommon Arrhythmias, hepatitis (may be fatal).

Interactions with other medicines (* indicates severe):

Amitriptyline: increased risk of arrhythmias and hypotension.

* **Chlorpromazine**: enhanced hypotensive effect.

Diazepam: enhanced sedative effect.

Enalapril: enhanced hypotensive effect.

Epinephrine (adrenaline): risk of arrhythmias.

* **Fluphenazine**: enhanced hypotensive effect.

Furosemide: enhanced hypotensive effect.

* **Haloperidol**: enhanced hypotensive effect.

Isoniazid: possible potentiation of isoniazid hepatotoxicity.

* **Levodopa**: risk of arrhythmias.

Spironolactone: enhanced hypotensive effect.

Suxamethonium: enhanced effects of suxamethonium.

Vancomycin: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

Vecuronium: enhanced effects of vecuronium.

* **Verapamil**: enhanced hypotensive effect and AV delay.

Notes: Preferred drug if intubation is likely to be difficult.

Does not augment salivary or bronchial secretions.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Ketamine

ATC code: N01AX03

Injection: 50 mg (as hydrochloride)/ml in 10 ml vial

Indications: Induction and maintenance of anaesthesia; analgesia for painful procedures of short duration.

Contraindications: Thyrotoxicosis; hypertension; severe cardiac disease; history of cerebrovascular accident, cerebral trauma, intracerebral mass or haemorrhage or other cause of raised intracranial pressure; eye injury and increased intraocular pressure; psychiatric disorders, particularly hallucinations; porphyria.

Precautions: Increased cerebrospinal fluid pressure; predisposition to hallucinations or nightmares; supplementary analgesia often required in surgical procedures involving visceral pain pathways (morphine may be used but addition of nitrous oxide will often suffice); administer an antisialogogue to prevent excessive salivation leading to respiratory difficulties; during recovery, patient must remain undisturbed but under observation.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Titrate dose to effect.

Induction and maintenance of anaesthesia (short procedures), analgesia for short painful procedures.

Intravenous injection over at least 60 seconds:

Neonate, Infant or **Child** 1–2 mg/kg produces 5–10 minutes of surgical anaesthesia, adjusted according to response.

Intramuscular injection:

Neonate 4 mg/kg for 15 minutes of surgical anaesthesia (adjusted according to response).

Infant or **Child** 4–13 mg/kg (4 mg/kg sufficient for some diagnostic procedures), adjusted according to response; 10 mg/kg usually produces 12–25 minutes of surgical anaesthesia.

Induction and maintenance of anaesthesia (longer procedures).

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.

Infant or **Child** initially 0.5–2 mg/kg followed by a continuous intravenous infusion of 0.6–2.7 mg/kg/hour adjusted according to response.

Adverse effects: Common Raised blood pressure and pulse rate, raised intracranial pressure, raised intraocular pressure, hypersalivation, increased muscle tone, emergence reactions including hallucinations, restlessness, confusion, irrational behaviour.

Uncommon Hypotension, bradycardia.

Rare Arrhythmias.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased risk of arrhythmias and hypotension.

* **Chlorpromazine**: enhanced hypotensive effect.

Diazepam: enhanced sedative effect.

Enalapril: enhanced hypotensive effect.

* **Fluphenazine**: enhanced hypotensive effect.

Furosemide: enhanced hypotensive effect.

* **Haloperidol**: enhanced hypotensive effect.

Isoniazid: possible potentiation of isoniazid hepatotoxicity.

Spironolactone: enhanced hypotensive effect.

Vancomycin: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

* **Verapamil**: enhanced hypotensive effect and AV delay.

Notes: For IV injection, dilute to a concentration of no more than 50 mg/ml with glucose 5% or sodium chloride 0.9% or water for injection.

For continuous IV infusion, dilute to a concentration of 1 mg/ml with glucose 5% or sodium chloride 0.9%; use microdrip infusion for maintenance of anaesthesia.

Premedication with an anticholinergic to reduce secretions is recommended before its use in anaesthesia.

Anaesthesia persists for up to 15 minutes after a single intravenous injection and is characterized by profound analgesia.

Subanaesthetic doses may be used to provide analgesia and sedation for painful procedures of short duration (e.g. dressing of burns, radiotherapeutic procedures, marrow sampling and minor orthopaedic procedures).

Recovery is relatively slow and associated with a high incidence of hallucinations and other emergence reactions, such as delirium.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Nitrous oxide

ATC code: N01AX13

Inhalation

Indications: Maintenance of anaesthesia in combination with other anaesthetic agents and muscle relaxants; analgesia for emergency management of injuries, during postoperative physiotherapy and for refractory pain in terminal illness.

Contraindications: Demonstrable collection of air in pleural (pneumothorax), pericardial or peritoneal space; intestinal obstruction; occlusion of middle ear; arterial air embolism; decompression sickness; chronic obstructive airway disease; emphysema.

Precautions: Minimize exposure of staff; vitamin B_{12} deficiency.

Dose:

Maintenance of light anaesthesia.
Inhalation using suitable anaesthetic apparatus:
Neonate, Infant or **Child** up to 66% in oxygen.

Analgesia.
Inhalation using suitable anaesthetic apparatus:
Neonate, Infant or **Child** up to 50% in oxygen, according to the child's needs.

Adverse effects: Common Nausea and vomiting.

Uncommon Arrhythmias.

Rare Malignant hyperthermia, after prolonged administration: megaloblastic anaemia, leukopenia, agranulocytosis, neuropathy and myeloneuropathy.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased risk of arrhythmias and hypotension.
* **Chlorpromazine**: enhanced hypotensive effect.
Diazepam: enhanced sedative effect.
Enalapril: enhanced hypotensive effect.
* **Fluphenazine**: enhanced hypotensive effect.
Furosemide: enhanced hypotensive effect.
* **Haloperidol**: enhanced hypotensive effect.
Isoniazid: possible potentiation of isoniazid hepatotoxicity.
* **Methotrexate**: increased antifolate effect (avoid concomitant use).
Spironolactone: enhanced hypotensive effect.
Vancomycin: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.
* **Verapamil**: enhanced hypotensive effect and AV delay.

Notes: Should not be used as a sole anaesthetic agent due to lack of potency.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Oxygen

ATC code: V03AN01

Inhalation (medicinal gas)

Fire hazard. Avoid use of cautery when oxygen is used with ether; reducing valves on oxygen cylinders must not be greased (risk of explosion).

Special Notes: Inhalation gas.

Indications: Maintain adequate tissue oxygenation in inhalational anaesthesia and other indications for use in neonates and children. Used during resuscitation and in the treatment of respiratory problems requiring supplemental oxygen.

Dose:

Concentration of oxygen in inspired anaesthetic gases should never be less than 21%, and preferably 30% or above.

The concentration required depends on the condition being treated.

Renal impairment: No dosage adjustment necessary.

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: Long-term use of concentrations greater than 80% have a toxic effect on the lungs leading to pulmonary congestion, exudation and atelectasis. Short-term use of 100% is not associated with these toxic effects.

The concentration required depends on the condition being treated; if available, monitoring of the oxygen delivered is strongly recommended, as inappropriate concentration may have serious or even lethal effects. Risks include morbidity, brain damage, and especially in pre-term neonates can cause retinopathy with blindness and chronic lung disease.

Use of 100% oxygen should not be withheld in an emergency situation.

Interactions with other medicines (* indicates severe):

* **Bleomycin**: serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia.

Notes: Monitoring of oxygen delivered is strongly recommended.

If available, use oxygen analyser to monitor inspired oxygen and pulse oximeter to monitor oxygen saturation.

Oxygen should be added routinely during anaesthesia with inhalational agents, even when air is used as the carrier gas, to protect against hypoxia.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Thiopental

ATC code: N01AF03

Powder for injection: 0.5 g; 1 g (sodium salt) in ampoule

Special Notes: Specialist skills required for administration and supportive management.

Indications: Induction of anaesthesia prior to administration of inhalational anaesthetic; anaesthesia of short duration.

Contraindications: Inability to maintain airway; hypersensitivity to barbiturates; severe cardiovascular disease; dyspnoea or obstructive respiratory disease; porphyria.

Precautions: Asthma; hypotension; cardiovascular disease; myotonic dystrophy; reconstituted solution is highly alkaline: extravasation can result in extensive tissue necrosis and sloughing; intra-arterial injection causes intense pain and may result in arteriospasm; rapid administration may result in severe hypotension and hiccups; renal impairment; hepatic impairment.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Titrate dose to effect.

Induction of anaesthesia, anaesthesia of short duration (< 15–20 minutes).
Slow IV injection usually as a 2.5% (25 mg/ml) solution over 10–15 seconds:
Neonate initially up to 2 mg/kg, then 1 mg/kg repeated as necessary (maximum total dose 4 mg/kg).
Infant or **Child** initially up to 5 mg/kg, then 1 mg/kg repeated as necessary (maximum total dose 7 mg/kg).

Renal impairment: May need to reduce dose in severe impairment; administer slowly.

Hepatic impairment: Reduce dose for induction in severe liver disease.

Adverse effects: Common Hypotension, transient erythema, injection site reactions, cardiorespiratory depression, myocardial depression, prolonged somnolence and recovery, cough, sneezing, cardiac arrhythmias.

Uncommon Laryngospasm, rash, allergic reactions.

Rare Anaphylaxis, bronchospasm, haemolytic anaemia.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased risk of arrhythmias and hypotension.

* **Chlorpromazine**: enhanced hypotensive effect.

Diazepam: enhanced sedative effect.

Enalapril: enhanced hypotensive effect.

* **Fluphenazine**: enhanced hypotensive effect.

Furosemide: enhanced hypotensive effect.

* **Haloperidol**: enhanced hypotensive effect.

Isoniazid: possible potentiation of isoniazid hepatotoxicity.

Silver sulfadiazine: enhanced effects of thiopental.

Spironolactone: enhanced hypotensive effect.

Sulfadiazine: enhanced effects of thiopental.

Sulfadoxine + pyrimethamine: enhanced effects of thiopental.

Sulfamethoxazole + trimethoprim: enhanced effects of thiopental.

Vancomycin: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

* **Verapamil**: enhanced hypotensive effect and AV delay.

Notes: For intravenous injection, dilute to a concentration of 25 mg/ml with water for injection; give over at least 10–15 seconds.

Avoid rapid IV injection (may cause hypotension or decreased cardiac output).

Induction is rapid and excitement does not usually occur.

Thiopental does not have analgesic properties.

Monitoring for hypotension and respiratory compromise is required.

Lower doses are needed in shock and low cardiac output states.

Repeated doses have a cumulative effect especially in neonates where recovery is slower.

References:
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

1.2 Local anaesthetics

Drugs used for conduction anaesthesia (also termed local or regional anaesthesia) reversibly block conduction along nerve fibres. Local anaesthetics have variable properties and a range of uses. These include topical (surface) anaesthesia, local anaesthesia and more specialized anaesthetic procedures requiring higher level technical skills (e.g. nerve blocks and regional, epidural and spinal anaesthesia).

Local anaesthetic toxicity

Local anaesthetic toxicity is usually due to excessively high plasma concentrations. Therefore, great care should be taken to avoid accidental intravascular injection or unwanted systemic absorption. Facilities for resuscitation should be available at all times.

Bupivacaine

ATC code: N01BB01

Injection: 0.25%; 0.5% (hydrochloride) in vial

Injection for spinal anaesthesia: 0.5% (hydrochloride) in 4 ml ampoule to be mixed with 7.5% glucose solution

Special Notes: Bupivacaine is a representative local anaesthetic. Various drugs can serve as alternatives.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Infiltration anaesthesia; peripheral and sympathetic nerve block; spinal or epidural anaesthesia (except in dehydrated or hypovolaemic patients); post-operative analgesia.

Contraindications: Local inflammation or infection; septicaemia; intravenous regional anaesthesia (e.g. Bier's block); use in intravenous infusions; spinal or epidural anaesthesia in patients taking anticoagulant therapy or with coagulation disorders; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patients; hypersensitivity to amide local anaesthetics.

Precautions: Respiratory impairment; hepatic impairment; epilepsy; porphyria; myasthenia gravis.

Dose:

Dose needs to be adjusted according to child's physical status and nature of procedure.

Do not use solutions containing preservatives for spinal, epidural or caudal anaesthesia.

Local infiltration.
0.5–2.5 mg/kg as a 0.25% or 0.5% solution; maximum dose 1 ml/kg of 0.25% solution, 0.5 ml/kg of 0.5% solution (2.5 mg/kg).

Peripheral nerve block.
0.3–2.5 mg/kg as a 0.25% or 0.5% solution; maximum dose 1 ml/kg of 0.25% solution, 0.5 ml/kg of 0.5% solution.

Epidural block in surgery, using 0.5% preservative free solution.
1–2.5 mg/kg.

Caudal block in surgery, using 0.5% preservative free solution.
1–2.5 mg/kg.

NOTE Use lower doses for debilitated patients, or in epilepsy or acute illness.

Renal impairment: No dosage adjustment necessary.

Hepatic impairment: Avoid (or reduce dose) in severe liver disease.

Adverse effects: Adverse effects generally occur only with excessive dosage or following intravascular injection.

Common Hypotension, lightheadedness, dizziness, blurred vision, restlessness, tremors, confusion, headache, paraesthesia, somnolence, constipation, nausea, vomiting, oedema, erythema at injection site, petechiae, skin irritation.

Uncommon Seizures, arrhythmias.

Rare Heart block, cardiac arrest, hypersensitivity reactions, respiratory failure.

Interactions with other medicines (* indicates severe):

Lidocaine: increased myocardial depression (interaction less likely when lidocaine used topically).

Procainamide: increased myocardial depression.

* **Propranolol**: increased risk of bupivacaine toxicity.

Quinidine: increased myocardial depression.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Lidocaine

ATC code: N01BB02

Injection: 1%; 2% (hydrochloride) in vial

Injection for spinal anaesthesia: 5% (hydrochloride) in 2 ml ampoule to be mixed with 7.5% glucose solution

Topical forms: 2% to 4% (hydrochloride)

Special Notes: Lidocaine is a representative local anaesthetic. Various drugs can serve as alternatives.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Local anaesthetic blocks, dental work and spinal anaesthesia.

Contraindications: Local inflammation or infection; septicaemia; spinal or epidural anaesthesia in patients taking anticoagulant therapy or with coagulation disorders; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patients; hypersensitivity to amide local anaesthetics.

Precautions: Bradycardia, impaired cardiac conduction; severe shock; respiratory impairment; renal impairment; hepatic impairment; epilepsy; porphyria; myasthenia gravis.

Dose:

Dose needs to be adjusted according to child's physical status and nature of procedure. Use the lowest effective dose and concentration.

Do not use solutions containing preservatives for spinal, epidural, caudal or intravenous regional anaesthesia.

Local infiltration and peripheral nerve block, using 1% or 2% solution.
Child up to 3 mg/kg (0.3 ml/kg of 1% solution and 0.15 ml/kg of 2% solution; maximum dose 200 mg), not repeated within 2 hours.

Surface anaesthesia of pharynx, larynx, trachea, using 4% topical solution.
Child up to 3 mg/kg (0.075 ml/kg), not repeated within 2 hours. Instil using a jet spray or apply with a swab.

Surface anaesthesia of urethra, using 4% topical solution.
Child up to 3 mg/kg (0.075 ml/kg), not repeated within 2 hours.

Spinal anaesthesia, using 5% solution (with glucose 7.5%).
Child up to 3 mg/kg (0.06 ml/kg), not repeated within 2 hours.

Renal impairment: Severe: use with caution.

Hepatic impairment: Avoid (or reduce dose) in severe liver disease.

Adverse effects: Adverse effects generally occur only with excessive dosage or following intravascular injection.

Common Hypotension, lightheadedness, dizziness, blurred vision, restlessness, tremors, confusion, headache, paraesthesia, somnolence, constipation, nausea, vomiting, oedema, erythema at injection site, petechiae, skin irritation.

Uncommon Seizures, arrhythmias.

Rare Heart block, cardiac arrest, hypersensitivity reactions and respiratory failure.

Interactions with other medicines (* indicates severe):

NOTE Interactions less likely when lidocaine is used topically.

* **Acetazolamide**: hypokalaemia caused by acetazolamide antagonizes action of lidocaine.

* **Atenolol**: increased myocardial depression.

  Bupivacaine: increased myocardial depression.

* **Furosemide**: action of lidocaine antagonized by hypokalaemia caused by furosemide.

* **Hydrochlorothiazide**: action of lidocaine antagonized by hypokalaemia caused by hydrochlorothiazide.

  Lopinavir: possibly increased plasma concentration of lidocaine.

* **Procainamide**: increased myocardial depression.

* **Propranolol**: increased myocardial depression; increased risk of lidocaine toxicity.

* **Quinidine**: increased myocardial depression.

  Suxamethonium: neuromuscular blockade enhanced and prolonged.

* **Timolol**: increased myocardial depression.

* **Verapamil**: increased myocardial depression.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Lidocaine + Epinephrine (Adrenaline)

ATC code: N01BB52

Dental cartridge: 2% (hydrochloride) + epinephrine 1:80 000

Injection: 1%; 2% (hydrochloride) + epinephrine 1:200 000 in vial

Special Notes: Do not use in digits and appendages, such as fingers, toes, ears, nose and penis, due to risk of ischaemic necrosis.

Mainly used for dental anaesthesia.

Indications: Dental anaesthesia; infiltration anaesthesia; peripheral nerve block.

Contraindications: LIDOCAINE Local inflammation or infection; septicaemia; spinal or epidural anaesthesia in patients taking anticoagulant therapy or with coagulation disorders; severe anaemia or heart disease; spinal or epidural anaesthesia in dehydrated or hypovolaemic patients; hypersensitivity to amide local anaesthetics.

EPINEPHRINE Cerebral arteriosclerosis; hypersensitivity to sympathomimetic amines.

Precautions: LIDOCAINE Bradycardia; impaired cardiac conduction; severe shock; respiratory impairment; renal impairment; hepatic impairment; epilepsy; porphyria; myasthenia gravis; avoid for ring block of digits or appendages (risk of ischaemic necrosis).

EPINEPHRINE Hypertension; heart block; heart disease; arrhythmias; cerebrovascular disease; thyroid disease; diabetes mellitus.

Dose:

Child *all ages* dose needs to be adjusted according to child's physical status and nature of procedure. Use the lowest effective dose and concentration. Do not repeat the dose within 2 hours. Maximum dose of lidocaine **with epinephrine** is 7 mg/kg/dose.

Renal impairment: LIDOCAINE Severe: use with caution.

Hepatic impairment: LIDOCAINE Avoid (or reduce dose) in severe liver disease.

Adverse effects: Adverse effects generally occur only with excessive dosage or following intravascular injection.

Common Hypotension, bradycardia, lightheadedness, dizziness, blurred vision, restlessness, tremors, confusion, headache, paraesthesia, somnolence, constipation, nausea, vomiting, oedema, erythema at injection site, petechiae, skin irritation.

Uncommon Seizures, arrhythmias.

Rare Heart block, cardiac arrest, hypersensitivity reactions, respiratory failure.

Interactions with other medicines (* indicates severe):

LIDOCAINE

NOTE Interactions less likely when lidocaine is used topically.

* **Acetazolamide**: hypokalaemia caused by acetazolamide antagonizes action of lidocaine.
* **Atenolol**: increased myocardial depression.

  Bupivacaine: increased myocardial depression.
* **Furosemide**: action of lidocaine antagonized by hypokalaemia caused by furosemide.
* **Hydrochlorothiazide**: action of lidocaine antagonized by hypokalaemia caused by hydrochlorothiazide.

  Lopinavir: possibly increased plasma concentration of lidocaine.
* **Procainamide**: increased myocardial depression.
* **Propranolol**: increased myocardial depression; increased risk of lidocaine toxicity.
* **Quinidine**: increased myocardial depression.

  Suxamethonium: neuromuscular blockade enhanced and prolonged.
* **Timolol**: increased myocardial depression.
* **Verapamil**: increased myocardial depression.

Notes: Do not administer intravenously or intra-arterially.

Before injecting for local anaesthesia, withdraw syringe plunger to make sure that injection is not into a vein or artery.

Use preservative free solutions for epidural or caudal use.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

1.3 Preoperative medication and sedation for short-term procedures

Appropriate premedication is an important consideration for procedures in children requiring conduction or general anaesthesia. Premedication may be used to help manage pain and anxiety and to improve the course of subsequent anaesthesia. A potent analgesic such as morphine (section 2.2) should be administered peri-operatively to patients in severe pain or for analgesia during and after surgery.

Atropine

ATC code: A03BA01

Injection: 1 mg (as sulfate) in 1 ml ampoule

Indications: Preoperative medication to inhibit salivation and secretions; reversal of the muscarinic effects of cholinergic agents such as neostigmine and pyridostigmine; treatment of bradycardia secondary to cholinergic stimulation.

Contraindications: Closed-angle glaucoma; myasthenia gravis; prostatic enlargement; severe gastrointestinal inflammatory disease; gastrointestinal obstruction.

Precautions: Down syndrome; children; ulcerative colitis; diarrhoea; heart failure; gastrointestinal disorders; hyperthyroidism; cardiac disorders; tachycardia; hypertension; hypoxia; fever and in warm environments (monitor temperature and keep patients cool); constipation; delirium.

CHILDREN Children are at increased risk for rapid rise in body temperature due to suppression of sweat gland activity. Large doses may cause paradoxical hyperexcitability.

DOWN SYNDROME Down syndrome children have both increased sensitivity to cardiac effects and mydriasis. Children with Down syndrome also have more secretions and may require atropine more frequently.

Dose:

Premedication.

IV:

Child *all ages* 20 micrograms/kg (max 600 micrograms) immediately before induction of anaesthesia.

SC:

Neonate 10–15 micrograms/kg 30–60 minutes before induction of anaesthesia.

Infant or **Child** 20 micrograms/kg (minimum dose 100 micrograms, maximum dose 600 micrograms) 30–60 minutes before induction of anaesthesia.

IM:

Infant or **Child** 20 micrograms/kg (minimum dose 100 micrograms, maximum dose 600 micrograms) 30–60 minutes before induction of anaesthesia.

Reversal of the muscarinic effects of cholinergic agents.

IV:

Neonate 20 micrograms/kg.

Infant or **Child** 20 micrograms/kg (maximum dose 600 micrograms).

Treatment of bradycardia secondary to cholinergic stimulation.

IV:

Neonate 20 micrograms/kg.

Infant or **Child** 10–20 micrograms/kg (maximum dose 600 micrograms).

Renal impairment: Use with caution. No dose adjustment necessary.

Hepatic impairment: Use with caution. No dose adjustment necessary.

Adverse effects: Common Dry mouth, blurred vision, photophobia, flushing and dryness of skin, rash, difficulty in micturition, constipation, arrhythmias, tachycardia, palpitations, fever.

Uncommon Nausea, vomiting, confusion.

Rare Closed-angle glaucoma, seizures.

Interactions with other medicines (* indicates severe):

NOTE Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase adverse effects such as dry mouth, urine retention and constipation.

Amitriptyline: increased antimuscarinic adverse effects.

Chlorphenamine: increased antimuscarinic adverse effects.

Chlorpromazine: increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration).

Haloperidol: possibly reduced effects of haloperidol.

Metoclopramide: antagonism of effects of metoclopramide on gastrointestinal activity.

Neostigmine: antagonism of effects of neostigmine. Late unopposed bradycardia may result.

Pyridostigmine: antagonism of effects of pyridostigmine.

Notes: For IV administration, administer undiluted by rapid IV injection; slow injection may result in paradoxical bradycardia.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Diazepam

ATC code: N05BA01

Injection: 5 mg/ml in 2 ml ampoule

Tablet: 5 mg

Special Notes: Drug subject to international control under the Convention on Psychotropic Substances (1971).

Diazepam is a representative benzodiazepine. Various drugs can serve as alternatives.

Intravenous diazepam can cause airway obstruction and hypoxia in exactly the same way as any other intravenous anaesthetic.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Premedication before major or minor surgery (for use in short-term procedures); sedation with amnesia for endoscopic procedures and surgery under local anaesthetic.

Contraindications: Central nervous system depression or coma; shock; respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; marked neuromuscular respiratory weakness including unstable myasthenia gravis.

Precautions: Respiratory disease; muscle weakness and myasthenia gravis; marked personality disorder; hepatic impairment; renal failure; close observation required until full recovery after sedation; porphyria.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Premedication and sedation for clinical procedures.

Oral:

Infant or **Child** 200–300 micrograms/kg (maximum 10 mg) 45–60 minutes prior to procedure.

Slow IV (over 2–5 minutes):

Infant or **Child** 100–200 micrograms/kg (maximum 5 mg) immediately before procedure.

Renal impairment: Severe: start with small doses; increased cerebral sensitivity.

Hepatic impairment: Can precipitate coma. Reduce dose by half.

Low doses could be used but a shorter acting agent would be preferable.

Adverse effects: Common Drowsiness, sedation, confusion, amnesia, muscle weakness, ataxia, slurred speech, pain on intravenous injection.

Uncommon Respiratory depression, hypotension, paradoxical insomnia, excitability, hallucinations and aggression, injection pain and thrombophlebitis.

Rare Blood dyscrasias including neutropenia, agranulocytosis, anaemia, leukopenia and thrombocytopenia.

Interactions with other medicines (* indicates severe):

Amitriptyline: enhanced sedative effect.

Chlorphenamine: enhanced sedative effect.

Chlorpromazine: enhanced sedative effect.

Codeine: enhanced sedative effect.

Enalapril: enhanced hypotensive effect.

Furosemide: enhanced hypotensive effect.

Haloperidol: enhanced sedative effect.

Halothane: enhanced sedative effect.

Isoniazid: metabolism of diazepam inhibited.

Ketamine: enhanced sedative effect.

Morphine: enhanced sedative effect.

Nitrous oxide: enhanced sedative effect.

Phenytoin: plasma phenytoin concentrations possibly increased or decreased by diazepam.

Rifampicin: metabolism of diazepam accelerated (reduced plasma concentration).

* **Ritonavir**: plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression; avoid concomitant use).

Spironolactone: enhanced hypotensive effect.

Thiopental: enhanced sedative effect.

Notes: Do not use via intramuscular injection as absorption is slow and erratic; route should only be used if oral or intravenous administration not possible.

Slow intravenous injection into large vein reduces risk of thrombophlebitis.

Resuscitation equipment must be available.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Morphine

ATC code: N02AA01

Injection: 10 mg (as sulfate or hydrochloride) in 1 ml ampoule

Special Notes: Risk of ten times overdose in small children. Extreme care required with dose calculation and preparation.

Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Indications: Preoperative sedative and analgesic.

Contraindications: Respiratory depression; severe respiratory disease; CNS depression; risk of paralytic ileus; raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma.

Precautions: Renal impairment; hepatic impairment; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; overdosage.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Sedation and analgesia for procedures.

IV:

Infant or **Child** 0.05–0.1 mg/kg 5 minutes before the procedure. Maximum dose 15 mg.

IM:

Infant or **Child** 0.1 mg/kg 20 minutes before the procedure. Maximum dose 15 mg. Only use IM route for premedication if patient has no IV access and there is adequate respiratory monitoring available.

Renal impairment: Moderate to severe: reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity.

Hepatic impairment: Avoid or reduce dose; may precipitate coma.

Adverse effects: Common Nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, postural hypotension, miosis.

Uncommon Respiratory depression (dose related), bradycardia, tachycardia, palpitations.

Rare Syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

Interactions with other medicines (* indicates severe):

Amitriptyline: possibly increased sedation.

Chlorpromazine: enhanced sedative and hypotensive effect.

Ciprofloxacin: avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis.

Diazepam: enhanced sedative effect.

Haloperidol: enhanced sedative and hypotensive effect.

Metoclopramide: antagonism of effect of metoclopramide on gastrointestinal activity.

* **Ritonavir**: possibly increases plasma concentration of morphine.

Notes: For intravenous administration, administer slowly over 5 minutes.

Risk of ten times overdose in small children.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).

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SECTION 2:
Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)

2 Analgesics, antipyretics, non-steroidal anti-inflammatory medicines (NSAIMs), medicines used to treat gout and disease modifying agents in rheumatoid disorders (DMARDs)

Pain management in children

In general terms, principles for drug management of pain in children follow the WHO Analgesic Ladder with the following recommendations for increasing pain:

- mild pain: non-opioid with or without non-steroidal anti-inflammatory medicine (NSAIM) and adjuvant
- moderate pain: mild opioid with non-opioid, NSAIM and adjuvant
- severe pain: strong opioid with non-opioid, NSAIM and adjuvant, with or without specialist techniques.

Non-drug strategies are also an important part of managing pain in children.

2.1 Non-opioids and non-steroidal anti-inflammatory medicines (NSAIMs)

Non-opioid analgesics include paracetamol and NSAIMs (section 2.1). These are particularly suitable for musculoskeletal pain. Combining a non-opioid with an opioid analgesic can provide more effective analgesia than either medication alone.

Ibuprofen

ATC code: M01AE01

Tablet: 200 mg; 400 mg

Special Notes: WHO age/weight restriction: > 3 months.

Indications: Mild to moderate pain.

Contraindications: Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAIM; active peptic ulceration or upper gastrointestinal bleeding; severe renal failure, hepatic failure or cardiac failure.

Precautions: Asthma; cardiac disease; volume depletion, such as in gastroenteritis or dehydration (increased risk of renal impairment); concomitant use of drugs that increase risk of bleeding; previous peptic ulceration; coagulation defects; allergic disorders; renal impairment; hepatic impairment.

Dose:

Mild to moderate pain.

Oral:

Infant or **Child** ***over 3 months*** 5–10 mg/kg three or four times daily with or after food. Maximum daily dose is 40 mg/kg/day.

Renal impairment: Mild: use lowest effective dose and monitor renal function; sodium and water retention may occur as may deterioration in renal function possibly leading to renal failure.

Moderate to severe: avoid.

Hepatic impairment: Use with caution: increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease.

Adverse effects: Common Nausea, diarrhoea, dyspepsia, headache, dizziness, fluid retention, raised blood pressure, gastrointestinal ulceration and bleeding.

Uncommon Rash, urticaria, photosensitivity, renal impairment.

Rare Angioedema, bronchospasm, hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), colitis, aseptic meningitis.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: avoid concomitant use (increased adverse effects).
* **Ciclosporin**: increased risk of nephrotoxicity.

  Dexamethasone: increased risk of gastrointestinal bleeding and ulceration.

  Digoxin: possibly exacerbation of heart failure, reduced renal function and increased plasma digoxin concentration.

  Enalapril: antagonism of hypotensive effect, increased risk of renal impairment.
* **Fluoxetine**: increased risk of bleeding.

  Furosemide: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

  Heparin: possibly increased risk of bleeding.

  Hydrocortisone: increased risk of gastrointestinal bleeding and ulceration.
* **Levofloxacin**: possibly increased risk of convulsions.
* **Lithium**: reduced excretion of lithium (increased risk of toxicity).
* **Methotrexate**: excretion of methotrexate reduced (increased risk of toxicity).
* **Ofloxacin**: possible increased risk of convulsions.

  Penicillamine: possible increased risk of nephrotoxicity.
* **Phenytoin**: effect of phenytoin possibly enhanced.

  Prednisolone: increased risk of gastrointestinal bleeding and ulceration.

  Propranolol: antagonism of hypotensive effect.

  Ritonavir: plasma concentration possibly increased by ritonavir.

  Spironolactone: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia.
* **Warfarin**: anticoagulant effect possibly enhanced.

  Zidovudine: increased risk of haematological toxicity.

Notes: Give with or after food.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Paracetamol

ATC code: N02BE01

Oral liquid: 25 mg/ml

Suppository: 100 mg

Tablet: 100 mg to 500 mg

Special Notes: Also referred to as acetaminophen.

Not recommended for anti-inflammatory use due to lack of proven benefit.

Indications: Mild to moderate pain; fever.

Precautions: Hepatic impairment; renal impairment; overdosage.

Dose:

Mild to moderate pain, fever.

Oral, rectal:

Neonate 10 mg/kg every 6–8 hours as necessary. Maximum 4 doses in 24 hours. If neonate is jaundiced, a 5 mg/kg dose is suitable.

Infant or **Child** 15 mg/kg, up to 1 g, every 4–6 hours as necessary. Maximum 4 doses, or 4 g, in 24 hours.

NOTE Infants under 3 months should not be given paracetamol unless advised by a doctor.

Hepatic impairment: Dose related toxicity; avoid large doses.

Adverse effects: Rare Rash, hypersensitivity, neutropenia, thrombocytopenia, pancytopenia.

HEPATOTOXICITY Hepatotoxicity (and less frequently renal damage) can occur after paracetamol overdosage. Children in the following situations may be at an increased risk of liver damage from paracetamol overdosage: malnourished, obese, febrile illness, prolonged course, not eaten for a few days or taking liver enzyme inducing drugs. Refer to section 4.2 for more information on paracetamol toxicity.

Interactions with other medicines (* indicates severe):

Metoclopramide: increased absorption of paracetamol.

Warfarin: prolonged regular use of paracetamol possibly enhances anticoagulant effect.

Notes: Shake suspension well before use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Acetylsalicylic acid

ATC code: N02BA01

Suppository: 50 mg to 150 mg

Tablet: 100 mg to 500 mg

Do not use acetylsalicylic acid in children who have or who are recovering from chickenpox (varicella), influenza, acute febrile illness or flu symptoms due to the rare association with Reye's syndrome. During treatment with acetylsalicylic acid, changes in behaviour may be an early sign of Reye's syndrome. Patients and carers should be instructed to contact the health-care provider if these symptoms develop.

Special Notes: Also referred to as aspirin.

Indications: Management of rheumatic fever, juvenile arthritis and Kawasaki disease.

Contraindications: Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAIM; for simple analgesia and antipyrexia in children under 16 years (risk of Reye syndrome); active peptic ulceration; haemophilia and other bleeding disorders; hepatic failure.

Precautions: Asthma; uncontrolled hypertension; concomitant use of drugs that increase risk of bleeding; previous peptic ulceration; G6PD deficiency; dehydration; renal impairment; hepatic impairment.

Dose:

Administer with or after food.

Juvenile arthritis, rheumatic fever.

Oral:

Infant or **Child** up to 130 mg/kg daily in 5–6 divided doses in acute conditions; 80–100 mg/kg daily in divided doses for maintenance.

Kawasaki disease.

Oral:

Neonate initially 8 mg/kg four times daily 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.

Infant or **Child** initially 7.5–12.5 mg/kg four times daily until afebrile, followed by 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.

Renal impairment: Increased risk of bleeding and acetylsalicylic acid induced renal impairment.

Severe: avoid; increased risk of sodium and water retention; deterioration in renal function; gastrointestinal bleeding.

Hepatic impairment: Avoid in severe hepatic impairment; increased risk of gastrointestinal bleeding.

Adverse effects: Common Nausea, dyspepsia, gastrointestinal ulceration or bleeding, tinnitus, vertigo, confusion, increased bleeding time.

Uncommon Hypersensitivity reactions including angioedema, bronchospasm and rash (including Stevens-Johnson syndrome), iron deficiency anaemia, renal impairment, oesophageal ulceration.

Rare Major haemorrhage (including gastrointestinal, subconjunctival or other), blood dyscrasias, oedema, myocarditis, Reye syndrome with subsequent encephalopathy and severe hepatic injury.

Interactions with other medicines (* indicates severe):

Dexamethasone: increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration.

Enalapril: antagonism of hypotensive effect; increased risk of renal impairment.

Fluoxetine: increased risk of bleeding.

* **Heparin**: enhanced anticoagulant effect of heparin.

Hydrocortisone: increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration.

* **Ibuprofen**: avoid concomitant use (increased adverse effects); antiplatelet effect of acetylsalicylic acid possibly reduced.

* **Methotrexate**: reduced excretion of methotrexate (increased toxicity).

Metoclopramide: enhanced effect of acetylsalicylic acid (increased rate of absorption).

Phenytoin: enhancement of effect of phenytoin.

Prednisolone: increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration.

Spironolactone: antagonism of diuretic effect.

Valproic acid: enhancement of effect of valproic acid.

* **Warfarin**: risk of bleeding due to antiplatelet effect.

Notes: Give with or after food.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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2.2 Opioid analgesics

Opioid analgesics act on the central nervous system. Morphine is effective in relieving moderate to severe pain, particularly of visceral origin; there is a large variation in patient response. Weaker opioids such as codeine are suitable for mild to moderate pain.

Opioid analgesic overdose

In overdose, opioids can cause respiratory depression and coma with pinpoint pupils. Naloxone (section 4.2) is a specific antidote.

Codeine

ATC code: R05DA04

Tablet: 15 mg (phosphate)

Special Notes: Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Indications: Mild to moderate pain.

Contraindications: Hypersensitivity to codeine or similar drugs; respiratory depression; risk of paralytic ileus.

Precautions: Renal impairment; hepatic impairment; reduced respiratory reserve; overdosage (see section 4.2).

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Mild to moderate pain.

Oral:

Neonate, Infant or ***Child*** 0.5–1 mg/kg every 4–6 hours when needed; maximum 240 mg daily.

Renal impairment: Moderate to severe: reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity.

Hepatic impairment: Avoid or reduce dose; may precipitate coma.

Adverse effects: Common Nausea, vomiting, constipation (mainly with long-term use), drowsiness, dizziness, urinary retention, dry mouth.

Uncommon Respiratory depression (dose related), sweating, facial flushing, dependence, euphoria, sedation, headache, pruritus.

Rare Syndrome of inappropriate antidiuretic hormone secretion (SIADH), seizures, anaphylaxis.

Interactions with other medicines (* indicates severe):

Amitriptyline: possibly increased sedation.

Chlorpromazine: enhanced sedative and hypotensive effect.

Diazepam: enhanced sedative effect.

Haloperidol: enhanced sedative and hypotensive effect.

Metoclopramide: antagonism of effect of metoclopramide on gastrointestinal activity.

* **Ritonavir**: ritonavir possibly increases plasma concentration of codeine.

Notes: Increase fluid and fibre intake to avoid constipation.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Morphine

ATC code: N02AA01

Injection: 10 mg (as hydrochloride or sulfate) in 1 ml ampoule

Oral liquid: 2 mg (as hydrochloride or sulfate)/ml

Tablet: 10 mg (as sulfate)

Tablet (prolonged release): 10 mg; 30 mg; 60 mg (as sulfate)

Special Notes: Extreme caution should be exercised in determining all drug doses in children. There is a risk of misplacing the decimal point with morphine, resulting in a 10 times overdose.

NOTE 0.1 milligrams = 100 micrograms.

Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Indications: Postoperative pain; severe acute and chronic pain.

Contraindications: Respiratory depression; severe respiratory disease; CNS depression; risk of paralytic ileus; raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma.

Precautions: Renal impairment; hepatic impairment; dependence (severe withdrawal symptoms if withdrawn abruptly); hypothyroidism; convulsive disorders; decreased respiratory reserve and acute asthma; hypotension; prostatic hypertrophy; overdosage.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Pain.

SC or *IM:*

Neonate 100 micrograms/kg every 6 hours, adjusted according to response.

Infant *1–6 months* initially 100–200 micrograms/kg every 6 hours, adjusted according to response.

Infant or **Child *6 months–2 years*** initially 100–200 micrograms/kg every 4 hours, adjusted according to response;

2–12 years initially 200 micrograms/kg every 4 hours, adjusted according to response. Usual maximum dose is 15 mg.

IV injection over at least 5 minutes:

Neonate initially 50 micrograms/kg every 6 hours, adjusted according to response.

Infant *1–6 months* initially 100 micrograms/kg every 6 hours, adjusted according to response.

Infant or **Child *6 months–12 years*** initially 100 micrograms/kg every 4 hours, adjusted according to response. Maximum dose is 15 mg.

IV 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 infusion* 10–30 micrograms/kg/hour adjusted to response;

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.

Oral:

Child *1–12 months* initially 80–200 micrograms/kg every 4 hours, adjusted according to response;

1–2 years initially 200–400 micrograms/kg every 4 hours, adjusted according to response;

2–12 years initially 200–500 micrograms/kg (maximum 20 mg) every 4 hours, adjusted according to response.

Oral (prolonged release):

Child initially 200–800 micrograms/kg every 12 hours, adjusted according to response.

Continuous SC infusion:

Child *1–3 months* 10 micrograms/kg/hour;

3 months–18 years 20 micrograms/kg/hour.

Renal impairment: Mild to moderate: reduce dose by 25%.

Severe: reduce dose by 50% or avoid; increased and prolonged effect; increased cerebral sensitivity.

Hepatic impairment: Avoid or reduce dose, may precipitate coma.

Adverse effects: Common Nausea, vomiting, constipation, lightheadedness, dizziness, sedation, sweating, dysphoria, euphoria, dry mouth, anorexia, spasm of urinary and biliary tract, pruritus, rash, sweating, postural hypotension, miosis.

Uncommon Respiratory depression (dose related), bradycardia, tachycardia, palpitations.

Rare Syndrome of inappropriate antidiuretic hormone secretion (SIADH), anaphylaxis.

Interactions with other medicines (* indicates severe):

Amitriptyline: possibly increased sedation.

Chlorpromazine: enhanced sedative and hypotensive effect.

Ciprofloxacin: manufacturer of ciprofloxacin advises avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis.

Diazepam: enhanced sedative effect.

Haloperidol: enhanced sedative and hypotensive effect.

Metoclopramide: antagonism of effect of metoclopramide on gastrointestinal activity.

* **Ritonavir**: ritonavir possibly increases plasma concentration of morphine.

Notes: Subcutaneous injection not suitable for oedematous patients.

Administer intravenous injection slowly over 5 minutes.

For continuous intravenous infusion, dilute with glucose 5% or 10% or sodium chloride 0.9%.

For neonatal intensive care infusions, dilute 2.5 mg/kg body weight to a final volume of 50 ml with infusion fluid.

Prolonged release morphine preparations must not be crushed or chewed. Child must be able to swallow the tablet whole.

Doses should be adjusted according to response.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

2.3 Medicines used to treat gout

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children.*

2.4 Disease modifying agents used in rheumatoid disorders (DMARDs)

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children.*

SECTION 3:
Antiallergics and medicines used in anaphylaxis

3 Antiallergics and medicines used in anaphylaxis

Allergic disorders are a common problem in children. Allergic conditions include asthma, eczema, urticaria, allergic rhinitis (hayfever) and allergies to foods, medicines and drugs.

Allergic reactions which are mild and of limited duration (e.g. urticaria and allergic rhinitis) may not require treatment. However, when symptoms are moderate or persistent, medications such as antihistamines and corticosteroids may be required.

Antihistamines inhibit the wheals, pruritus, sneezing and nasal secretory responses that characterize allergy, and thus relieve allergic symptoms.

Corticosteroids suppress or prevent almost all symptoms of inflammation associated with allergy. Steroids should be used for short-term suppression of inflammation, but long-term use of steroids should be avoided, due to the risk of significant side-effects.

Allergic emergencies

Severe allergic reactions such as anaphylaxis and angioedema are life-threatening emergencies. First-line treatment for these conditions is epinephrine with appropriate resuscitation. Use of other medications in these conditions is secondary.

Chlorphenamine

ATC code: R06AB04

Injection: 10 mg (hydrogen maleate) in 1 ml ampoule

Oral liquid: 2 mg/5 ml

Tablet: 4 mg (hydrogen maleate)

Special Notes: Also referred to as chlorpheniramine maleate.

WHO age/weight restriction: > 1 year.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Allergic conditions including urticaria, angioedema, rhinitis, conjunctivitis and in pruritic skin disorders.

Intravenously as an adjunct in the emergency treatment of anaphylactic shock.

Contraindications: Hypersensitivity to chlorphenamine or dexchlorpheniramine.

Precautions: Asthma; bladder neck obstruction; hepatic insufficiency; narrow angle glaucoma; pyloroduodenal obstruction; sedative effects; stenosing peptic ulcer; symptomatic prostatic hypertrophy.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Allergy.
Oral:
Child *under 1 year* not recommended;
1–2 years 1 mg twice daily;
2–6 years 1 mg every 4–6 hours (maximum 6 mg daily);
6–12 years 2 mg every 4–6 hours (maximum 12 mg daily).

Allergic reactions, anaphylaxis (adjunct).
SC, IM or *IV:*
Child *under 1 year* not recommended;
1–6 years 2.5–5 mg;
6–12 years 5–10 mg.

Renal impairment: Severe: dose reduction may be required.

Hepatic impairment: Sedation caused by chlorphenamine inappropriate in severe liver disease; avoid.

Adverse effects: Common Anorexia, nausea, vomiting, epigastric distress, diarrhoea, constipation, drowsiness, somnolence, dry mouth, blurred vision, urinary retention, drying effect throughout the respiratory tract and a thickening of bronchial mucus, headache, weight gain.

Uncommon Exfoliative dermatitis, cardiac dysrhythmia, hypotension (more severe when used intravenously), paradoxical excitation.

Rare Disturbances in smell and taste, facial dyskinesias, blood dyscrasias (including agranulocytosis, thrombocytopenia, pancytopenia and aplastic anaemia), EEG changes, psychotic disorder, liver dysfunction, tremor, seizures, confusion, depression, sleep disturbances.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased antimuscarinic and sedative effects.

Atropine: increased antimuscarinic adverse effects.

Diazepam: enhanced sedative effect.

Lopinavir: possibly increased plasma concentration of chlorphenamine.

Notes: Give intravenous injection over 1 minute.

If necessary, injection solution can be diluted with sodium chloride 0.9% injection.

Chlorphenamine may cause excitability in children.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Dexamethasone

ATC code: H02AB02

Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1 ml ampoule

Indications: Adjunct in the emergency treatment of anaphylaxis; short-term suppression of inflammation in allergic disorders.

Contraindications: Not relevant to emergency use.

Precautions: Increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis; amoebiasis; strongyloidiasis; risk of severe chickenpox in non-immune patients (varicella zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; corneal perforation; osteoporosis; myasthenia gravis.

Dose:

Inflammatory and allergic disorders.
IM or *slow IV injection* or *infusion:*
Infant or **Child** 100–400 micrograms/kg in 1–2 divided doses (maximum 24 mg daily).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

Common Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (see below).

INTRAVENOUS Transient itching, burning or tingling in perineal area (after intravenous bolus).

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis.

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis is less common.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration.

Albendazole: plasma albendazole concentration possibly increased.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions).

* **Carbamazepine**: accelerated metabolism of dexamethasone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of dexamethasone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of dexamethasone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

* **Lopinavir**: possibly reduced plasma lopinavir concentration.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.
* **Phenobarbital**: metabolism of dexamethasone accelerated (reduced effect).
* **Phenytoin**: metabolism of dexamethasone accelerated (reduced effect).

Praziquantel: plasma praziquantel concentration reduced.

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of dexamethasone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Saquinavir: possibly reduced plasma saquinavir concentration.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of dexamethasone impair immune response.

* **Vaccine, live**: high doses of dexamethasone impair immune response; avoid use of live vaccines.
* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
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Epinephrine (Adrenaline)

ATC code: C01CA24

Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1 ml ampoule (1:1000)

Intravenous epinephrine should be used with extreme care by specialists only.

Special Notes: 1 mg/ml = 1:1000 or 0.1%.

Indications: Severe anaphylactic reaction; severe angioedema.

Contraindications: Closed-angle glaucoma; use during halothane or cyclopropane anaesthesia.

Precautions: Hyperthyroidism; hypertension; diabetes mellitus; heart disease; arrhythmias; psychoneurosis; cerebrovascular disease; phaeochromocytoma; susceptibility to closed-angle glaucoma.

Dose:

Anaphylaxis.
IM:
Infant ***under 6 months*** 50 micrograms (0.05 ml of 1 mg/ml solution);
Infant or **Child** ***6 months–6 years*** 150 micrograms (0.15 ml of 1 mg/ml solution);
Child ***6–12 years*** 300 micrograms (0.3 ml of 1 mg/ml solution).
These doses may be repeated at 5 minute intervals, several times if necessary, depending on blood pressure, pulse and respiratory function.
IV (if circulation inadequate):
Infant or **Child** 10 micrograms/kg (0.1 ml/kg of the dilute 1 mg/10 ml solution) given over several minutes.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, anxiety, headache, fear, palpitations, tachycardia, restlessness, tremor, dizziness, dyspnoea, weakness, sweating, pallor, hyperglycaemia.

Uncommon Excessive increase in blood pressure, ventricular arrhythmias, pulmonary oedema (on excessive dosage or extreme sensitivity), angina, cold extremities, peripheral ischaemia and necrosis (at injection site).

Rare Allergic reaction (sodium metabisulfite in some products).

OVERDOSE OR RAPID INTRAVENOUS ADMINISTRATION Arrhythmias (ventricular and supraventricular), severe hypertension, cerebral haemorrhage, pulmonary oedema.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased effect or toxicity of epinephrine.

* **Cyclopropane**: may precipitate ventricular arrhythmias.

* **Ergot derivatives**: may precipitate hypertensive crisis

Fluoxetine: increased effect or toxicity of epinephrine.

* **Halothane**: may precipitate ventricular arrhythmias.

Propranolol: hypertension, bradycardia, resistance to epinephrine effect.

Notes: 1 mg/ml = 1:1000 or 0.1%.

Inject intramuscular epinephrine into anterolateral aspect of thigh; do not inject into hands, feet, ears, nose, genitals or buttocks.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Hydrocortisone

ATC code: H02AB09

Powder for injection: 100 mg (as sodium succinate) in vial

Indications: Adjunct in the emergency treatment of anaphylaxis.

Contraindications: Not relevant to emergency use.

Precautions: Not relevant to emergency use.

Dose:

Anaphylaxis.
IM or *IV:*
Infant *under 6 months* initially 25 mg up to four times daily adjusted according to response.
Infant or **Child *6 months–6 years*** initially 50 mg up to four times daily adjusted according to response.
Child *6–12 years* initially 100 mg up to four times daily adjusted according to response.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

Common Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (including euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour).

INTRAVENOUS Transient itching, burning or tingling in perineal area (after intravenous bolus).

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis, psychiatric effects (including delirium or psychosis).

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

* **Carbamazepine**: accelerated metabolism of hydrocortisone (reduced effect).

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of hydrocortisone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

* **Phenobarbital**: metabolism of hydrocortisone accelerated (reduced effect).

* **Phenytoin**: metabolism of hydrocortisone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of hydrocortisone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of hydrocortisone impairs immune response.

* **Vaccine, live**: high doses of hydrocortisone impairs immune response; avoid use of live vaccines.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Prednisolone

ATC code: H02AB06

Oral liquid: 5 mg/ml

Tablet: 5 mg; 25 mg

Special Notes: Prednisone should be considered equivalent to prednisolone.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Short-term suppression of inflammation.

Contraindications: Untreated systemic infection; administration of live vaccines: usually not relevant to emergency treatment.

Precautions: Most precautions do not apply for emergency or short-term use.

Increased severity of viral infections; recent myocardial infarction; congestive heart failure; renal impairment; hepatic impairment; diabetes mellitus; osteoporosis; glaucoma; corneal perforation; severe psychosis; epilepsy; psoriasis; peptic ulcer; hypothyroidism; history of steroid myopathy.

Dose:

Oral:

Infant or **Child** 1–2 mg/kg once daily (usual maximum 60 mg), reducing after a few days if appropriate. Increased frequency may be required in certain clinical indications.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Adverse effects more common.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

Common Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (including euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour).

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis, psychiatric effects (including delirium and psychosis).

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration.

* **Amphotericin B**: increased risk of hypokalaemia.

* **Carbamazepine**: accelerated metabolism of prednisolone (reduced effect).

Ciclosporin: increased plasma concentration of prednisolone.

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of prednisolone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of prednisolone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.
* **Phenobarbital**: metabolism of prednisolone accelerated (reduced effect).
* **Phenytoin**: metabolism of prednisolone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of prednisolone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with prednisolone.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of prednisolone impair immune response.

* **Vaccine, live**: high doses of prednisolone impair immune response; avoid use of live vaccines.
* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose prednisolone enhances anticoagulant effect).

Notes: Take the tablets or oral liquid with food to help reduce stomach upset.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

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SECTION 4:
Antidotes and other substances used in poisonings

4 Antidotes and other substances used in poisonings

The following notes on treatment of poisoning are guidelines only. It is strongly recommended that poisons information centres or other local sources of expertise be consulted in cases of suspected poisoning.

A diagnosis of poisoning is based on history, including details of the poisoning agent, the amount ingested, the time of ingestion, and the results of investigations when appropriate. Symptoms and signs depend on the agent involved and therefore vary widely.

Check for burns in or around the mouth, or stridor (abnormal respiratory sounds suggesting laryngeal damage), due to ingestion of corrosives. Admit all children who have ingested iron, pesticides, paracetamol, aspirin, narcotics, antidepressant drugs, paraquat, lithium or warfarin; or who have taken modified-release or prolonged-release dose forms. Children who have ingested corrosives or petroleum products should not be sent home within 6 hours.

Supportive care

Few patients require active removal of the poison, and most are treated symptomatically with supportive care and monitoring of vital signs.

Decontamination

Depending on the substance involved and circumstances of poisoning, decontamination of the skin and eyes (with appropriate protection of staff and carers) should be undertaken. For inhaled poisons, removal from the source of poisoning, administration of oxygen and further airway support may be required.

Gastric decontamination

Gastric decontamination (removal of poisons from the stomach) is most effective within 1 hour of ingestion; after this time it is usually of little benefit. Administration of activated charcoal to prevent further absorption is the treatment of choice for gastric decontamination.

Gastric lavage is rarely required. Induction of emesis for treatment of poisoning is not recommended.

4.1 Non-specific

Charcoal, activated

ATC code: A07BA01

Powder

Indications: Reduction of absorption of poisons; active elimination of poisons.

Contraindications: Poisoning by hydrocarbons with high potential for harm if aspirated; poisoning by corrosive substances (may prevent visualization of lesions caused by poison); unprotected airway; gastrointestinal tract not intact; bowel obstruction.

Precautions: Drowsy or unconscious child (risk of aspiration (intubate before administration via nasogastric or gastric tube)); not effective for poisoning with alcohols, clofenotane (dicophane, dichlorodiphenyltrichloroethane (DDT)), cyanides, malathion, and metal salts including iron and lithium.

Dose:

Reduction of absorption of poisons.

Oral:

Neonate, Infant or **Child** 1 g/kg (maximum 50 g) as a single dose as soon as possible after ingestion of poison.

Active elimination of poisons.

Oral:

Neonate, Infant or **Child** 1 g/kg (maximum 50 g) every 4 hours.

Renal impairment: Not absorbed; no dose adjustment necessary.

Hepatic impairment: Not absorbed; no dose adjustment necessary.

Adverse effects: Common Black stools, colicky abdominal pain, nausea, vomiting, constipation or diarrhoea.

Rare Bowel obstruction, aspiration, pneumonitis.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Administer as soon as possible after ingestion if significant toxicity is anticipated, preferably within 1 hour for greatest effect.

Administration after 1 hour is only of any potential benefit in selected poisonings. Refer to specialist texts for advice.

The powder should be mixed with fluid such as soft drinks, fruit juice, fruit syrup or chocolate syrup to mask the taste and form a drinkable solution. Mix well immediately prior to ingestion.

Do not mix with milk or ice cream.

Child must drink slowly to reduce risk of vomiting.

Palatability is improved by chilling.

Drinking may be easier if mixture is covered or the child drinks with their eyes closed.

Unconscious patients in whom decontamination is indicated require intubation to protect their airway. Activated charcoal can be administered via an orogastric or nasogastric tube after aspiration of stomach contents. This route may also be used in conscious patients who refuse, or cannot take, oral charcoal.

Laxatives should not be used concurrently with repeat dose activated charcoal because of the risk of fluid and electrolyte disturbances.

References:

American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. *Clinical Toxicology,* 1999, 37(6):731–751.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

4.2 Specific

Acetylcysteine

ATC code: V03AB23

Injection: 200 mg/ml in 10 ml ampoule

Oral liquid: 10% and 20%

Indications: Paracetamol overdosage.

Contraindications: There are no contraindications to acetylcysteine when used for paracetamol toxicity.

Precautions: Asthma (observe child carefully while slowly administering loading dose over 1–2 hours; do not delay treatment).

Dose:

Paracetamol overdosage.

IV infusion:

Neonate, Infant or **Child** ***up to 5 years and 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.
over 5 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.

NOTE Continued infusion beyond 20 hours may be required in late presentations or repeated supratherapeutic ingestions if there is evidence of liver toxicity. In such cases, continue the final infusion rate until hepatic transaminases are falling.

Oral:

Neonate, Infant or **Child** initially 140 mg/kg, followed by 70 mg/kg every 4 hours for 17 doses, starting 4 hours after loading dose.

Renal impairment: No dosage adjustment recommended.

Hepatic impairment: No dosage adjustment recommended.

Adverse effects: Common Flushing, urticaria, itch.

Uncommon Anaphylactoid reaction.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: For oral therapy, all doses should be given even if paracetamol plasma level has dropped below toxic range.

Repeat oral dose if vomiting occurs within 1 hour of administration.

Emergency treatments such as antihistamines and H_2-blockers should be readily available in case of adverse effects.

Manufacturer also recommends other infusion fluids, but glucose 5% is preferable.

Hypersensitivity-like reactions may be managed by reducing infusion rate or suspending infusion until reaction has settled; specialist advice may be needed.

Rash may be managed with an antihistamine, for example chlorphenamine.

Acute asthma may be managed with a short-acting beta$_2$-agonist such as salbutamol.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO 17th expert committee on the selection and use of essential medicines. Unedited draft report of the 17th expert committee on the selection and use of essential medicines. *WHO Technical Report Series,* 18 May 2009 (http://www.who.int/selection_medicines/committees/expert/17/WEBuneditedTRS_2009.pdf).
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Atropine

ATC code: A03BA01

Injection: 1 mg (as sulfate) in 1 ml ampoule

Indications: Treatment of cholinergic effects associated with organophosphate or carbamate poisoning.

Contraindications: There are no contraindications to use of atropine for treatment of organophosphate or carbamate poisoning.

Precautions: Down syndrome; children; ulcerative colitis; diarrhoea; heart failure; closed-angle glaucoma; myasthenia gravis; gastrointestinal disorders; hyperthyroidism; cardiac disorders; tachycardia; hypertension; hypoxia; fever and in warm environments (monitor temperature and keep patients cool); constipation; delirium.

CHILDREN Children are at increased risk for rapid rise in body temperature due to suppression of sweat gland activity. Large doses may cause paradoxical hyperexcitability.

DOWN SYNDROME Down syndrome children have both increased sensitivity to cardiac effects and mydriasis. Children with Down syndrome also have more secretions and may require atropine more frequently.

Dose:

Organophosphate or carbamate poisoning.
IM or *IV:*
Infant or **Child** 20 micrograms/kg (maximum dose 2 mg) every 5–10 minutes (depending on the severity of poisoning) until the skin becomes flushed and dry, the pupils dilate and tachycardia develops.

Dose may be repeated every 1–4 hours for at least 24 hours to maintain atropine effect.

Renal impairment: Use with caution. No dosage adjustment necessary.

Hepatic impairment: Use with caution. No dosage adjustment necessary.

Adverse effects: Common Dry mouth, blurred vision, photophobia, flushing and dryness of skin, rash, difficulty in micturition, constipation, arrhythmias, tachycardia, palpitations, fever.

Uncommon Nausea, vomiting, confusion.

Rare Closed-angle glaucoma, seizures.

Interactions with other medicines (* indicates severe):

NOTE Many drugs have antimuscarinic effects; concomitant use of two or more such drugs can increase adverse effects such as dry mouth, urine retention and constipation.

Please consider in the context of poisoning treatment whether interactions are clinically relevant.

Amitriptyline: increased antimuscarinic adverse effects.

Chlorphenamine: increased antimuscarinic adverse effects.

Chlorpromazine: increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration).

Haloperidol: possibly reduced effects of haloperidol.

Metoclopramide: antagonism of effects of metoclopramide on gastrointestinal activity.

Neostigmine: antagonism of effects of neostigmine. Late unopposed bradycardia may result.

Pyridostigmine: antagonism of effects of pyridostigmine.

Notes: Administer undiluted via rapid intravenous injection as slow injection may result in paradoxical bradycardia.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Calcium gluconate

ATC code: A12AA03

Injection: 100 mg/ml in 10 ml ampoule

Indications: Magnesium toxicity; severe hyperkalaemia not due to digoxin toxicity; acute hypocalcaemia (including hypocalcaemia caused by ethylene glycol toxicity, hydrofluoric acid ingestion and oxalate poisoning); calcium channel blocker toxicity; topical treatment of hydrofluoric acid burns.

Contraindications: There are no contraindications to the use of calcium gluconate for treatment of toxicity or poisoning.

Precautions: Conditions associated with hypercalcaemia and hypercalciuria; digoxin therapy; renal impairment.

Dose:

Urgent correction of acute hypocalcaemia, hyperkalaemia or hypermagnesaemia; calcium channel blocker toxicity.
IV:
Neonate, Infant or **Child** 50 mg/kg as a single dose. Maximum dose 200 mg (20 ml). Repeat dose after 10 minutes if necessary. If effective, consider intravenous infusion.

Maintenance correction of acute hypocalcaemia, hyperkalaemia or hypermagnesaemia; maintenance treatment of calcium channel blocker toxicity.
Continuous IV infusion:
Neonate 200 mg/kg daily over 24 hours, adjusted to response.
Infant or **Child *under 2 years*** 500 mg/kg daily (usual maximum 4 g) over 24 hours.
Child *over 2 years* 4 g over 24 hours.

Hydrofluoric acid burns.
Topical:
Child *all ages* apply 2.5% calcium gluconate gel to the affected area for at least 30 minutes, usually longer.

NOTE To extemporaneously prepare 2.5% calcium gluconate gel, combine 2.5 ml (250 mg) of injection solution in 100 ml of water soluble lubricant, such as K-Y Jelly®.

Renal impairment: Moderate to severe impairment: may require dosage adjustment depending on calcium level. Risk of hypercalcaemia and renal calculi.

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: Common Gastrointestinal disturbances, constipation, injection site reactions, fall in blood pressure.

Uncommon Bradycardia, arrhythmia, peripheral vasodilation.

Rare Renal calculi, severe tissue damage with extravasation.

Interactions with other medicines (* indicates severe):

Please consider in the context of poisoning treatment whether interactions are clinically relevant.

Ciprofloxacin: reduced absorption of ciprofloxacin.

Digoxin: large intravenous doses of calcium salts can precipitate arrhythmias.

Hydrochlorothiazide: increased risk of hypercalcaemia.

Levothyroxine: reduced absorption of levothyroxine.

Ofloxacin: reduced absorption of ofloxacin.

Notes: For intravenous infusion, dilute to 20 mg/ml with glucose 5% or sodium chloride 0.9%. Maximum administration rate is 20 mg/kg/hour (or 10 mg/kg/hour in neonates).

For intravenous injection, administer via slow intravenous injection over 5–10 minutes.

Avoid extravasation; should not be given by intramuscular or subcutaneous injection.

Continuous ECG monitoring is recommended during intravenous calcium administration.

Significant hydrofluoric acid poisoning (> 3% of body surface area) may result in marked systemic hypocalcaemia requiring intravenous therapy.

References:

Brent J et al. *Critical care toxicology.* Philadelphia, Elsevier Mosby, 2005.
Dart R, ed. *Medical toxicology. 3rd ed.* Philadelphia, Lippincott Williams & Wilkins, 2004.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Deferoxamine

ATC code: V03AC01

Powder for injection: 500 mg (as mesilate) in vial

Special Notes: Also referred to as desferrioxamine.

Indications: Acute iron poisoning; chronic iron overload.

Precautions: Renal impairment; eye and ear examinations before and at 3 month intervals during treatment are necessary to assess toxicity; aluminium encephalopathy (may exacerbate neurological dysfunction); for all children monitor body weight and height at 3 month intervals (risk of growth restriction with excessive doses).

Dose:

Acute iron poisoning.

Slow IV infusion:

Neonate, Infant or **Child** initially 15 mg/kg/hour, reduced after 4–6 hours so that total dose does not exceed 80 mg/kg in 24 hours. Maximum dose 6 g/day.

IM:

50 mg/kg/dose every 6 hours. Maximum dose 6 g/day.

The preferred route of administration is IV.

NOTE It is uncommon to require more than 24 hours therapy for acute iron overdose. Therapeutic end-points to cease infusion are poorly defined but may be indicated by clinically stable patient and serum iron < 60 micromol/l.

Chronic iron overload.

SC or *IV infusion:*

Infant or **Child** initially up to 30 mg/kg over 8–12 hours, on 3–7 days per week. For established iron overload the dose is usually between 20 and 50 mg/kg daily. The dose should reflect the degree of iron overload. Use the lowest effective dose.

Diagnosis of iron overload.

IM:

Child 500 mg.

Renal impairment: Metal complexes excreted by kidneys (in severe renal impairment dialysis increases rate of elimination).

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: Common Injection site reactions including redness, pain, swelling, rashes and itch, hypotension (especially when given too rapidly by intravenous injection), fever, arthralgia, myalgia, rash, anaphylactoid reactions.

CHRONIC USE Growth retardation, bone deformities (both with high doses).

Uncommon Renal failure, non-cardiogenic pulmonary oedema, disturbances of hearing and vision (including lens opacity and retinopathy).

CHRONIC USE Neurosensory deafness.

Rare Anaphylaxis, acute respiratory distress syndrome, neurological disturbances.

CHRONIC USE Bone marrow depression, ocular toxicity, mucormycosis and other unusual infections.

Interactions with other medicines (* indicates severe):

There are no known significant interactions where it is recommended to avoid concomitant use.

Notes: 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%.

For intramuscular or subcutaneous administration, reconstitute powder with water for injection to a concentration of 100 mg/ml. No further dilution required.

For all children, monitor body weight and height at 3 month intervals (risk of growth restriction with excessive doses).

Iron excretion induced by deferoxamine is enhanced by ascorbic acid and ascorbic acid is sometimes prescribed for this purpose.

References:

Dart R, ed. *Medical toxicology. 3rd ed.* Philadelphia, Lippincott Williams & Wilkins, 2004.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Dimercaprol

ATC code: V03AB09

Injection in oil: 50 mg/ml in 2 ml ampoule

Indications: Acute heavy metal poisoning by antimony, arsenic, bismuth, gold, mercury, possibly thallium; adjunct (with sodium calcium edetate) in lead poisoning.

Contraindications: Not indicated for iron, selenium or cadmium poisoning; severe hepatic impairment (unless due to arsenic poisoning).

Precautions: Hypertension; renal impairment; any abnormal reaction such as hyperpyrexia should be assessed; peanut allergy (peanut oil in injection); G6PD deficiency.

Dose:

Heavy metal poisoning.
IM:
Infant or **Child** 2.5–3 mg/kg every 4 hours for 2 days, 2–4 times on the third day, then 1–2 times daily for 10 days or until recovery.

Renal impairment: Discontinue or use with extreme caution if impairment develops during treatment. Haemodialysis may be required to remove the chelate in renal failure. Urinary alkalinization prior to commencing treatment may reduce nephrotoxicity caused by dissociation of dimercaprol-metal complexes in acid urine.

Hepatic impairment: Severe: avoid use (unless arsenic poisoning).

Adverse effects: Common Hypertension, fever, tachycardia, malaise, nausea, vomiting, abdominal pain, salivation, lacrimation, sweating, burning sensation in the mouth, throat and eyes, injection site pain, headache, muscle spasms, tingling of the extremities, feeling of constriction in throat and chest.

Uncommon Abscess at injection site.

Interactions with other medicines (* indicates severe):

* **Ferrous salts**: avoid concomitant use.

Notes: Administer undiluted via deep intramuscular injection.

References:

Dart R, ed. *Medical toxicology. 3rd ed.* Philadelphia, Lippincott Williams & Wilkins, 2004.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Naloxone

ATC code: V03AB15

Injection: 400 micrograms/ml (hydrochloride) in 1 ml ampoule

Indications: Opioid overdosage.

Contraindications: There are no contraindications to use of naloxone for treatment of opioid toxicity.

Precautions: Physical dependence on opioids or other situations where acute withdrawal syndrome may be precipitated; cardiovascular disease; postoperative patients (may reverse analgesia and increase blood pressure).

Dose:

Opioid overdosage.

IV:

Neonate, Infant or **Child** 10 micrograms/kg; if no response give subsequent dose of 100 micrograms/kg. Review diagnosis if respiratory function does not improve. Further doses may be required if respiratory function deteriorates.

NOTE Naloxone hydrochloride may be administered in the same doses by intramuscular or subcutaneous injection, but only if the intravenous route is not feasible (slower onset of action).

Continuous IV infusion using an infusion pump:
Neonate, Infant or **Child** 5–20 micrograms/kg/hour, adjusted according to response.

Renal impairment: Excretion of some opioids and/or their active metabolites (codeine, dextropropoxyphene, dihydrocodeine, morphine, pethidine, oxycodone) is delayed in impairment and they will accumulate; extended treatment with naloxone infusion may be required to reverse opioid effect.

Hepatic impairment: No dose adjustment necessary.

Adverse effects: Common Nausea, vomiting, sweating.

Uncommon Tachycardia, ventricular arrhythmias.

Rare Cardiac arrest.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is advised to avoid concomitant use.

Notes: For continuous intravenous infusion, dilute to a concentration of 4 micrograms/ml with glucose 5% or sodium chloride 0.9%.

For intravenous bolus, administer over 30 seconds as undiluted preparation.

Intravenous dose may be repeated every 2–3 minutes until response.

After initial response, intravenous dose may need to be repeated every 20–60 minutes due to short duration of action.

Do not give naloxone to neonates of mothers who have been taking methadone or heroin.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Penicillamine

ATC code: M01CC01

Solid oral dosage form: 250 mg

Penicillamine has been associated with fatalities due to agranulocytosis, aplastic anaemia, thrombocytopenia, Goodpasture syndrome and myasthenia gravis. Discontinue therapy if white blood cell count < 3.5 x 10^9/L. Temporarily discontinue treatment if the platelet count < 100 x 10^9/L. Patients and carers should be warned to promptly report any symptoms suggesting toxicity.

Special Notes: Also referred to as D-penicillamine.

Consider use of other metal chelators with better side-effect profile, including sodium calcium edetate and 2,3-dimercaptosuccinic acid if available.

Indications: Heavy metal poisoning, particularly lead and copper.

Contraindications: Hypersensitivity; lupus erythematosus; pregnancy.

Precautions: Monitor blood counts and urine tests throughout treatment; concomitant nephrotoxic drugs; renal impairment; avoid concurrent gold, chloroquine or immunosuppressive treatment; avoid oral iron within 2 hours of a dose; penicillin hypersensitivity (risk of cross-reactivity).

PATIENT ADVICE Warn patient or carer to tell doctor immediately if sore throat, fever, infection, non-specific illness, unexplained bleeding and bruising, purpura, mouth ulcers or rash develop.

Dose:

Heavy metal poisoning, particularly lead and copper.
Oral:
Child *all ages* 7.5 mg/kg 3–4 times daily.
Duration of therapy depends on pretreatment blood levels and may vary from 4–12 weeks.

Renal impairment: Mild impairment: reduce dose and monitor renal function or avoid.

Moderate to severe impairment: avoid.

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: Common Rash, anorexia, nausea, vomiting, taste disturbance.

Uncommon Mouth ulcers, fever, allergy, itching, urticaria, proteinuria.

Rare Haematuria, thrombocytopenia, leukopenia, agranulocytosis, aplastic anaemia, haemolytic anaemia, nephrotic syndrome, lupus erythematosus, Goodpasture syndrome, myasthenia gravis, polymyositis, breast enlargement, hepatic dysfunction, alopecia, pemphigus, dermatomyositis, Stevens-Johnson syndrome.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of penicillamine.

Digoxin: plasma concentration of digoxin possibly reduced.

Ferrous salts: oral ferrous salts reduce absorption of penicillamine.

Ibuprofen: possible increased risk of nephrotoxicity.

Isoniazid: penicillamine potentiates isoniazid.

Zinc sulfate: absorption of penicillamine and zinc sulfate reduced.

Notes: Give on an empty stomach, at least 1 hour before meals or 2 hours after. Separate from milk, food or other drugs by at least 1 hour.

For lead poisoning, continue treatment until urinary lead stabilized at less than 500 micrograms/day.

Adverse effects may be minimized by starting with a small dose and gradually increasing while monitoring for adverse effects.

Monitoring is strongly recommended.

Measure urine and blood concentration of the intoxicating metal weekly.

Perform complete blood count and urinalysis twice weekly for the first month, then every 2 weeks for 6 months and monthly thereafter.

Monitor liver function every 6 months.

Monitor patient's skin, lymph nodes and body temperature.

References:

Dart R, ed. *Medical toxicology. 3rd ed.* Philadelphia, Lippincott Williams & Wilkins, 2004.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Sodium calcium edetate

ATC code: V03AB03

Injection: 200 mg/ml in 5 ml ampoule

Patients with lead encephalopathy and cerebral oedema may experience a lethal increase in intracranial pressure following intravenous infusion; the intramuscular route is preferred for these patients. In cases where the intravenous route is necessary, avoid rapid infusion.

Special Notes: Also referred to as calcium disodium edetate, calcium disodium versenate, ethylenediaminetetraacetic acid, calcium disodium ethylenediaminetetraacetic acid, calcium disodium edathamil, calcium EDTA, calcium disodium EDTA and edetate calcium disodium.

Usually given in conjunction with dimercaprol for lead poisoning.

To avoid potentially serious errors, the abbreviation EDTA should never be used.

Consider use of oral succimer (2,3-dimercaptosuccinic acid) if available in asymptomatic or minimally symptomatic patients due to better safety profile.

Indications: Heavy metal poisoning, particularly lead; lead encephalopathy.

Contraindications: Anuria; active renal disease; hepatitis.

Precautions: Renal impairment; establish urine flow before treatment.

Dose:

Heavy metal poisoning, particularly lead, without encephalopathy.

Continuous IV infusion:

Child *all ages* 20–30 mg/kg per day for up to 5 days.

OR

Deep IM:

Child *all ages* 20–30 mg/kg per day in 2–3 divided doses every 8–12 hours for up to 5 days.

NOTE Depending on blood lead level, additional courses may be necessary. A second course can be given with a 48 hour interval between the first and second courses, and a third course can be given with a 48 hour interval after the second course.

Specialist texts should be consulted for further information on heavy metal poisoning other than lead.

Lead encephalopathy.

Continuous IV infusion:

Child *all ages* 30 mg/kg per day for 5 days.

OR

If evidence of cerebral oedema or increased intracranial pressure, intramuscular administration is recommended.

Deep IM:

Child *all ages* 30 mg/kg per day in 2–3 divided doses every 8–12 hours for 5 days.

NOTE Depending on blood lead level, additional courses may be necessary. A second course can be given with a 48 hour interval between the first and second courses, and a third course can be given with a 48 hour interval after the second course.

Renal impairment: Reduce dose in all degrees of renal impairment. Use with extreme caution.

Hepatic impairment: No dosage reduction necessary.

Adverse effects: Common Sneezing, nasal congestion, numbness, tingling, nausea, diarrhoea, abdominal cramps, fever, malaise, headache, myalgia, thirst, chills.

Uncommon Renal tubular necrosis, pain at injection site, thrombophlebitis (if given too rapidly or as too concentrated a solution), lacrimation, transient hypotension.

Rare Mucocutaneous (mucous membrane) lesions.

Interactions with other medicines (* indicates severe):

Zinc insulin: interferes with zinc insulin by chelating zinc.

Steroids: enhanced renal toxicity.

Notes: For intravenous infusion, dilute to a concentration not more than 30 mg/ml with glucose 5% or sodium chloride 0.9%; give over at least 1 hour.

Dimercaprol concomitant therapy recommended in symptomatic lead poisoning.

Blood lead levels will determine if subsequent courses are required.

References:

Dart R, ed. *Medical toxicology. 3rd ed.* Philadelphia, Lippincott Williams & Wilkins, 2004.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

SECTION 5:
Anticonvulsants/antiepileptics

5 Anticonvulsants/antiepileptics

Guiding principles for drug treatment of epilepsy in children

The aim of drug treatment for epilepsy is to prevent the recurrence of seizures. Treatment of epilepsy in children should also include counselling of the patient and family, treatment of underlying causes where possible, avoidance of precipitating factors, and safety education.

Guiding principles for drug treatment include the following:

- Start with a low dose and increase gradually until seizures are controlled, the maximum dose is reached or there are significant side-effects.
- Aim for single drug therapy (approximately 70% of children will achieve seizure control on a single drug).
- Monitor plasma drug concentrations in some situations.
- Use combination therapy when single drug therapy has failed to control seizures.
- Avoid sudden cessation of medication, since this can precipitate uncontrolled seizures. If a drug fails to control seizures, it should be gradually substituted with another, and the first drug should be withdrawn only when the new regimen is mainly established.

Interactions

Anticonvulsant medication interactions are complex. It is important to check for potential interactions when making any changes to the medication schedule of a child on anticonvulsants.

Carbamazepine

ATC code: N03AF01

Oral liquid: 20 mg/ml

Tablet (chewable): 100 mg; 200 mg

Tablet (scored): 100 mg; 200 mg

The US Food and Drug Administration (FDA) has issued a warning that all patients who are taking, or starting, any antiepileptic should be monitored for changes in behaviour that could indicate the emergence, or worsening, of suicidal thoughts or behaviour or depression.

Rare but potentially fatal blood cell abnormalities (aplastic anaemia and agranulocytosis) have been reported in association with carbamazepine treatment. These mostly occur in the first 3–4 months of treatment.

Stevens-Johnson syndrome and toxic epidermal necrolysis may occur.

Patients and/or carers should be told how to recognize possible blood disorders and severe skin conditions, and to seek medical attention should they occur.

Special Notes: May be referred to as CBZ.

Indications: Generalized tonic-clonic and partial seizures.

Contraindications: Atrioventricular conduction abnormalities; history of bone marrow depression; porphyria.

Precautions: Hepatic impairment; renal impairment; cardiac disease; skin reactions (see Adverse effects); history of blood disorders (monitor blood counts before and during treatment); glaucoma; avoid sudden withdrawal.

Dose:

Generalized tonic-clonic and partial seizures.

Oral:

Infant or **Child** initially 5 mg/kg at night or 2.5 mg/kg twice daily, increased by 2.5–5 mg/kg every 3–7 days if necessary; usual maintenance dose 5 mg/kg 2–3 times daily (up to 20 mg/kg daily may be needed).

Renal impairment: Use with caution.

Severe impairment: administer 75% of dose and monitor serum levels.

Hepatic impairment: Metabolism impaired in advanced liver disease.

Adverse effects: Common Drowsiness, ataxia, dizziness, blurred vision, diplopia, headache (all dose related), rash, dry mouth, abdominal pain, nausea, vomiting, anorexia, diarrhoea, constipation, asymptomatic hyponatraemia, leukopenia, thrombocytopenia, increased liver enzymes (usually not clinically significant).

Rare Severe skin reactions (see below), systemic lupus erythematosus, agranulocytosis, aplastic anaemia, cholestatic jaundice, multi-organ hypersensitivity syndrome (including fever, lymphadenopathy, haematological abnormalities, hepatitis), psychosis, arrhythmia, orofacial dyskinesia, hepatitis, gynaecomastia, galactorrhoea, aggression, jaundice, osteomalacia, confusion, arthralgia.

SEVERE SKIN REACTIONS Include exfoliative dermatitis, Stevens-Johnson syndrome and toxic epidermal necrolysis; may also occur as part of multi-organ hypersensitivity syndrome. Serious reactions mostly occur within the first few months of treatment and are more common in those with the HLA-B*1502 allele, which occurs predominantly in people of Han Chinese or Thai ancestry.

Interactions with other medicines (* indicates severe):

* **Amitriptyline**: antagonism of anticonvulsant effect (seizure threshold lowered); accelerated metabolism of amitriptyline (reduced plasma concentration; reduced antidepressant effect).

  Chloroquine: possibly increased risk of seizures.

* **Chlorpromazine**: antagonism of anticonvulsant effect (seizure threshold lowered).

  Ciclosporin: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* **Dexamethasone**: accelerated metabolism of dexamethasone (reduced effect).

  Doxycycline: accelerated metabolism of doxycycline (reduced effect).

* **Erythromycin**: increased plasma carbamazepine concentration.

  Ethosuximide: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of ethosuximide possibly reduced.

  Fluoxetine: plasma concentration of carbamazepine increased.

  Furosemide: increased risk of hyponatraemia.

* **Haloperidol**: antagonism of anticonvulsant effect (seizure threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration).

  Hydrochlorothiazide: increased risk of hyponatraemia.

* **Hydrocortisone**: accelerated metabolism of hydrocortisone (reduced effect).

* **Isoniazid**: increased plasma carbamazepine concentration (also isoniazid hepatotoxicity possibly increased).

  Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

* **Lopinavir**: possibly reduced plasma lopinavir concentration.

  Mebendazole: reduced plasma mebendazole concentration (possibly increase mebendazole dose for tissue infection).

* **Mefloquine**: antagonism of anticonvulsant effect.

  Miconazole: plasma concentration of carbamazepine possibly increased.

  Phenobarbital: may be enhanced toxicity without corresponding increase in anticonvulsant effect; reduced plasma concentration of carbamazepine. Incidence of serious side-effects such as Stevens-Johnson syndrome may increase when used in combination.

* **Phenytoin**: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered. Incidence of serious side-effects such as Stevens-Johnson syndrome may increase when used in combination.

  Praziquantel: plasma praziquantel concentration reduced.

* **Prednisolone**: accelerated metabolism of prednisolone (reduced effect).

* **Ritonavir**: plasma concentration possibly increased by ritonavir.

  Saquinavir: possibly reduced plasma saquinavir concentration.

  Spironolactone: increased risk of hyponatraemia.

  Valproic acid: may be enhanced toxicity without corresponding increase in anticonvulsant effect; reduced plasma concentration of valproic acid; plasma concentration of active metabolite of carbamazepine increased.

  Vecuronium: antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated).

* **Warfarin**: accelerated metabolism of warfarin (reduced anticoagulant effect).

Notes: Therapeutic drug monitoring (TDM) is available for carbamazepine but routine monitoring is not required for the majority of patients.

Plasma concentration for optimum response 4–12 mg/litre (17–50 micromol/litre).

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Diazepam

ATC code: N05BA01

Rectal solution or gel: 5 mg/ml in 0.5 ml; 2 ml and 4 ml tubes.

Special Notes: Drug subject to international control under the Convention on Psychotropic Substances (1971).

Indications: Status epilepticus; emergency management of recurrent seizures.

Contraindications: CNS depression or coma; shock; respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; marked neuromuscular respiratory weakness including unstable myasthenia gravis.

Precautions: Respiratory disease; muscle weakness and myasthenia gravis; marked personality disorder; hepatic impairment; renal impairment; close observation required until full recovery after sedation; porphyria; neonates and infants.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Status epilepticus, emergency management of recurrent seizures.

Rectal:

Neonate 1.25–2.5 mg repeated once after 10 minutes if necessary.

Infant or **Child** ***less than 2 years*** 5 mg repeated once after 10 minutes if necessary;

greater than 2 years 10 mg repeated once after 10 minutes if necessary.

NOTE Repeat doses should only be administered under medical supervision.

Renal impairment: Severe impairment: consider dose reduction; increased cerebral sensitivity.

Hepatic impairment: Reduce dose as may precipitate coma.

Severe impairment: avoid use.

Adverse effects: Common Drowsiness, sedation, confusion, amnesia, muscle weakness, ataxia, slurred speech.

Uncommon Respiratory depression especially with repeat doses, hypotension, paradoxical insomnia, excitability, hallucinations, aggression, injection pain, thrombophlebitis.

Rare Blood dyscrasias including neutropenia, agranulocytosis, anaemia, leukopenia and thrombocytopenia.

Interactions with other medicines (* indicates severe):

Amitriptyline: enhanced sedative effect.

Chlorphenamine: enhanced sedative effect.

Chlorpromazine: enhanced sedative effect.

Codeine: enhanced sedative effect.

Enalapril: enhanced hypotensive effect.

Furosemide: enhanced hypotensive effect.

Haloperidol: enhanced sedative effect.

Halothane: enhanced sedative effect.

Isoniazid: metabolism of diazepam inhibited.

Ketamine: enhanced sedative effect.

Morphine: enhanced sedative effect.

Nitrous oxide: enhanced sedative effect.

Phenytoin: plasma phenytoin concentrations possibly increased or decreased by diazepam.

Rifampicin: metabolism of diazepam accelerated (reduced plasma concentration).

* **Ritonavir**: plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression; avoid concomitant use).

Spironolactone: enhanced hypotensive effect.

Thiopental: enhanced sedative effect.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Lorazepam

ATC code: N05BA06

Parenteral formulation: 2 mg/ml in 1 ml ampoule; 4 mg/ml in 1 ml ampoule

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Status epilepticus.

Contraindications: CNS depression or coma; shock; respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; marked neuromuscular respiratory weakness including unstable myasthenia gravis.

Precautions: Respiratory disease; muscle weakness and myasthenia gravis; marked personality disorder; hepatic impairment; renal impairment; close observation required until full recovery after sedation; porphyria; neonates and infants.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Status epilepticus.

Slow IV injection:

Neonate, Infant or **Child** 50–100 micrograms/kg (maximum 4 mg) as a single dose, repeated once after 10 minutes if necessary.

Renal impairment: Increased sensitivity to CNS effects in renal impairment; use a lower initial dose in severe impairment.

Hepatic impairment: Contraindicated in severe hepatic impairment, particularly when hepatic encephalopathy is present.

In mild to moderate impairment, use low doses of a short acting benzodiazepine to reduce risk of precipitating coma.

Adverse effects: Common Drowsiness, oversedation, light-headedness, memory loss, hypersalivation, ataxia, slurred speech.

Uncommon Headache, vertigo, disorientation, confusion, paradoxical excitation, euphoria, aggression, hostility, anxiety, anterograde amnesia, respiratory depression, hypotension.

IV INJECTION Pain and thrombophlebitis, severe hypotension, arrhythmias, respiratory arrest.

Rare Blood disorders, including leukopenia and leukocytosis, jaundice, transient elevated liver function tests, allergic reactions, including rash and anaphylaxis.

Interactions with other medicines (* indicates severe):

Amitriptyline: enhanced sedative effect.

Chlorphenamine: enhanced sedative effect.

Chlorpromazine: enhanced sedative effect.

Codeine: enhanced sedative effect.

Enalapril: enhanced hypotensive effect.

Furosemide: enhanced hypotensive effect.

Haloperidol: enhanced sedative effect.

Halothane: enhanced sedative effect.

Isoniazid: metabolism of lorazepam inhibited.

Ketamine: enhanced sedative effect.

Morphine: enhanced sedative effect.

Nitrous oxide: enhanced sedative effect.

Phenytoin: plasma phenytoin concentrations possibly increased or decreased by lorazepam.

Rifampicin: metabolism of lorazepam accelerated (reduced plasma concentration).

* **Ritonavir**: plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression; avoid concomitant use).

Spironolactone: enhanced hypotensive effect.

Notes: Facilities for managing respiratory depression and hypoventilation such as mask, bag and/or mechanical ventilation should be at hand.

ADMINISTRATION For intravenous injection, dilute with an equal volume of sodium chloride 0.9% or water for injection (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.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Phenobarbital

ATC code: N03AA02

Injection: 200 mg/ml (phenobarbital sodium)

Oral liquid: 3 mg/ml (phenobarbital)

Tablet: 15 mg to 100 mg (phenobarbital)

Special Notes: Also known as phenobarbitone.

Drug subject to international control under the Convention on Psychotropic Substances (1971).

Indications: Status epilepticus; generalized tonic-clonic seizures; partial seizures; neonatal seizures.

Contraindications: Porphyria; absence seizures.

Precautions: Renal impairment; hepatic impairment; respiratory depression; debilitated; depression or suicidal tendencies; may cause behavioural changes in children; avoid sudden withdrawal.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Status epilepticus.
Slow IV injection:
Neonate, Infant or **Child** initially 20 mg/kg followed by 2.5–5 mg/kg once or twice daily.

Generalized tonic-clonic seizures, partial seizures.
Slow IV injection followed by *oral:*
Neonate initial dose 20 mg/kg by slow IV injection followed by 2.5–5 mg/kg orally once daily.
Oral:
Infant or **Child** 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.

Neonatal seizures.
Slow IV injection:
Neonate 5–10 mg/kg every 20–30 minutes until control is achieved. Careful clinical monitoring and dosage adjustment are necessary in order to minimize the risk of adverse effects.

THERAPEUTIC DRUG MONITORING Therapeutic drug monitoring should be carried out. Trough plasma concentration for optimum response 15–40 mg/litre (65–170 micromol/litre).

Renal impairment: Use with caution. Avoid large doses in severe impairment.

Hepatic impairment: May precipitate coma. Avoid in severe impairment.

Adverse effects: Prolonged use may cause physical dependence.

Common Sedation, mental depression, paradoxical insomnia, altered mood and behaviour.

Uncommon Ataxia, nystagmus, restlessness, confusion, hypotension.

Rare Exfoliative dermatitis, toxic epidermal necrolysis and Stevens-Johnson syndrome (erythema multiforme), aggression, hyperactivity in children, megaloblastic anaemia, osteomalacia, Dupuytren contracture, multi-organ hypersensitivity syndrome (including fever, severe skin disease, lymphadenopathy, haematological abnormalities, hepatitis).

Interactions with other medicines (* indicates severe):

Abacavir: plasma concentration of abacavir possibly reduced.

* **Amitriptyline**: antagonism of anticonvulsant effect (seizure threshold lowered); metabolism of amitriptyline possibly accelerated (reduced plasma concentration).

* **Carbamazepine**: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of carbamazepine reduced. The incidence of serious side effects such as Stevens-Johnson syndrome may increase when used in combination.

* **Chloramphenicol**: metabolism of chloramphenicol accelerated (reduced chloramphenicol concentration).

* **Chlorpromazine**: antagonism of anticonvulsant effect (seizure threshold lowered).

* **Ciclosporin**: metabolism of ciclosporin accelerated (reduced effect).

* **Dexamethasone**: metabolism of dexamethasone accelerated (reduced effect).

Doxycycline: metabolism of doxycycline accelerated (reduced plasma concentration).

Ethosuximide: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of ethosuximide possibly reduced.

Etoposide: possibly reduced plasma concentration of etoposide.

Fluoxetine: antagonism of anticonvulsant effect (seizure threshold lowered).

Folic acid and folinic acid: plasma concentration of phenobarbital possibly reduced.

Griseofulvin: reduction in absorption of griseofulvin (reduced effect).

* **Haloperidol**: antagonism of anticonvulsant effect (seizure threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration).

* **Hydrocortisone**: metabolism of hydrocortisone accelerated (reduced effect).

Levothyroxine: metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism).

* **Lopinavir**: plasma concentration of lopinavir possibly reduced.

Mebendazole: reduced plasma mebendazole concentration (possibly increase mebendazole dose for tissue infection).

Metronidazole: metabolism of metronidazole accelerated (reduced plasma concentration).

Phenytoin: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised. The incidence of serious side-effects such as Stevens-Johnson syndrome may be increased when used in combination.

* **Prednisolone**: metabolism of prednisolone accelerated (reduced effect).

Quinidine: metabolism of quinidine accelerated (reduced plasma concentration).

* **Saquinavir**: plasma concentration of saquinavir possibly reduced.

Valproic acid: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of valproic acid reduced; phenobarbital concentration increased.

* **Warfarin**: metabolism of warfarin accelerated (reduced anticoagulant effect).

Notes: 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).

Tablets may be crushed before administration.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Phenytoin

ATC code: N03AB02

Capsule: 25 mg; 50 mg; 100 mg (sodium salt)

Injection: 50 mg/ml in 5 ml vial (sodium salt)

Oral liquid: 5 mg or 6 mg/ml* (base)

Tablet: 25 mg; 50 mg; 100 mg (sodium salt)

Tablet (chewable): 50 mg

*NOTE The possible availability of such similar strengths can cause confusion in prescribing and dispensing; extreme care must be taken when prescribing or dispensing this dose form.

Indications: Status epilepticus; generalized tonic-clonic seizures; partial seizures.

Contraindications: Porphyria; sinus bradycardia; heart block.

Precautions: Hepatic impairment; avoid sudden withdrawal; renal impairment; monitor blood counts; injection solution alkaline (irritant to tissues); avoid intramuscular administration

BLOOD OR SKIN DISORDERS Patients or their carers should be told how to recognize signs of blood or skin disorders and advised to seek immediate medical attention if symptoms such as sore throat, rash, mouth ulcers, bruising or bleeding develop. Leukopenia which is severe, progressive or associated with clinical symptoms requires withdrawal (if necessary under cover of suitable alternative).

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Status epilepticus.

IV:

Neonate, Infant or **Child** 18 mg/kg as a loading dose, then 2.5–5 mg/kg twice daily.

Generalized tonic-clonic seizures, partial seizures.

Oral:

Infant or **Child** initially 1.5–2.5 mg/kg twice daily, increased gradually according to clinical response and plasma phenytoin concentrations to 2.5–5 mg/kg twice daily. Usual maximum 7.5 mg/kg or 300 mg daily.

THERAPEUTIC DRUG MONITORING Therapeutic drug monitoring is required for optimum response and to avoid unnecessary toxicities. Therapeutic plasma phenytoin concentrations are reduced in the 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–12 years: 10–20 mg/litre (40–80 micromol/litre).

Renal impairment: No specific dose adjustment is necessary. However, serum phenytoin protein binding is altered in uraemia which can affect proper interpretation/evaluation of serum phenytoin concentrations. The fraction of unbound phenytoin increases as renal function decreases, partially explained by decreases in serum albumin. In these cases clinical outcomes should be considered before changing doses according to blood levels.

Hepatic impairment: Reduce dose to avoid toxicity.

Adverse effects: Common Gastric intolerance, sleeplessness, agitation, sedation, confusion, ataxia, nystagmus, diplopia, blurred vision, slurred speech, cerebellar/vestibular symptoms, behavioural disorders, impaired learning (dose related), gingival hypertrophy, acne, coarse facies, hirsutism, impaired cognition, increased seizure frequency, lymph node enlargement, vertigo, rash (discontinue; if mild, reintroduce cautiously but discontinue if recurrence).

IV Thrombophlebitis, local skin necrosis.

Rare Hallucinations, neurological changes including peripheral neuropathy, choreiform movements, cerebellar atrophy, blood dyscrasias, hyperglycaemia, osteomalacia and rickets, Stevens-Johnson syndrome, toxic epidermal necrolysis, systemic lupus erythematosus, multi-organ hypersensitivity syndrome (including fever, severe skin disease, lymphadenopathy, haematological abnormalities, hepatitis).

IV Cardiovascular and central nervous system depression (particularly if administered too rapidly) with arrhythmias, hypotension and cardiovascular collapse, and alterations in respiratory function (including respiratory collapse), 'purple glove' syndrome (progressive distal limb oedema, discoloration and pain; may lead to soft tissue necrosis and limb ischaemia).

Interactions with other medicines (* indicates severe):

Abacavir: plasma concentration of abacavir possibly reduced.

Acetylsalicylic acid: enhancement of effect of phenytoin.

* **Amitriptyline**: antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma amitriptyline concentration.

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of phenytoin.

Azathioprine: possibly reduced absorption of phenytoin.

Bleomycin: possibly reduced absorption of phenytoin.

* **Carbamazepine**: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of carbamazepine often lowered. Incidence of serious side-effects such as Stevens-Johnson syndrome may be increased in combination therapy.

* **Chloramphenicol**: plasma phenytoin concentration increased (increased risk of toxicity).

Chloroquine: possible increased risk of seizures.

* **Chlorpromazine**: antagonism of anticonvulsant effect (convulsive threshold lowered).

* **Ciclosporin**: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

Ciprofloxacin: plasma phenytoin concentration can be increased or decreased by ciprofloxacin.

Cyclophosphamide: possibly reduced absorption of phenytoin.

Cytarabine: reduced absorption of phenytoin.

Dacarbazine: possibly reduced absorption of phenytoin.

Dactinomycin: possibly reduced absorption of phenytoin.

Daunorubicin: possibly reduced absorption of phenytoin.

* **Dexamethasone**: metabolism of dexamethasone accelerated (reduced effect).

Diazepam: plasma phenytoin concentration possibly increased or decreased by diazepam.

Digoxin: plasma concentration of digoxin possibly reduced.

Doxorubicin: possibly reduced absorption of phenytoin.

Doxycycline: increased metabolism of doxycycline (reduced plasma concentration).

* **Ethosuximide**: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly reduced.

Etoposide: possibly reduced absorption of phenytoin and possibly reduced plasma concentration of etoposide.

* **Fluconazole**: plasma concentration of phenytoin increased (consider reducing dose of phenytoin).

Fluorouracil: metabolism of phenytoin possibly inhibited (increased risk of toxicity).

* **Fluoxetine**: plasma concentration of phenytoin increased.

Folic acid and folinic acid: plasma phenytoin concentration possibly reduced.

* **Haloperidol**: antagonism of anticonvulsant effect (convulsive threshold lowered).
* **Hydrocortisone**: metabolism of hydrocortisone accelerated (reduced effect).
* **Ibuprofen**: effect of phenytoin possibly enhanced.
* **Isoniazid**: metabolism of phenytoin inhibited (enhanced effect).

Levamisole: plasma phenytoin concentration possibly increased.

Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism); plasma concentration of phenytoin possibly increased.

Lopinavir: plasma lopinavir concentration possibly reduced.

Mebendazole: reduced plasma mebendazole concentration (possibly increase mebendazole dose for tissue infections).

* **Mefloquine**: antagonism of anticonvulsant effect.

Mercaptopurine: possibly reduced absorption of phenytoin.

Methotrexate: reduced absorption of phenytoin; antifolate effect of methotrexate increased.

* **Metronidazole**: metabolism of phenytoin inhibited (increased plasma phenytoin concentration).

Phenobarbital: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of phenytoin often lowered but may be raised; plasma concentration of phenobarbital often raised. Incidence of serious side-effects such as Stevens-Johnson syndrome may be increased in combination therapy.

Praziquantel: plasma praziquantel concentration reduced.

* **Prednisolone**: metabolism of prednisolone accelerated (reduced effect).

Procarbazine: reduced absorption of phenytoin.

* **Pyrimethamine**: antagonism of anticonvulsant effect; increased antifolate effect.
* **Quinidine**: accelerated metabolism of quinidine (reduced plasma quinidine concentration).
* **Rifampicin**: accelerated metabolism of phenytoin (reduced plasma concentration).

Saquinavir: plasma saquinavir concentration possibly reduced.

Silver sulfadiazine: possibly increased plasma concentration of phenytoin.

Sulfadiazine: plasma phenytoin concentration possibly increased.

* **Sulfadoxine + pyrimethamine**: plasma phenytoin concentration possibly increased; increased antifolate effect.
* **Sulfamethoxazole + trimethoprim**: antifolate effect and plasma phenytoin concentration increased.
* **Trimethoprim**: antifolate effect and plasma phenytoin concentration increased.

Vaccine, influenza: enhanced effect of phenytoin.

Valproic acid: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of valproic acid reduced; plasma concentration of phenytoin increased or possibly reduced.

Vecuronium: antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade).

Vinblastine: possibly reduced absorption of phenytoin.

Vincristine: possibly reduced absorption of phenytoin.

* **Warfarin**: accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported).

Zidovudine: plasma phenytoin concentration increased or decreased by zidovudine.

Notes: 100 mg phenytoin sodium contains approximately 92 mg phenytoin.

Monitoring of therapeutic concentrations in plasma can improve safety and efficacy.

Preferably take with or after food.

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. Preferably give phenytoin with or after food. To ensure consistent absorption, administer at the same time in regard to meals.

For intravenous 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 (maximum 50 mg/minute).

For intravenous infusion: dilute to a concentration not exceeding 10 mg/ml with sodium chloride 0.9% and give through an inline filter (0.22–0.5 micron) at a rate not exceeding 1 mg/kg/minute (maximum 50 mg/minute); complete administration within 1 hour of preparation.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Valproic acid (sodium valproate)

ATC code: N03AG01

Oral liquid: 40 mg/ml

Tablet (crushable): 100 mg

Tablet (enteric coated): 200 mg; 500 mg (sodium valproate)

Hepatic failure resulting in death may occur.

Cases of life-threatening pancreatitis (including fatalities) have been reported in children.

HYPERSENSITIVITY SYNDROME Usually occurs in first 6 weeks and can be fatal; symptoms include fever, rash, lymphadenopathy, hepatitis, haematological abnormalities; hepato-renal syndrome may occur.

Indications: All forms of epilepsy and seizure disorders including infantile spasms.

Contraindications: Active liver disease; family history of severe hepatic dysfunction; pancreatitis; porphyria; previous history of Stevens-Johnson syndrome.

Precautions: Monitor liver function before and during first 6 months of therapy, especially in patients at most risk (children under 3 years of age, those with metabolic disorders, degenerative disorders, organic brain disease or severe seizure disorders associated with mental retardation, or multiple antiepileptic therapy); ensure no undue potential for bleeding before starting and before major surgery or anticoagulant therapy; renal impairment; hepatic impairment; systemic lupus erythematosus; false-positive urine tests for ketones; avoid sudden withdrawal, unless under medical supervision.

BLOOD OR HEPATIC DISORDERS Patients or their carers should be told how to recognize signs of blood or liver disorders, and advised to seek immediate medical attention if symptoms including loss of seizure control, malaise, weakness, anorexia, lethargy, oedema, vomiting, abdominal pain, drowsiness, jaundice, or spontaneous bruising or bleeding develop.

PANCREATITIS Patients or their carers should be told how to recognize signs of pancreatitis and advised to seek immediate medical attention if symptoms such as abdominal pain, nausea and vomiting develop; discontinue sodium valproate if pancreatitis diagnosed.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

Dose:

All forms of epilepsy and seizure disorders including infantile spasms.

Oral:

Neonate initially 20 mg/kg once daily. Usual maintenance dose is 10 mg/kg twice daily.

Infant or **Child** initially 5–7.5 mg/kg twice daily. Usual maintenance dose is 12.5–15 mg/kg twice daily. Up to 30 mg/kg twice daily in infantile spasms may be required. If dose exceeds 20 mg/kg twice daily, monitor clinical chemistry and haematological parameters.

Renal impairment: Reduce dose and alter dosage according to free serum valproic acid concentration. Renal impairment reduces protein binding; monitoring only total valproic acid serum concentrations may be misleading.

Hepatic impairment: Avoid if possible; hepatotoxicity and hepatic failure may occasionally occur (usually in first 6 months).

Adverse effects: Common Increased appetite and weight gain, gastrointestinal irritation, nausea, hyperammonaemia, ataxia, tremor, impaired hepatic function, sedation, increased alertness, behavioural disturbances, hearing loss.

Uncommon Transient hair loss (regrowth may be curly), inhibition of platelet aggregation, fibrinogen reduction, irregular periods, amenorrhoea, gynaecomastia, toxic epidermal necrolysis, Stevens-Johnson syndrome (erythema multiforme), vasculitis, hirsutism, acne.

Rare Oedema, thrombocytopenia, fatal hepatic failure (see Precautions; withdraw treatment immediately if malaise, weakness, lethargy, oedema, abdominal pain, vomiting, anorexia, jaundice, drowsiness or loss of seizure control), pancreatitis (see Precautions; measure plasma amylase if acute abdominal pain), extrapyramidal symptoms, blood disorders (see Precautions; leukopenia, pancytopenia, red cell hypoplasia, Fanconi syndrome), dementia.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: enhancement of effect of valproic acid.

* **Amitriptyline**: antagonism of anticonvulsant effect (seizure threshold lowered).

Carbamazepine: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of valproic acid reduced; plasma concentration of active metabolite of carbamazepine increased.

* **Chloroquine**: possible increased risk of seizures.

* **Chlorpromazine**: antagonism of anticonvulsant effect (seizure threshold lowered).

Erythromycin: metabolism of valproic acid possibly inhibited (increased plasma concentration).

Ethosuximide: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of ethosuximide possibly increased.

* **Haloperidol**: antagonism of anticonvulsant effect (seizure threshold lowered).

* **Mefloquine**: antagonism of anticonvulsant effect.

Phenobarbital: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of valproic acid reduced; phenobarbital concentration increased.

Phenytoin: may be enhanced toxicity without corresponding increase in anticonvulsant effect; plasma concentration of valproic acid reduced; plasma concentration of phenytoin increased or possibly reduced.

Warfarin: anticoagulant effect possibly enhanced.

Zidovudine: plasma concentration of zidovudine possibly increased (risk of toxicity).

Notes: Plasma concentrations in therapeutic range of 40–100 mg/litre (280–700 micromol/litre); not generally considered useful in assessing control, but higher levels associated with increased incidence of adverse effects; low or undetectable plasma levels are not necessarily an indicator of non-adherence. In patients with confirmed adherence, dose change or co-medication may be needed.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Ethosuximide

ATC code: N03AD01

Capsule: 250 mg

Oral liquid: 50 mg/ml

Indications: Absence seizures.

Precautions: Hepatic impairment; renal impairment; blood counts and hepatic and renal function tests recommended; avoid sudden withdrawal; porphyria.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

BLOOD DISORDERS Children or their carers should be told how to recognize signs of blood disorders such as fever, sore throat, mouth ulcers, bruising or bleeding and be advised to seek immediate medical attention if these symptoms occur.

Dose:

Absence seizures.

Oral:

Infant or **Child** ***1 month–6 years*** initially 5 mg/kg (maximum 125 mg) twice daily, increased gradually over 2–3 weeks to a maintenance dose of 10–20 mg/kg (maximum 500 mg) twice daily; ***6–12 years*** initially 250 mg twice daily, increased by 250 mg at intervals of 4–7 days to a usual dose of 500–750 mg twice daily (occasionally, up to a maximum of 1 g twice daily may be needed).

Renal impairment: Use with caution. Dose reduction not necessary.

Hepatic impairment: Use with caution. Dose reduction not necessary.

Adverse effects: Common Gastrointestinal disturbances including anorexia, hiccups, nausea and vomiting, epigastric pain (particularly during initial treatment), weight loss, drowsiness, dizziness, ataxia, headache, depression, euphoria.

Uncommon Irritability, hyperactivity, sleep disturbances, night terrors, aggressiveness.

Rare Rash including Stevens-Johnson syndrome (erythema multiforme), systemic lupus erythematosus, disturbances of liver and renal function, haematological disorders (including leukopenia, agranulocytosis, aplastic anaemia, thrombocytopenia and pancytopenia), gum hyperplasia, swelling of tongue, increased mental state depression with overt suicidal ideation, psychosis, increased libido, myopia, vaginal bleeding.

Interactions with other medicines (* indicates severe):

* **Amitriptyline**: antagonism of anticonvulsant effect.

  Carbamazepine: may enhance toxicity of carbamazepine without corresponding increase in anticonvulsant effect; possibly reduced plasma concentration of ethosuximide.

  Chloroquine: possible increased risk of seizures.

* **Chlorpromazine**: antagonism of anticonvulsant effect.

* **Haloperidol**: antagonism of anticonvulsant effect (seizure threshold lowered).

* **Isoniazid**: metabolism of ethosuximide inhibited (increased plasma ethosuximide concentration and risk of toxicity).

* **Mefloquine**: antagonism of anticonvulsant effect.

  Phenobarbital: may enhance toxicity of phenobarbital without corresponding increase in anticonvulsant effect; possibly reduced plasma concentration of ethosuximide.

* **Phenytoin**: may enhance toxicity without corresponding increase in anticonvulsant effect; plasma concentration of phenytoin possibly increased; plasma concentration of ethosuximide possibly reduced.

  Valproic acid: may enhance toxicity of valproic acid without corresponding increase in anticonvulsant effect; possibly increased plasma concentration of ethosuximide.

Notes: Administer with food or milk to reduce gastrointestinal upset.

Therapeutic drug monitoring (TDM) is available for ethosuximide but routine monitoring is not required for the majority of patients. Plasma concentration for optimum response 40–100 mg/litre (300–700 micromol/litre).

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf.

SECTION 6:
Anti-infective medicines

6 Anti-infective medicines

6.1 Anthelminthics

6.1.1 Intestinal anthelminthics

Cestode tapeworm infections

Cestode infections include intestinal taeniasis and cysticercosis, hymenolepiasis (dwarf tapeworm), diphyllobothriasis and echinococcosis (hydatid disease). Intestinal tapeworm infections are often asymptomatic. There may be loss of appetite, nausea and abdominal pain. Further symptoms may become apparent due to worm migration, depending on the site affected, which can include the pancreas, bile duct and appendix.

Intestinal nematode infections

Intestinal nematode infections include ascariasis, capillariasis, enterobiasis, hookworm infection, strongyloidiasis, trichostrongyliasis and trichuriasis.

Tissue nematode infections

Tissue nematode infections include angiostrongyliasis, anisakiasis, cutaneous larva migrans, dracunculiasis, trichinellosis and visceral larva migrans.

Albendazole

ATC code: P02CA03

Tablet (chewable): 400 mg

Indications: Treatment of hydatid disease *(Echinococcus granulosus, E. multilocularis)* prior to or not amenable to surgery; hookworms; roundworms; pinworms; threadworms; tapeworm (taeniasis); strongyloidiasis; neurocysticercosis; whipworm; filariasis; hairworm; cutaneous larva migrans; visceral larva migrans and trichinosis.

Contraindications: Known hypersensitivity to benzimidazoles; pregnancy.

Precautions: Liver function tests and blood counts before treatment and every 2 weeks while on therapy; neurocysticercosis (consider steroid and anticonvulsant therapy); retinal cysticercosis.

Dose:

Hydatid disease *(E. granulosus, E. multilocularis).*
Oral:
Child *over 2 years* 7.5 mg/kg twice daily with food (maximum 400 mg twice daily) for 28 days, followed by 14 day break, then repeat for 2–3 cycles.

Hookworms, roundworms, pinworms, threadworms (ancylostomiasis, necatoriasis, ascariasis, enterobiasis).
Oral:
Child *12 months–2 years* 200 mg as a single dose;
greater than 2 years or < 10 kg 400 mg as a single dose before food. Treatment may be repeated in 3 weeks.

Tapeworm (taeniasis), strongyloidiasis.
Oral:
Child *less than 10 kg* 200 mg daily before food for 3 days;
greater than 10 kg 400 mg daily before food for 3 days. Treatment may be repeated in 3 weeks.

Neurocysticercosis.
Oral:
Child *under 60 kg* 7.5 mg/kg (maximum dose 400 mg) twice daily after food for 7–30 days.

Whipworm (Trichuriasis).
Oral:
Child *greater than 2 years* 200–400 mg as a single dose, or in heavier infections, 400 mg daily for 3 days. Treatment may be repeated in 3 weeks.

Filariasis for community eradication programmes in combination with diethylcarbamazine or ivermectin.
Oral:
Child *less than 10 kg* 200 mg once annually for 5 years;
greater than 10 kg 400 mg annually for 5 years.

Hairworm (Trichostrongyliasis).
Oral:
Child *greater than 10 kg* 400 mg as a single dose.

Cutaneous larva migrans.
Oral:
Child *greater than 10 kg* 400 mg as a single dose, or 400 mg daily for 3 days.

Visceral larva migrans (toxocariasis).
Oral:
Child *all ages* 10 mg/kg daily (maximum 400 mg daily) for 5 days.

Trichinosis.
Oral:
Child *greater than 10 kg* 400 mg daily for 8–14 days.

Renal impairment: Renal elimination of albendazole is minimal. Dosage adjustment in patients with impaired renal function does not appear necessary.

Hepatic impairment: Patients with liver disease may be more susceptible to bone marrow suppression.

Adverse effects: Common or uncommon Headache, nausea, vomiting, diarrhoea, abdominal pain, increased liver function tests, dizziness, fever.

Rare Hypersensitivity (itch, rash, urticaria), alopecia, bone marrow depression, hepatitis, cholestatic jaundice, Stevens-Johnson syndrome, pancytopenia, allergic shock if cyst leakage, convulsions and meningism in cerebral disease.

Interactions with other medicines (* indicates severe):

Dexamethasone: plasma albendazole concentration possibly increased.

Praziquantel: increased plasma concentration of active metabolite of albendazole.

Notes: To aid administration, tablets may be dispersed in water, or crushed or chewed.

Patients being treated for neurocysticercosis should receive appropriate steroid and anticonvulsant therapy as required. Oral or intravenous corticosteroids should be considered to prevent cerebral hypertensive episodes during the first week of treatment.

Blood counts should be monitored at the beginning of each 28 day cycle of therapy, and every 2 weeks while on therapy with albendazole in all patients.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Levamisole

ATC code: P02CE01

Tablet: 50 mg; 150 mg (as hydrochloride)

Indications: Treatment of ascariasis; hookworm and mixed ascariasis with hookworm infections.

Precautions: Epilepsy; juvenile idiopathic arthritis; Sjogren syndrome.

Dose:

Ascariasis (roundworm).
Oral:
Infant and **Child** ***all ages*** 2.5–3 mg/kg (maximum dose 150 mg) as a single dose.

Hookworm and mixed ascariasis with hookworm.
Oral:
Infant and **Child** ***all ages*** 2.5 mg/kg (maximum dose 150 mg) as a single dose repeated after 7 days if severe infection.

Renal impairment: Dose reduction not necessary as only small amounts (approximately 3%) of a dose of levamisole are excreted unchanged in the urine.

Hepatic impairment: Use with caution; dose adjustment may be necessary.

Adverse effects: Uncommon Abdominal pain, nausea, vomiting, dizziness and headache.

Rare Taste disturbances (on prolonged treatment), insomnia, seizures (especially at high doses), influenza-like syndrome, blood disorders, vasculitis, arthralgia, myalgia, rash.

Interactions with other medicines (* indicates severe):

Alcohol: possibility of disulfiram-like reaction.

Phenytoin: plasma phenytoin concentration possibly increased.

* **Warfarin**: anticoagulant effect possibly enhanced.

Notes: Leukocyte and platelet counts should be monitored regularly during levamisole therapy.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Mebendazole

ATC code: P02CA01

Tablet (chewable): 100 mg; 500 mg

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Treatment of pinworm; threadworm; roundworm; whipworm and hookworm infections. Also for the gastrointestinal phase of trichinosis *(Trichinella spiralis)* and for capillariasis *(Capillaria philippinensis)*.

As a second-line agent in the treatment of hydatid disease *(Echinococcus granulosus* and *E. multilocularis)* before surgery or not amenable to surgery and also for toxocariasis.

Contraindications: Known hypersensitivity to benzimidazoles; pregnancy.

Precautions: Blood counts and liver function tests should be monitored (with high-dose regimens); children < 6 months old.

Dose:

Threadworms, pinworms.

Oral:

Child *from 6 months up to 10 kg* 50 mg as a single dose, if reinfection occurs second dose may be needed after 2 weeks;

greater than 10 kg or from 1 year 100 mg as a single dose, if reinfection occurs second dose may be needed after 2 weeks.

Whipworms, roundworms, hookworms.

Oral:

Child *from 6 months up to 10 kg* 50 mg twice daily for 3 days;

greater than 10 kg or from 1 year 100 mg twice daily for 3 days.

Capillariasis.

Oral:

Child *all ages from 2 years* 200 mg twice daily for 20 days.

Echinococcus (mebendazole is second-line therapy, albendazole is preferred).

Oral:

Child *all ages from 2 years* 15mg/kg/dose three times daily.

Toxocariasis: visceral larva migrans (mebendazole is second-line therapy, albendazole is preferred).

Oral:

Child *all ages from 2 years* 100–200 mg twice daily for 5 days although doses of up to 1 g/day have been used for 21 days. Severe disease may warrant corticosteroid use.

Trichinosis (gastrointestinal phase of illness only).

Oral:

Child *all ages from 2 years* 5 mg/kg (maximum 200 mg) twice daily with food for 7 days, severe infection may require concomitant corticosteroid use, late phase anthelminthic therapy not indicated.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Extensively metabolized in the liver.

Hepatic insufficiency: lower dose to prevent toxic levels of mebendazole.

Adverse effects: Rare Gastrointestinal disturbances, headache, dizziness, with high doses, allergic reactions, raised liver enzymes, alopecia, bone marrow depression.

Interactions with other medicines (* indicates severe):

Carbamazepine: reduced plasma mebendazole concentration (possibly increase mebendazole dose for tissue infection).

Phenobarbital: reduced plasma mebendazole concentration (possibly increase mebendazole dose for tissue infection).

Phenytoin: reduced plasma mebendazole concentration (possibly increase mebendazole dose for tissue infection).

Notes: Doses should be taken between meals.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Bartlett JG, ed. *Johns Hopkins Point of Care Information Technology (POC-IT) Abx Guide.* (PDA reference.) 2003 (with updates 2004–2009).
Drugs for parasitic infection. *The Medical Letter on Drugs and Therapeutics,* 2004, 46:1–12.
Gilbert DN et al. *The Sanford guide to antimicrobial therapy. 38th ed.* Sperryville, Antimicrobial Therapy, 2008.
Guerrant RL, Walker DH, Weller PF. *Tropical infectious diseases: principles, pathogens, & practice. 2nd ed.* Philadelphia, Churchill Livingstone, 2006.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Niclosamide

ATC code: P02DA01

Tablet (chewable): 500 mg

Special Notes: Niclosamide is listed for use only when praziquantel fails.

Indications: A second-line agent for the treatment of tapeworm *(Taenia saginata, T. solium, Diphyllobothrium latum, Dipylidium caninum* and *Hymenolepis nana)* infections.

Precautions: Chronic constipation (restore regular bowel movement before treatment); give antiemetic before treatment; only active against adult stage of tapeworm (i.e. intestinal stage in host), not effective against larval stage (cysticercosis) (i.e. tissue stage in host).

Dose:

T. solium infection.
Oral:
Child *under 2 years* 500 mg;
2–6 years 1 g;
over 6 years 2 g.
Doses should be given after a light breakfast, followed after 2 hours by a laxative.

T. saginata, Dipylidium caninum and *Diphyllobothrium latum* infection.
Oral:
As for *T. solium* but half the dose may be taken after breakfast and the remainder 1 hour later followed by a laxative after 2 hours.

Symptomatic persisting *Hymenolepis nana* infection.
Oral:
Child *under 2 years* 500 mg on the first day then 250 mg daily for 6 days;
2–6 years 1 g on first day then 500 mg daily for 6 days;
over 6 years 2 g as a single dose on first day then 1 g daily for 6 days, or 2 g daily for 7 days.
Repeated treatment may be necessary to cure intense infections or to eliminate the parasite within a family group or institution.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, retching, abdominal pain.

Uncommon Lightheadedness.

Rare Pruritus, autoinfection.

Notes: Niclosamide must be chewed thoroughly and then swallowed with a small amount of water. Tablets may be crushed to a fine powder for administration to young children and mixed with a small amount of water to form a paste. The drug has a vanilla taste which is palatable for most children.

Niclosamide is effective but may cause disintegration of *T. solium* segments and release viable eggs with subsequent cysticercosis (disease secondary to cysticercus encystment of larvae of *T. solium* in tissues and CNS). Concomitant laxative use 2 hours after niclosamide, although only specifically indicated for *T. solium* infections, is widely recommended, as the precise species of worm may not be confirmed.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Bartlett JG, ed. *Johns Hopkins Point of Care Information Technology (POC-IT) Abx Guide.* [PDA reference] 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Niclocide Product Information. Bayer, 1995 (http://www.drugs.com/mmx/niclocide.html, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Praziquantel

ATC code: P02BA01

Tablet: 150 mg; 600 mg

Indications: Cestodiasis (tapeworm including *Taenia solium, Taenia saginata, Diphyllobothrium latum, Hymenolepsis nana).*

Precautions: SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Ocular or neurocysticercosis; cardiac arrhythmias.

NOTE Praziquantel use in neurocysticercosis is controversial, and depends on activity status of disease. Multidisciplinary expert consultation strongly advised (infectious diseases physician, neurosurgeon (if cerebral or spinal), ophthalmologist (if ocular)).

Dose:

Taenia saginata and *T. solium* infections.
Oral:
Child *over 4 years* 5–10 mg/kg as a single dose.

Symptomatic and persisting *Hymenolepis nana* infection.
Oral:
Child *over 4 years* 15–25 mg/kg as a single dose.
Repeated treatment may be necessary to cure intense infections or to eliminate the parasite within a family group or institution.

Diphyllobothrium latum infection.
Oral:
Child *over 4 years* 10–25 mg/kg as a single dose.

Cysticercosis, dermal cysticercosis.
Oral:
Child *over 4 years* 60 mg/kg daily in three divided doses for 6 days.

Active parenchymal neurocysticercosis.
Oral:
17–33 mg/kg/dose three times daily for 14 days or for 30 days if giant cysts or subarachnoid cysts are present. Albendazole may be preferred over praziquantel.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Consider reducing dose in moderate to severe impairment (increases concentration and half-life).

Adverse effects: Usually mild and transitory with short courses. Many adverse effects result from death of the parasite and are more severe with a high parasite burden.

Symptoms such as papilloedema, retinal haemorrhages, focal seizures and motor weakness may occur in people with neurocysticercosis (due to an intense inflammatory response to dying larvae in CNS).

Others such as skin reactions, eosinophilia and fever are also thought to be responses to antigens released from dying parasites.

Common Dizziness (dose dependent), headache, malaise, drowsiness, nausea, vomiting, abdominal discomfort (dose dependent), diarrhoea, rectal bleeding, anorexia, colic, reversible rises in hepatic aminotransferases, pruritus, rash.

Rare Hypersensitivity reactions including fever, eosinophilia (may be due to dead and dying parasites), arrhythmia.

Interactions with other medicines (* indicates severe):

Albendazole: increased plasma concentration of active metabolite of albendazole.

* **Carbamazepine**: may significantly decrease praziquantel serum concentration.

Chloroquine: plasma praziquantel concentration possibly reduced.

* **Dexamethasone**: plasma praziquantel concentration reduced.

* **Efavirenz**: may significantly decrease praziquantel serum concentration.

Erythromycin: may increase praziquantel serum concentrations.

* **Nevirapine**: may significantly decrease praziquantel serum concentration.

* **Phenobarbital**: may significantly decrease praziquantel serum concentration.

* **Phenytoin**: plasma praziquantel concentration reduced.

* **Rifampicin**: increases metabolism of praziquantel and may reduce its concentration to ineffective levels.

Ritonavir: may increase praziquantel serum concentrations.

Notes: If the tablets or parts of the tablets are kept in the mouth, a bitter taste (which can promote gagging or vomiting) may be experienced.

Swallow whole (unchewed) and take with water during meals. Tablet may be cut into halves or quarters, but do not chew.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Bartlett JG, ed. *Johns Hopkins Point of Care Information Technology (POC-IT) Abx Guide.* (PDA reference.) 2003 (with updates 2004–2009).

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.

Biltricide Product Information. Bayer Schering Pharma AG, 2010 (http://www.drugs.com/pro/biltricide.html, accessed 10 February 2010).

Drugs for parasitic infection. *The Medical Letter on Drugs and Therapeutics,* 2004, 46:1–12.

Garcia HH et al. A trial of antiparasitic treatment to reduce the rate of seizures due to cerebral cysticercosis. *New England Journal of Medicine,* 2004, 350:249–258.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

Maguire JH. Tapeworms and seizures - treatment and prevention. *New England Journal of Medicine,* 2004, 350:215–217.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Pyrantel

ATC code: P02CC01

Oral liquid: 50 mg (as embonate)/ml

Tablet (chewable): 250 mg (as embonate)

Special Notes: Also referred to as pyrantel embonate (EUR), pyrantel pamoate (US).

Indications: Treatment of intestinal nematode infections such as roundworm, hairworm, hookworm, pinworm, threadworm and trichinosis.

Precautions: Liver disease (reduce dose).

Dose:

Roundworm (ascariasis), hairworm (trichostrongyliasis).
Oral:
Child *all ages* 10 mg/kg as a single dose.

Hookworm *(Ancylostoma* and *Necator americanus)* infections.
Oral:
Child *all ages* 10 mg/kg as a single dose; in severe infections, 10 mg/kg daily for 4 days.

Pinworm or threadworm (enterobiasis).
Oral:
Child *all ages* 10 mg/kg as a single dose with a second dose after 2–4 weeks.

Trichinosis.
Oral:
Child *all ages* 10 mg/kg daily for 5 days.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Reduce dose in hepatic impairment.

Adverse effects: Rare Mild gastrointestinal disturbances, headache, dizziness, drowsiness, insomnia, rash and elevated liver enzymes.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Primaquine: may decrease the effect and levels of pyrantel.

Notes: Doses are expressed as base, dose forms expressed as salt.

1 mg of pyrantel base is equivalent to 2.88 mg of pyrantel pamoate or embonate salt.

All family members should be treated.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).

6.1.2 Antifilarials

Loiasis

Loiasis is an infection with the filarial nematode *Loa loa*, and is transmitted by the biting tabanid fly *Chrysops*. Most infections remain asymptomatic, although the classical migration of the adult worm may be seen across the eye.

Lymphatic filariasis

Lymphatic filariasis is caused by infection with *Wuchereria bancrofti* (bancroftian filariasis), *Brugia malayi*, or *B. timori* (brugian filariasis). It is characterized by early fevers and lymphangitis, then progressive lymphatic obstruction of the affected area, often a limb. Occult filariasis (tropical pulmonary eosinophilia) is a clinical variant of *W. bancrofti* infection.

Onchocerciasis

Onchocerciasis (filariasis or river blindness) is caused by infection with the filarial nematode, *Onchocerca volvulus*. The vector is the black fly which breeds near fast flowing rivers. Clinically it appears as an itchy papular rash progressing to skin thickening with loss of elasticity and subcutaneous nodules. The eyes are often also involved.

Ivermectin

ATC code: P02CF01

Tablet (scored): 3 mg; 6 mg

Indications: Suppressive treatment of onchocerciasis (also known as river blindness), lymphatic filariasis and strongyloidiasis.

Contraindications: Pregnancy (delay treatment until after delivery).

Precautions: Loiasis coinfection: may develop life-threatening encephalopathy.

Hyper-reactive onchodermatitis: more likely to have serious adverse reactions especially oedema, transient worsening of onchodermatitis.

Dose:

Onchocerciasis and lymphatic filariasis.
Oral:
Child *over 5 years and over 15 kg* 150 micrograms/kg as a single dose once a year or as necessary.

Strongyloidiasis. Uncomplicated disease.
Oral:
Child *over 5 years and over 15 kg* 200 micrograms/kg once daily for 2 days, take with fatty food.

Strongyloidiasis. Immunocompromised patients, complicated or disseminated infection.
Oral:
Child *over 5 years and over 15 kg* an extended course of 200 micrograms/kg once daily on days 1, 2, 15 and 16.

Cutaneous larva migrans.
Oral:
Child *over 5 years and over 15 kg* 200 micrograms/kg daily for 1–2 days.
In complicated or disseminated infection, daily dosing may be required and expert advice should be sought.
Treatment is not always successful, especially in immunosuppressed patients, and may need to be repeated at monthly intervals or a longer course given.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: In onchocerciasis, adverse effects are more frequent and more severe due to allergic or inflammatory responses to death of the parasite (Mazzotti reaction; see below).

Common Urticaria, vertigo, tremor, raised liver enzymes (ALT and AST), decreased leukocyte count, eosinophilia, increased haemoglobin.

STRONGYLOIDIASIS Diarrhoea, nausea, dizziness, somnolence, abdominal pain.

ONCHOCERCIASIS Mazzotti reaction (see below).

Uncommon Pruritus, rash, mild ocular irritation.

STRONGYLOIDIASIS Fatigue, constipation, vomiting, tremor, rash, itch.

ONCHOCERCIASIS Headache.

Rare Postural hypotension, leukopenia, anaemia, toxic epidermal necrolysis, Stevens-Johnson syndrome.

MAZZOTTI REACTION Occurs within 3 days of treatment, resulting from death of microfilariae; fever, headache, sore throat, cough, rash, conjunctivitis, arthralgia, myalgia, lymphadenopathy, lymphadenitis, oedema, weakness, tachycardia, nausea and vomiting, diarrhoea.

Interactions with other medicines (* indicates severe):

Alcohol: may increase bioavailability of ivermectin.

Notes: PATIENT ADVICE Absorption of ivermectin is enhanced when dosage is taken following ingestion of a fatty meal. Orange juice modestly reduces ivermectin absorption.

Onchocerciasis This treatment does not kill the adult worm, so you may need further treatment.

Strongyloidiasis You will need to have your stools checked to see if the treatment was effective.

Drug of choice for strongyloidiasis.

After a single dose to treat onchocerciasis, skin microfilariae levels are low for up to 9 months (ivermectin does not kill the adult worm).

References:

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.
eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
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Diethylcarbamazine

ATC code: P02CB02

Tablet: 50 mg; 100 mg (dihydrogen citrate)

Indications: Systemic lymphatic filariasis and occult filariasis; loiasis (Loa loa).

Contraindications: Pregnancy (delay treatment until after delivery).

Precautions: Renal impairment; cardiac disorders; other severe acute disease: delay diethylcarbamazine treatment until after recovery.

Alkaline urine (e.g. pH 7.5 to 8); in certain regions (e.g. Ghana), the diet is predominantly vegetarian, which promotes alkaline urine, clinical significance of this is unknown but a dose reduction may be necessary; risk of precipitating meningoencephalitis with heavy Loa loa microfilaraemia.

Dose:

Lymphatic filariasis (bancroftian).
Oral:
Adult and **Child *over 10 years*** 1 mg/kg as a single dose on first day, increased gradually over 3 days to 6 mg/kg daily, preferably in divided doses after meals, for 12 days;
under 10 years half the adult dose.

Lymphatic filariasis (bancroftian). Mass treatment control programmes.
Oral:
Adult and **Child *over 10 years*** 6 mg/kg in divided doses over 24 hours, once a year;
under 10 years half the adult dose.

Lymphatic filariasis (brugian).
Oral:
Adult and **Child *over 10 years*** 1 mg/kg as a single dose on first day, increased gradually over 3 days to 3–6 mg/kg daily, preferably in divided doses after meals, for 6–12 days;
under 10 years half the adult dose.

Lymphatic filariasis (brugian). Mass treatment control programmes.
Oral:
Adult and **Child *over 10 years*** 3–6 mg/kg in divided doses over 24 hours, 6 times at weekly or monthly intervals;
under 10 years half the adult dose.

Filariasis for community eradication programmes.
Oral:
Child *all ages* 6 mg/kg once annually.

Loiasis (Loa Loa).
Oral:
Child *all ages* 6 mg/kg/day in three divided doses for 12 days.

NOTE Corticosteroid and antihistamine cover should be considered for the first 2–3 days of therapy.

The above dose regimens are intended only as a guide, since many countries have developed specific treatment regimens.

Renal impairment: Moderate to severe: reduce dose; plasma half-life prolonged and urinary excretion considerably reduced.

Dose reductions are indicated in patients with renal insufficiency, especially those with an alkaline urine (e.g. pH 8) yet specific dosing guidelines are not available.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Usually mild and transitory with short courses. Many adverse effects result from death of the parasite and are more severe and more common with a high parasite burden.

Immunological reactions (see below), nodules (palpable subcutaneously and along spermatic cord, formed by recently killed worms), transient lymphangitis and exacerbation of lymphoedema.

Uncommon or rare Headache, dizziness, drowsiness, nausea and vomiting.

IMMUNOLOGICAL REACTIONS Usually occur within a few hours of the first dose, subsiding by the fifth day of treatment, including fever, headache, joint pain, dizziness, anorexia, malaise, transient haematuria, urticaria, vomiting, asthma in asthmatics (similar to Mazzotti reaction, induced by disintegrating microfilariae).

Interactions with other medicines (* indicates severe):

Urinary acidifiers: increased loss of diethylcarbamazine, clinical importance of this is unknown.

Urinary alkalinisers (e.g. sodium bicarbonate): decreased loss of diethylcarbamazine, clinical importance of this is unknown.

Notes: Should not be used first line for onchocerciasis.

Diethylcarbamazine should be administered after meals.

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).

References:

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

6.1.3 Antischistosomals and antitrematode medicines

Fluke infections

The intestinal flukes include *Fasciolopsis buski*, *Metagonimus yokogawai*, *Heterophyes heterophyes*, *Echinostoma* spp. and *Gastrodiscoides hominis*. The liver flukes include *Clonorchis sinensis*, *Opisthorchis viverrini*, *O. felineus* and *Fasciola hepatica*. The lung flukes are of the genus *Paragonimus*.

Schistosomiasis

Schistosomiasis, a waterborne parasitic infection, is caused by several species of trematode worms (blood flukes). Intestinal schistosomiasis is caused principally by *Schistosoma mansoni* as well as *S. japonicum*, *S. mekongi* and *S. intercalatum*. Urinary schistosomiasis is caused by *S. haematobium*.

Praziquantel

ATC code: P02BA01

Tablet: 600 mg

Indications: Intestinal schistosomiasis; urinary schistosomiasis, intestinal, liver and lung fluke infections.

Contraindications: Ocular cysticercosis.

Precautions: SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Neurocysticercosis (see section 6.1.1 Praziquantel); cardiac arrhythmias.

Dose:

Trematodiasis. Schistosomiasis.
Oral:
Child *over 4 years* 20 mg/kg/dose three times daily for 1 day.
Or

Schistosoma haematobium and *S. mansoni.*
Oral:
Child *over 4 years* 20 mg/kg/dose twice daily for 1 day.

S. japonicum and *S. mekongi.*
Oral:
Child *over 4 years* 20 mg/kg/dose three times daily for 1 day.

Chlonorchiasis and opisthorchiasis.
Oral:
Child *over 4 years* 25 mg/kg/dose three times daily (at 5 hour intervals) for 1 day.

Paragonimus westermani.
Oral:
Child over 4 years 25 mg/kg dose three times daily for 2 days.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Consider reducing dose in moderate to severe impairment (increases concentration and half-life).

Adverse effects: Usually mild and transitory with short courses. Many adverse effects result from death of the parasite and are more severe with a high parasite burden.

Symptoms may include skin reactions, eosinophilia and fever, which are also thought to be responses to antigens released from dying parasites.

Common Dizziness (dose-dependent), headache, malaise, drowsiness, nausea, vomiting, abdominal discomfort (dose-dependent), diarrhoea, rectal bleeding, anorexia, colic, reversible rises in hepatic aminotransferases.

Rare Hypersensitivity reactions including fever, pruritus, eosinophilia (may be due to dead and dying parasites), arrhythmia.

Interactions with other medicines (* indicates severe):

Albendazole: increased plasma concentration of active metabolite of albendazole.

* **Carbamazepine**: may significantly decrease praziquantel serum concentration.

Chloroquine: plasma praziquantel concentration possibly reduced.

* **Dexamethasone**: plasma praziquantel concentration reduced.

* **Efavirenz**: may significantly decrease praziquantel serum concentration.

Erythromycin: may increase praziquantel serum concentration.

* **Nevirapine**: may significantly decrease praziquantel serum concentration.

* **Phenobarbital**: may significantly decrease praziquantel serum concentration.

* **Phenytoin**: plasma praziquantel concentration reduced.

* **Rifampicin**: increases metabolism of praziquantel and may reduce its concentration to ineffective levels.

Ritonavir: may increase praziquantel serum concentration.

Notes: If the tablets or parts of the tablets are kept in the mouth, a bitter taste (which can promote gagging or vomiting) may be experienced. Swallow tablets whole (unchewed) and take with water during meals. Tablet may be cut into halves or quarters, but do not chew.

References:

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Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Triclabendazole

ATC code: P02BX04

Tablet: 250 mg

Indications: Fascioliasis; paragonimiasis.

Precautions: Paragonimus infections: treatment in hospital as there may be central nervous system involvement; severe fascioliasis: biliary colic, due to obstruction by dying worms.

Dose:

Fascioliasis.

Oral:

Child *over 4 years* 10 mg/kg as a single dose.

Paragonimiasis.

Oral:

Child *over 4 years* 10 mg/kg/dose twice daily for 1 day.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Abdominal pain (predominately right upper quadrant), dizziness, headache, fever, chills.

Rare Leukopenia.

Notes: Take with food.

Ingestion of barley may reduce anthelminthic effectiveness.

References:

Aronson JK, ed. *Meyler's side effects of drugs. 15th ed.* Amsterdam, Elsevier, 2006.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Oxamniquine

ATC code: P02BA02

Capsule: 250 mg

Oral liquid: 50 mg/ml

Special Notes: Oxamniquine is listed for use when praziquantel treatment fails.

Indications: Intestinal schistosomiasis due to *Schistosoma mansoni* (acute stage and chronic hepatosplenic disease).

Contraindications: Pregnancy: delay treatment until after delivery unless immediate intervention necessary.

Precautions: SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Epilepsy or a history of seizures.

Dose:

Intestinal schistosomiasis due to *S. mansoni* (west Africa, South America, Caribbean islands).
Oral:
Child *under 30 kg* 20 mg/kg in 2 divided doses;
30 kg and over 15 mg/kg as a single dose.

Intestinal schistosomiasis due to *S. mansoni* (east and central Africa, Arabian peninsula).
Oral:
Child *all ages* 30 mg/kg in 2 divided doses.

Intestinal schistosomiasis due to *S. mansoni* (Egypt and southern Africa).
Oral:
Child *all ages* 60 mg/kg in divided doses over 2–3 days (maximum single dose 20 mg/kg).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Dizziness, drowsiness, headache, nausea, vomiting, diarrhoea, intense reddish discoloration of urine, EEG abnormalities, ECG abnormalities, scattered pulmonary infiltrates (Loeffler syndrome).

Uncommon Urticaria, pruritic skin rashes, fever, raised liver enzyme values.

Rare Changes in creatine kinase, proteinuria, haematuria, myalgia, eosinophilia, epileptiform seizures, hallucinations, excitement.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: To minimize gastrointestinal side effects, administration after a meal or late in the daytime is recommended.

Used in the treatment of schistosomiasis caused by *S. mansoni*, but not by other *Schistosoma* spp.

References:

Aronson JK, ed. *Meyler's side effects of drugs. 15th ed.* Amsterdam, Elsevier, 2006.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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6.2 Antibacterials

Choice of a suitable antibacterial drug

The choice of an antibacterial drug is based on the identity of the likely pathogen and its antibacterial sensitivity, as well as consideration of various factors relating to the patient (e.g. history of allergy, renal and hepatic function, immune status, severity of illness, ethnic origin and age).

Antibacterial policy

Local policies often limit the availability of antibacterials in order to achieve reasonable economy consistent with adequate antibacterial cover, and to reduce the development of resistant organisms. A policy may allow a range of drugs for general use, and permit use of other drugs only on the advice of a microbiologist or physician responsible for the control of infectious diseases. Guidelines for the management of specific diseases should be consulted when selecting an antibacterial agent.

Before starting therapy

The following should be considered before starting antimicrobial therapy:

- Viral infections should not be treated with antibacterials. Viral upper respiratory tract infections and uncomplicated diarrhoea do not require antibacterial medications.
- When possible, samples should be taken for culture and sensitivity testing. "Blind" antibacterial prescribing for unexplained fever 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.
- The **choice** of an antibiotic for a particular infection should be as specific as possible, reserving broad-spectrum cover for very unwell patients (e.g. those with severe acute malnutrition) when the infecting organism is either unknown or may be one many different species. Narrowing the spectrum, when possible, minimizes potential resistance and limits toxic effects to the patient.
- 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; 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 its toxic and therapeutic doses (e.g. an aminoglycoside), it is equally important to avoid an excessive dose. In such cases, 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 generally require intravenous therapy. However, antibacterials that are well absorbed can be given by mouth even for some serious infections. When 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 this encourages resistance, and prolonged therapy may also lead to unwanted side-effects and unnecessary expense. However, in certain infections, such as tuberculosis or chronic osteomyelitis, it is necessary to treat for prolonged periods.

6.2.1 Beta-lactam medicines

Beta-lactam antibiotics include penicillins, cefalosporins and carbapenems. These share a common structure and are bactericidal, through a mechanism of action directed at the bacterial cell wall.

Hypersensitivity

The most important adverse effect of penicillins is hypersensitivity, which causes a rash, and occasionally anaphylaxis, which can be fatal. Allergic reactions to penicillins occur in 1–10% of exposed individuals, while anaphylactic reactions occur in fewer than 0.05%. Individuals with a history of anaphylaxis, urticaria or rash immediately after penicillin administration are at risk of immediate hypersensitivity with subsequent exposure to penicillins. These individuals should not receive a penicillin, cefalosporin or any other beta-lactam antibiotic. Patients who are allergic to one penicillin will be allergic to them all because hypersensitivity is related to the basic penicillin structure. About 10–15% of penicillin-sensitive patients will be allergic to cefalosporins and other beta-lactams.

Individuals with a history of a minor rash (a non-confluent rash restricted to a small area of the body) or a rash occurring more than 72 hours after penicillin administration are possibly not allergic to penicillin. In these individuals, a penicillin should not be withheld unnecessarily for a serious infection.

Amoxicillin

ATC code: J01CA04

Powder for oral liquid: 125 mg (anhydrous)/5 ml; 250 mg (anhydrous)/5 ml

Solid oral dosage form: 250 mg; 500 mg (anhydrous)

Indications: Urinary tract infections, upper respiratory tract infections, bronchitis; pneumonia; otitis media; dental abscess and other oral infections; osteomyelitis; Lyme disease; endocarditis prophylaxis; post-splenectomy prophylaxis; gynaecological infections; gonorrhoea; anthrax.

Contraindications: Hypersensitivity to penicillins (see section notes); penicillin-associated jaundice or hepatic dysfunction.

Precautions: History of allergy (see section notes); renal impairment; erythematous rashes common in glandular fever, cytomegalovirus infection, chronic lymphatic leukaemia and possibly HIV infection; maintain adequate hydration with high doses (risk of crystalluria).

Dose:

Infections due to sensitive organisms.

Oral:

Child *up to 10 years* 125 mg every 8–12 hours, doubled in severe infections;
over 10 years 250 mg every 8–12 hours, doubled in severe infections.

Otitis media.

Oral:

40 mg/kg daily in three divided doses (maximum 3 g daily).

Renal impairment: Mild to moderate: risk of crystalluria with high doses.

Severe: reduce dose; rashes more common and risk of crystalluria.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, superinfection (including candidiasis), especially during prolonged treatment with broad-spectrum penicillins, allergy.

Uncommon Fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, tooth discoloration, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, electrolyte disturbances (due to their sodium or potassium content), neurotoxicity (e.g. seizures with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment), thrombocytopenia), nephropathy (with parenteral use), Stevens-Johnson syndrome, toxic epidermal necrolysis.

Interactions with other medicines (* indicates severe):

Allopurinol: increased risk of rash.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Warfarin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Amoxicillin + Clavulanic acid

ATC code: J01CR02

Oral liquid: 125 mg amoxicillin + 31.25 mg clavulanic acid/5 ml; 250 mg amoxicillin + 62.5 mg clavulanic acid/5 ml

Tablet: 500 mg + 125 mg

Indications: Infections due to beta-lactamase producing bacteria (where amoxicillin alone not appropriate) including respiratory tract infections, otitis media, genitourinary and abdominal infections, cellulitis, animal bites, severe dental infections, *Haemophilus influenzae*, osteomyelitis and surgical prophylaxis.

Contraindications: Hypersensitivity to penicillins (see section notes); history of penicillin or amoxicillin with clavulanic acid-associated jaundice or hepatic dysfunction.

Precautions: History of allergy (see section notes); renal impairment; erythematous rashes common in glandular fever, cytomegalovirus infection, chronic lymphatic leukaemia and possibly HIV infection; maintain adequate hydration with high doses (risk of crystalluria); hepatic impairment.

Dose:

Infections due to susceptible beta-lactamase producing organisms.
Oral (expressed in terms of amoxicillin):
Child *under 1 year* 20 mg/kg daily in three divided doses;
1–6 years 125 mg every 8 hours;
6–12 years 250 mg every 8 hours;
over 12 years 250 mg every 8 hours.
This dose can be doubled in severe infections.

Renal impairment: Risk of crystalluria with high doses (particularly during parenteral therapy); reduce dose if creatinine clearance less than 30 ml/minute.

Hepatic impairment: Monitor liver function in liver disease.

Cholestatic jaundice reported either during or shortly after treatment; more common in patients over the age of 65 years and in males; duration of treatment should not usually exceed 14 days.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy, transient increases in liver enzymes and bilirubin.

Uncommon Dizziness, headache, fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, tooth discoloration, interstitial nephritis, hepatitis, jaundice, serum sickness-like syndrome, haemolytic anaemia, electrolyte disturbances (due to their sodium or potassium content), neurotoxicity (e.g. seizures with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment), thrombocytopenia), nephropathy (with parenteral use), Stevens-Johnson syndrome, toxic epidermal necrolysis, acute generalised exanthematous pustulosis, cholestatic hepatitis (generally less severe than flucloxacillin hepatitis and is usually reversible. Symptoms may appear during, or several weeks after, treatment and may persist for 5–6 weeks. The risk increases with age (> 55 years), male sex and length of treatment).

Interactions with other medicines (* indicates severe):

Allopurinol: increased risk of rash.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Warfarin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin.

Notes: The risk of acute liver toxicity has been estimated to be about six times higher with amoxicillin + clavulanic acid than amoxicillin.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Ampicillin

ATC code: J01CA01

Powder for injection: 500 mg; 1 g (as sodium salt) in vial

> Not to be given by intrathecal injection as can cause encephalopathy which may be fatal.

Indications: Mastoiditis; gynaecological infections; septicaemia; peritonitis; endocarditis; meningitis; cholecystitis; osteomyelitis.

Contraindications: Hypersensitivity to penicillins (see section notes).

Precautions: History of allergy (see section notes); renal impairment; erythematous rashes common in glandular fever, acute or chronic lymphocytic leukaemia and cytomegalovirus infection.

Dose:

Severe infections due to sensitive organisms (e.g. meningitis).

IV or *IM:*

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–12 years* 50 mg/kg every 4–6 hours (maximum 2 g every 4 hours).

ADMINISTRATION IV administration is preferred. If IM injection is required, lidocaine can be used to reconstitute the injection to reduce local pain.

IV: give over 30 minutes when using doses greater than 50 mg/kg to avoid CNS toxicity, including convulsions.

Renal impairment: Severe: reduce dose or frequency.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site, superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy.

Uncommon Fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, electrolyte disturbances (due to their sodium or potassium content), neurotoxicity (e.g. convulsions with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment), thrombocytopenia), nephropathy (with parenteral use), Stevens-Johnson syndrome, toxic epidermal necrolysis.

Interactions with other medicines (* indicates severe):

Allopurinol: increased risk of rash.

Aminoglycosides: separate in terms of IV administration by 1 hour, preferably, due to inactivation of the aminoglycoside by the penicillin.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Warfarin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin.

Notes: IV penicillins are physically incompatible with many substances (including aminoglycosides); give separately.

Avoid rapid IV administration of large doses as it may result in seizures.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Benzathine benzylpenicillin

ATC code: J01CE08

Powder for injection: 900 mg benzathine benzylpenicillin (= 1.2 million IU) in 5 ml vial; 1.8 g benzathine benzylpenicillin (= 2.4 million IU) in 5 ml vial

Do not give by intravenous injection.

Indications: Streptococcal pharyngitis; diphtheria; syphilis and other treponemal infections (yaws, pinta, bejel); rheumatic fever prophylaxis.

Contraindications: Penicillin hypersensitivity (see section notes); intravascular injection; neurosyphilis.

Precautions: History of allergy (see section notes); renal failure.

Dose:

Do not give by intravenous injection.

Streptococcal pharyngitis; primary prophylaxis of rheumatic fever.
Deep IM:
Child *under 30 kg* 450–675 mg (600 000–900 000 IU) as a single dose;
30 kg and over 900 mg (1.2 million IU) as a single dose.

Secondary prophylaxis of rheumatic fever.
Deep IM:
Child *under 30 kg* 450 mg (600 000 IU) once every 3–4 weeks;
30 kg and over 900 mg (1.2 million IU) once every 3–4 weeks.

Congenital syphilis (where no evidence of CSF involvement).
Deep IM:
Child *up to 2 years* 37.5 mg/kg (50 000 IU/kg) as a single dose.

Yaws, pinta and bejel.
Deep IM:
Child 450 mg (600 000 IU) as a single dose.

Renal impairment: Severe: neurotoxicity; high doses may cause convulsions.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site, superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy.

Uncommon Fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, tooth discoloration, joint pain, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, electrolyte disturbances (due to their sodium or potassium content), neurotoxicity (e.g. seizures with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment), thrombocytopenia), nephropathy (with parenteral use), Stevens-Johnson syndrome, toxic epidermal necrolysis, Jarisch-Herxheimer reaction. This consists of fever, chills, headache, hypotension and flare-up of lesions (due to release of pyrogens from the organisms and endotoxins) during treatment for syphilis and other spirochaete infections. Lasts for 12–24 hours; symptoms can be alleviated by acetylsalicylic acid (aspirin) or prednisolone; can be dangerous in cardiovascular syphilis or where there is serious risk of local damage, e.g. optic atrophy.

ACCIDENTAL INTRAVASCULAR ADMINISTRATION May result in severe neurovascular damage. CNS effects, including anxiety, agitation, fear of death and hallucinations (usually resolving in 15–30 minutes, but rarely lasting for up to 24 hours) may also occur.

Interactions with other medicines (* indicates severe):

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Notes: Give by deep IM injection only.

Give doses > 900 mg (1.2 million IU) as two injections at separate sites.

It may require that the dose to be divided into two sites if there is reduced muscle bulk.

Absorbed slowly into circulation and hydrolysed to benzylpenicillin; use when prolonged, low concentrations of benzylpenicillin are appropriate and adequate.

In adults duration of effect of 900 mg (1.2 million IU) dose is 2–4 weeks.

Syringes are not graduated; part syringe dosing is not accurate but is used.

Benzathine benzylpenicillin 900 mg = 720 mg benzylpenicillin = 1.2 million IU.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Benzylpenicillin

ATC code: J01CE01

Powder for injection: 600 mg (= 1 million IU); 3 g (= 5 million IU) (sodium or potassium salt) in vial

Special Notes: Also known as penicillin G.

Indications: Pneumonia; throat infections; otitis media; Lyme disease; streptococcal endocarditis; meningococcal disease; necrotizing enterocolitis; necrotizing fasciitis; leptospirosis; neurosyphilis; anthrax; relapsing fever; actinomycosis; brain abscess; gas gangrene; cellulitis; osteomyelitis.

Contraindications: Penicillin hypersensitivity (see section notes); avoid intrathecal route (see section notes).

Precautions: History of allergy (see section notes); renal failure; heart failure.

Dose:

Mild to moderate infections due to sensitive organisms.
IV or *IM:*
Neonate *under 1 week* 50 mg/kg daily in two divided doses;
Neonate *1–4 weeks* 75 mg/kg daily in three divided doses.
Child *1 month–12 years* 100 mg/kg daily in four divided doses.
Higher doses are used in severe infections (see also below).

Meningococcal disease.
IV or *IM:*
Premature infant and **Neonate *under 1 week*** 100 mg/kg daily in two divided doses.
Neonate *1–4 weeks* 150 mg/kg daily in three divided doses.
Child *1 month–2 years* 180–300 mg/kg daily in 4–6 divided doses.

Suspected meningococcal disease (before transfer to hospital).
IV or *IM:*
Infant *under 1 year* 300 mg.
Child *1–9 years* 600 mg;
10 years and over 1.2 g.

Congenital syphilis.
IV:
Infant and **Child *up to 2 years*** 30 mg/kg twice daily for the first 7 days of life, then 30 mg/kg three times daily for 3 days.
IV or *IM:*
Child *2 years and over* 120–180 mg/kg (to a maximum of 1.44 g) daily in 4–6 divided doses for 10–14 days.

Renal impairment: Severe: maximum 6 g daily; neurotoxicity (high doses may cause convulsions).

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site, superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy.

Uncommon Fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, tooth discoloration, joint pains, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, electrolyte disturbances (due to their sodium or potassium content), neurotoxicity (e.g. seizures with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment), thrombocytopenia), nephropathy (with parenteral use), Stevens-Johnson syndrome, toxic epidermal necrolysis, Jarisch-Herxheimer reaction. This consists of fever, chills, headache, hypotension and flare-up of lesions (due to release of pyrogens from the organisms and endotoxins) during treatment for syphilis and other spirochaete infections. Lasts for 12–24 hours; symptoms can be alleviated by acetylsalicylic acid (aspirin) or prednisolone; can be dangerous in cardiovascular syphilis or where there is serious risk of local damage, e.g. optic atrophy.

Interactions with other medicines (* indicates severe):

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Notes: Intravenous route preferred for neonates and infants; doses over 1.2 g by intravenous route only.

IV penicillins are physically incompatible with many substances (including aminoglycosides); give separately.

Avoid rapid IV administration of large doses as it may result in convulsions. Longer administration time is particularly important when using doses of ≥ 50 mg/kg to avoid CNS toxicity.

Contains 3.4 mmol (78 mg) sodium per 1.2 g injection.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Cefalexin

ATC code: J01DB01

Powder for reconstitution with water: 25 mg/ml; 50 mg/ml

Solid oral dosage form: 250 mg

Special Notes: Also referred to as cephalexin.

Indications: Infection due to sensitive organisms, urinary tract infections, mild cellulitis.

Contraindications: Cefalosporin hypersensitivity.

Precautions: Renal impairment; impaired vitamin K synthesis, low vitamin K stores (chronic disease and malnutrition) as increased risk of bleeding; allergy to cefalosporins; a severe or immediate allergic reaction (including urticaria, anaphylaxis or interstitial nephritis) to a penicillin.

Dose:

Oral:

Infant and **Child** 6.25–12.5 mg/kg/dose every 6 hours. Up to maximum of 25 mg/kg/dose every 6 hours may be used in severe infections.

The same daily dose may be given twice daily for uncomplicated urinary tract infections, streptococcal pharyngitis and tonsillitis, skin and soft tissue infections, however this is not recommended if > 500 mg per dose is required.

Renal impairment: Reduce dose in moderate impairment.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, electrolyte disturbances.

Uncommon Vomiting, headache, dizziness, oral and vaginal candidiasis, *Clostridium difficile*-associated disease, superinfection, eosinophilia, drug fever.

Rare Anaphylactic shock, bronchial obstruction, cholestatic hepatitis, urticaria, haemolytic anaemia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome, neurotoxicity (including seizures), blood dyscrasias (e.g. neutropenia (related to dose and treatment duration), thrombocytopenia), bleeding, renal impairment.

Interactions with other medicines (* indicates severe):

Cefalosporins can cause renal impairment; administration with other drugs which also have this effect may increase risk of nephrotoxicity.

Metformin: increase in metformin plasma levels and may increase risk of metformin side-effects (nausea, vomiting, diarrhoea, asthenia, headache).

Typhoid vaccine, live: a decreased immunological response to the typhoid vaccine.

Notes: Hypersensitivity to cefalosporins occurs in about 0.5–6.5% of penicillin sensitive patients.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Cefazolin

ATC code: J01DB04

Powder for injection: 1 g (as sodium salt) in vial

Special Notes: WHO age/weight restriction: > 1 month.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Prophylaxis of infection in surgery; treatment of MSSA in non-anaphylactic penicillin allergy.

Contraindications: Cefalosporin hypersensitivity (see section 6.2.1).

Precautions: Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction; see section 6.2.1); moderate renal impairment; false-positive urinary glucose (if tested for reducing substances) and false-positive Coombs' test; seizure disorders.

Dose:

Surgical prophylaxis.

Deep IM or *IV:*

Infant *over 1 month* 25 mg/kg (maximum 1 g dose) as a single dose at induction of anaesthesia, repeated if necessary if surgery lasts over 3 hours. Further doses may be given every 6–8 hours postoperatively for 24 hours if necessary, or for up to 5 days in continued risk of infection. Intramuscular administration may be painful and should be avoided where possible. If IM injection is required/necessary cefazolin can be reconstituted with lidocaine 0.5%.

Renal impairment: Moderate: reduce dose.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site.

Uncommon Vomiting, headache, dizziness, oral and vaginal candidiasis, *Clostridium difficile*-associated disease, superinfection, eosinophilia, drug fever.

Rare Confusion (after large doses in renal failure), anaphylaxis, bronchial obstruction, urticaria, haemolytic anaemia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, renal impairment including interstitial nephritis, abnormal liver function tests, arthritis, serum sickness-like syndrome, neurotoxicity (including seizures), blood dyscrasias including neutropenia, eosinophilia, thrombocytopenia, leukopenia, thrombocythaemia and bleeding.

Interactions with other medicines (* indicates severe):

Cefalosporins can cause renal impairment; administration with other drugs which also have this effect may increase risk of nephrotoxicity.

Typhoid vaccine, live: a decreased immunological response to the typhoid vaccine.

* **Warfarin**: possibly enhanced anticoagulant effect.

Notes: IV products are physically incompatible with many substances; avoid mixing with other drugs.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Pharmacy Department, The Royal Children's Hospital. *Paediatric Injectable Guidelines. 3rd ed.* Melbourne, The Royal Children's Hospital, 2006.
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WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Ceftriaxone

ATC code: J01DD04

Powder for injection: 250 mg; 1 g (as sodium salt) in vial

Use with calcium (see Contraindications) and avoid in infants with hyperbilirubinaemia.

Special Notes: WHO age/weight restriction: > 41 weeks corrected gestational age.

Indications: Serious infections due to sensitive bacteria, including septicaemia, pneumonia and meningitis; osteomyelitis, septic arthritis; *Haemophilus influenzae* epiglottitis; surgical prophylaxis; prophylaxis of meningococcal meningitis; shigellosis, invasive salmonellosis; endocarditis; gonococcal conjunctivitis; gonorrhoea; pelvic inflammatory disease; Lyme disease.

Contraindications: Cefalosporin hypersensitivity (see section 6.2.1); porphyria; neonates with jaundice, hypoalbuminaemia, acidosis or impaired bilirubin binding; concomitant treatment with calcium (ceftriaxone should not be used in neonates less than 28 days of age if they are receiving (or are expected to receive) calcium-containing intravenous products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid).

Precautions: Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction; see also section 6.2.1); severe renal impairment; hepatic impairment if accompanied by renal impairment; premature neonates (may displace bilirubin from serum albumin); treatment longer than 14 days, renal failure, dehydration or concomitant total parenteral nutrition (risk of ceftriaxone precipitation in gallbladder); false-positive urinary glucose (if tested for reducing substances) and false-positive Coombs' test.

Dose:

Infections due to susceptible organisms.

Deep IM or *IV:*

Neonate ***7 days or under*** 50 mg/kg daily (maximum dose 1 g);
Neonate ***over 7 days*** 75 mg/kg daily (maximum dose 1 g).
Infant and **Child** ***under 50 kg*** 50–100 mg/kg daily (maximum dose 1 g); higher dose reserved for severe infections.

Neonatal gonococcal conjunctivitis.

IM:

Neonate 50 mg/kg as a single dose (maximum 125 mg).

Prophylaxis of secondary case of meningococcal meningitis.

IM:

Child ***1 month–12 years*** 125 mg as a single dose;
12–18 years 250 mg as a single dose.

ADMINISTRATION Doses of 50 mg/kg and over should be given by intravenous infusion only.

Intramuscular doses over 1 g divided between more than one site.

For IM injection: ceftriaxone may be mixed with lidocaine 1% to 450 mg/ml to reduce pain at intramuscular site.

Administer by intravenous injection (over at least 3 minutes) or by intravenous infusion (over 30 minutes).

Intravenous infusions for neonates should be over 60 minutes (see also Contraindications).

Renal impairment: Severe: maximum 50 mg/kg daily (maximum 2 g daily); also monitor plasma concentration if both severe renal impairment and hepatic impairment.

Hepatic impairment: Reduce dose and monitor plasma concentration if both hepatic and severe renal impairment.

Adverse effects: Common Diarrhoea, nausea, rash, electrolyte disturbances, abnormalities in liver function enzymes, pain and inflammation at injection site, thrombocytosis, leukopenia.

Uncommon Vomiting, headache, dizziness, oral and vaginal candidiasis, *Clostridium difficile*-associated disease, superinfection, eosinophilia, drug fever.

Rare Anaphylaxis, bronchial obstruction, urticaria, haemolytic anaemia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome, neurotoxicity (including seizures), blood dyscrasias (including thrombocytopenia, neutropenia, haemolytic anaemia, anaemia, haemolysis), prolongation of prothrombin time, renal impairment, pancreatitis, increased bilirubin, jaundice, pseudolithiasis (dose-dependent, asymptomatic and reversible biliary sludge formation due to calcium-ceftriaxone complex; has been mistaken for gallstones on ultrasound scans and usually resolves after stopping treatment), nephrolithiasis (formation of calcium-ceftriaxone renal stones, sometimes requiring treatment; usually reversible).

Interactions with other medicines (* indicates severe):

Calcium salts.

Ciclosporin: increased risk of ciclosporin toxicity (renal dysfunction, cholestasis, paraesthesia).

Lactated Ringer's solution: formation of ceftriaxone-calcium precipitates and is contraindicated.

Ringer's solution: formation of ceftriaxone-calcium precipitates and is contraindicated.

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

* **Warfarin**: possibly enhanced anticoagulant effect.

Notes: Cefotaxime is preferred to ceftriaxone for Gram-negative septicaemia in neonates as ceftriaxone displaces bilirubin from albumin and may increase risk of bilirubin encephalopathy. However, single dose ceftriaxone is used to treat neonatal gonococcal conjunctivitis.

Concomitant use of ceftriaxone and intravenous calcium-containing products is contraindicated in neonates (< 28 days of age). Ceftriaxone should not be used in neonates (< 28 days of age) if they are receiving (or are expected to receive) calcium-containing intravenous products.

In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid. Ceftriaxone must not be administered simultaneously with intravenous calcium-containing solutions via a Y-site in any age group.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Pharmacy Department, The Royal Children's Hospital. *Paediatric Injectable Guidelines. 3rd ed.* Melbourne, The Royal Children's Hospital, 2006.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Cloxacillin

ATC code: J01CF02

Capsule: 500 mg; 1 g (sodium salt)

Powder for injection: 500 mg (as sodium salt) in vial

Powder for oral liquid: 125 mg (as sodium salt)/5 ml

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Infections due to beta-lactamase-producing staphylococci including impetigo, cellulitis and other soft-tissue infections; pyomyositis; staphylococcal endocarditis, septicaemia, pneumonia, septic arthritis and osteomyelitis; otitis externa.

Contraindications: Hypersensitivity to penicillins (see sections notes).

Precautions: History of allergy (see section notes); renal and hepatic impairment; heart failure.

Dose:

Infections due to susceptible beta-lactamase-producing staphylococci.

Oral:

Child *all ages* 12.5–50 mg/kg/dose four times daily, depending upon severity of infection.

Oral cloxacillin is not optimal for the treatment of severe infections. Parenteral therapy would be preferred.

IM or *IV:*

Child *all ages* 12.5–50 mg/kg/dose four times daily, depending upon severity of infection.

Renal impairment: Severe: reduce dose.

Hepatic impairment: Dose reduction not necessary; observe for worsening hepatic function.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site, phlebitis or thrombophlebitis at injection sites, transient increases in liver enzymes and bilirubin, superinfection (including candidiasis).

Uncommon Fever, vomiting, *Clostridium difficile*-associated disease.

Rare Contact dermatitis, nail damage, electrolyte disturbances (due to their sodium or potassium content), agranulocytosis, coagulation disorders, jaundice, cholestatic hepatitis, hepatotoxicity, nephrotoxicity, interstitial nephritis, serum sickness-like syndrome, immune hypersensitivity reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Interactions with other medicines (* indicates severe):

Aminoglycosides: concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine. Suggestion: allow 24 hours or more to elapse between the last dose of antibiotic and the administration of oral live typhoid vaccine.

Warfarin: increased risk of bleeding.

Notes: Take on an empty stomach 30 minutes before meals as the presence of food in the stomach decreases absorption.

Cholestatic jaundice may occur up to several weeks after treatment has been stopped; administration for more than 2 weeks and increasing age are risk factors.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
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Phenoxymethylpenicillin

ATC code: J01CE02

Powder for oral liquid: 250 mg (as potassium salt)/5 ml

Tablet: 250 mg (as potassium salt)

Special Notes: Also referred to as penicillin V.

Indications: Streptococcal pharyngitis; otitis media; cellulitis; mouth infections; secondary prophylaxis of rheumatic fever; post-splenectomy prophylaxis.

Contraindications: Hypersensitivity to penicillins (see section notes); serious infections (see section notes).

Precautions: History of allergy (see section notes); infectious mononucleosis (high incidence of rash).

Dose:

Infections due to sensitive organisms.

Oral:

Child *all ages* 10–12.5 mg/kg/dose (maximum 500 mg) every 6 hours. Dose may be doubled in severe infections.

Secondary prophylaxis of rheumatic fever.

Oral:

Child *all ages* 10–12.5 mg/kg/dose (maximum 500 mg) twice daily.

Renal impairment: Dosage adjustment not necessary.

Hepatic impairment: Dosage adjustment may be necessary in patients with impaired liver function when they also have renal failure.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy.

Uncommon Fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, tooth discoloration, joint pains, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, neurotoxicity (e.g. seizures with high doses or impaired renal function), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment), thrombocytopenia), nephropathy (with parenteral use), Stevens-Johnson syndrome, toxic epidermal necrolysis.

Interactions with other medicines (* indicates severe):

Aminoglycosides: concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.

Chloramphenicol: decreased antibacterial effectiveness.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine.

Notes: Relatively acid-stable, so it can be given orally.

PATIENT ADVICE Phenoxymethylpenicillin should be taken at least 30 minutes before or 2 hours after food.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Procaine benzylpenicillin

ATC code: J01CE09

Powder for injection: 1 g (= 1 million IU); 3 g (= 3 million IU) in vial

Accidental intravascular administration may result in severe neurovascular damage. CNS effects including anxiety, agitation, fear of death and hallucinations (usually resolving in 15–30 minutes, but rarely lasting for up to 24 hours) may also occur.

Special Notes: Also referred to as penicillin G procaine.

Indications: Syphilis; anthrax; pneumonia; diphtheria; cellulitis; mouth infections; bites.

Contraindications: Hypersensitivity to penicillins (see section notes); intravascular injection.

Precautions: History of allergy (see section notes); renal failure; sodium restriction, heart failure (some parenteral penicillins have high sodium content); infectious mononucleosis (high incidence of rash).

Dose:

Never administer intravenously.

Pneumonia.
Deep IM:
Child *all ages* 50 mg/kg (maximum 1.2 g) daily for 10 days.

Congenital syphilis.
Deep IM:
Child *up to 2 years* 50 mg/kg daily for 10 days.

Renal impairment: Severe: neurotoxicity; high doses may cause convulsions.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, urticaria, pain and inflammation at injection site (less common with benzylpenicillin), superinfection (including candidiasis) especially during prolonged treatment with broad-spectrum penicillins, allergy.

Uncommon Fever, vomiting, erythema, exfoliative dermatitis, angioedema, *Clostridium difficile*-associated disease.

Rare Anaphylaxis, bronchospasm, interstitial nephritis, serum sickness-like syndrome, haemolytic anaemia, electrolyte disturbances (due to sodium or potassium content), neurotoxicity, Hoigné syndrome (bizzare behaviour, neurological reactions), coagulation disorders, blood dyscrasias (e.g. neutropenia (related to dose and duration of treatment)), nephropathy (with parenteral use), muscular contractures in neonates and infants, Stevens-Johnson syndrome, toxic epidermal necrolysis, Jarisch-Herxheimer reaction (fever, chills, headache, hypotension and flare-up of lesions (due to release of pyrogens from the organisms and endotoxins) during treatment for syphilis and other spirochaete infections. Lasts for 12–24 hours; symptoms can be alleviated by acetylsalicylic acid (aspirin) or prednisolone; can be dangerous in cardiovascular syphilis or where there is serious risk of local damage, e.g. optic atrophy).

Interactions with other medicines (* indicates severe):

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Methotrexate: reduced excretion of methotrexate (increased risk of toxicity).

Notes: Inject at a slow, steady rate to avoid blockage of the needle.

Procaine benzylpenicillin is not recommended as first-line treatment for neonatal sepsis except in settings with high neonatal mortality, when given by trained health workers in cases where hospital care is not achievable.

Dose equivalence: 1 g = 1 million units.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
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Cefotaxime

ATC code: J01DA10

Powder for injection: 250 mg per vial

Indications: Serious infections due to sensitive bacteria, including septicaemia, pneumonia and meningitis; osteomyelitis, septic arthritis; *Haemophilus influenzae* epiglottis; surgical prophylaxis; prophylaxis of meningococcal meningitis; shigellosis, invasive salmonellosis; endocarditis; gonococcal conjunctivitis; gonorrhoea; pelvic inflammatory disease; Lyme disease.

Contraindications: Cefalosporin hypersensitivity.

Precautions: Renal impairment; sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction: see section 6.2.1); impaired vitamin K synthesis, low vitamin K stores (chronic disease and malnutrition) as increased risk of bleeding.

Dose:

Infections due to sensitive Gram-positive and Gram-negative bacteria, surgical prophylaxis, *haemophilus* epiglottitis and meningitis.
IV or *IM:*
Neonate *under 7 days* 25 mg/kg every 12 hours;
Neonate *7–21 days* 25 mg/kg every 8 hours;
Neonate *21–28 days* 25 mg/kg every 6–8 hours.
Child *1 month–18 years* 50 mg/kg every 8–12 hours, increase to every 6 hours in severe infection and meningitis (maximum 12 g daily).
Neonatal doses may be doubled in severe infection and meningitis.

Gonorrhoea.
IV or *IM:*
Child *1 month–18 years* 500 mg as a single dose.

ADMINISTRATION IV administration is preferred. Inject IV over 3–5 minutes to avoid arrhythmias.

If IM injection is required cefotaxime may be reconstituted with lidocaine 0.5% to 300 mg/ml.

Renal impairment: Reduce dose in moderate renal impairment.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site.

Uncommon Vomiting, headache, dizziness, oral and vaginal candidiasis, *Clostridium difficile*-associated disease, superinfection, eosinophilia, drug fever.

Rare Life-threatening arrhythmias with rapid IV administration, anaphylactic shock, bronchial obstruction, urticaria, haemolytic anaemia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome, neurotoxicity (including seizures), blood dyscrasias (e.g. neutropenia (related to dose and treatment duration), thrombocytopenia), bleeding, renal impairment.

Interactions with other medicines (* indicates severe):

Cefalosporins can cause renal impairment; administration with other drugs which also have this effect may increase risk of nephrotoxicity.

Aminoglycosides: concomitant cefalosporins and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by one hour.

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine. Suggestion: allow 24 hours or more to elapse between the last dose of antibiotic and the administration of oral live typhoid vaccine.

Notes: Rapid IV administration of large doses may result in seizures, especially if inappropriately high doses are used in renal impairment.

Use instead of ceftriaxone for Gram-negative septicaemia in neonates.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Ceftazidime

ATC code: J01DD02

Powder for injection: 250 mg or 1 g (as pentahydrate) in vial

Indications: Infections due to sensitive bacteria, especially those due to *Pseudomonas* spp. and including those resistant to aminoglycosides.

Contraindications: Cefalosporin hypersensitivity (see section 6.2.1).

Precautions: Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction; see section 6.2.1); aztreonam allergy: person may cross-react to ceftazidime; renal impairment; false-positive urinary glucose (if tested for reducing substances) and false-positive Coombs' test; porphyria.

Dose:

Infections due to sensitive Gram-positive and Gram-negative bacteria.
Deep IM or *IV:*
Neonate *under 7 days* 25–50 mg/kg every 24 hours;
Neonate *7–21 days* 25–50 mg/kg every 12 hours;
Neonate *21–28 days* 25–50 mg/kg every 8 hours.
Child *1 month–18 years* 25-50 mg/kg every 8 hours (maximum 6 g daily).

Renal impairment: Reduce dose in mild renal impairment.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Diarrhoea, nausea, rash, electrolyte disturbances, pain and inflammation at injection site, blood dyscrasias (including thrombocytosis, leukopenia and drug-induced eosinophilia), elevations in liver enzymes.

Uncommon Vomiting, headache, dizziness, oral and vaginal candidiasis, *Clostridium difficile*-associated disease, superinfection, drug fever.

Rare Anaphylaxis, bronchial obstruction, urticaria, haemolytic anaemia, angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial nephritis, arthritis, serum sickness-like syndrome, neurotoxicity (including seizures), blood dyscrasias (including thrombocytopenia and haemolytic anemia), prothrombin time elevations, renal impairment.

Interactions with other medicines (* indicates severe):

Cefalosporins can cause renal impairment; administration with other drugs which also have this effect may increase risk of nephrotoxicity.

Aminoglycosides: concomitant cefalosporins and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine. Suggestion: allow 24 hours or more to elapse between the last dose of antibiotic and the administration of oral live typhoid vaccine.

Notes: IV products are physically incompatible with many substances; avoid mixing with other drugs.

Carbon dioxide is released during reconstitution; a gas relief needle may be needed to relieve positive pressure.

References:

Aronson JK, ed. *Meyler's side effects of drugs. 15th ed.* Amsterdam, Elsevier, 2006.
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hansten PD, Horn JH. *Drug interactions analysis and management.* St Louis, Wolters Kluwer Health, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Imipenem + Cilastatin

ATC code: J01DH51

Powder for injection: 250 mg (as monohydrate) + 250 mg (as sodium salt); 500 mg (as monohydrate) + 500 mg (as sodium salt) in vial

Special Notes: Only listed for the treatment of life-threatening hospital-based infection due to suspected or proven multi-resistant infection.

Indications: Severe aerobic and anaerobic Gram-positive and Gram-negative infections in hospital (not indicated for CNS infections), including infections caused by resistant *Pseudomonas* and *Acinetobacter* spp.

Contraindications: Meningitis.

Precautions: Sensitivity to beta-lactam antibacterials (avoid if history of immediate hypersensitivity reaction; see also section 6.2.1); renal impairment; CNS disorders, such as epilepsy; neutropenia: drug-related nausea and vomiting is more likely to occur.

Dose:

Infections due to aerobic and anaerobic Gram-positive and Gram-negative organisms, hospital acquired septicaemia.
IV (expressed in terms of imipenem):
Neonate *under 7 days* 20 mg/kg every 12 hours;
Neonate *7–21 days* 20 mg/kg every 8 hours;
Neonate *21–28 days* 20 mg/kg every 6 hours.
Infant *1–3 months* 20 mg/kg every 6 hours.
Child *3 months–18 years* and ***under 40 kg*** 15 mg/kg (maximum 500 mg) every 6 hours;
3 months–18 years and ***over 40 kg*** 250–500 mg every 6 hours.
Dose may be doubled for less susceptible organisms.

ADMINISTRATION Follow manufacturers instructions dependent on product.

Caution: complex administration.

Reconstitute with 10 ml NaCl 0.9% to form a cloudy suspension.

Do not administer this suspension without further dilution.

Further dilute to 5 mg/ml with a compatible fluid to give a clear solution.

500 mg or less: over 20–30 minutes.

More than 500 mg: over 40–60 minutes.

Renal impairment: Reduce dose in mild renal impairment.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, diarrhoea, local injection site reactions, e.g. phlebitis.

Uncommon Rash, pruritus, urticaria, taste alteration, fever, dizziness, somnolence, confusion, tremor, paraesthesia, headache, psychiatric disturbances, encephalopathy, convulsions (risk of convulsions is higher in people with pre-existing CNS disorders or renal impairment (especially when excessive doses are used). Imipenem is thought to have similar epileptogenic potential to high-dose benzylpenicillin), hypotension, positive Coombs' test, increases in liver function tests and bilirubin, raised urea and creatinine, *Clostridium difficile*-associated disease, itch, rash.

Rare Red discoloration of the urine in children, anaphylaxis, hepatitis, Stevens-Johnson syndrome, angioedema, tachycardia, renal toxicity, blood dyscrasias.

Interactions with other medicines (* indicates severe):

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine. Suggestion: allow 24 hours or more to elapse between the last dose of antibiotic and the administration of oral live typhoid vaccine.

Valproic acid: decreased valproic acid plasma concentrations and loss of anticonvulsant effect.

Notes: Suitability of this preparation for intravenous or intramuscular administration varies dependent on product. Check product and instructions carefully. The intramuscular preparation must not be administered intravenously and the infusion preparation must not be administered intramuscularly.

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6.2.2 Other antibacterials

This section contains a number of antibiotics from different classes which do not fit within other categories but should be available to treat serious infections.

They should all be available in centres providing secondary or tertiary level hospital care, and particularly in those with intensive care facilities.

The use of some of these agents may be restricted by local policy to ensure their cost effective and efficacious use.

Azithromycin

ATC code: J01FA10

Capsule: 250 mg; 500 mg

Oral liquid: 40 mg/ml

Indications: Trachoma.

Contraindications: Severe hepatic impairment.

Precautions: Prolongation of QT interval; renal impairment; hepatic impairment; myasthenia gravis.

Dose:

Trachoma.
Oral:
Child *all ages* 20 mg/kg (maximum 1 g) as a single dose.

Renal impairment: Use with caution in patients with severe renal impairment.

Hepatic impairment: Mild or moderate hepatic impairment: no modification of dosage is necessary, despite its hepatic metabolism.

Severe impairment: avoid; jaundice reported.

Adverse effects: Common Gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain and cramps), headache, candida infections.

Uncommon Dizziness, cough, wheeze, dyspnoea, agitation, taste disturbances, rash, fixed drug eruptions.

Rare Prolonged QT interval, torsades de pointes, interstitial nephritis, pyloric stenosis, leukopenia, thrombocytopenia, anaphylaxis, acute respiratory distress, Stevens-Johnson syndrome, psychiatric disturbances, hearing loss, seizures, *Clostridium difficile*-associated disease, pancreatitis, cholestatic jaundice, hepatotoxicity.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of azithromycin.

* **Artemether with lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.

* **Ciclosporin**: possible inhibition of metabolism of ciclosporin (increased plasma concentration).

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Digoxin: increased plasma concentration of digoxin (increased risk of toxicity).

Ritonavir: plasma concentration of azithromycin possibly increased.

* **Warfarin**: possibly enhanced anticoagulant effect of warfarin.

Notes: Capsules should be taken at least 1 hour before or 2 hours after food.

Mixture should be taken on an empty stomach.

Of all the macrolide antibiotics, azithromycin causes the least inhibition of cytochrome P450 3A4.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
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Chloramphenicol

ATC code: J01BA01

Capsule: 250 mg

Oily suspension for injection*: 0.5 g (as sodium succinate)/ml in 2 ml ampoule

Oral liquid: 30 mg (as palmitate)/ml

Powder for injection: 1 g (sodium succinate) in vial

Serious and fatal blood dyscrasias (aplastic anaemia, hypoplastic anaemia, thrombocytopenia and granulocytopenia) have occurred after both short-term and prolonged therapy.
Monitor full blood count with platelets frequently in all patients; discontinue if evidence of myelosuppression. Irreversible bone marrow suppression may occur weeks or months after therapy. Avoid repeated courses of treatment. Warn patient or carer to report pale skin, sore throat, fever, tiredness or weakness, or unusual bleeding or bruising in the months after stopping this medicine.

Should be reserved for the treatment of life-threatening infections.

Grey baby syndrome may follow excessive doses in neonates with immature hepatic metabolism; monitoring of plasma concentrations is required.

Special Notes: *Oily suspension for injection is included on the list only for the presumptive treatment of epidemic meningitis in children older than 2 years. In children under 2 years, use ceftriaxone which is approved for use from > 41 weeks corrected gestational age.

Some strains of *Haemophilus influenzae* type b and *Salmonella typhi* are resistant to chloramphenicol.

Indications: Severe life-threatening infections; presumptive treatment of bacterial meningitis in meningococcal epidemic in children older than 2 years.

Contraindications: Pregnancy; porphyria; breastfeeding.

Precautions: Avoid repeated courses and prolonged use; hepatic impairment; renal impairment; blood counts required before and during treatment; monitor plasma concentrations in neonates (see Warnings); G6PD deficiency.

Dose:

Severe life-threatening infections.
IV injection or *infusion:*
Neonate *under 2 weeks* 12.5 mg/kg every 12 hours.
Neonate *over 2 weeks* 12.5 mg/kg every 6 hours.
Oral, IV injection or *infusion:*
Infant or **Child** 12.5 mg/kg every 6 hours. Maximum daily dose 4 g. Up to 25 mg/kg every 6 hours may be required in severe infections provided plasma concentrations are measured and high doses reduced as soon as possible.

THERAPEUTIC DRUG MONITORING Plasma concentration monitoring required in neonates and high doses; preferred in those under 4 years of age and in hepatic impairment.

Recommended peak plasma chloramphenicol concentration (approximately 1 hour after intravenous injection or infusion, or 2 hours after oral administration): 15–25 mg/litre.

Pre-dose trough concentration should not exceed 15 mg/litre.

Presumptive treatment of bacterial meningitis in meningococcal epidemic.
IM injection (using oily injection):
Child *over 2 years* 100 mg/kg as a single dose. Maximum dose 3 g.

Renal impairment: Severe: avoid unless no alternative; dose-related depression of haematopoiesis.

Hepatic impairment: Avoid if possible; increased risk of bone marrow depression; reduce dose and monitor plasma chloramphenicol concentration.

Adverse effects: Common Nausea, vomiting, dry mouth, reversible bone marrow suppression, headache.

Uncommon Diarrhoea, glossitis, stomatitis, enterocolitis, mild depression, *Clostridium difficile* infection, confusion, delirium.

Rare Peripheral neuropathy, peripheral neuritis, contact dermatitis, urticaria, angioedema, anaphylaxis, onycholysis, irreversible bone marrow suppression (aplastic anaemia, leukopenia, thrombocytopenia, haemolytic anaemia and leukaemia), hepatotoxicity, optic atrophy, optic neuritis, ototoxicity, bronchospasm, Jarisch-Herxheimer reaction, metabolic acidosis, grey baby syndrome (see below).

GREY BABY SYNDROME Vomiting, greenish diarrhoea, abdominal distension, hypothermia, pallid cyanosis, irregular respiration, circulatory collapse; may follow excessive doses in neonates with immature hepatic metabolism; also reported in infants born to mothers treated in late pregnancy.

Interactions with other medicines (* indicates severe):

Atazanavir: may increase chloramphenicol serum concentration. Monitor carefully for bone marrow suppression.

* **Ciclosporin (+ calcineurin inhibitors)**: plasma concentration of ciclosporin possibly increased.

Hydroxocobalamin: response to hydroxocobalamin reduced.

Iron: systemic chloramphenicol increases serum iron concentration due to chloramphenicol-induced bone marrow toxicity; if myelosuppression occurs, monitor iron stores and decrease iron dose as needed; consider stopping chloramphenicol, seek specialist advice.

Lopinavir + ritonavir: may increase chloramphenicol serum concentration. Monitor carefully for bone marrow suppression.

* **Phenobarbital**: metabolism of chloramphenicol accelerated (reduced chloramphenicol concentration).

* **Phenytoin**: plasma phenytoin concentration increased (increased risk of toxicity).

Protease inhibitors: may increase chloramphenicol serum concentration. Monitor carefully for bone marrow suppression.

Rifampicin: accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration).

Ritonavir: may increase chloramphenicol serum concentration. Monitor carefully for bone marrow suppression.

Saquinavir: may increase chloramphenicol serum concentration. Monitor carefully for bone marrow suppression.

* **Warfarin**: enhanced anticoagulant effect.

Notes: Chloramphenicol should be reserved for life-threatening infections including (but not limited to) typhoid fever, septicaemia, meningitis, epiglottitis, pneumonia, cerebral abscess, mastoiditis, rickettsia, listeriosis, Whipple disease, Q fever and psittacosis.

Systemic use is limited by its toxicity; if using a high dose, reduce it as soon as possible; avoid repeated courses and prolonged treatment. Obtain complete blood picture before and during treatment (this will not warn of aplastic anaemia); consider stopping treatment if haematological changes occur. Stop treatment if peripheral neuropathy or optic neuritis occur.

RECONSTITUTION AND ADMINISTRATION Reconstitute according to manufacturer's directions. For intermittent intravenous infusion, dilute reconstituted solution further in glucose 5% or sodium chloride 0.9%. The oily injection is for intramuscular use only (see notes above).

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Ciprofloxacin

ATC code: J01MA02

Oral liquid: 50 mg/ml

Solution for IV infusion: 2 mg/ml

Tablet: 250 mg (as hydrochloride)

Achilles tendinitis and tendon rupture have been reported with fluoroquinolones in patients of all ages.

Indications: Treatment of infections due to susceptible organisms including *Pseudomonas,* cholera, shigellosis, *Campylobacter,* typhoid and gonorrhoea. Local resistance patterns need to taken into account.

Contraindications: History of tendon disorders related to quinolone use; pregnancy; breastfeeding.

Precautions: History of epilepsy; conditions that predispose to seizures; G6PD deficiency; myasthenia gravis; avoid exposure to excessive sunlight (discontinue if photosensitivity occurs); tendon damage; renal impairment; avoid excessive alkalinity of urine and ensure adequate fluid intake as risk of crystalluria.

The drug should be discontinued if psychiatric, neurological or hypersensitivity reactions, including severe rash, occur.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

TENDON DAMAGE Tendon damage (including rupture) has been reported rarely in patients receiving quinolones. Tendon rupture may occur within 48 hours of starting treatment. Health-care workers should be aware that the risk of tendon rupture is increased by the concomitant use of corticosteroids; if tendinitis is suspected, the quinolone should be discontinued immediately.

Dose:

Complicated urinary tract infection.
Oral:
Neonate 7.5 mg/kg twice daily.
Infant 5–7.5 mg/kg twice daily. Dose may be doubled in severe infection.
Child 10 mg/kg twice daily. Dose may be doubled in severe infections. Maximum dose 750 mg twice daily.
IV infusion:
Neonate 5 mg/kg every 12 hours.
Infant 4 mg/kg every 12 hours. Dose may be doubled in severe infections.
Child 6 mg/kg every 8 hours, increased to 10 mg/kg every 8 hours in severe infections. Maximum dose 400 mg every 8 hours.

Severe respiratory tract infections, gastrointestinal infections.
Oral:
Neonate 7.5 mg/kg twice daily.
Infant 5–7.5 mg/kg twice daily. Dose may be doubled in severe infections.
Child 20 mg/kg twice daily. Maximum dose 750 mg twice daily.
IV infusion:
Neonate 5 mg/kg every 12 hours.
Infant 4 mg/kg every 12 hours. Dose may be doubled in severe infections.
Child 10 mg/kg every 8 hours. Maximum dose 400 mg every 8 hours.

Pseudomonal lower respiratory tract infection in cystic fibrosis.
Oral:
Infant 15 mg/kg twice daily.
Child 20 mg/kg twice daily. Maximum dose 750 mg twice daily.
IV:
Infant 4–8 mg/kg every 12 hours.
Child 10 mg/kg every 8 hours. Maximum dose 400 mg every 8 hours.

Treatment and post-exposure prophylaxis of anthrax.
Oral:
Infant or **Child** 15 mg/kg twice daily. Maximum 500 mg twice daily.
IV:
Infant or **Child** 10 mg/kg every 12 hours. Maximum 400 mg per dose.

NOTE Cutaneous anthrax should be treated for 7 days, inhalational or gastrointestinal should be treated for 60 days. Post-exposure prophylaxis should be administered for 60 days. Other antibiotics may be used if and when sensitivities are known.

Renal impairment: Reduce dose if CrCl < 30 ml/minute.

Adverse effects: Common Rash, itch, gastrointestinal intolerance (nausea, vomiting, dyspepsia, diarrhoea, abdominal pain), metallic taste.

Uncommon Headache, dizziness, insomnia, depression, restlessness, tremors, arthralgia, arthritis, myalgia, tendinitis, raised liver enzymes, erythema, pain or thrombophlebitis at intravenous infusion site.

Rare Interstitial nephritis, blood dyscrasias (including agranulocytosis, aplastic anaemia, haemolytic anaemia, leukopenia, methaemoglobinaemia, pancytopenia and thrombocytopenia), orofacial dyskinesia, disturbances in vision, transient hearing impairment, movement disorders, seizures, psychotic reactions, peripheral oedema, angioedema, anaphylaxis, *Clostridium difficile* infection, tendon inflammation and rupture, vasculitis, crystalluria, renal failure, pancreatitis, hepatitis, cholestatic jaundice, peripheral neuropathy, photosensitivity, fixed drug eruption, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, Jarisch-Herxheimer reaction, hyperglycaemia, blood coagulation disorder.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of ciprofloxacin.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Calcium salts: reduced absorption of ciprofloxacin.

* **Ciclosporin**: increased risk of nephrotoxicity.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Dairy products: reduced absorption of ciprofloxacin.

Ferrous salts: absorption of ciprofloxacin reduced by oral ferrous salts.

* **Ibuprofen**: possibly increased risk of seizures.

Methotrexate: increased methotrexate concentration and risk of toxicity when high-dose methotrexate is given; monitor methotrexate concentration carefully as increased rescue treatment with calcium folinate may be needed.

Morphine: manufacturer of ciprofloxacin advises to avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis.

Phenytoin: plasma phenytoin concentration can be increased or decreased by ciprofloxacin.

Theophylline: may result in increased plasma levels of theophylline and significant adverse effects.

Thyroid hormones: ciprofloxacin may interfere with absorption of thyroxine, resulting in hypothyroidism; separate drug administration times during a long ciprofloxacin course, and monitor thyroid function.

* **Warfarin**: enhanced anticoagulant effect.

Zinc sulfate: reduced absorption of ciprofloxacin.

Notes: Best taken on an empty stomach. Separate doses from iron, antacids and milk by 2 hours.

Important to maintain an adequate fluid intake.

Consider the necessity for intravenous administration as adequate levels can be achieved using oral formulations due to high bioavailability.

Can cause photosensitivity. Use sunscreen, wear protective clothing and a hat.

ADMINISTRATION For intravenous administration, administer by slow intravenous infusion over 60 minutes. Final concentration for administration should not exceed 2 mg/ml.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Doxycycline

ATC code: J01AA02

Oral liquid: 5 mg/ml; 10 mg/ml

Solid oral dosage form: 50 mg; 100 mg (hydrochloride)

Special Notes: WHO age/weight restriction: > 8 years (except for serious infections, e.g. cholera).

Indications: Bacterial infections.

Contraindications: Pregnancy; breastfeeding; porphyria; systemic lupus erythematosus.

Precautions: Children under 8 years (avoid unless life-threatening infection when no other alternative exists); avoid exposure to sunlight or sunlamps (photosensitivity reported); renal impairment; hepatic impairment; concomitant hepatotoxic drugs; myasthenia gravis.

Dose:

Bacterial infections.

Oral:

Child *over 8 years* 2 mg/kg (maximum 100 mg) twice daily on day 1, then 2 mg/kg (maximum 100 mg) daily, or twice daily in severe infections such as rickettsia. Maximum daily dose 200 mg.

Renal impairment: Use with caution; avoid excessive doses.

Hepatic impairment: Avoid (or use with caution).

Adverse effects: Common Gastrointestinal intolerance (nausea, vomiting, diarrhoea, epigastric burning), tooth discoloration (permanent in children aged < 8 years), enamel dysplasia, reduced bone growth (in children < 8 years), photosensitivity (depends on dose and degree of sun exposure).

Uncommon Rash, stomatitis, bone deformity, fungal overgrowth.

Rare Photo-onycholysis and nail discoloration, oesophageal ulcers (due to partly swallowed tablets or capsules), antibiotic-associated colitis *(Clostridium difficile*-associated disease), hepatitis, fatty liver degeneration (with high doses, especially in pregnancy), pancreatitis, hepatotoxicity, headache and visual disturbances may indicate benign intracranial hypertension, bulging fontanelles in infants, allergic reactions including anaphylaxis (less common than with penicillins), toxic epidermal necrolysis, worsening of systemic lupus erythematosus, serum sickness-like reactions, Jarisch-Herxheimer reaction when treating spirochetal infections.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of doxycycline.

Carbamazepine: accelerated metabolism of doxycycline (reduced effect).

* **Ciclosporin**: possibly increased plasma ciclosporin concentration.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Ferrous salts: absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts.

Methotrexate: increased risk of methotrexate toxicity.

Phenobarbital: metabolism of doxycycline accelerated (reduced plasma concentration).

Phenytoin: increased metabolism of doxycycline (reduced plasma concentration).

Rifampicin: plasma doxycycline concentration possibly reduced.

* **Warfarin**: anticoagulant effect possibly enhanced.

Notes: Separate dose from antacids and iron supplements by 2 hours. Swallow whole with plenty of water and remain upright (do not lie down) for an hour after taking doxycycline to prevent oesophageal irritation. Single daily doses are best taken in the morning rather than at night.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
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Erythromycin

ATC code: J01FA01

Powder for oral liquid: 25 mg/ml (as stearate or ethyl succinate)

Solid oral dosage form: 250 mg (as stearate or ethyl succinate)

Indications: Treatment of susceptible infections as an alternative to penicillin in hypersensitive patients; treatment of susceptible infections such as *Campylobacter* enteritis, cholera, oral infections, respiratory tract infections (including pneumonia, legionnaires' disease, streptococcal pharyngitis) and diphtheria; prevention of secondary case of diphtheria and pertussis in non-immune patients.

Contraindications: Hypersensitivity to erythromycin or other macrolides; porphyria; severe hepatic impairment; treatment with cisapride.

Precautions: Hepatic impairment; renal impairment; predisposition to QT interval prolongation; neonates under 2 weeks; porphyria.

Dose:

Treatment of susceptible infections.
Oral:
Neonate 12.5 mg/kg every 6 hours.
Infant or **Child** ***under 2 years*** 125 mg every 6 hours, doubled in severe infections;
2–8 years 250 mg every 6 hours, doubled in severe infections;
over 8 years 250–500 mg every 6 hours, doubled in severe infections.

Prevention of secondary case of diphtheria in non-immune patient.
Oral:
Infant or **Child** ***under 2 years*** 125 mg every 6 hours for 7 days;
2–8 years 250 mg every 6 hours for 7 days;
over 8 years 500 mg every 6 hours for 7 days.
Treat for a further 10 days if nasopharyngeal swabs are positive after first 7 days of treatment.

Prevention of secondary case of pertussis in non-immune patient.
Oral:
Infant or **Child** ***under 2 years*** 125 mg every 6 hours for 7 days;
2–8 years 250 mg every 6 hours for 7 days;
over 8 years 500 mg every 6 hours for 7 days.

Renal impairment: Severe impairment: reduce dose. Risk of ototoxicity.

Hepatic impairment: May cause idiosyncratic hepatotoxicity.

Mild to moderate impairment: use with caution; hepatic impairment may worsen.

Severe impairment: avoid use.

Adverse effects: Common Gastrointestinal intolerance (nausea, vomiting, abdominal discomfort, diarrhoea), headache, dyspnoea, cough, candidal infections, phlebitis, infantile hypertrophic pyloric stenosis (see below).

Uncommon Rash, fixed drug eruptions, urticaria, reversible hearing loss after large doses.

Rare Myasthenia-like syndrome, anaphylaxis, acute respiratory distress, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, psychiatric disturbances, hearing loss, seizures, *Clostridium difficile* infection, cholestatic jaundice, pancreatitis, prolonged QT interval, torsades de pointes.

INFANTILE HYPERTROPHIC PYLORIC STENOSIS Has occurred in about 5% of a cohort of infants receiving erythromycin for pertussis prophylaxis; risk increased with increasing length of treatment; no increased risk in infants receiving erythromycin after 2 weeks of age.

Interactions with other medicines (* indicates severe):

Erythromycin has multiple drug-drug interactions as it is a potent inhibitor of cytochrome P450 3A4 and 1A2.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Carbamazepine**: increased plasma carbamazepine concentration.
* **Ciclosporin**: increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin).

Dexamethasone: erythromycin possibly inhibits metabolism of dexamethasone.

Digoxin: increased plasma concentration of digoxin (increased risk of toxicity).

Hydrocortisone: erythromycin possibly inhibits metabolism of hydrocortisone.

Prednisolone: erythromycin possibly inhibits metabolism of prednisolone.

* **Quinidine**: increased risk of ventricular arrhythmias with parenteral erythromycin.

Ritonavir: plasma concentration possibly increased by ritonavir.

* **Theophylline**: may increase theophylline concentration and toxicity; erythromycin levels may concurrently decrease, possibly affecting its efficacy.

Valproic acid: metabolism of valproic acid possibly inhibited (increased plasma concentration).

* **Verapamil**: increased risk of cardiotoxicity and serious prolongation of QT interval.
* **Vinblastine**: increased toxicity of vinblastine (avoid concomitant use).
* **Warfarin**: enhanced anticoagulant effect.

Notes: Total oral daily dose may be halved and given every 12 hours, however diarrhoea is a common side effect.

Stop erythromycin if severe hepatic dysfunction develops.

The ethyl succinate (EES) salt is given without regard to food. The base and stearate salt are given on an empty stomach 1 hour before or 2 hours after meals.

Parents of neonates: tell your doctor if your baby develops vomiting or is irritable when feeding while taking erythromycin.

Warn patients or carers that erythromycin interacts with many drugs and even herbal products so inform doctor or pharmacist before taking additional medication.

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Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Gentamicin

ATC code: J01GB03

Injection: 10 mg; 40 mg (as sulfate)/ml in 2 ml vial

Aminoglycosides are associated with significant nephrotoxicity; vestibular and permanent bilateral auditory ototoxicity can occur; tinnitus or vertigo are indications of vestibular injury and impending bilateral irreversible deafness. Risk of nephrotoxicity and ototoxicity is increased in patients with impaired renal function, high-dose therapy or prolonged therapy. Risk of nephrotoxicity increases when used concurrently with other potentially nephrotoxic drugs; renal damage is usually reversible. Risk of ototoxicity increases with use of potent diuretics.

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Treatment of infections with susceptible organisms taking local resistance factors into account, including septicaemia, pneumonia, acute pyelonephritis and meningitis.

Contraindications: Myasthenia gravis.

Precautions: Renal impairment; neonates and infants (use with caution and monitor renal, auditory and vestibular function, and serum gentamicin concentrations); avoid prolonged use; conditions characterized by muscular weakness; obesity (use ideal body weight to calculate dose and monitor serum gentamicin concentration closely).

Dose:

Treatment of infections with susceptible organisms.
IV or *IM:*
Term neonate 3.5–5 mg/kg once daily.
Infant or **Child** ***under 10 years*** 7.5 mg/kg once daily;
over 10 years 6 mg/kg once daily (maximum dose 240–360 mg).

THERAPEUTIC DRUG MONITORING Monitor serum gentamicin concentration and reduce doses or increase dosing intervals, or both, as necessary. Pre-dose ("trough") concentration should be less than 1 mg/litre.

Renal impairment: Reduce dose frequency. Monitor renal, auditory and vestibular function. Monitor serum gentamicin concentration.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nephrotoxicity (see below), ototoxicity (see below).

Rare Hypomagnesaemia, hypokalaemia, hypocalcaemia, anaphylaxis (probably due to sulfites in some formulations), bronchospasm, neuromuscular blockade (see below), oliguria, peripheral neuropathy, antibiotic-associated colitis.

NEPHROTOXICITY Usually reversible and can be anticipated if treatment lasts > 7–10 days; usually presents as gradually worsening non-oliguric renal failure with increasing serum creatinine and proteinuria, but may present as acute tubular necrosis.

OTOTOXICITY Clinically evident vestibular ototoxicity (nausea, vomiting, vertigo, nystagmus, difficulties with gait) and cochlear ototoxicity (noticeable hearing loss, tinnitus, feeling of fullness in ear) have been associated with gentamicin use. As the patient is unaware of the first symptoms of cochlear toxicity, it may appear to begin after stopping treatment. Ototoxicity caused by gentamicin can be irreversible; permanent deafness may occur.

NEUROMUSCULAR BLOCKADE May result in respiratory depression; can usually be reversed with prompt administration of IV calcium gluconate; the effect of neostigmine is variable.

Interactions with other medicines (* indicates severe):

Amphotericin B: increased risk of nephrotoxicity.

Capreomycin: increased risk of nephrotoxicity and ototoxicity.

* **Ciclosporin**: increased risk of nephrotoxicity.

Digoxin: possibly increased plasma concentration of digoxin.

* **Furosemide**: increased risk of ototoxicity.

Magnesium sulfate: additive neuromuscular blocking effect with aminoglycosides and parenteral magnesium sulfate; use combinations cautiously, monitor respiratory function.

* **Neostigmine**: antagonism of effect of neostigmine.

Nondepolasing neuromuscular blockers: aminoglycosides prolong effect of nondepolarising neuromuscular blockers; may lead to respiratory insufficiency.

Other nephrotoxic agents: co-administration with other drugs which are ototoxic or nephrotoxic may increase risk of these adverse effects.

Penicillins: concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.

* **Pyridostigmine**: antagonism of effect of pyridostigmine.

* **Suxamethonium**: enhanced muscle relaxant effect.

Vancomycin: increased risk of nephrotoxicity and ototoxicity.

* **Vecuronium**: enhanced muscle relaxant effect.

Notes: In obese or severely oedematous children use the ideal weight for height to calculate dose.

ADMINISTRATION For intravenous infusion, dilute in glucose 5% or sodium chloride 0.9%; infuse over 30–60 minutes. Final concentration of intravenous administration should not exceed 10 mg/ml.

Administer other antibiotics, such as cefalosporins and penicillins, at least 1 hour before or after gentamicin.

Target serum concentrations may vary depending on indication and institution.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
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Metronidazole

ATC code: J01XD01

Injection: 500 mg in 100 ml vial

Oral liquid: 40 mg (as benzoate)/ml

Tablet: 200 mg to 500 mg

Indications: Anaerobic bacterial infections including ulcerative gingivitis, acute oral infections, tetanus, skin and soft tissue infections, and *Clostridium difficile* infection (oral therapy); surgical prophylaxis.

Precautions: Hepatic impairment; disulfiram-like reaction with alcohol; clinical and laboratory monitoring in courses lasting longer than 10 days.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Anaerobic bacterial infections.

Oral:

Neonate initially 15 mg/kg then 7.5 mg/kg every 12 hours.

Infant or **Child** 7.5 mg/kg every 8 hours. Maximum dose 400 mg.

IV infusion:

Neonate 15 mg/kg as a single loading dose, followed by 7.5 mg/kg every 12 hours starting 24 hours after loading dose.

Infant or **Child** 7.5 mg/kg every 8 hours. Maximum dose 500 mg.

NOTE Acute ulcerative gingivitis is usually successfully treated in 3 days, *Clostridium difficile* infection should be treated orally, and is usually treated for 7–10 days, while other anaerobic and oral anaerobic conditions usually treated for only 7 days.

Surgical prophylaxis.

Oral or *IV infusion:*

Infant or **Child** 7.5 mg/kg 2 hours before surgery. Up to 3 further doses of 7.5 mg/kg may be given every 8 hours for high-risk procedures. Maximum dose 500 mg.

Renal impairment: Metabolites may accumulate in severe impairment possibly causing adverse effects. Dose adjustment is not usually necessary.

Hepatic impairment: Severe impairment: reduce total daily dose to one third and give once daily.

Use with caution in hepatic encephalopathy.

Adverse effects: Common Gastrointestinal intolerance (nausea, abdominal pain, vomiting, diarrhoea), anorexia, metallic taste, CNS effects (e.g. dizziness, headache), thrombophlebitis (IV).

Uncommon Furry tongue, glossitis, stomatitis, paraesthesia.

Rare Pancreatitis, abnormal liver function tests, jaundice, hepatitis, optic neuritis, thrombocytopenia, *Clostridium difficile*-associated disease, hypersensitivity reactions (e.g. rash, itch, flushing, fever), anaphylaxis, angioedema, erythema multiforme, Stevens-Johnson syndrome, leukopenia, peripheral neuropathy, seizures, darkening of the urine.

HIGH-DOSE AND/OR PROLONGED TREATMENT Leukopenia is reversible and usually only occurs after prolonged treatment; peripheral neuropathy (usually reversible) and/or CNS toxicity (including seizures) may occur.

Interactions with other medicines (* indicates severe):

Alcohol: disulfiram-like reaction.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Fluorouracil: metabolism of fluorouracil inhibited (increased toxicity).

Lithium: increased lithium toxicity reported.

Lopinavir liquid: disulfuram-like reaction.

Phenobarbital: metabolism of metronidazole accelerated (reduced plasma concentration).

* **Phenytoin**: metabolism of phenytoin inhibited (increased plasma phenytoin concentration).

* **Warfarin**: enhanced anticoagulant effect.

Notes: Well absorbed orally and the intravenous route is normally reserved for severe infections.

Oral absorption from the suspension is lower than from the tablets.

Patients should be advised to swallow tablets whole with water, during or after food; suspension is best taken 1 hour before food (or on an empty stomach).

ADMINISTRATION For intravenous infusion, infuse over 20–30 minutes.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Nitrofurantoin

ATC code: J01XE01

Oral liquid: 5 mg/ml

Tablet: 100 mg

Indications: Treatment of acute uncomplicated urinary tract infection; prophylaxis of urinary tract infection.

Contraindications: Renal impairment; infants less than 3 months; G6PD deficiency; pregnancy, at term; porphyria.

Precautions: Pulmonary disease; hepatic impairment; monitor lung and liver function on long-term therapy (discontinue if lung function deteriorates); electrolyte imbalance; susceptibility to peripheral nephritis; anaemia; diabetes mellitus; vitamin B and folate deficiency; false-positive urinary glucose (if testing for reducing substances); urine may be coloured yellow or brown.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Treatment of acute uncomplicated urinary tract infection.

Oral:

Infant or **Child** ***over 3 months*** 750 micrograms/kg four times daily for 3–7 days. Maximum dose 100 mg.

Prophylaxis of urinary tract infection.

Oral:

Infant or **Child** ***over 3 months*** 1 mg/kg at night. Maximum dose 100 mg.

Renal impairment: Avoid in all degrees of renal impairment. Risk of peripheral neuropathy. Treatment may be ineffective because of inadequate urine concentrations.

Hepatic impairment: Cholestatic jaundice and chronic active hepatitis reported.

Adverse effects: Common Dose related gastrointestinal disorders (including nausea and vomiting, anorexia, diarrhoea and abdominal pain), hypersensitivity reactions (including urticaria, rash, sialadenitis, pruritus, angioedema), headache.

Uncommon Drowsiness, vertigo, dizziness.

Rare Peripheral polyneuropathy (see below), cholestatic jaundice, hepatitis, hepatotoxicity (see below), acute and chronic pulmonary reactions (see below), skin reactions including erythema multiforme, Stevens-Johnson syndrome, exfoliative dermatitis, lupus-like syndrome, anaphylaxis, drug fever, blood disorders including eosinophilia, arthralgia, pancreatitis, benign intracranial hypertension.

HEPATOTOXICITY Acute hepatocellular or cholestatic reactions generally occur in the first 6 weeks of treatment, sometimes with fever, eosinophilia, rash and are usually reversible. Chronic active hepatitis (sometimes reversible) mostly occurs in women, usually after about 6 months treatment; may be associated with pulmonary toxicity (see below). Both types can be fatal.

PULMONARY TOXICITY Pulmonary fibrosis has been reported. Possible association with lupus erythematosus-like syndrome.

PERIPHERAL POLYNEUROPATHY Begins with peripheral paraesthesia and sensory loss (usually in lower limbs); can progress to motor loss and muscle atrophy. Improvement usually occurs after stopping treatment, but it may be incomplete. The main predisposing factor appears to be renal impairment.

Interactions with other medicines (* indicates severe):

Fluconazole: concurrent use may result in increased risk of hepatic and pulmonary toxicity.

Norfloxacin: may result in antagonism of the antibacterial effect of norfloxacin.

Folic acid: concurrent use may result in decreased folic acid serum levels.

Notes: Give with food or milk to reduce nausea and to improve absorption.

PATIENT ADVICE Patients and their carers should be advised to tell their doctor immediately if they have difficulty breathing, develop a cough or get any numbness or tingling.

MONITORING During long-term treatment monitor the following: pulmonary function; liver function every month for 3 months, then every 3 months, as onset of hepatotoxicity may be insidious; renal function as peripheral polyneuropathy is more likely to occur if this is impaired; for development of paraesthesia as stopping treatment early can prevent severe neuropathy.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Sulfamethoxazole + Trimethoprim

ATC code: J01EE01

Injection: 80 mg + 16 mg/ml in 5 ml ampoule; 80 mg + 16 mg/ml in 10 ml ampoule

Oral liquid: 40 mg + 8 mg/ml

Tablet: 100 mg + 20 mg; 400 mg + 80 mg

Special Notes: Also referred to as co-trimoxazole.

Indications: Treatment of infections with susceptible organisms including urinary tract infections, respiratory tract infection, typhoid fever and otitis media. Local antimicrobial patterns need to be taken into account.

Contraindications: Hypersensitivity to sulfonamides or trimethoprim; porphyria; megaloblastic anaemia; severe renal impairment; severe hepatic impairment.

Precautions: Mild to moderate renal impairment; maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts on prolonged treatment; discontinue immediately if blood disorder develops; rash (discontinue immediately); predisposition to folate deficiency; asthma; G6PD deficiency; avoid in infants under 6 weeks.

Dose:

Doses are expressed in terms of the trimethoprim component.

Treatment of infections with susceptible organisms.

Oral:

Infant or **Child** ***over 6 weeks*** 4 mg/kg/dose twice daily. Maximum 160 mg twice daily.

IV infusion:

Infant or **Child** ***over 6 weeks*** 3 mg/kg every 12 hours. Maximum 160 mg twice daily.

Renal impairment: Severe impairment: avoid use.

Moderate impairment: use half normal dose.

Plasma monitoring may be required with high doses in renal impairment; seek expert advice.

Hepatic impairment: Severe impairment: avoid use.

Adverse effects: Some adverse effects may be hypersensitivity reactions (see below).

Incidence of some adverse effects (rash, fever, nausea, neutropenia, thrombocytopenia, raised hepatic aminotransferases) is substantially higher in patients with AIDS.

Common Fever, nausea, vomiting, diarrhoea, anorexia, rash, itch, stomatitis, hyperkalaemia, thrombocytopenia, photosensitivity.

Uncommon Headache, drowsiness, hyperkalaemia, blood disorders (including neutropenia, leukopenia, thrombocytopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia).

Rare Erythema, vasculitis, hyponatraemia, hypoglycaemia, pancreatitis, hepatitis, jaundice, hepatic necrosis, crystalluria, urinary obstruction with anuria/oliguria, lowered mental acuity, depression, tremor, ataxia (after IV use in HIV patients), nephrotoxicity, antibiotic-associated colitis, *Clostridium difficile*-associated disease, aseptic meningitis.

HYPERSENSITIVITY May present with fever, dyspnoea, cough, rash, eosinophilia; the most serious effects include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like syndrome, lupus-like syndrome, pneumonitis, hepatitis, interstitial nephritis, systemic vasculitis and pancytopenia.

Interactions with other medicines (* indicates severe):

Trimethoprim is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g. pyrimethamine.

Trimethoprim can cause hyperkalaemia; administration with potassium supplements or other drugs which also cause potassium retention can further increase potassium concentration.

Trimethoprim with sulfamethoxazole can cause nephrotoxicity; giving with other nephrotoxic drugs may cause additional renal adverse effects.

* **Azathioprine**: increased risk of haematological toxicity.

* **Ciclosporin**: increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim.

Dapsone: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.

Digoxin: plasma concentration of digoxin possibly increased.

Lamivudine: competes for renal excretion, increasing lamivudine concentration and risk of toxicity.

* **Mercaptopurine**: increased risk of haematological toxicity.

* **Methotrexate**: antifolate effect of methotrexate increased (avoid concomitant use).
* **Phenytoin**: antifolate effect and plasma phenytoin concentration increased.
* **Pyrimethamine**: increased antifolate effect.

  Rifampicin: decreases concentrations of trimethoprim and sulfamethoxazole when used for prophylaxis in HIV-positive patients, decreasing its efficacy.
* **Sulfadoxine + pyrimethamine**: increased antifolate effect.

  Warfarin: possibly enhanced anticoagulant effect.

Notes: Oral dose is best given with or after food.

Attention should be paid to the folate status of the patient should treatment be prolonged or high dose.

DILUTION AND ADMINISTRATION For intermittent intravenous infusion may be further diluted in glucose 5% and 10% or sodium chloride 0.9% or Ringer's intravenous solution. Must be further diluted; dilute each 5 ml of injection solution to 125 ml. Infuse over 60–90 minutes (but may be adjusted according to fluid requirements). If fluid restriction necessary, 5 ml may be diluted with 75 ml of glucose 5% and the required dose infused over a maximum of 60 minutes. Check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Trimethoprim

ATC code: J01EA01

Oral liquid: 10 mg/ml

Tablet: 100 mg; 200 mg

Special Notes: WHO age/weight restriction: > 6 months.

Indications: Treatment of urinary tract infection and respiratory tract infection; prophylaxis of urinary tract infection.

Contraindications: Blood disorders including megaloblastic anaemia due to folate deficiency; severe renal impairment.

Precautions: Mild to moderate renal impairment; hepatic impairment; predisposition to folate deficiency; blood counts on long-term therapy; porphyria; neonates and infants < 6 months.

BLOOD DISORDERS On long-term treatment, patients and their carers should be told how to recognize 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.

Dose:

Treatment of urinary tract infection and respiratory tract infection.
Oral:
Infant or **Child** ***over 6 months*** 4 mg/kg twice daily. Maximum 200 mg twice daily.

Prophylaxis of urinary tract infection.
Oral:
Infant or **Child** ***over 6 months*** 2 mg/kg (maximum 100 mg) at night.

Renal impairment: Mild to moderate impairment: use half normal dose if CrCl 15–30 ml/minute.

Moderate to severe impairment: avoid use if CrCl less than 15 ml/minute.

Hepatic impairment: Use with caution. Dose reduction not required.

Adverse effects: Common Fever, pruritus, rash, nausea, vomiting, glossitis, hyperkalaemia (see below), superinfection (*Candida* species).

Uncommon Sore mouth, increase in serum creatinine.

Rare Leukopenia, thrombocytopenia, megaloblastic anaemia, methaemoglobinaemia (especially with high doses or prolonged treatment), allergy including anaphylaxis, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, aseptic meningitis.

HYPERKALAEMIA Trimethoprim causes potassium retention. Hyperkalaemia can occur with usual doses but is more likely to be clinically significant as dose increases. Average onset is 4–5 days. Risk factors are high doses, renal impairment and use of other potassium-retaining drugs (see Interactions).

Interactions with other medicines (* indicates severe):

Trimethoprim is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g. pyrimethamine.

* **Azathioprine**: increased risk of haematological toxicity.
* **Ciclosporin**: increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim.

Dapsone: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.

Digoxin: plasma concentration of digoxin possibly increased.

Enalapril: increased risk of hyperkalaemia.

Lamivudine: competes for renal excretion, increasing lamivudine concentration and risk of toxicity.

* **Mercaptopurine**: increased risk of haematological toxicity.
* **Methotrexate**: antifolate effect of methotrexate increased (avoid concomitant use).
* **Phenytoin**: antifolate effect and plasma phenytoin concentration increased.
* **Pyrimethamine**: increased antifolate effect.
* **Sulfadoxine + pyrimethamine**: increased antifolate effect.

Warfarin: possibly enhanced anticoagulant effect.

Notes: Monitor complete blood picture and folate status during prolonged or high-dose treatment.

Monitor serum potassium, beginning on day 3, if the patient has renal impairment, is taking drugs which can cause hyperkalaemia or is taking a high dose.

Give at night to maximize urinary concentration for urinary tract infection prophylaxis.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

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Clindamycin

ATC code: J01FF01

Capsule: 150 mg

Injection: 150 mg (as phosphate)/ml

Oral liquid: 15 mg/ml

Antibiotic-associated colitis *(Clostridium difficile* infection) may be fatal, discontinue treatment immediately if diarrhoea develops.

Special Notes: Clindamycin is a complementary drug when penicillin is not appropriate.

Indications: Treatment of infections with susceptible organisms where allergy to penicillin and resistance to first-line drugs, including staphylococcal bone and joint infections, peritonitis and pneumonia.

Contraindications: Diarrhoeal states; avoid injections containing benzyl alcohol in neonates; porphyria.

Precautions: Discontinue immediately if diarrhoea or colitis develop; hepatic impairment; renal impairment; monitor liver and renal function on prolonged therapy and in neonates and infants; females; avoid rapid intravenous administration; avoid taking with antidiarrhoeal medication.

Dose:

Treatment of infections with susceptible organisms where allergy to penicillin and resistance to first-line drugs.

Oral:

Neonate *under 14 days* 3–6 mg/kg three times daily;

Neonate *14–28 days* 3–6 mg/kg four times daily.

Infant or **Child** 3–6 mg/kg four times daily (body weight under 10 kg, minimum dose 37.5 mg three times daily). Maximum dose 450 mg four times daily.

IV infusion or *deep IM injection:*

Infant or **Child** 3.75–6.25 mg/kg four times daily; increased up to 10 mg/kg four times daily in severe infections. Total daily dose may alternatively be given in three divided doses. In life-threatening infection, up to 1.2 g four times daily may be used. Single doses over 600 mg must be given by intravenous infusion.

Renal impairment: Severe impairment: reduce dose.

Hepatic impairment: Severe impairment: reduce dose.

Adverse effects: Common Diarrhoea (mild to severe: discontinue treatment), nausea, vomiting, abdominal discomfort, rash, pruritus, urticaria.

Uncommon Antibiotic-associated colitis *(Clostridium difficile* infection).

Rare Taste disturbance, oesophagitis, anaphylaxis (often related to the tartrazine in the capsule preparation), blood dyscrasias (neutropenia, eosinophilia, agranulocytosis and thrombocytopenia), polyarthritis, jaundice and altered liver function tests, hepatotoxicity (with high doses), Stevens-Johnson syndrome, exfoliative and vesiculobullous dermatitis, toxic epidermal necrolysis ("slow" red man syndrome).

IV Hypotension, cardiac arrest (rapid injection), thrombophlebitis.

IM Pain, induration, sterile abscess.

Interactions with other medicines (* indicates severe):

Neostigmine: antagonism of effects of neostigmine.

Pyridostigmine: antagonism of effects of pyridostigmine.

* **Suxamethonium**: enhanced effects of suxamethonium.
* **Vecuronium**: enhanced muscle relaxant effect.

Notes: Consider the necessity for IV administration as adequate levels can be achieved using oral formulations due to high bioavailability.

PATIENT ADVICE Patients should discontinue immediately and contact doctor if diarrhoea develops; capsules should be swallowed with a glass of water.

ADMINISTRATION ADVICE For intravenous infusion, dilute in glucose 5% or sodium chloride 0.9% to concentration not > 12 mg/ml and infuse slowly IV over 30–40 minutes to reduce risk of adverse cardiac effects (hypotension, cardiac arrest).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Vancomycin

ATC code: J01XA01

Powder for injection: 250 mg (as hydrochloride) in vial

Special Notes: Vancomycin is a complementary antibacterial drug for use only when there is significant resistance to other drugs on the WHO Model List of Essential Medicines for Children.

Indications: Treatment of infections with susceptible organisms including methicillin-resistant staphylococcal pneumonia, staphylococcal meningitis, antibiotic-associated colitis, endocarditis treatment and prophylaxis. Local antimicrobial patterns need to be taken into account.

Contraindications: History of deafness.

Precautions: Avoid rapid infusion (risk of anaphylactoid reactions, see Adverse effects); rotate infusion sites; renal impairment; monitor plasma vancomycin concentration (after three or four doses in normal renal function, earlier if renal impairment), blood counts, urine analysis and renal function tests: use only in hospital setting; monitor auditory function and plasma vancomycin concentrations in renal impairment.

Dose:

Treatment of infections with susceptible organisms.

IV infusion:

Neonate, Infant or **Child** 15 mg/kg every 8 hours, adjusted according to plasma concentration. Maximum daily dose 2 g.

THERAPEUTIC DRUG MONITORING Plasma concentration monitoring required; pre-dose (trough) concentration should be 10–15 mg/litre (15–20 mg/litre for less sensitive strains of methicillin-resistant *Staphylococcus aureus).*

Antibiotic-associated colitis.

Oral (using the injection solution):

Infant or **Child *under 5 years*** 5 mg/kg four times daily for 7–10 days;

5–12 years 62.5 mg four times daily for 7–10 days.

Renal impairment: Increase dose interval or reduce dose, or both, in renal impairment.

Monitor plasma vancomycin concentration and renal function regularly.

Adverse effects: Common IV: local pain (may be severe), thrombophlebitis. Oral: usually only causes gastrointestinal adverse effects if significant serum concentrations occur, e.g. in renal impairment. Nausea, vomiting, diarrhoea and chills.

Uncommon Nephrotoxicity including renal failure (see below).

Rare Ototoxicity (discontinue if tinnitus occurs), interstitial nephritis, serious skin reactions (e.g. linear IgA bullous disease, exfoliative dermatitis, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, vasculitis, drug rash with eosinophilia and systemic symptoms (DRESS)). Blood disorders including thrombocytopenia (may be immune-mediated), neutropenia (more likely after at least 1 week and total dose > 25 g), leukopenia, agranulocytosis, flushing of the upper body ("red man" syndrome (see below)), anaphylaxis, severe hypotension (with shock, cardiac arrest), superinfection, *Clostridium difficile*-associated disease.

NEPHROTOXICITY Although reports of frequency are conflicting, it is more common when used with aminoglycosides and in renal impairment. It appears to be related to vancomycin serum concentration.

OTOTOXICITY Dizziness, vertigo and tinnitus can occur. Vancomycin alone rarely causes ototoxicity; risk is higher with prolonged use, in renal impairment and when given with other ototoxic drugs, e.g. aminoglycosides; deafness may be permanent.

RED MAN SYNDROME Usually due to infusion being given too quickly. It is not an allergic reaction although symptoms are partly due to histamine release; they include fever, chills, erythema, facial and upper torso rash, which may be followed by hypotension, angioedema and itch. May be treated with antihistamines (e.g. promethazine); successful administration is usually possible by increasing the infusion time (e.g. to 120 minutes).

Interactions with other medicines (* indicates severe):

Amikacin: increased risk of nephrotoxicity and ototoxicity.

Amphotericin B: possibly increased risk of nephrotoxicity.

Capreomycin: increased risk of nephrotoxicity and ototoxicity.

* **Ciclosporin**: increased risk of nephrotoxicity.

* **Furosemide**: increased risk of ototoxicity.

Gentamicin: increased risk of nephrotoxicity and ototoxicity.

Halothane: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

Ketamine: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

Nitrous oxide: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

Paromomycin: increased risk of otoxicity.

Streptomycin: increased risk of nephrotoxicity and ototoxicity.

* **Suxamethonium**: enhanced effects of suxamethonium.

Thiopental: hypersensitivity-like reactions can occur with concomitant intravenous vancomycin.

Notes: Injection may be given orally for *Clostridium difficile* infection (see Dose); flavouring syrups may be added to the solution at the time of administration.

ADMINISTRATION Give over at least 60 minutes (rate not to exceed 10 mg/minute for doses > 500 mg) via central venous catheter if possible; avoid extravasation; never give IM. Do not mix with other drugs in parenteral solutions.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

6.2.3 Antileprosy medicines

Leprosy is a chronic mycobacterial infection due to *Mycobacterium leprae*, which is a slow-growing intracellular bacillus that infiltrates the skin, peripheral nerves, the nasal and other mucosa and the eyes; it affects people of all ages and both sexes. The incubation period between infection and appearance of leprosy is normally between 2 and 10 years, but may be up to 20 years. It is transmitted from person to person when bacilli are shed from the nose. For treatment purposes, patients may be classified as having either paucibacillary (PB) or multibacillary (MB) leprosy. The two forms may be distinguished by skin smears, but facilities are not always available to process them and their reliability is often doubtful. In practice, most leprosy programmes classify patients and choose a regimen based on the number of skin lesions, i.e. PB leprosy: one to five skin lesions; MB leprosy, more than five skin lesions.

Rifampicin, clofazimine and **dapsone** are used in the treatment of leprosy and should always be used as combination therapy; this is essential to prevent the emergence of resistance.

Lepra reactions are episodes of sudden increase in the activity of leprosy, and are often accompanied by neuritis. Reactions must always be treated promptly to prevent permanent nerve damage and disability. Leprosy multidrug therapy should continue without interruption during a lepra reaction. This reduces the frequency and severity of lepra reactions.

Type 1 lepra reactions (reversal reactions) are delayed hypersensitivity reactions, characterized by redness and swelling of pre-existing skin lesions and possible increased motor/sensory loss before ulceration of the lesion. This may occur in either PB or MB leprosy.

The type 2 lepra reaction (erythema nodosum leprosum [ENL]), characterized by fever and multiple red tender nodules, is an antibody response to dead leprosy bacteria and occurs only in MB leprosy.

Clofazimine

ATC code: J04BA01

Capsule: 50 mg; 100 mg

Special Notes: Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance.

Indications: Treatment of multibacillary (MB) leprosy (and where classification between MB and paucibacillary leprosy cannot be made) as part of combination therapy; treatment of type 2 lepra reactions (erythema nodosum leprosum).

Precautions: Pre-existing gastrointestinal symptoms (reduce dose, increase dose interval or discontinue if symptoms develop during treatment); liver and renal impairment; may discolour soft contact lenses.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for about 24 hours.

Dose:

Multibacillary leprosy (in combination with dapsone and rifampicin).

Oral:

Child *under 10 years* 100 mg once a month and 50 mg twice a week. Continue treatment for 12 months;

10–12 years 150 mg once a month and 50 mg on alternate days. Continue treatment for 12 months.

Type 2 lepra reaction (erythema nodosum leprosum).

Oral:

Child *all ages* 100 mg two or three times daily. Continue treatment for 3 months. 4–6 weeks treatment may be required before effect is seen.

Adverse effects: Uncommon Reversible discoloration of skin, hair, cornea, conjunctiva, tears, sweat, sputum, faeces and urine, gastrointestinal pain, nausea, vomiting, diarrhoea, weight loss, gastrointestinal bleeding, severe mucosal and submucosal oedema, dry skin, acne-like eruptions, rashes, pruritus, photosensitivity, decreased sweat production, dry eyes.

Rare Headache, drowsiness, dizziness, taste disorders, elevation of blood glucose concentration.

Interactions with other medicines (* indicates severe):

* **Phenytoin**: reduced phenytoin serum concentrations and loss of phenytoin efficacy.

Notes: The drug is well tolerated and virtually non-toxic in the dosage used for multidrug therapy (MDT). The drug causes brownish black discoloration and dryness of skin. However, this disappears within a few months after stopping treatment. This should be explained to patients starting a MDT regimen for MB leprosy.

References:

Estrada B. Leprosy. *eMedicine.* New York, WebMD, 2009 (http://emedicine.medscape.com/article/965605-overview, accessed 10 February 2010).

WHO-recommended multi-drug therapy (MDT) regimens. Geneva, World Health Organization, 2010 (http://www.who.int/lep/mdt/regimens/en/, accessed 10 February 2010).

Dapsone

ATC code: J04BA02

Tablet: 25 mg; 50 mg; 100 mg

Special Notes: Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance.

Indications: Treatment of leprosy as part of combination therapy (paucibacillary and multibacillary).

Contraindications: Hypersensitivity to sulfones; severe anaemia.

Precautions: Anaemia (treat severe anaemia before therapy, and monitor blood counts during treatment); susceptibility to haemolysis including G6PD deficiency (including breastfeeding affected infants); porphyria.

BLOOD DISORDERS On long-term treatment, patients and their carers should be told how to recognize blood disorders and advised to seek immediate medical attention if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Paucibacillary leprosy (in combination with rifampicin).

Oral:

Child *under 10 years* 25 mg once daily. Continue treatment for 6 months;
10–12 years 50 mg once daily. Continue treatment for 6 months.

Multibacillary leprosy (in combination with rifampicin and clofazimine).

Oral:

Child *under 10 years* 25 mg once daily. Continue treatment for 12 months;
10–12 years 50 mg once daily. Continue treatment for 12 months.

Renal impairment: Increased levels can occur in renal impairment.

Adverse effects: Common Gastrointestinal irritation, photosensitivity.

Rare Haemolysis, methaemoglobinaemia, allergic dermatitis (rarely including toxic epidermal necrolysis and Stevens-Johnson syndrome), hepatitis, agranulocytosis, "dapsone syndrome" resembling mononucleosis (rare hypersensitivity reaction with symptoms including rash, fever, jaundice and eosinophilia), tachycardia, headache, nervousness, insomnia, blurred vision, paraesthesia, reversible peripheral neuropathy, psychoses.

Interactions with other medicines (* indicates severe):

Rifampicin: reduced plasma dapsone concentration.

Sulfamethoxazole + trimethoprim: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.

Trimethoprim: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.

Notes: May cause photosensitivity.

Patients with high acetylation rates or who are receiving treatment that affects acetylation may require a dosage adjustment.

May be taken with food to reduce stomach upset.

Tablets should be taken whole and small doses should be made up from 25 mg tablets. Do not split the tablet.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).

Rifampicin

ATC code: J04AB02

Solid oral dosage form: 150 mg; 300 mg

Special Notes: Medicines used in the treatment of leprosy should never be used except in combination. Combination therapy is essential to prevent the emergence of drug resistance.

Indications: Treatment of leprosy as part of combination therapy (paucibacillary and multibacillary).

Contraindications: Hypersensitivity to rifamycins; jaundice.

Precautions: Hepatic impairment; monitor liver function tests and blood counts in patients with liver disorders or on prolonged therapy; renal impairment (if dose above 600 mg daily); porphyria; discolours soft contact lenses.

IMPORTANT Advise patients on hormonal contraceptives to use additional means.

NOTE Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis or thrombocytopenia; discontinue permanently if serious adverse effects occur.

LIVER DISORDERS Patients or their carers should be told how to recognize signs of liver disorders and advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Dose:

Paucibacillary leprosy (in combination with dapsone).

Oral:

Child *under 10 years* 300 mg once a month. Continue treatment for 6 months;
10–12 years 450 mg once a month. Continue treatment for 6 months.

Multibacillary leprosy (in combination with dapsone and clofazimine).

Oral:

Child *under 10 years* 300 mg once a month. Continue treatment for 12 months;
10–12 years 450 mg once a month. Continue treatment for 12 months.

PATIENT ADVICE Take dose at least 30 minutes before a meal, since absorption is reduced by food.

Hepatic impairment: Impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily.

Adverse effects: Common Urine, tears, saliva and sputum coloured orange-red.

Rare Alterations of liver function, jaundice, potentially fatal hepatitis (dose related; do not exceed maximum dose of 600 mg daily), anorexia, nausea, vomiting, diarrhoea, antibiotic-associated colitis, headache, drowsiness, rashes, fever, influenza-like syndrome, respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, thrombocytopenic purpura, oedema, muscular weakness, myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, menstrual disturbances.

Interactions with other medicines (* indicates severe):

Abacavir: plasma concentration of abacavir possibly reduced.

Amitriptyline: plasma concentration of amitriptyline possibly reduced.

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of rifampicin.

Chloramphenicol: accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration).

* **Ciclosporin**: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).

* **Contraceptives, oral**: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Dapsone: reduced plasma dapsone concentration.

* **Dexamethasone**: accelerated metabolism of dexamethasone (reduced effect).

Diazepam: metabolism of diazepam accelerated (reduced plasma concentration).

Digoxin: plasma concentration of digoxin possibly reduced.

Doxycycline: plasma doxycycline concentration possibly reduced.

Efavirenz: reduced plasma concentration of efavirenz (increase efavirenz dose).

* **Fluconazole**: accelerated metabolism of fluconazole (reduced plasma concentration).

* **Glibenclamide**: possibly accelerated metabolism (reduced effect) of glibenclamide.

* **Haloperidol**: accelerated metabolism of haloperidol (reduced plasma haloperidol concentration).

* **Hydrocortisone**: accelerated metabolism of hydrocortisone (reduced effect).

* **Indinavir**: metabolism accelerated by rifampicin (plasma indinavir concentration reduced; avoid concomitant use).
* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

  Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).
* **Lopinavir**: reduced plasma concentration of lopinavir (avoid concomitant use).
* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Nelfinavir**: plasma concentration of nelfinavir significantly reduced (avoid concomitant use).
* **Nevirapine**: reduced plasma concentration of nevirapine (avoid concomitant use).
* **Nifedipine**: accelerated metabolism of nifedipine (plasma concentration significantly reduced).
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).
* **Phenytoin**: accelerated metabolism of phenytoin (reduced plasma concentration).
* **Prednisolone**: accelerated metabolism of prednisolone (reduced effect).

  Propranolol: metabolism of propranolol accelerated (significantly reduced plasma concentration).
* **Quinidine**: accelerated metabolism of quinidine (reduced plasma quinidine concentration).
* **Saquinavir**: plasma concentration of saquinavir significantly reduced; avoid concomitant use.
* **Verapamil**: accelerated metabolism of verapamil (plasma concentration significantly reduced).
* **Warfarin**: accelerated metabolism of warfarin (reduced anticoagulant effect).

  Zidovudine: avoidance of rifampicin advised by manufacturer of zidovudine.

Notes: Capsules should be swallowed whole. Avoid contact during dosing/preparation due to risk of contact sensitization.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

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6.2.4 Antituberculosis medicines

Antituberculosis treatment in children

The main objectives of **antituberculosis** treatment are to:

1. cure the patient of tuberculosis (TB) (by rapidly eliminating most of the bacilli)
2. prevent death from active TB or its late effects
3. prevent relapse of TB (by eliminating the dormant bacilli)
4. prevent the development of drug resistance (by using a combination of drugs)
5. decrease TB transmission to others.

Children with TB usually have paucibacillary (low organism numbers) pulmonary disease. They also develop extrapulmonary TB more often than adults. Severe and disseminated TB (e.g. TB meningitis and miliary TB) occurs more frequently in young children (less than 3 years old). Both the bacillary load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are generally good, even in young and immunocompromised children, provided treatment is started promptly. Studies demonstrate that very few of the drug adverse events more commonly reported in adults occur as commonly in children, when used in doses suggested in WHO treatment regimens.

Treatment regimens

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. Daily treatment is preferred for therapy, but treatment can be given three times weekly provided the treatment is directly observed. Three times weekly therapy is not recommended in settings where there is high HIV-prevalence, or for HIV-positive individuals.

Recommended dosages

Note that dose recommendations for several first-line anti-TB medications have recently been revised. Recommended doses for several medications have been increased, because current evidence suggests that serum drug levels may be lower in children than in adults. Children with TB must be followed up regularly and have dosages adjusted for weight gained.

Two or more new drugs should be added to any re-treatment regimen in cases of genuine failure of treatment.

Children with TB who are co-infected with HIV

HIV-infected children are at greater risk for TB infection and TB disease than children not infected with HIV. HIV-infected children also have a poorer response to TB treatment and higher rates of mortality associated with TB disease. The majority of deaths in HIV-infected children being treated for TB occur in the first 2 months of TB treatment during the intensive phase.

Management of relapse and drug-resistant TB in children

In childhood TB cases when anti-TB treatment fails or a relapse occurs, every effort should be made to find the most likely cause for the failure or relapse. Mycobacterial culture and drug susceptibility testing should be performed for all re-treatment cases.

Drug-resistant TB is a public health problem in many countries. Second-line drugs are required to manage these infections. There is limited experience with the safety of many of these drugs in children. No drug is absolutely contraindicated in children; however, benefits have to be carefully weighed against risks. These drugs are indicated for the treatment of multidrug-resistant TB in children and should only be used in specialized centres.

Ethambutol

ATC code: J04AK02

Oral liquid: 25 mg/ml

Tablet: 100 mg; 400 mg (hydrochloride)

Indications: Treatment of tuberculosis, in combination with other drugs.

Contraindications: Optic neuritis; severe renal impairment.

Precautions: Visual disturbances; renal impairment.

VISUAL DISTURBANCES Patients should report visual disturbances immediately and discontinue treatment.

Dose:

Treatment of tuberculosis, in combination with other drugs.

Oral:

Infant or **Child** 20 mg/kg (range 15–25 mg/kg) once daily.

NOTE Serum ethambutol concentrations should be monitored.

The doses in this monograph are based on the 2009 WHO "Dosing instructions for the use of currently available fixed-dose combination TB medicines for children". Therefore, they may differ from other paediatric TB treatment guidelines.

Renal impairment: Mild/moderate: reduce dose; if creatinine clearance less than 30 ml/minute monitor plasma ethambutol concentration.

Severe: avoid.

Adverse effects: Uncommon Optic neuritis (reduced visual acuity and red/green colour blindness (early changes usually reversible, prompt withdrawal may prevent blindness)), gout, peripheral neuritis (especially in legs).

Rare Rash, pruritus, urticaria, thrombocytopenia.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Geneva, World Health Organization, 2009 (http://www.stoptb.org/gdf/assets/documents/Interim Paediatric FDCs detailed dosing instructions_Sept09.pdf, accessed 10 February 2010).

Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children. Geneva, World Health Organization, 2006 (http://www.who.int/tb/publications/2006/en/index.html, accessed 10 February 2010).

Graham SM et al. Ethambutol in tuberculosis: time to reconsider? *Archives of Disease in Childhood,* 1998, 79:274–278.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

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Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

Trebucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *International Journal of Tuberculosis and Lung Disease,* 1997(1):12–15.

Isoniazid

ATC code: J04AC01

Oral liquid: 10 mg/ml

Tablet: 100 mg; 300 mg

Tablet (scored): 50 mg

Severe and sometimes fatal hepatitis may occur; usually occurs within the first 3 months of treatment. Patients or their carers must be advised to report any prodromal symptoms of hepatitis, such as fatigue, weakness, malaise, anorexia, nausea or vomiting, immediately.

Special Notes: Also referred to as INH.

Indications: Treatment of tuberculosis, in combination with other drugs; prophylaxis of tuberculosis.

Contraindications: Drug-induced hepatic disease.

Precautions: Hepatic impairment; risk of peripheral neuritis (prophylactic pyridoxine recommended) in patients with malnutrition, chronic renal failure, diabetes mellitus or HIV infection; epilepsy; slow acetylator status; history of psychosis; porphyria; renal impairment.

LIVER DISORDERS Patients or their carers should be told how to recognize signs of liver disease and be advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Dose:

Treatment of tuberculosis (in combination with other drugs), prophylaxis of tuberculosis.
Oral:
Infant or **Child** ***greater than 3 months*** 10 mg/kg (range 10–15 mg/kg) once daily (maximum 300 mg daily).

The doses in this monograph are based on the 2009 WHO "Dosing instructions for the use of currently available fixed-dose combination TB medicines for children". Therefore, they may differ from other paediatric TB treatment guidelines.

Renal impairment: Severe: reduce dose to maximum 4 mg/kg daily or 200 mg daily; risk of peripheral neuropathy.

Hepatic impairment: Use with caution; monitor liver function regularly and frequently in the first 2 months.

Adverse effects: Uncommon Nausea, vomiting, diarrhoea, gastrointestinal pain, constipation, dry mouth.

Rare Hepatotoxicity (withdraw treatment), peripheral neuropathy, blood disorders (including agranulocytosis, haemolytic anaemia, aplastic anaemia), optic neuritis, toxic psychoses, seizures, hypersensitivity reactions (including fever, rashes, joint pain, erythema multiforme and purpura), systemic lupus erythematosus-like syndrome, pellagra, hyper-reflexia, difficulty with micturition, hyperglycaemia, gynaecomastia.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased plasma concentration of isoniazid.

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of isoniazid.

* **Carbamazepine**: increased plasma carbamazepine concentration (also isoniazid hepatotoxicity possibly increased).

Cycloserine: increased risk of CNS toxicity.

Diazepam: metabolism of diazepam inhibited.

* **Ethosuximide**: metabolism of ethosuximide inhibited (increased plasma ethosuximide concentration and risk of toxicity).

Halothane: possible potentiation of isoniazid hepatotoxicity.

Ketamine: possible potentiation of isoniazid hepatotoxicity.

Nitrous oxide: possible potentiation of isoniazid hepatotoxicity.

p-Aminosalicylic acid: increased plasma concentration of isoniazid.

* **Phenytoin**: metabolism of phenytoin inhibited (enhanced effect).

Thiopental: possible potentiation of isoniazid hepatotoxicity.

Notes: PATIENT ADVICE Isoniazid should be taken on an empty stomach; if taken with food to reduce gastrointestinal irritation, oral absorption and bioavailability may be impaired.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Donald PR. *A literature review of the pharmacokinetics of rifampicin, isoniazid and pyrazinamide and a recommendation for the dosages to be used in children.* Geneva, World Health Organization, Unpublished 2007.

Donald PR. *Hepatotoxicity of antituberculosis agents in children: a literature review.* Geneva, World Health Organization, Unpublished 2009.

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Frydenberg AR, Graham SM. Toxicity of first-line drugs for treatment of tuberculosis in children: review. *Tropical Medicine and International Health,* 2009, 14(11):1329–1337.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

Pyrazinamide

ATC code: J04AK01

Oral liquid: 30 mg/ml

Tablet: 400 mg

Tablet (dispersible): 150 mg

Tablet (scored): 150 mg

Special Notes: Also referred to as PZA.

Indications: Treatment of tuberculosis, in combination with other medicines.

Contraindications: Severe hepatic impairment; porphyria.

Precautions: Hepatic impairment; renal impairment; diabetes mellitus (monitor blood glucose, may change suddenly); gout; concurrent medications associated with liver injury (particulary rifampicin).

LIVER DISORDERS Patients or their carers should be told how to recognize signs of liver disease and be advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Dose:

Treatment of tuberculosis, in combination with other medicines.

Oral:

Infant or **Child** 35 mg/kg (range 30–40 mg/kg) once daily. Maximum 2 g daily.

The doses in this monograph are based on the 2009 WHO "Dosing instructions for the use of currently available fixed-dose combination TB medicines for children". Therefore, they may differ from other paediatric TB treatment guidelines.

Renal impairment: Severe impairment: reduce dose.

Hepatic impairment: Monitor hepatic function, idiosyncratic hepatotoxicity more common.

Severe hepatic impairment: avoid use.

Adverse effects: Common Nausea, vomiting.

Uncommon Rash, photosensitivity.

Rare Flushing, dysuria, arthralgia, gout, sideroblastic anaemia, hepatotoxicity (including fever, anorexia, hepatomegaly, splenomegaly, jaundice, liver failure).

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: reduced ciclosporin serum concentrations and potentially reduced immunosuppressive efficacy.

Rifampicin: risk of severe hepatic injury.

Zidovudine: decreased serum concentration and efficacy of pyrazinamide.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
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Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

Rifampicin

ATC code: J04AB02

Oral liquid: 20 mg/ml

Solid oral dosage form: 150 mg; 300 mg

Special Notes: Also referred to as rifampin.

Indications: Treatment of tuberculosis, in combination with other drugs.

Contraindications: Hypersensitivity to rifamycins; jaundice.

Precautions: Hepatic impairment; liver function tests and blood counts required in liver disorders and on prolonged therapy; porphyria; discolours soft contact lenses.

IMPORTANT Advise patients on hormonal contraceptives to use additional means.

NOTE Resumption of rifampicin treatment after a long interval may cause serious immunological reactions, resulting in renal impairment, haemolysis or thrombocytopenia; discontinue permanently if serious adverse effects occur.

LIVER DISORDERS Patients or their carers should be told how to recognize signs of liver disease and be advised to discontinue treatment and seek immediate medical attention if symptoms such as persistent nausea, vomiting, malaise or jaundice develop.

Dose:

Treatment of tuberculosis, in combination with other drugs.

Oral:

Infant or **Child** 15 mg/kg (range 10–20 mg) once daily. Maximum 600 mg daily.

The doses in this monograph are based on the 2009 WHO "Dosing instructions for the use of currently available fixed-dose combination TB medicines for children". Therefore, they may differ from other paediatric TB treatment guidelines.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Impaired elimination; monitor liver function; avoid or do not exceed 8 mg/kg daily.

Adverse effects: Common Urine, tears, saliva and sputum coloured orange-red.

Rare Alterations of liver function, jaundice, potentially fatal hepatitis, anorexia, nausea, vomiting, diarrhoea, headache, drowsiness, rashes, fever, influenza-like syndrome, respiratory symptoms, collapse, shock, haemolytic anaemia, acute renal failure, thrombocytopenic purpura, oedema, muscular weakness, myopathy, exfoliative dermatitis, toxic epidermal necrolysis, pemphigoid reactions, leukopenia, eosinophilia, menstrual disturbances.

Interactions with other medicines (* indicates severe):

Abacavir: plasma concentration of abacavir possibly reduced.

Amitriptyline: plasma concentration of amitriptyline possibly reduced.

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of rifampicin.

Chloramphenicol: accelerated metabolism of chloramphenicol (reduced plasma chloramphenicol concentration).

* **Ciclosporin**: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).
* **Contraceptives, oral**: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Dapsone: reduced plasma dapsone concentration.

* **Dexamethasone**: accelerated metabolism of dexamethasone (reduced effect).

Diazepam: metabolism of diazepam accelerated (reduced plasma concentration).

Digoxin: plasma concentration of digoxin possibly reduced.

Doxycycline: plasma doxycycline concentration possibly reduced.

Efavirenz: reduced plasma concentration of efavirenz (increase efavirenz dose).

* **Fluconazole**: accelerated metabolism of fluconazole (reduced plasma concentration).
* **Glibenclamide**: possibly accelerated metabolism (reduced effect) of glibenclamide.
* **Haloperidol**: accelerated metabolism of haloperidol (reduced plasma haloperidol concentration).
* **Hydrocortisone**: accelerated metabolism of hydrocortisone (reduced effect).
* **Indinavir**: metabolism accelerated by rifampicin (plasma indinavir concentration reduced; avoid concomitant use).
* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Levothyroxine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

* **Lopinavir**: reduced plasma concentration of lopinavir (avoid concomitant use).
* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Nelfinavir**: plasma concentration of nelfinavir significantly reduced (avoid concomitant use).
* **Nevirapine**: reduced plasma concentration of nevirapine (avoid concomitant use).
* **Nifedipine**: accelerated metabolism of nifedipine (plasma concentration significantly reduced).
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).
* **Phenytoin**: accelerated metabolism of phenytoin (reduced plasma concentration).
* **Prednisolone**: accelerated metabolism of prednisolone (reduced effect).

Propranolol: metabolism of propranolol accelerated (significantly reduced plasma concentration).

* **Quinidine**: accelerated metabolism of quinidine (reduced plasma quinidine concentration).
* **Saquinavir**: plasma concentration of saquinavir significantly reduced; avoid concomitant use.
* **Verapamil**: accelerated metabolism of verapamil (plasma concentration significantly reduced).
* **Warfarin**: accelerated metabolism of warfarin (reduced anticoagulant effect).

Zidovudine: avoidance of rifampicin advised by manufacturer of zidovudine.

Notes: PATIENT ADVICE Take dose at least 30 minutes before a meal, as absorption is reduced when taken with food.

Capsules should be swallowed whole. Avoid contact during dosing/preparation due to risk of contact sensitization.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Dosing instructions for the use of currently available fixed-dose combination TB medicines for children. Geneva, World Health Organization, 2009 (http://www.stoptb.org/gdf/assets/documents/Interim Paediatric FDCs detailed dosing instructions_Sept09.pdf, accessed 10 February 2010).
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

Streptomycin

ATC code: J01GA01

Powder for injection: 1 g (as sulfate) in vial

Special Notes: Intramuscular injection of streptomycin is very painful.

Indications: Treatment of tuberculosis, in combination with other drugs.

Contraindications: Hearing disorders; myasthenia gravis; hypersensitivity to aminoglycoside antibiotics.

Precautions: Children (painful injection, avoid use if possible); renal impairment; infants (monitor renal, auditory and vestibular function, and plasma streptomycin concentrations); neuromuscular disorders; vertigo; tinnitus; hearing loss.

Dose:

Treatment of tuberculosis, in combination with other drugs.
Deep IM injection:
Infant or **Child** 20–40 mg/kg once daily. Maximum 1 g daily.

NOTE 1 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).

Renal impairment: Mild to moderate: extend dosing frequency. Monitor plasma concentrations.

Severe: avoid use.

Adverse effects: Common Pain and abscess at injection site.

Uncommon Vestibular and auditory damage, nephrotoxicity, hypersensitivity reactions (withdraw treatment), paraesthesia of mouth, nausea, vomiting, rash, hypomagnesaemia on prolonged therapy.

Rare Antibiotic-associated colitis, haemolytic anaemia, aplastic anaemia, agranulocytosis, thrombocytopenia.

Interactions with other medicines (* indicates severe):

* **Alcuronium**: enhanced muscle relaxant effect.

  Amphotericin B: increased risk of nephrotoxicity.
* **Ciclosporin**: increased risk of nephrotoxicity.
* **Cisplatin**: increased risk of nephrotoxicity and possibly of ototoxicity.
* **Furosemide**: increased risk of ototoxicity.
* **Neostigmine**: antagonism of effect of neostigmine.
* **Pyridostigmine**: antagonism of effect of pyridostigmine.

* **Suxamethonium**: enhanced muscle relaxant effect.

Vancomycin: increased risk of nephrotoxicity and ototoxicity.

* **Vecuronium**: enhanced muscle relaxant effect.

Notes: RECONSTITUTION AND ADMINISTRATION Reconstitute following manufacturer's instructions.

For IM injection, inject deep intramuscularly into a large muscle mass. Administer at a concentration not to exceed 500 mg/mL. Rotate injection sites.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf, accessed 10 February 2010).
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Amikacin

ATC code: J01GB06

Powder for injection: 100 mg; 500 mg; 1 g in vial

Special Notes: Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Indications: Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Contraindications: Hypersensitivity to amikacin or aminoglycoside antibiotics.

Precautions: Renal impairment; pre-existing vestibular or auditory impairment; concomitant anaesthesia or neuromuscular blockers; conditions characterized by muscle weakness; myasthenia gravis; concomitant neurotoxic, ototoxic or nephrotoxic drugs; neonates and infants; dehydration.

Dose:

Treatment of multidrug-resistant tuberculosis, in combination with other drugs.
IV or *IM:*
Infant or **Child** 15–30 mg/kg once daily (maximum 1 g).

NOTE Pre-dose (trough) concentration should be less than 5 mg/litre for once daily dosing.

Renal impairment: Dosage adjustment is required in patients with renal impairment. Patients should receive the usual loading dose; however, subsequent doses and/or dosing intervals should be adjusted. Adjustment may be based on amikacin serum levels. Target amikacin serum levels for once daily dosing: pre-dose (trough) concentration should be < 5 mg/litre.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Ototoxicity, nephrotoxicity.

Uncommon Rash, purpura, urticaria and alopecia.

Rare Exfoliative dermatitis, myasthenia gravis.

Interactions with other medicines (* indicates severe):

* **Alcuronium**: enhanced effects of alcuronium.

Amphotericin B: increased risk of nephrotoxicity.

* **Benzylpenicillin**: concomitant penicillin and aminoglycoside therapy has been reported to result in inactivation of the aminoglycoside. Preferable to separate administration by 1 hour.
* **Ciclosporin**: increased risk of nephrotoxicity.
* **Cisplatin**: increased risk of nephrotoxicity and possibly of ototoxicity.
* **Furosemide**: increased risk of ototoxicity.
* **Neostigmine**: antagonism of effects of neostigmine.
* **Pyridostigmine**: antagonism of effects of pyridostigmine.
* **Suxamethonium**: enhanced effects of suxamethonium.

  Vancomycin: increased risk of nephrotoxicity and ototoxicity.
* **Vecuronium**: enhanced effects of vecuronium.

Notes: ADMINISTRATION Administer by intramuscular injection or slow intermittent intravenous infusion over 30 minutes at a final concentration not to exceed 10 mg/ml. For intravenous infusion, dilute with glucose 5% or sodium chloride 0.9% or compound sodium lactate.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

Capreomycin

ATC code: J04AB30

Powder for injection: 1 g in vial

The use of capreomycin in patients with renal insufficiency or pre-existing auditory impairment must be undertaken with great caution. Risk of additional cranial nerve VIII impairment or renal injury.

Since other parenteral antituberculosis agents (streptomycin, viomycin) also have similar and sometimes irreversible toxic effects, particularly on cranial nerve VIII and renal function, simultaneous administration of these agents with capreomycin is not recommended. Use with non-antituberculosis drugs (polymyxin A sulfate, colistin sulfate, amikacin, gentamicin, tobramycin, vancomycin, kanamycin and neomycin) having ototoxic or nephrotoxic potential, should be undertaken only with great caution.

Special Notes: Monitor body weight monthly and adjust dose accordingly.

Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Indications: Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Contraindications: Hypersensitivity to aminoglycoside antibiotics.

Precautions: Auditory impairment; concomitant use with streptomycin or viomycin; renal impairment; renal injury; myasthenia gravis.

Dose:

Treatment of multidrug-resistant tuberculosis, in combination with other drugs.
IV or *IM:*
Child 15–30 mg/kg (maximum 1 g) once daily.

Renal impairment: Use with caution. In all degrees of impairment, dosing frequency should be reduced to 2–3 times weekly.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Injection site pain, eosinophilia, leukopenia, electrolyte disturbances (including hypokalaemia, hypocalcaemia, hypomagnesaemia, hyponatraemia and hypochloraemia), ototoxicity.

Uncommon Urticaria and rash, changes in liver function tests, neuromuscular blockade.

Rare Thrombocytopenia, nephrotoxicity.

Interactions with other medicines (* indicates severe):

* **Alcuronium**: enhanced or prolonged neuromuscular blockade.

Amikacin: amikacin toxicity (ototoxicity, nephrotoxicity).

* **Atracurium**: enhanced or prolonged neuromuscular blockade.
* **Cisatracurium**: enhanced or prolonged neuromuscular blockade.
* **Doxacurium**: enhanced or prolonged neuromuscular blockade.
* **Fazadinium**: enhanced or prolonged neuromuscular blockade.
* **Gallamine**: enhanced or prolonged neuromuscular blockade.

Gentamicin: gentamicin toxicity (ototoxicity, nephrotoxicity).

* **Hexafluorenium**: enhanced or prolonged neuromuscular blockade.

Kanamycin: kanamycin toxicity (ototoxicity, nephrotoxicity).

* **Metocurine**: enhanced or prolonged neuromuscular blockade.
* **Mivacurium**: enhanced or prolonged neuromuscular blockade.

Netilmicin: netilmicin toxicity (ototoxicity, nephrotoxicity).

* **Pancuronium**: enhanced or prolonged neuromuscular blockade.
* **Pipecuronium**: enhanced or prolonged neuromuscular blockade.
* **Rapacuronium**: enhanced or prolonged neuromuscular blockade.
* **Rocuronium**: enhanced or prolonged neuromuscular blockade.

Streptomycin: streptomycin toxicity (ototoxicity, nephrotoxicity).

* **Suxamethonium**: enhanced or prolonged neuromuscular blockade.

Tobramycin: tobramycin toxicity (ototoxicity, nephrotoxicity).

* **Tubocurarine**: enhanced or prolonged neuromuscular blockade.
* **Vecuronium**: enhanced or prolonged neuromuscular blockade.

Notes: ADMINISTRATION Reconstitute with 0.9% sodium chloride or water for injection. Administer by deep intramuscular injection into a large muscle or dilute further with 0.9% sodium chloride and infuse over 60 minutes.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Capastat Product Information. Aspen, 2010 (http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=16185, accessed 10 February 2010).

Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf, accessed 10 February 2010).
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Cycloserine

ATC code: J04AB01

Solid oral dosage form: 250 mg

Special Notes: Safety and effectiveness in paediatrics have not been established.

Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Indications: Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Contraindications: Epilepsy; depression; severe anxiety; psychosis; porphyria; severe renal impairment.

Precautions: Neuropsychiatric status assessed at least monthly, more frequently if symptoms develop; renal impairment.

Dose:

Treatment of multidrug-resistant tuberculosis, in combination with other drugs.
Oral:
Child 5–10 mg/kg twice daily (initially 5 mg/kg/dose and adjust according to blood concentration and response). Maximum 1 g daily.

NOTE Serum concentration measurements aiming for a peak concentration of 20–35 mg/ml are often useful in determining the optimum dose for a given patient. Measure 3–4 hours after dose.

Renal impairment: Avoid use in all degrees of renal impairment.

Adverse effects: Common Neurological (headache, dizziness, vertigo, drowsiness, tremor, seizures, confusion, psychosis, depression).

Uncommon Rash.

Rare Megaloblastic anaemia, changes in liver function tests, heart failure.

Interactions with other medicines (* indicates severe):

* **Alcohol**: increased risk of seizures.

Isoniazid: increased risk of CNS toxicity.

Notes: Penetrates the cerebrospinal fluid.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf, accessed 10 February 2010).
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

Ethionamide

ATC code: J04AD03

Tablet: 125 mg; 250 mg

Special Notes: Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Indications: Treatment of multidrug-resistant tuberculosis and tuberculosis meningitis.

Contraindications: Severe hepatic impairment.

Precautions: AIDS infection (drug malabsorption may be a problem); diabetes mellitus; renal impairment; hepatic impairment.

Dose:

Treatment of multidrug-resistant tuberculosis and tuberculosis meningitis.

Oral:

Child 15–20 mg/kg once daily if tolerated; divided doses if necessary. Maximum 1 g/day.

Renal impairment: Severe: reduce to 50% of dose.

Hepatic impairment: Mild and moderate impairment: use with caution.

Severe impairment: avoid use.

Adverse effects: Common Gastrointestinal disturbance (see below).

Uncommon Hepatotoxicity.

Rare Hypotension, rash, fever, hypoglycaemia, hypothyroidism, gynaecomastia, photosensitivity, thrombocytopenia, encephalopathy, neuropathy, seizures, visual disturbances, ototoxicity.

GASTROINTESTINAL ADVERSE EFFECTS Gastrointestinal irritation is the major limiting factor in the therapeutic use of ethionamide. The most frequent adverse effects of ethionamide are nausea, vomiting and diarrhoea. Anorexia, excessive salivation, stomatitis and a metallic taste in the mouth occur less frequently. Abdominal discomfort, described as epigastric pain or burning, is common with therapeutic doses. These effects appear to be dose related. In general, half of the patient population is unable to tolerate 1 g of ethionamide as a single dose. Gastrointestinal effects are more common in females than males, and are less common in children. Persons of Asian or African descent reportedly tolerate this drug better than those of European descent.

Interactions with other medicines (* indicates severe):

Aminosalicylic acid: excessive adverse effects (GI distress and hepatotoxicity).

Cycloserine: neurological adverse effects, including seizures.

Ethambutol: excessive adverse effect (GI distress, headache, confusion, neuritis and hepatotoxicity).

Isoniazid: increased isoniazid levels, peripheral neuritis, hepatotoxicity and encephalopathy.

Pyrazinamide: hepatotoxicity.

Rifampicin: hepatotoxicity.

Notes: Concurrent administration of pyridoxine may reduce peripheral neuropathy.

Administration of an antiemetic agent 30 minutes prior to ethionamide and administration of ethionamide at bedtime have been suggested in patients experiencing gastrointestinal adverse effects.

Baseline liver function tests including serum transaminases, bilirubin and alkaline phosphatase should be obtained and regularly monitored (e.g. every 2–4 weeks) during ethionamide therapy.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf, accessed 10 February 2010).
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Kanamycin

ATC code: J01GB04

Powder for injection: 1 g vial

Special Notes: Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Indications: Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Contraindications: Intestinal obstruction.

Precautions: Concomitant administration with nephrotoxic or ototoxic antibiotics; concomitant administration with rapid acting diuretic agents; cross-allergenicity among other aminoglycosides (see Notes); infant botulism; myasthenia gravis; impaired neuromuscular transmission; parkinsonism; renal impairment; hepatic impairment; vestibular impairment.

Dose:

Treatment of multidrug-resistant tuberculosis, in combination with other drugs.
IM or *IV:*
Neonate with ***birth weight of less than 2 kg and aged 7 days or less*** 7.5 mg/kg every 12 hours;
birth weight of more than 2 kg and aged 7 days or less 10 mg/kg every 12 hours;
birth weight of 2 kg or less and aged greater than 7 days 10 mg/kg every 12 hours;
birth weight of more than 2 kg and aged greater than 7 days 10 mg/kg every 8 hours.
Infant or **Child** 15–30 mg/kg once daily (maximum 1 g daily).

NOTE Whenever possible, dosage should be guided by kanamycin serum concentrations. Maintain optimal peak serum levels of 15–30 micrograms/ml. Suitable times to collect blood for kanamycin assays are 1 hour after an IM dose or 30 minutes after an IV dose (peak) then just prior to the next dose (trough).

Renal impairment: The dosage of kanamycin must be reduced in patients with impaired renal function.

Mild impairment: 60–90% of the normal dose every 8–12 hours.

Moderate impairment: 30–70% of the dose every 12 hours.

Severe impairment: 20–30% of the dose every 24–48 hours.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nephrotoxicity, ototoxicity, local irritation or pain after IM injection.

Uncommon Neuromuscular blockade.

Rare Skin rash, drug fever, headache, paraesthesia, nausea, vomiting and diarrhoea.

Interactions with other medicines (* indicates severe):

* **Penicillins**: loss of kanamycin activity.
* **Neuromuscular blocking drugs**: enhanced and/or prolonged neuromuscular blockade which may lead to respiratory depression and paralysis.

Loop diuretics: an increased risk of ototoxicity (tinnitus, transient or permanent hearing loss, dizziness, vertigo).

Carboplatin: increased ototoxicity.

Cidofovir: nephrotoxicity.

Ciclosporin: renal dysfunction or nephrotoxicity.

Tacrolimus: additive or synergistic renal function impairment.

Typhoid vaccine, live: decreased immunological response to the typhoid vaccine.

Notes: 62.2% of patients allergic to kanamycin demonstrated cross-sensitivity to gentamicin. Amikacin and kanamycin are very similar and have almost 100% cross-resistance.

Occasionally, some vials may darken during the shelf-life of the product, but this does not indicate a loss of potency.

ADMINISTRATION INSTRUCTIONS The minimum dilution of kanamycin is 2.5–5 mg/ml administered over 30–60 minutes. Direct intravenous push is not recommended.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Ofloxacin

ATC code: J01MA01

Tablet: 200 mg; 400 mg

Special Notes: Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Levofloxacin may be an alternative based on availability and programme considerations.

Indications: Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Contraindications: Pregnancy; breastfeeding.

Precautions: Tendinitis and tendon rupture; central nervous system disorders (may predispose patient to seizures or lower seizure threshold); co-administration with class IA (e.g. procainamide, quinidine) or class III (e.g. amiodarone, sotalol) antiarrhythmic agents should be avoided; diabetic patients, especially patients receiving oral hypoglycemic agents or insulin (may cause hyperglycaemia or hypoglycaemia); excessive sunlight (risk for phototoxic reactions); hepatic impairment; renal impairment.

Dose:

Treatment of multidrug-resistant tuberculosis, in combination with other drugs.
Oral:
Child 7.5–10 mg/kg twice daily. Maximum 800 mg/day.

Renal impairment: All degrees of renal impairment: increased risk of seizure; dosage adjustment recommended; seek specialist advice.

Hepatic impairment: Elimination may be reduced; reduce dose in severe liver disease.

Adverse effects: Common Rash, photosensitivity, nausea, vomiting, arthropathy, arthritis, diarrhoea, taste disturbance, insomnia, headache, dizziness.

Uncommon Seizures, hypoglycaemia or hyperglycaemia.

Rare Arrhythmias including QT prolongation, hepatic impairment/failure, blood dyscrasias, myopathy, arthralgia, tendon rupture, nephrotoxicity.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of ofloxacin.

* **Amiodarone**: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.

* **Ciclosporin**: increased risk of nephrotoxicity.

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Ferrous salts: absorption of ofloxacin reduced by oral ferrous salts.

* **Flecainide**: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

* **Ibuprofen**: possible increased risk of convulsions.

* **Quinidine**: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

* **Sotalol**: an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

Theophylline: an increased risk of elevated theophylline concentrations.

Typhoid vaccine, live: a decreased immunological response to the typhoid vaccine.

* **Warfarin**: enhanced anticoagulant effect.

Zinc sulfate: reduced absorption of ofloxacin.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546956_eng.pdf, accessed 10 February 2010).

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p-Aminosalicylic acid

ATC code: J04AA01

Granules: 4 g in sachet

Tablet: 500 mg

Special Notes: Also referred to as PAS and as 4-aminosalicylic acid (4-ASA).

Second-line medicines should be reserved for the treatment of multidrug-resistant tuberculosis (MDR-TB) and should be used in specialized centres adhering to WHO standards for TB control.

Indications: Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Contraindications: Hypersensitivity to aminosalicylic acid products; end-stage renal disease.

Precautions: Glucose-6-phosphate dehydrogenase (G6PD) deficiency (risk of haemolysis); hepatic impairment; peptic ulcer disease; renal impairment; congestive heart failure; patients on therapy of more than 1 month should be considered for maintenance vitamin B_{12}.

Dose:

Treatment of multidrug-resistant tuberculosis, in combination with other drugs.

Oral:

Child 200–300 mg/kg per day in 2–4 divided doses. Maximum 10 g daily.

Renal impairment: Not recommended to be used in patients with severe renal impairment.

Hepatic impairment: Use with caution. Increase laboratory and clinical monitoring. Dose reduction not considered necessary.

Adverse effects: Common Nausea, vomiting, diarrhoea, abdominal pain.

Rare Hepatotoxicity, haemolysis, fever, rash, blood dyscrasias, hypoglycaemia, crystalluria, encephalopathy.

Interactions with other medicines (* indicates severe):

* **Digoxin**: reduced digoxin serum concentrations.

Ethionamide: excessive adverse effects (GI distress and hepatotoxicity).

Isoniazid: reduction in the acetylation of isoniazid (increased isoniazid levels).

Vitamin B_{12}: reduced absorption of vitamin B_{12}.

Notes: PATIENT ADVICE Should be taken with acidic food or drink (yoghurt, apple sauce or fruit juice).

Granules should be stored in the refrigerator. Can be stored at room temperature for short periods of time.

Do not use granules if packet is swollen or the granules have lost their tan colour and have turned dark brown or purple.

Sprinkle granules on apple sauce or yogurt or suspend in tomato, orange, grapefruit, grape, cranberry, apple or fruit juice containing drinks.

Patients should be advised that the skeleton of the granules may be seen in the stool.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

Paser Product Information. Jacobus, 2004 (http://www.rxlist.com/paser-drug.html, accessed 10 February 2010).

Treatment of tuberculosis guidelines. 4th ed. Geneva, World Health Organization, 2010 (http://whqlibdoc.who.int/publications/2010/9789241547833_eng.pdf, accessed 10 February 2010).

Treatment of tuberculosis. American Thoracic Society, CDC, and Infectious Diseases Society of America, 2003 (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm, accessed 10 February 2010).

6.3 Antifungal medicines

Fungal infections are increasing in prevalence globally, and can be classified as superficial or systemic. Superficial infections affect the skin, hair, nails or mucous membranes; systemic fungal infections affect the body as a whole. Systemic fungal infections may occur as opportunistic infections in patients who are immunocompromised, and are associated with high mortality rates.

Duration of therapy depends on the initial severity of the infection and the clinical response of the patient. In some infections, a satisfactory response is only obtained after several months or more of continuous treatment.

Fluconazole

ATC code: J02AC01

Capsule: 50 mg

Injection: 2 mg/ml in vial

Oral liquid: 10 mg/ml

Rare cases of fluconazole-associated hepatotoxicity, including fatalities, have been reported.

Indications: Systemic mycoses including histoplasmosis, non-meningeal coccidioidomycosis, paracoccidioidomycosis and blastomycosis; treatment and, in HIV and other immunosuppressed patients, prophylaxis of cryptococcal meningitis; prevention of fungal infections in immunocompromised patients; oesophageal and oropharyngeal candidiasis, vaginal candidiasis and systemic candidiasis.

Contraindications: Acute porphyria.

Precautions: Renal impairment; monitor liver function: discontinue if signs or symptoms of hepatic disease (risk of hepatic necrosis); concomitant hepatotoxic drugs; susceptibility to QT interval prolongation; patients with proarrhythmic conditions.

Dose:

Systemic mycoses.
Oral or *IV:*
Child *over 2 years* 3–6 mg/kg (maximum 200 mg) daily for at least 6 months.

Cryptococcal meningitis following amphotericin B induction therapy or systemic candidiasis (in patients unable to tolerate amphotericin B).
Oral or *IV:*
Neonate *under 2 weeks* 6–12 mg/kg every 72 hours;
2–4 weeks 6–12 mg/kg every 48 hours.
Infant or **Child** 6–12 mg/kg (maximum 800 mg) daily.
Treatment should continue according to response and should be for at least 8 weeks for cryptococcal meningitis.

Prevention of relapse of cryptococcal meningitis in AIDS patients after completion of primary therapy.
Oral or *IV:*
Infant or **Child** 6 mg/kg (maximum 200 mg) daily.

Mucosal candidiasis (except genital).
Oral or *IV:*
Neonate *under 2 weeks* 3–6 mg/kg on first day then 3 mg/kg every 72 hours;
2–4 weeks 3–6 mg/kg on first day then 3 mg/kg every 48 hours.
Infant or **Child** 3–6 mg/kg on the first day, then 3 mg/kg daily (maximum 100 mg) for 7–14 days.
Treat for 14–30 days for other mucosal infections such as oesophagitis, candiduria and non-invasive bronchopulmonary infections.

Vaginal candidiasis.
Oral:
Child *post-puberty* 150 mg as a single dose.

Prevention of fungal infections in immunocompromised patients.
Oral or *IV:*
Neonate *under 2 weeks* 3–12 mg/kg every 72 hours according to duration and extent of neutropenia;
2–4 weeks 3–12 mg/kg every 48 hours according to duration and extent of neutropenia.
Infant or **Child** 3–12 mg/kg (maximum 400 mg) daily according to duration and extent of neutropenia.
Commence treatment before anticipated onset of neutropenia and continue for 7 days after neutrophil count in desirable range.

Renal impairment: Reduce dose in mild to severe impairment by 50%.

Hepatic impairment: Use with caution.

Adverse effects: Common Rash, headache, nausea, vomiting, abdominal pain, diarrhoea, elevated liver enzymes.

Uncommon Anorexia, fatigue, dizziness, constipation.

Rare Oliguria, hypokalaemia, seizures, paraesthesia, alopecia, Stevens-Johnson syndrome, toxic epidermal necrolysis (severe skin reactions more common in patients with AIDS), prolonged QT interval, torsades de pointes, thrombocytopenia, other blood dyscrasias, serious hepatotoxicity including hepatic failure, angioedema, anaphylactic/anaphylactoid reactions.

Interactions with other medicines (* indicates severe):

Fluconazole can cause prolonged QT interval and torsades de pointes; avoid concomitant use of other cardiotoxic or arrhythmogenic drugs.

Amphotericin B: possible antagonism of effect of amphotericin.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Carbamazepine: fluconazole may inhibit metabolism of carbamazepine and may increase concentration and risk of adverse effects; monitor carbamazepine concentration and for adverse effects.

* **Ciclosporin**: metabolism of ciclosporin inhibited (increased plasma concentration).

Contraceptives, oral: anecdotal reports of failure of estrogen containing contraceptives.

Diazepam: fluconazole may inhibit diazepam's metabolism, increasing the risk of adverse effects.

Ibuprofen: fluconazole may inhibit ibuprofen's metabolism, increasing its concentration and may increase risk of adverse effects.

* **Nevirapine**: increased plasma concentration of nevirapine.

* **Phenytoin**: plasma concentration of phenytoin increased (consider reducing dose of phenytoin).

* **Rifampicin**: accelerated metabolism of fluconazole (reduced plasma concentration).

Ritonavir: plasma concentration of fluconazole increased by ritonavir.

Saquinavir: plasma concentration of saquinavir possibly increased.

* **Warfarin**: enhanced anticoagulant effect.

* **Zidovudine**: increased plasma concentration of zidovudine (increased risk of toxicity).

Notes: For intravenous infusion, give over 60 minutes at a maximum rate of 200 mg/hour. Higher doses are best infused over 2 hours.

Food decreases the rate but not the extent of absorption. Bioavailability is excellent at > 90%.

Fluconazole oral liquid may contain sodium benzoate and should be used with caution in neonates.

References:
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Griseofulvin

ATC code: D01BA01

Oral liquid: 25 mg/ml

Solid oral dosage form: 125 mg; 250 mg

Special Notes: The formulations and doses in this formulary refer to microsize (fine particle) griseofulvin and these are not equivalent to ultramicrosize (ultra microfine crystal) formulations.

Indications: Fungal infections of the skin, scalp or hair where topical treatment has failed or is inappropriate.

Contraindications: Severe liver disease; pregnancy (avoid pregnancy and use additional non-hormonal contraception during and for 1 month after treatment; men should not father children within 6 months of treatment); porphyria; systemic lupus erythematosus (risk of exacerbation).

Precautions: Avoid exposure to intense sunlight to prevent photosensitivity reactions; penicillin hypersensitivity (cross-reactivity with griseofulvin is possible); pre-existing hepatic insufficiency (closely monitor hepatic function throughout treatment); blood disorders (monitor blood count weekly during first month of treatment).

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Fungal infections of the skin, scalp or hair where topical treatment has failed or is inappropriate.
Oral:
Infant or **Child** 10–20 mg/kg (maximum 1 g) once daily or in divided doses. Up to 25 mg/kg/day for 6–8 weeks may be required for the treatment of tinea capitis.

Duration of treatment depends on the infection and thickness of keratin at site of infection. As a guide: at least 4 weeks for skin and hair, at least 6 weeks for scalp ringworm and in severe hair, skin and scalp infections, up to 3 months.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Contraindicated in severe liver disease.

Adverse effects: Common Headache, nausea, diarrhoea, anorexia.

Uncommon Photosensitivity, urticaria, rash, blurred vision, confusion, fatigue, dizziness, taste disturbance.

Rare Precipitation/exacerbation of systemic lupus erythematosus, vomiting, severe diarrhoea, menstrual irregularities, leukopenia, hepatotoxicity, hypersensitivity, e.g. serum sickness-like reaction, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Interactions with other medicines (* indicates severe):

Ciclosporin: plasma ciclosporin concentration possibly reduced.

* **Contraceptives, oral**: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).
* **Ethanol**: disulfiram-like reaction (nausea, vomiting, diarrhoea, flushing, tachycardia, hypotension).
* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).
* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).

  Phenobarbital: reduction in absorption of griseofulvin (reduced effect).
* **Warfarin**: reduced anticoagulant effect.

Notes: Fatty meals will increase griseofulvin absorption. Administer with a fatty meal or with food or milk to improve absorption and to avoid gastrointestinal upset.

PATIENT ADVICE Avoid consumption of alcoholic beverages during treatment with griseofulvin.

Avoid sun exposure, wear protective clothing and use sunscreen as griseofulvin may make you more sensitive to sunlight.

The contraceptive pill will not be as effective while you are taking griseofulvin; you should use additional contraception, e.g. condoms, during treatment and for 4 weeks afterwards.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Nystatin

ATC code: A07AA02

Lozenge: 100 000 IU

Oral liquid: 10 mg/ml; 100 000 IU/ml

Tablet: 100 000 IU; 500 000 IU

Special Notes: Nystatin should not be used for the treatment of systemic mycoses.

Indications: Oral, oesophageal and intestinal candidiasis.

Dose:

Treatment of oral candidiasis.

Oral:

Child *all ages* 100 000 units four times daily after feeds. Treatment is usually given for 7 days and continued for 2 days after lesions have healed.

Treatment of intestinal and oesophageal candidiasis.

Oral:

Child *all ages* 100 000 units four times daily after feeds. Immunocompromised children may require 500 000 units four times daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, diarrhoea (more severe with doses > 5 million units daily).

Rare Oral irritation and sensitization, rash and erythema multiforme (Stevens-Johnson syndrome).

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Each mg of nystatin contains not less than 4400 units of activity.

PATIENT ADVICE Oral liquid: shake well before use. It is best to use the oral liquid after (rather than before) a meal or drink. Should be swished around mouth and retained for as long as possible then swallowed.

Continue to use for 2 days after your symptoms/lesions disappear.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Amphotericin B

ATC code: J02AA01

Powder for injection: 50 mg in vial

As deoxycholate or liposomal

Amphotericin B is available as deoxycholate, lipid complex and liposomal; these should not be considered interchangeable.

Care with product formulation. Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid based or liposomal products. Single daily doses of conventional amphotericin B formulation never exceed 1.5 mg/kg.

Anaphylaxis has been reported with amphotericin B containing drugs; facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction.

Intravenous amphotericin B is used primarily for the treatment of patients with progressive fungal infections; not to be used for non-invasive forms of fungal disease.

Special Notes: Also known as amphotericin.

Amphotericin B is available as the conventional deoxycholate complex and liposomal forms. It is also available in a lipid complex form (not included in the 2nd WHO Model list of essential medicines for children).

Indications: Life-threatening fungal infections including histoplasmosis, coccidioidomycosis, paracoccidioidomycosis, blastomycosis, aspergillosis, cryptococcosis, mucormycosis, sporotrichosis and candidiasis.

Contraindications: Known hypersensitivity.

Precautions: Close medical supervision throughout treatment and initial test dose required (see Anaphylaxis, below); renal impairment; hepatic and renal function tests; blood counts and plasma electrolyte (including potassium and magnesium concentration) monitoring; avoid rapid infusion (risk of arrhythmias).

LIPOSOMAL Diabetes as each 50 mg vial of liposomal amphotericin B contains 900 mg of sucrose.

ANAPHYLAXIS Anaphylaxis occurs rarely with intravenous amphotericin B and a test dose is advisable before the first infusion. The patient should be 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 B is essential).

Dose:

Conventional amphotericin B (as deoxycholate)

Systemic fungal infections.

IV:

Neonate, Infant or **Child** initial test dose of 100 micrograms/kg (maximum 1 mg) included as part of first dose, then 250 micrograms/kg daily, gradually increased up to 1 mg/kg daily or in severe infection, up to maximum of 1.5 mg/kg daily.

Prolonged treatment is usually necessary. For prolonged treatment, a higher dose (maximum 1.5 mg/kg) may be given on alternate days. If treatment is interrupted for longer than 7 days, recommence at 250 micrograms/kg daily and increase gradually.

Liposomal amphotericin B

Systemic fungal infections.

IV:

Neonate, Infant or **Child** initial test dose 100 micrograms/kg (maximum 1 mg) then 1 mg/kg once daily, increased in steps of 1 mg/kg daily up to 3 mg/kg once daily; maximum 5 mg/kg once daily if necessary for severe infection.

Renal impairment: Mild to severe: use only if no alternative. No dosage reduction is necessary, but further impairment is likely with conventional (as deoxycholate) amphotericin B. Nephrotoxicity may be reduced with use of liposomal formulations.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Adverse effects are similar for all amphotericin B formulations; the rates depend on the formulation used; liposomal formulations are generally better tolerated.

Common Fever, headache, nausea and vomiting, anorexia, hypokalaemia, hypomagnesaemia, diarrhoea, epigastric pain, muscle and joint pain, infusion reactions (see below), thrombophlebitis, anaemia, nephrotoxicity (see below).

Uncommon Hypotension, hypertension, cardiac arrest, arrhythmias (rapid infusion of conventional amphotericin B), blood dyscrasias, gastrointestinal bleeding, elevated liver enzymes, hepatotoxicity, rash, neurological effects (e.g. seizures, confusion, blurred vision, hearing loss, tinnitus).

Rare Anaphylactoid reactions, hyperkalaemia (especially in renal impairment), cardiovascular toxicity (including arrhythmias, ECG changes).

NEPHROTOXICITY Conventional (as deoxycholate) amphotericin B affects renal function in all patients; changes are dose related and generally reversible (except with cumulative doses > 3–5 g). Distal tubular damage may lead to loss of concentrating ability, renal tubular acidosis, nephrocalcinosis, hypokalaemia and hypomagnesaemia. Anuria or oliguria may occur. Risk is greater in those with renal impairment or when used with other nephrotoxic drugs. Nephrotoxicity may be associated with sodium depletion.

Liposomal amphotericin B is less nephrotoxic than conventional (deoxycholate) amphotericin B.

INFUSION REACTIONS Include fever, chills, hypotension, anorexia, nausea, vomiting, headache, malaise, muscle and joint pain; usually lessen with continued treatment.

Continuous infusion of conventional (as deoxycholate) amphotericin B reduces infusion reactions.

With liposomal amphotericin B one or more acute infusion reactions (chest pain, hypoxia, dyspnoea, severe abdominal, flank or leg pain, flushing and urticaria) may occur; these may be related to the liposomal component; frequency is very variable.

Interactions with other medicines (* indicates severe):

Amphotericin B is nephrotoxic; administration with other nephrotoxic drugs or cytotoxic drugs may cause additional renal impairment.

It may also reduce potassium concentration; administration with other drugs with this effect may worsen hypokalaemia. Monitor potassium concentration; supplements may be needed.

Amikacin: increased risk of nephrotoxicity.

Azoles (e.g. fluconazole): possible antagonistic effect; potentially reduced antifungal efficacy.

* **Ciclosporin**: increased risk of nephrotoxicity.

* **Dexamethasone**: increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions).

* **Digoxin**: hypokalaemia caused by amphotericin B increases cardiac toxicity of digoxin.

Fluconazole: possible antagonism of effect of amphotericin B.

Flucytosine: renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased).

Furosemide: increased risk of hypokalaemia.

Gentamicin: increased risk of nephrotoxicity.

Hydrochlorothiazide: increased risk of hypokalaemia.

* **Hydrocortisone**: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

Miconazole: possible antagonism of effects of amphotericin B.

Paromomycin: possible increased risk of nephrotoxicity.

Pentamidine: possible increased risk of nephrotoxicity.

* **Prednisolone**: increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions).

Streptomycin: increased risk of nephrotoxicity.

Vancomycin: possible increased risk of nephrotoxicity.

Notes: Check renal function before starting treatment; monitor renal function and electrolytes (especially potassium, magnesium and sodium) at least three times a week and complete blood picture and hepatic function twice a week during treatment and until stable after treatment stops.

Liposomal formulations of amphotericin B are less nephrotoxic than conventional amphotericin B; the few comparative clinical trials between conventional and liposomal formulations appear to show similar efficacy.

Conventional (as deoxycholate): use an antihistamine, paracetamol and/or hydrocortisone in patients who have previously experienced acute adverse reactions to prevent or treat infusion reactions.

ADMINISTRATION ADVICE (both formulations). Incompatible with sodium chloride solutions; flush existing line with glucose 5% or use a separate line.

Do not mix with any other drugs.

After initial reconstitution, do not administer without further dilution.

Conventional amphotericin B (as deoxycholate) Reduce risk of thrombophlebitis by using large peripheral veins or a central venous catheter, changing venous access sites frequently and infusing over longer periods.

Reconstitute as per product instructions including further dilution with glucose 5% to produce a final concentration of 0.1 mg/ml (in fluid restricted children up to 0.4 mg/ml if given via a central line).

Initial test dose should be given over 20–30 minutes. To minimize infusion related reactions, infuse the initial treatment dose slowly over 4–6 hours; tolerance to infusion reactions increases with subsequent doses, which may allow a shorter infusion, however, do not give over < 2 hours.

Liposomal amphotericin B Reconstitute as per product instructions including filtering through a 5 micron filter and further dilute with glucose 5% to produce a final concentration of 0.2–2 mg/ml.

Initial test dose should be given over 10 minutes. Then infuse subsequent doses over 30–60 minutes.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Flucytosine

ATC code: J02AX01

Capsule: 250 mg

Infusion: 10 mg/ml in 250 ml

Keep flucytosine injection at 15–25 °C (forms fluorouracil above 25 °C and can precipitate below 15 °C).

Use with extreme caution in patients with impaired renal function. Close monitoring of haematological, renal and hepatic status of all patients is essential.

Special Notes: Also known as 5-FC.

Indications: Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis; adjunct to amphotericin B in systemic candidiasis.

Precautions: Renal impairment; use with amphotericin B (both nephrotoxic); hepatic impairment; liver and kidney function tests and blood counts required (weekly in renal impairment or in blood disorders); bone marrow depression, myelosuppressive drugs, radiation treatment, patients with AIDS have an increased risk of blood dyscrasias; monotherapy due to emergent resistance.

Dose:

Adjunct to amphotericin B (or fluconazole) in cryptococcal meningitis; adjunct to amphotericin B in systemic candidiasis.
Oral or *IV:*
Neonate 50 mg/kg every 12 hours.
Infant or **Child** 50 mg/kg every 6 hours. In infections due to extremely sensitive organisms, 25–37.5 mg/kg every 6 hours may be sufficient. Treatment does not usually extend beyond 7 days. Continue for at least 4 months in cryptococcal meningitis.

Renal impairment: Reduce dose and monitor plasma flucytosine concentration.

Mild renal impairment: usual dose every 12 hours.

Moderate renal impairment: usual dose every 24 hours.

Severe renal impairment: usual dose every 24–48 hours.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, diarrhoea, rashes, thrombocytopenia, photosensitivity.

Uncommon Cardiotoxicity, confusion, hallucinations, psychosis, seizures, headache, sedation, vertigo, gastrointestinal haemorrhage, alterations in liver function tests including hepatitis, toxic epidermal necrolysis, peripheral neuropathy.

Rare Anaphylaxis, hepatic necrosis, blood disorders including thrombocytopenia, leukopenia and aplastic anaemia.

Interactions with other medicines (* indicates severe):

Flucytosine depresses the bone marrow; administration with other drugs which also have this effect may increase the risk of myelosuppression.

If it is given with nephrotoxic drugs, its renal excretion may be reduced, increasing the risk of toxicity.

Amphotericin B: renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased).

Cytarabine: plasma flucytosine concentration possibly reduced.

Zidovudine: concomitant administration may increase the risk of haematological toxicity. Caution if used together.

Notes: Monitoring is essential in renal impairment, when using with amphotericin B, or if there is an increased risk of bone marrow suppression, e.g. in patients with AIDS.

Resistance to flucytosine can develop during therapy and sensitivity testing is essential before and during treatment.

Take the capsules with food to reduce stomach upset.

PLASMA CONCENTRATION MONITORING For plasma concentration monitoring, blood should be taken shortly before starting the next infusion (or before next dose by mouth). Plasma concentration for optimum response 25–50 mg/l (200–400 micromol/l) and should not exceed 80 mg/l (620 micromol/l).

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
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Jarvis JN et al. Managing cryptococcosis in the immunocompromised host. *Current Opinion in Infectious Diseases,* 2008, 21(6):596–603.
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McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Potassium iodide

ATC code: D01BA

Saturated solution

Special Notes: Also referred to as saturated solution of potassium iodide or SSKI®. Easily confused with potassium iodide and iodine (strong iodide solution, or Lugol's solution).

Indications: Sporotrichosis; subcutaneous phycomycosis.

Contraindications: Hypersensitivity to iodides; acute bronchitis or active tuberculosis.

Precautions: Not for long-term use; Addison disease; cardiac disease; hyperthyroidism; myotonia congenita; renal impairment.

Dose:

Sporotrichosis and subcutaneous phycomycosis.

Oral:

Child *all ages* initiate at 1 drop three times daily, increasing as tolerated, up to a maximum of 1 drop per kg of body weight or 40–50 drops three times daily, whichever is lowest. Treatment should be continued for at least 4 weeks after resolution or stabilization of lesions.

NOTE If signs of iodism occur, suspend treatment temporarily and restart after a few days at lower dosage. These doses assume a solution of 1 g/ml.

Renal impairment: Use with caution.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Hypothyroidism, hyperthyroidism, metallic taste, increased salivation, coryza-like symptoms and irritation and swelling of the eyes, lacrimation, conjunctivitis, gastrointestinal disturbances, diarrhoea, skin reactions including acneiform.

Uncommon Pulmonary oedema, bronchitis, depression, insomnia, headache, laryngitis, goitre.

Rare Pain or inflammation of salivary glands, hypersensitivity reactions, Jod-Basedow phenomenon (iodine-induced thyrotoxicosis).

Interactions with other medicines (* indicates severe):

Potassium iodide contains potassium and can cause hyperkalaemia. Potassium salts and medicines which may increase serum potassium concentrations should be used with caution.

* **Ciclosporin**: increased risk of hyperkalaemia.
* **Enalapril**: increased risk of severe hyperkalaemia.
* **Spironolactone**: risk of hyperkalaemia.

Notes: ADMINISTRATION Give after meals with food or milk.

References:

Aronson JK, ed. *Meyler's side effects of drugs. 15th ed.* Amsterdam, Elsevier, 2006.
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6.4 Antiviral medicines

6.4.1 Antiherpes medicines

Herpes simplex infections

Aciclovir is active against herpes viruses but does not eradicate them. It is indicated in children for herpes simplex virus (HSV) infections but is only effective if started early in the course of infection. HSV infections can be primary or reactivation infections, and include superficial infections, genital herpes, eczema herpeticum, herpetic whitlow and eye involvement. HSV encephalitis is a serious, treatable condition that should not be missed. Invasive and disseminated infection can occur in immunocompromised patients.

Varicella-zoster infection (chickenpox)

Chickenpox in neonates should be treated with parenteral **aciclovir** to reduce the risk of severe disease. Otherwise, antiviral treatment is generally not required except for immunocompromised patients and those at special risk (e.g. those with severe cardiovascular or respiratory disease or a chronic skin disorder).

While most HIV-positive patients with herpes zoster (shingles) experience only one self-limiting disease course, some will suffer repeated episodes. Treatment should be reserved for debilitating disease and when there is a high risk of serious complications, such as in advanced HIV disease.

Aciclovir

ATC code: J05AB01

Oral liquid: 40 mg/ml

Powder for injection: 250 mg (as sodium salt) in vial

Tablet: 200 mg

Special Notes: Also referred to as acyclovir.

Indications: Treatment and prophylaxis of herpes simplex infections; zoster infections.

Precautions: Maintain adequate hydration; renal impairment.

Dose:

Herpes simplex (non-encephalitis) treatment including genital herpes.
Immunocompetent patients.
Oral:
Child *less than 2 years* 100 mg five times daily;
2 years and over 200 mg five times daily.
Treatment usually for 5 days; longer if new lesions appear during treatment or if healing incomplete.
Immunocompromised patients.
Oral:
Child *1 month–2 years* 200 mg five times daily for 7–14 days;
2–12 years 400 mg five times daily for 7–14 days.

Disseminated herpes simplex treatment.
IV:
Neonate to **Infant *under 3 months*** 20 mg/kg every 8 hours for 10–14 days (21 days if CNS involvement).
Child *3 months–12 years* 250 mg/m^2 every 8 hours, usually for 5 days.

Herpes simplex prophylaxis in immunocompromised patients.
Oral:
Child *less than 2 years* 100–200 mg four times daily;
2 years and over 200–400 mg four times daily.

Chickenpox treatment (usually only prescribed if immunocompromised).
Oral:
Child *less than 2 years* 200 mg four times daily;
2–5 years 400 mg four times daily;
over 5 years 800 mg four times daily.

Varicella zoster treatment.
Immunocompetent patients.
IV:
Neonate to **Infant *under 3 months*** 10–20 mg/kg every 8 hours for at least 7 days.
Child *3 months–12 years* 250 mg/m^2 every 8 hours usually for 5 days.
Immunocompromised patients.
IV:
Neonate to **Infant *under 3 months*** 20 mg/kg every 8 hours for at least 7 days.
Child *3 months–12 years* 500 mg/m^2 every 8 hours usually for 5 days.

Herpes simplex encephalitis treatment.
IV:
Child *3 months–12 years* 500 mg/m^2 every 8 hours usually for 14–21 days.

Renal impairment: Intravenous dose reduction required in mild to severe impairment.

Oral dose reduction required in moderate to severe impairment.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, diarrhoea, hallucinations (high dose), headache, encephalopathy (reported in 1% patients with IV use), injection site reactions.

Uncommon Agitation, vertigo, confusion, dizziness, oedema, renal impairment, arthralgia, sore throat, abdominal pain, constipation, rash, weakness.

Rare Coma, seizures, neutropenia, leukopenia, anaemia, thrombocytopenia, crystalluria, anorexia, fatigue, hepatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, anaphylaxis.

Interactions with other medicines (* indicates severe):

Ciclosporin: increased risk of nephrotoxicity.

Zidovudine: neurotoxicity.

Notes: Make sure that you drink plenty of fluids.

If you wish, you can disperse tablets in water.

$$\text{Body surface area (m}^2\text{)} = \sqrt{\frac{\text{height (cm) x weight (kg)}}{3600}}$$

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

6.4.2 Antiretrovirals

Antiretroviral therapy in children

Antiretroviral (ART) medicines are essential for the treatment and prevention of HIV infection in children, prevention of mother-to-child transmission (MTCT) and post-exposure prophylaxis. Studies of ART in children demonstrate that similar improvements to those obtained in adults are seen in morbidity, mortality and surrogate markers with many different potent ART regimens.

ART in children is aimed at reducing the plasma viral load as much as possible for as long as possible, in order to improve immune function, reduce risk of opportunistic infections and other complications of human immunodeficiency virus (HIV) infection (e.g. encephalopathy and malignancy) and facilitate improved growth, development and quality of life.

In all populations, drug therapy should be designed to minimize the risk of toxicity and development of resistance, and maximize long-term compliance.

Unique considerations for the use of ART in children include the following:

- fewer drug choices than for adults (e.g. **efavirenz** is not approved for children less than 3 years of age)
- limitations of formulations for paediatric patients (e.g. large volumes required [e.g. **stavudine** liquid], poor palatability [e.g. **ritonavir**], the need for refrigeration [e.g. **lopinavir**] and short shelf-life [e.g. **didanosine**])
- limitations of currently available pharmacokinetic data for children, leading to uncertain dosing regimens for some medications

- the need for dose adjustment as children grow (to avoid under-dosing and drug resistance)
- less data regarding toxicity for children and non-specific clinical manifestations of toxicity in infants
- longer potential cumulative treatment duration.

Prevention of mother-to-child transmission

To prevent the transmission of HIV from mother to baby, WHO promotes a comprehensive approach, which includes the following four components:

- primary prevention of HIV infection among women of childbearing age
- preventing unintended pregnancies among women living with HIV
- preventing HIV transmission from a woman living with HIV to her infant
- providing appropriate treatment, care and support to mothers living with HIV and to their children and families.

Detailed recommendations for prevention of MTCT of HIV, including the role of ART, can be accessed at the following website:

http://www.who.int/hiv/topics/mtct/en/index.html

Post-exposure prophylaxis

Treatment with antiretroviral drugs may be appropriate following exposure to HIV-contaminated materials and sexual assault. Current WHO guidelines on post-exposure prophylaxis to prevent HIV infection are accessible at the following website: http://www.who.int/hiv/topics/prophylaxis/en/

Fixed-dose drug combinations

- Fixed-dose drug combinations, now available in many regions, allow for easier administration of antiretroviral medications based on age or weight bands. They have the advantages of being relatively more affordable, more tolerable for children than multiple tablets, avoiding dosing errors and potentially improving adherence.

Lamivudine + Nevirapine + Stavudine

ATC code: J05AR07

Tablet: 150 mg + 200 mg + 30 mg

Tablet (dispersible): 30 mg + 50 mg + 6 mg; 60 mg + 100 mg + 12 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as 3TC+NVP+d4T.

Indications: HIV infection (alone as a complete regimen, or in combination with other antiretroviral drugs).

Contraindications: NEVIRAPINE Moderate or severe hepatic impairment; post-exposure prophylaxis.

Precautions: LAMIVUDINE Pancreatitis (see below); renal impairment; chronic hepatitis B or C; hepatic disease (see below).

Pancreatitis If no suitable alternative exists, use with extreme caution in children with advanced HIV infection, previous history of pancreatitis or risk factors for pancreatitis.

Hepatic disease Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; caution in children with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.

NEVIRAPINE Hepatic impairment; chronic hepatitis B or C; high CD4 cell count.

Hepatic disease Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in the first 6 weeks; close monitoring required during first 18 weeks; discontinue permanently if liver abnormalities accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe liver abnormalities but no hypersensitivity reaction; discontinue permanently if significant liver function abnormalities recur, monitor patient closely if mild to moderate liver abnormalities 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.

PATIENT ADVICE Patients and/or caregivers should be told how to recognize hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if symptoms of hepatitis, severe skin reaction or hypersensitivity reactions develop.

STAVUDINE Peripheral neuropathy (see below); pancreatitis (see below); chronic hepatitis B or C; hepatic disease (see below); renal impairment.

Peripheral neuropathy Suspend if peripheral neuropathy develops (characterized by persistent numbness, tingling or pain in feet or hands); if symptoms resolve satisfactorily on withdrawal and if stavudine needs to be continued, resume treatment at half previous dose.

Pancreatitis Avoid use or use extreme caution in patients with history of pancreatitis. If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if asymptomatic), suspend treatment until diagnosis of pancreatitis excluded; on return to normal values, re-initiate treatment only if essential (using low dose increased gradually if appropriate). Whenever possible, avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example, intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis, monitor closely if elevated.

Hepatic disease Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Dose:

HIV infection (alone as a complete regimen, or in combination with other antiretroviral drugs).

SPECIAL CONSIDERATIONS FOR DOSING A lead-in dose of nevirapine, half of the normal daily dosage, is used for 2 weeks to decrease the likelihood of rash incidence. For children < 30 kg, use of 14 day lead-in decreases the incidence of rash.

If the child experiences a rash in the lead-in period, then remain on the half dosage until the rash resolves. Wait no longer than 28 days for the rash to resolve then seek an alternative regimen.

Contains a fixed dose of nevirapine, therefore cannot be used for nevirapine induction as nevirapine dose escalation is required; use individual components during induction period. See individual drug monographs for dose recommendations.

Lamivudine + Nevirapine + Stavudine: recommended dosing based on weight bands

Weight range (kg)		Target doses	Dose (tablets)	
		Lamivudine 4 mg/kg twice daily Nevirapine 160–200 mg/m² twice daily after 2 week induction dose Stavudine 1 mg/kg twice daily		
Bottom	Top	Formulation Lamivudine/ nevirapine/ stavudine tablets	a.m.	p.m.
3	3.9	30 mg/50 mg/6 mg	1	1
4	4.9	30 mg/50 mg/6 mg	1	1
5	5.9	30 mg/50 mg/6 mg	1	1
6	6.9	30 mg/50 mg/6 mg	2	1
7	7.9	30 mg/50 mg/6 mg	2	1
8	8.9	30 mg/50 mg/6 mg	2	1
9	9.9	30 mg/50 mg/6 mg	2	1
10	10.9	30 mg/50 mg/6 mg	2	2
11	11.9	30 mg/50 mg/6 mg	2	2
12	13.9	30 mg/50 mg/6 mg	2	2
14	16.9	30 mg/50 mg/6 mg	3	2
17	19.9	30 mg/50 mg/6 mg	3	2
20	24.9	30 mg/50 mg/6 mg	3	3
25	29.9	150 mg/200 mg/30 mg	1	1
30	34.9	150 mg/200 mg/30 mg	1	1

Renal impairment: LAMIVUDINE Moderate to severe: reduce dose.

NEVIRAPINE Mild and moderate: no dosage adjustment required. Severe: use with caution.

STAVUDINE Mild: reduce dose to 50%. Moderate: reduce dose to 25%.

Hepatic impairment: LAMIVUDINE Dosage adjustment not required; use with caution in patients with decompensated liver disease. See notes in Precautions.

NEVIRAPINE Avoid in moderate or severe hepatic impairment. Use with caution in mild and moderate impairment. See notes in Precautions.

STAVUDINE Dosage adjustment not required; use with caution in patients with liver disease. See notes in Precautions.

Adverse effects: LAMIVUDINE **Common** Headache, fatigue, nausea, anorexia, diarrhoea, skin rash, abdominal pain, pancreatitis (more commonly reported in children; up to 14%).

Uncommon Peripheral neuropathy, anaemia, decreased neutrophil count, increased liver enzymes, fat redistribution (see Lipodystrophy, below), lactic acidosis, severe hepatomegaly with steatosis.

NEVIRAPINE **Common** Rash, nausea, headache, fever.

Uncommon Hepatotoxicity (can be severe, life threatening and possibly fatal), vomiting, abdominal pain, fatigue, myalgia, Stevens-Johnson syndrome.

Rare Toxic epidermal necrolysis, diarrhoea, angioedema, hypersensitivity reactions, arthralgia, anaemia and granulocytopenia.

STAVUDINE **Common** Headache, gastrointestinal disturbances, skin rashes.

Uncommon Peripheral neuropathy, pancreatitis, fat redistribution (see Lipodystrophy, below), lactic acidosis, severe hepatomegaly with steatosis, sleep disorders.

Rare Increased liver enzymes, rapidly progressive ascending neuromuscular weakness.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

LAMIVUDINE

* **Emtricitabine**: no information available; manufacturer advises avoid concomitant use.
* **Interferon alfa**: increased risk of hepatic toxicity.
* **Ribavirin**: increased risk of hepatic toxicity.

Sulfamethoxazole + trimethoprim: plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim).

NEVIRAPINE

* **Contraceptives, oral**: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Efavirenz: plasma efavirenz concentration reduced.

* **Fluconazole**: increased plasma concentration of nevirapine.

Indinavir: nevirapine reduces plasma concentration of indinavir.

* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Lopinavir: plasma concentration of lopinavir possibly reduced.

* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).
* **Rifampicin**: reduced plasma concentration of nevirapine (avoid concomitant use).

Saquinavir: plasma concentration of saquinavir reduced.

* **St John's wort *(Hypericum)***: reduced plasma concentration of nevirapine (avoid concomitant use).
* **Voriconazole**: increased plasma concentration of nevirapine and reduced concentration of voriconazole.
* **Warfarin**: enhanced or reduced anticoagulant effect.

STAVUDINE

* **Didanosine**: increased risk of adverse effects.
* **Ribavirin**: may decrease stavudine levels, also increased risk of fatal and non-fatal lactic acidosis.
* **Zidovudine**: may antagonize effect of stavudine (concomitant use contraindicated).

Notes: Can be given without regard to food.

Contains a fixed dose of nevirapine, therefore cannot be used for nevirapine induction as dose escalation required.

During induction period, give individual drugs separately.

Twice daily fixed dose tablet can be started if no rash or liver function test abnormalities present.

Tablets should preferably not be split unless scored.

References:

Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, Forthcoming 2010.

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WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Lamivudine + Nevirapine + Zidovudine

ATC code: J05AR05

Tablet: 30 mg + 50 mg + 60 mg; 150 mg + 200 mg + 300 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as 3TC+NVP+ZDV.

Zidovudine also referred to as AZT.

Indications: HIV infection.

Contraindications: NEVIRAPINE Severe hepatic impairment; post-exposure prophylaxis.

ZIDOVUDINE Abnormally low neutrophil counts or haemoglobin; neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase; acute porphyria.

Precautions: LAMIVUDINE Pancreatitis (see below); renal impairment; chronic hepatitis B or C; hepatic disease (see below).

Pancreatitis If no suitable alternative exists, use with extreme caution in children with advanced HIV infection and previous history of pancreatitis or risk factors for pancreatitis.

Hepatic disease Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; caution in children with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.

NEVIRAPINE Hepatic impairment; chronic hepatitis B or C; high CD4 cell count.

Hepatic disease Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in the first 6 weeks; close monitoring required during first 18 weeks; discontinue permanently if liver abnormalities accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe liver abnormalities but no hypersensitivity reaction; discontinue permanently if significant liver function abnormalities recur, monitor patient closely if mild to moderate liver abnormalities 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.

PATIENT ADVICE Patients and caregivers should be told how to recognize hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if symptoms of hepatitis, severe skin reaction or hypersensitivity reactions develop.

ZIDOVUDINE Haematological toxicity, including vitamin B_{12} deficiency, anaemia and myelosuppression; renal impairment; chronic hepatitis B or C; hepatic disease (see below).

Hepatic disease Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Exercise caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if there is any rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Dose:

HIV infection (alone as a complete regimen, or in combination with other antiretroviral drugs).

SPECIAL CONSIDERATIONS FOR DOSING A lead-in dose of nevirapine, half of the normal daily dosage, is used for 2 weeks to decrease the likelihood of rash incidence. For children < 30 kg, use of 14 day lead-in decreases the incidence of rash.

If the child experiences a rash in the lead-in period, then remain on the half dosage until the rash resolves. Wait no longer than 28 days for the rash to resolve then seek an alternative regimen.

Contains a fixed dose of nevirapine, therefore cannot be used for nevirapine induction as nevirapine dose escalation required; use individual components during induction period. See individual drug monographs for dose recommendations.

Lamivudine + Nevirapine + Zidovudine: recommended dosing based on weight bands

Weight range (kg)		Target doses	Dose (tablets)	
		Lamivudine 4 mg/kg twice daily Nevirapine 160–200 mg/m² twice daily after 2 week induction dose Zidovudine 180–240 mg/m² twice daily		
Bottom	Top	Formulation Lamivudine/ nevirapine/ zidovudine tablets	a.m.	p.m.
3	3.9	30 mg/50 mg/60 mg	1	1
4	4.9	30 mg/50 mg/60 mg	1	1
5	5.9	30 mg/50 mg/60 mg	1	1
6	6.9	30 mg/50 mg/60 mg	2	1
7	7.9	30 mg/50 mg/60 mg	2	1
8	8.9	30 mg/50 mg/60 mg	2	1
9	9.9	30 mg/50 mg/60 mg	2	1
10	10.9	30 mg/50 mg/60 mg	2	2
11	11.9	30 mg/50 mg/60 mg	2	2
12	13.9	30 mg/50 mg/60 mg	2	2
14	16.9	30 mg/50 mg/60 mg	3	2
17	19.9	30 mg/50 mg/60 mg	3	2
20	24.9	30 mg/50 mg/60 mg	3	3
25	29.9	150 mg/200 mg/300 mg	1	1
30	34.9	150 mg/200 mg/300 mg	1	1

Renal impairment: LAMIVUDINE Reduce dose in moderate and severe impairment.

NEVIRAPINE Mild and moderate: no dosage adjustment required. Severe: use with caution.

ZIDOVUDINE Severe: reduce dose.

Hepatic impairment: LAMIVUDINE Dosage adjustment not required; use with caution in patients with decompensated liver disease. See notes in Precautions.

NEVIRAPINE Avoid in moderate and severe hepatic impairment. Use with caution in mild impairment. See notes in Precautions.

ZIDOVUDINE Dosage adjustment may be required; accumulation may occur. Use with caution; monitor for haematological toxicities frequently.

Adverse effects: LAMIVUDINE **Common** Headache, fatigue, nausea, anorexia, diarrhoea, skin rash, abdominal pain, pancreatitis (more commonly reported in children; up to 14%).

Uncommon Peripheral neuropathy, anaemia, decreased neutrophil count, increased liver enzymes, fat redistribution (see Lipodystrophy, below), lactic acidosis, severe hepatomegaly with steatosis.

NEVIRAPINE **Common** Rash, nausea, headache, fever.

Uncommon Hepatotoxicity (can be severe, life threatening and possibly fatal), vomiting, abdominal pain, fatigue, myalgia, including Stevens-Johnson syndrome.

Rare Toxic epidermal necrolysis, diarrhoea, angioedema, hypersensitivity reactions, arthralgia, anaemia and granulocytopenia.

ZIDOVUDINE **Common** Haematological toxicity including neutropenia, leukopenia and anaemia, severe headache, malaise, nausea, vomiting, anorexia.

Uncommon Myopathy (associated with prolonged use), myositis, liver toxicity, lactic acidosis, severe hepatomegaly with steatosis, fat redistribution (see Lipodystrophy, below), skin and nail pigmentation, neuropathy.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

LAMIVUDINE

* **Emtricitabine**: no information available; manufacturer advises avoid concomitant use.
* **Interferon alfa**: increased risk of hepatic toxicity.
* **Ribavirin**: increased risk of hepatic toxicity.

Sulfamethoxazole + trimethoprim: plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim).

NEVIRAPINE

* **Contraceptives, oral**: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Efavirenz: plasma efavirenz concentration reduced.

* **Fluconazole**: increased plasma concentration of nevirapine.

Indinavir: nevirapine reduces plasma concentration of indinavir.

* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Lopinavir: plasma concentration of lopinavir possibly reduced.

* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).
* **Rifampicin**: reduced plasma concentration of nevirapine (avoid concomitant use).

Saquinavir: plasma concentration of saquinavir reduced.

* **St John's wort *(Hypericum)***: reduced plasma concentration of nevirapine (avoid concomitant use).
* **Voriconazole**: increased plasma concentration of nevirapine and reduced concentration of voriconazole.
* **Warfarin**: enhanced or reduced anticoagulant effect.

ZIDOVUDINE

NOTE Increased risk of toxicity with nephrotoxic and myelosuppressive drugs.

Fluconazole: increased plasma concentration of zidovudine (increased risk of toxicity).

Ganciclovir: increased risk of haematological toxicity.

* **Interferon alfa**: increased risk of hepatic and haematological toxicity.

Phenytoin: plasma phenytoin concentration increased or decreased by zidovudine.

Pyrimethamine: increased antifolate effect.

* **Ribavirin**: increased risk of hepatic and haematological toxicity.

Rifampicin: avoidance of rifampicin advised by manufacturer of zidovudine.

Stavudine: may antagonize effect of stavudine (concomitant use contraindicated).

Valproic acid: plasma concentration of zidovudine possibly increased (risk of toxicity).

Notes: Can be given without regard to food.

Contains a fixed dose of nevirapine, therefore cannot be used for nevirapine induction as dose escalation required.

During induction period, give individual drugs separately.

Twice daily fixed dose tablet can be started if no rash or liver function test abnormalities present.

Tablets should preferably not be split unless scored (to ensure accurate dosing); they may be crushed and mixed with a small amount of food or water and taken immediately.

References:

Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, Forthcoming 2010.

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Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Lamivudine + Zidovudine

ATC code: J05AR01

Tablet: 30 mg + 60 mg; 150 mg + 300 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach)*. At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as 3TC + ZDV.

Zidovudine also referred to as AZT.

Indications: HIV infection (in combination with other antiretroviral drugs).

Contraindications: ZIDOVUDINE Abnormally low neutrophil counts or haemoglobin; neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase; acute porphyria.

Precautions: LAMIVUDINE Pancreatitis (see below); renal impairment; chronic hepatitis B or C; hepatic disease (see below).

Pancreatitis If no suitable alternative exists, use with extreme caution in children with advanced HIV infection and a previous history of pancreatitis or risk factors for pancreatitis.

Hepatic disease Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; caution in children with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.

ZIDOVUDINE Haematological toxicity including vitamin B_{12} deficiency, anaemia and myelosuppression; renal impairment; chronic hepatitis B or C; hepatic disease (see below).

Hepatic disease Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Exercise caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if there is any rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Dose:

HIV infection (alone as a complete regimen, or in combination with other antiretroviral drugs).

Lamivudine + Zidovudine: recommended dosing based on weight bands

Weight range (kg)		Target doses	Dose (tablets)	
		Lamivudine 4 mg/kg twice daily Zidovudine 180–240 mg/m² twice daily		
Bottom	Top	Formulation Lamivudine/zidovudine tablets	a.m.	p.m.
3	3.9	30 mg/60 mg	1	1
4	4.9	30 mg/60 mg	1	1
5	5.9	30 mg/60 mg	1	1
6	6.9	30 mg/60 mg	2	1
7	7.9	30 mg/60 mg	2	1
8	8.9	30 mg/60 mg	2	1
9	9.9	30 mg/60 mg	2	1
10	10.9	30 mg/60 mg	2	2
11	11.9	30 mg/60 mg	2	2
12	13.9	30 mg/60 mg	2	2
14	16.9	30 mg/60 mg	3	2
17	19.9	30 mg/60 mg	3	2
20	24.9	30 mg/60 mg	3	3
25	29.9	150 mg/300 mg	1	1
30	34.9	150 mg/300 mg	1	1

Renal impairment: LAMIVUDINE Moderate or severe: reduce dose.

ZIDOVUDINE Severe: reduce dose.

Hepatic impairment: LAMIVUDINE Dosage adjustment not required; use with caution in patients with decompensated liver disease. See notes in Precautions.

ZIDOVUDINE Dosage adjustment may be required; accumulation may occur. Use with caution; monitor for haematological toxicities frequently.

Adverse effects: LAMIVUDINE **Common** Headache, fatigue, nausea, anorexia, diarrhoea, skin rash, abdominal pain, pancreatitis (more commonly reported in children; up to 14%).

Uncommon Peripheral neuropathy, anaemia, decreased neutrophil count, increased liver enzymes, fat redistribution (see Lipodystrophy below), lactic acidosis, severe hepatomegaly with steatosis.

ZIDOVUDINE **Common** Haematological toxicity including neutropenia, leukopenia and anaemia, severe headache, malaise, nausea, vomiting, anorexia.

Uncommon Myopathy (associated with prolonged use), myositis, liver toxicity, lactic acidosis, severe hepatomegaly with steatosis, fat redistribution (see Lipodystrophy below), skin and nail pigmentation, neuropathy.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

LAMIVUDINE

* **Emtricitabine**: no information available; manufacturer advises to avoid concomitant use.
* **Interferon alfa**: increased risk of hepatic toxicity.

* **Ribavirin**: increased risk of hepatic toxicity.

Sulfamethoxazole + trimethoprim: plasma concentration of lamivudine increased (avoid concomitant use of high dose sulfamethoxazole + trimethoprim).

ZIDOVUDINE

NOTE Increased risk of toxicity with nephrotoxic and myelosuppressive drugs.

Fluconazole: increased plasma concentration of zidovudine (increased risk of toxicity).

Ganciclovir: increased risk of haematological toxicity.

* **Interferon alfa**: increased risk of hepatic and haematological toxicity.

Phenytoin: plasma phenytoin concentration increased or decreased by zidovudine.

Pyrimethamine: increased antifolate effect.

* **Ribavirin**: increased risk of hepatic and haematological toxicity.

Rifampicin: avoidance of rifampicin advised by manufacturer of zidovudine.

Stavudine: may inhibit effect of stavudine (avoid concomitant use).

Valproic acid: plasma concentration of zidovudine possibly increased (risk of toxicity).

Notes: No food restrictions apply.

Tablets should not be split unless they are scored. Tablets can be crushed and mixed with a small amount of water or food and taken immediately.

References:

Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, Forthcoming 2010.

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

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6.4.2.1 Nucleoside/nucleotide reverse transcriptase inhibitors

Abacavir

ATC code: J05AF06

Oral liquid: 20 mg (as sulfate)/ml

Tablet: 300 mg (as sulfate)

Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir: approximately 5% of adults and children (rate varies by race/ethnicity) receiving abacavir develop a potentially fatal hypersensitivity reaction.

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases, the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as ABC.

Indications: HIV infection, in combination with other antiretroviral drugs.

Contraindications: Severe renal impairment; severe hepatic impairment; previous hypersensitivity reaction to abacavir.

Precautions: Chronic hepatitis B or C; hepatic impairment; renal impairment.

HYPERSENSITIVITY REACTIONS Life-threatening hypersensitivity reactions characterized by fever or rash and possibly nausea, vomiting, diarrhoea, abdominal pain, dyspnoea, cough, lethargy, malaise, headache and myalgia, less frequently by mouth ulceration, oedema, hypotension, sore throat, adult respiratory distress syndrome, paraesthesia, arthralgia, conjunctivitis, lymphadenopathy, lymphocytopenia, renal failure and anaphylaxis (hypersensitivity reactions presenting as sore throat, influenza-like illness, cough and breathlessness identified); and rarely by myolysis. Laboratory abnormalities may include raised liver enzymes (see below) and creatine kinase. Symptoms usually appear in the first 6 weeks, but may occur at any time; monitor patients for symptoms every 2 weeks for 2 months; 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. Studies have shown an association between abacavir hypersensitivity and a specific HLA genotype (HLA-B*5701). This genetic screening for HLA-B*5701 is recommended prior to initiation of abacavir based therapy. The incidence of abacavir hypersensitivity reaction is lower in the non-Caucasian population.

PATIENT ADVICE Patients and caregivers should be told the importance of regular dosing (intermittent therapy may increase sensitization), how to recognize signs of hypersensitivity, and advised to seek immediate medical attention if symptoms develop or before restarting treatment.

HEPATIC DISEASE Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis have been reported. Caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis (including alcohol abuse); discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Dose:

HIV infection, in combination with other antiretroviral drugs.

Oral:

Infant or **Child** 8 mg/kg/dose given twice daily, maximum 300 mg twice daily.

Simplified dosing tables based on weight bands are designed around 60 mg tablets (not on the 2nd WHO Model List of Essential Medicines for Children).

Abacavir: recommended dosing based on weight bands using 60 mg and 300 mg tablets

Weight range (kg)		Target dose	Dose (tablets)	
		< 16 years or < 37.5 kg: 8 mg/kg/dose given twice daily		
		Maximum dose > 16 years or ≥ 37.5 kg: 300 mg/dose given twice daily		
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
3	3.9	60 mg tablet	1	1
4	4.9	60 mg tablet	1	1
5	5.9	60 mg tablet	1	1
6	6.9	60 mg tablet	2	1
7	7.9	60 mg tablet	2	1
8	8.9	60 mg tablet	2	1
9	9.9	60 mg tablet	2	1
10	10.9	60 mg tablet	2	2
11	11.9	60 mg tablet	2	2
12	13.9	60 mg tablet	2	2
14	16.9	60 mg tablet	3	2
17	19.9	60 mg tablet	3	2
20	24.9	60 mg tablet	3	3
25	29.9	300 mg tablet	1	1
30	34.9	300 mg tablet	1	1

Abacavir: recommended dosing based on weight bands using oral liquid and 300 mg tablets

Weight range (kg)		Target dose < 16 years or < 37.5 kg: 8 mg/kg/dose given twice daily Maximum dose > 16 years or ≥ 37.5 kg: 300 mg/dose given twice daily	Dose (ml or tablets)	
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	20 mg/ml syrup	3 ml	3 ml
4	4.9	20 mg/ml syrup	3 ml	3 ml
5	5.9	20 mg/ml syrup	3 ml	3 ml
6	6.9	20 mg/ml syrup	4 ml	4 ml
7	7.9	20 mg/ml syrup	4 ml	4 ml
8	8.9	20 mg/ml syrup	4 ml	4 ml
9	9.9	20 mg/ml syrup	4 ml	4 ml
10	10.9	20 mg/ml syrup	6 ml	6 ml
11	11.9	20 mg/ml syrup	6 ml	6 ml
12	13.9	20 mg/ml syrup	6 ml	6 ml
14	16.9	300 mg tablet	0.5	0.5
17	19.9	300 mg tablet	0.5	0.5
20	24.9	300 mg tablet	1	0.5
25	29.9	300 mg tablet	1	1
30	34.9	300 mg tablet	1	1

Renal impairment: Severe: avoid.

Hepatic impairment: Moderate: avoid unless essential.

Severe: avoid.

Adverse effects: Common Nausea, vomiting, fever, headache, diarrhoea, rash, anorexia, fatigue.

Uncommon Lactic acidosis, severe hepatomegaly with steatosis, pancreatitis, hypersensitivity, lipodystrophy (see below).

Rare Increased liver enzymes, elevated blood glucose, elevated triglycerides, possible increased risk of myocardial infarction.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

Methadone: plasma concentration of methadone possibly reduced.

Phenobarbital: plasma concentration of abacavir possibly reduced.

Phenytoin: plasma concentration of abacavir possibly reduced.

Rifampicin: plasma concentration of abacavir possibly reduced.

Notes: Parents and carers must be warned about potential hypersensitivity reaction.

Abacavir should be stopped permanently if hypersensitivity reaction occurs.

Can be given without regard to food.

Store oral solution at room temperature (20–25 ºC); may be refrigerated.

Tablets may be crushed with a small amount of water or food and administered immediately.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

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Didanosine

ATC code: J05AF02

Buffered powder for oral liquid: 100 mg; 167 mg; 250 mg packets

Capsule (unbuffered enteric coated): 125 mg; 200 mg; 250 mg; 400 mg

Tablet (buffered chewable, dispersible): 25 mg; 50 mg; 100 mg; 150 mg; 200 mg

Fatal and non-fatal pancreatitis have been reported during therapy.

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as ddI.

Didanosine is usually reserved for second-line regimens.

NOTE Antacids in formulation may affect absorption of other drugs; see interactions.

Indications: HIV infection, in combination with at least two other antiretroviral drugs.

Precautions: Pancreatitis; peripheral neuropathy; hyperuricaemia; lactic acidosis or severe hepatomegaly with steatosis; chronic hepatitis B or C; retinal or optic nerve changes; renal impairment; hepatic impairment.

PANCREATITIS Avoid use or use extreme caution in patients with history of pancreatitis. If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if asymptomatic), suspend treatment until diagnosis of pancreatitis excluded; on return to normal values, re-initiate treatment only if essential (using low dose increased gradually if appropriate). Whenever possible, avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example intravenous pentamidine isetionate, stavudine and hydroxyurea); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis, monitor closely if elevated.

PERIPHERAL NEUROPATHY Dose related, especially in advanced HIV infection. Suspend treatment; a reduced dose may be tolerated when symptoms resolve. Please note that giving a lower dose may result in suboptimal therapy and an increased risk of treatment failure and the development of resistant mutations; it may be advisable to change to another drug at full dose.

HYPERURICAEMIA Suspend treatment if significant elevation occurs.

HEPATIC DISEASE Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; exercise caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

RETINAL OR OPTIC NERVE CHANGES Dilated retinal examinations recommended (especially in children) every 6 months, or if visual changes occur. Asymptomatic peripheral retinal depigmentation in < 5% of children can also occur. Not associated with vision loss and reverses when treatment is stopped.

Dose:

HIV infection, in combination with at least two other antiretroviral drugs.

Oral:

Infant *under 3 months* 50 mg/m^2/dose twice daily.

Infant *over 3 months* or **Child** 90–120 mg/m^2/dose twice daily (maximum 200 mg/dose twice daily or 400 mg once daily).

Simplified dosing tables based on weight bands are designed around the 25 mg tablets.

Didanosine: recommended dosing based on weight bands using 25 mg tablets

Weight range (kg)		Target dose < 3 months: 50 mg/m²/dose twice daily 3 months to < 13 years: 90–120 mg/m²/dose twice daily Maximum dose (≥ 13 years or > 60 kg): 200 mg/dose twice daily or 400 mg once daily	Dose (tablets)	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
3	3.9	25 mg tablet	NR	NR
4	4.9	25 mg tablet	NR	NR
5	5.9	25 mg tablet	2	2
6	6.9	25 mg tablet	3	2
7	7.9	25 mg tablet	3	2
8	8.9	25 mg tablet	3	2
9	9.9	25 mg tablet	3	2
10	10.9	25 mg tablet	3	3
11	11.9	25 mg tablet	3	3
12	13.9	25 mg tablet	3	3
14	16.9	25 mg tablet	4	3
17	19.9	25 mg tablet	4	3
20	24.9	25 mg tablet	4	4
25	29.9	25 mg tablet	5	5
30	34.9	25 mg tablet	5	5

Didanosine: recommended dosing based on weight bands using oral suspension and 25 mg tablets

Weight range (kg)		Target dose < 3 months: 50 mg/m²/dose twice daily 3 months to < 13 years: 90–120 mg/m²/dose twice daily Maximum dose (≥ 13 years or > 60 kg): 200 mg/dose twice daily or 400 mg once daily	Dose (ml or tablets)	
Bottom	**Top**	**Formulation**	**a.m.**	**p.m.**
3	3.9	10 mg/ml suspension	3 ml	3 ml
4	4.9	10 mg/ml suspension	3 ml	3 ml
5	5.9	10 mg/ml suspension	3 ml	3 ml
6	6.9	10 mg/ml suspension	5 ml	5 ml
7	7.9	10 mg/ml suspension	5 ml	5 ml
8	8.9	10 mg/ml suspension	5 ml	5 ml
9	9.9	10 mg/ml suspension	5 ml	5 ml
10	10.9	10 mg/ml suspension	6 ml	6 ml
11	11.9	10 mg/ml suspension	6 ml	6 ml
12	13.9	10 mg/ml suspension	6 ml	6 ml
14	16.9	25 mg tablet	4	3
17	19.9	25 mg tablet	4	3
20	24.9	25 mg tablet	4	4
25	29.9	25 mg tablet	5	5
30	34.9	25 mg tablet	5	5

Renal impairment: Reduce dose in all degrees of impairment; consult product information for individual preparations for further specific dosing information.

Hepatic impairment: No dose adjustment recommended. Possible increased risk of toxicity in patients with hepatic impairment; monitor for toxicity.

Adverse effects: Common Diarrhoea (sometimes severe, may be related to the antacid present in the preparation), abdominal pain, nausea, vomiting.

Uncommon Peripheral neuropathy, electrolyte abnormalities, hyperuricaemia, lactic acidosis, severe hepatomegaly with steatosis, pancreatitis, increased liver enzymes, retinal depigmentation, retinal changes, optic neuritis, hepatic toxicity, hepatic failure, lipodystrophy (see below).

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

* **Allopurinol**: possibly increased plasma concentration of didanosine.
* **Hydroxyurea**: increased risk of adverse effects. Avoid concurrent use if possible.
* **Ribavirin**: increased risk of toxicity, hepatic reactions, peripheral neuropathy and pancreatitis.
* **Ritonavir**: simultaneous administration can inactivate both drugs. Give didanosine 1 hour before or 2 hours after ritonavir.
* **Stavudine**: increased risk of adverse effects. Avoid concurrent use if possible.
* **Tenofovir**: plasma concentration of didanosine increased (increased risk of toxicity; avoid concomitant use).

Notes: Best given on an empty stomach 30 minutes before or at least 2 hours after a meal.

Didanosine is degraded rapidly unless given as an enteric formulation or combined with buffering agents or antacids. In children, this degradation effect may be less marked and didanosine may not have to be administered on an empty stomach.

ORAL SUSPENSION Is not easy to use and should be avoided if possible; should be kept refrigerated; stable for 30 days; must be well shaken.

TABLETS At least two tablets of appropriate strength must be used at any one time for adequate buffering (e.g. if the child's dose is 50 mg, administer two 25 mg tablets instead of one 50 mg tablet); didanosine tablets should be chewed, crushed or dispersed in water or clear juice before they are taken; tablets should not be swallowed whole.

ENTERIC-COATED BEADLETS IN CAPSULES Can be opened and sprinkled on a small amount of food, but this may decrease the area under the curve; do not crush or chew beadlets.

References:

Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf, accessed 10 February 2010).

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WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Emtricitabine

ATC code: J05AF09

Capsule: 200 mg

Oral liquid: 10 mg/ml

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

Special Notes: Also referred to as FTC.

Emtricitabine is an acceptable alternative to lamivudine, based on knowledge of the pharmacology, the resistance patterns and clinical trials of antiretrovirals.

WHO age/weight restriction: > 3 months.

Indications: HIV infection, in combination with at least two other antiretroviral drugs.

Contraindications: Avoid concomitant use with lamivudine.

Precautions: Renal impairment; hepatic disease.

HEPATIC DISEASE Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Exercise caution in patients with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of emtricitabine; monitoring required.

Dose:

NOTE Oral liquid and capsules are not bioequivalent.

240 mg oral solution ≡ 200 mg capsule; where appropriate, capsules may be used instead of oral solution; oral solution contains propylene glycol as an excipient.

HIV infection, in combination with other antiretroviral drugs.

Oral:

Child *over 3 months* 6 mg/kg (maximum 200 mg) daily.

Renal impairment: Mild or worse impairment: reduce dose or increase dosing interval. Consult product literature.

Hepatic impairment: Dosage adjustment not required; use with caution in patients with liver disease. See notes in Precautions.

Adverse effects: Common Diarrhoea, nausea, rash (may be higher in African Americans; up to 32% incidence reported), hyperpigmentation of palms and/or soles (more common in children, females and non-Caucasian people).

Uncommon Neutropenia, lactic acidosis, severe hepatomegaly with steatosis, lipodystrophy (see below).

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

* **Ganciclovir**: possible increased toxicity of emtricitabine.

  Lamivudine: avoid concomitant use.

* **Ribavirin**: possible increased toxicity of emtricitabine.

* **Valganciclovir**: possible increased toxicity of emtricitabine.

Notes: Can be given without regard to food.

Oral solution should be refrigerated. Can be kept at room temperature up to 25 °C if used within 3 months.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine,* 2009, 10(10):591–613.

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Lamivudine

ATC code: J05AF05

Oral liquid: 10 mg/ml

Tablet: 150 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as 3TC.

Indications: HIV infection, in combination with at least two other antiretroviral drugs.

Precautions: Pancreatitis (see below); renal impairment; chronic hepatitis B or C; hepatic disease (see below).

PANCREATITIS If no suitable alternative exists, use with extreme caution in children with advanced HIV infection, previous history of pancreatitis or risk factors for pancreatitis.

HEPATIC DISEASE Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported; caution in children with hepatomegaly, hepatitis (especially hepatitis C treated with interferon alfa and ribavirin), liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis. Exacerbation of hepatitis in patients with chronic hepatitis B may occur on discontinuation of lamivudine.

Dose:

HIV infection, in combination with other antiretroviral drugs.

Oral:

Neonate 2 mg/kg/dose given twice daily.

Infant or **Child** 4 mg/kg/dose given twice daily, maximum 150 mg twice daily.

Simplified dosing tables based on weight bands are designed around 30 mg tablets (not on the 2nd WHO Model List of Essential Medicines for Children).

Lamivudine: recommended dosing based on weight bands using 30 mg and 150 mg tablets

Weight range (kg)		Target dose	Dose (tablets)	
		Infant or Child: 4 mg/kg twice daily to a maximum of 150 mg twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	30 mg tablet	1	1
4	4.9	30 mg tablet	1	1
5	5.9	30 mg tablet	1	1
6	6.9	30 mg tablet	2	1
7	7.9	30 mg tablet	2	1
8	8.9	30 mg tablet	2	1
9	9.9	30 mg tablet	2	1
10	10.9	30 mg tablet	2	2
11	11.9	30 mg tablet	2	2
12	13.9	30 mg tablet	2	2
14	16.9	30 mg tablet	3	2
17	19.9	30 mg tablet	3	2
20	24.9	30 mg tablet	3	3
25	29.9	150 mg tablet	1	1
30	34.9	150 mg tablet	1	1

Lamivudine: recommended dosing based on weight bands using the oral liquid and 150 mg tablets

Weight range (kg)		Target dose	Dose (ml or tablets)	
		Infant or Child: 4 mg/kg twice daily to a maximum of 150 mg twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	10 mg/ml solution	3 ml	3 ml
4	4.9	10 mg/ml solution	3 ml	3 ml
5	5.9	10 mg/ml solution	3 ml	3 ml
6	6.9	10 mg/ml solution	4 ml	4 ml
7	7.9	10 mg/ml solution	4 ml	4 ml
8	8.9	10 mg/ml solution	4 ml	4 ml
9	9.9	10 mg/ml solution	4 ml	4 ml
10	10.9	10 mg/ml solution	6 ml	6 ml
11	11.9	10 mg/ml solution	6 ml	6 ml
12	13.9	10 mg/ml solution	6 ml	6 ml
14	16.9	150 mg tablet	0.5	0.5
17	19.9	150 mg tablet	0.5	0.5
20	24.9	150 mg tablet	1	0.5
25	29.9	150 mg tablet	1	1
30	34.9	150 mg tablet	1	1

Renal impairment: Moderate to severe: reduce dose.

Hepatic impairment: Dosage adjustment not required; use with caution in patients with decompensated liver disease. See notes in Precautions.

Adverse effects: Common Headache, fatigue, nausea, anorexia, diarrhoea, skin rash, abdominal pain, pancreatitis (more commonly reported in children; up to 14%).

Uncommon Peripheral neuropathy, anaemia, decreased neutrophil count, increased liver enzymes, fat redistribution (see Lipodystrophy below), lactic acidosis, severe hepatomegaly with steatosis.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

* **Emtricitabine**: no information available; manufacturer advises to avoid concomitant use.
* **Interferon alfa**: increased risk of hepatic toxicity.
* **Ribavirin**: increased risk of hepatic toxicity.

Sulfamethoxazole + trimethoprim: plasma concentration of lamivudine increased (avoid concomitant use of high dose sulfamethoxazole + trimethoprim).

Notes: Well tolerated.

Can be given without regard to food.

Store oral solution at room temperature. Use within 1 month of opening.

Tablets may be crushed with a small amount of water or food and administered immediately.

Also active against hepatitis B. Patients co-infected with HIV and hepatitis B should receive the HIV doses of lamivudine as above.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).

PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine,* 2009, 10(10):591–613.

Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Stavudine

ATC code: J05AF04

Capsule: 15 mg; 20 mg; 30 mg

Powder for oral liquid: 1 mg/ml

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach)*. At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as d4T.

Higher incidence of lactic acidosis and hepatic steatosis than with other NRTIs.

Indications: HIV infection, in combination with at least two other antiretroviral drugs.

Precautions: Peripheral neuropathy (see below); pancreatitis (see below); chronic hepatitis B or C; hepatic disease (see below); renal impairment.

PERIPHERAL NEUROPATHY Suspend if peripheral neuropathy develops (characterized by persistent numbness, tingling or pain in feet or hands); if symptoms resolve satisfactorily on withdrawal, and if stavudine needs to be continued, resume treatment at half previous dose. Please note that giving a lower dose may result in suboptimal therapy and an increased risk of treatment failure and the development of resistance mutations; it may be advisable to change to another drug at full dose.

PANCREATITIS Avoid use or use extreme caution in patients with history of pancreatitis. If symptoms of pancreatitis develop or if serum amylase or lipase is raised (even if asymptomatic), suspend treatment until diagnosis of pancreatitis excluded; on return to normal values, re-initiate treatment only if essential (using low dose increased gradually if appropriate). Whenever possible, avoid concomitant treatment with other drugs known to cause pancreatic toxicity (for example intravenous pentamidine isetionate); monitor closely if concomitant therapy unavoidable. Since significant elevations of triglycerides cause pancreatitis, monitor closely if elevated.

HEPATIC DISEASE Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis; discontinue if rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis occurs.

Dose:

HIV infection, in combination with other antiretroviral drugs.

Oral:

Infant or **Child** 1 mg/kg twice daily up to 30 mg twice daily.

Simplified dosing tables based on weight bands are designed around 6 mg capsules (not on the 2nd WHO Model List of Essential Medicines for Children).

Stavudine: recommended dosing based on weight bands using 6 mg and 30 mg capsules

Weight range (kg)		Target dose	Dose (capsules)	
		1 mg/kg twice daily up to 30 mg/kg twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	6 mg capsule	1	1
4	4.9	6 mg capsule	1	1
5	5.9	6 mg capsule	1	1
6	6.9	6 mg capsule	2	1
7	7.9	6 mg capsule	2	1
8	8.9	6 mg capsule	2	1
9	9.9	6 mg capsule	2	1
10	10.9	6 mg capsule	2	2
11	11.9	6 mg capsule	2	2
12	13.9	6 mg capsule	2	2
14	16.9	6 mg capsule	3	2
17	19.9	6 mg capsule	3	2
20	24.9	6 mg capsule	3	3
25	29.9	30 mg capsule	1	1
30	34.9	30 mg capsule	1	1

Stavudine: recommended dosing based on weight bands using oral liquid and 15 mg, 20 mg and 30 mg capsules

Weight range (kg)		Target dose	Dose (ml or capsules)	
		1 mg/kg twice daily up to 30 mg twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	1 mg/ml syrup	6 ml	6 ml
4	4.9	1 mg/ml syrup	6 ml	6 ml
5	5.9	1 mg/ml syrup	6 ml	6 ml
6	6.9	1 mg/ml syrup	9 ml	9 ml
7	7.9	1 mg/ml syrup	9 ml	9 ml
8	8.9	1 mg/ml syrup	9 ml	9 ml
9	9.9	1 mg/ml syrup	9 ml	9 ml
10	10.9	15 mg capsule	1	1
11	11.9	15 mg capsule	1	1
12	13.9	15 mg capsule	1	1
14	16.9	20 mg capsule	1	1
17	19.9	20 mg capsule	1	1
20	24.9	20 mg capsule	1	1
25	29.9	30 mg capsule	1	1
30	34.9	30 mg capsule	1	1

Renal impairment: Mild: reduce dose to 50%.

Moderate to severe: reduce dose to 25%.

Hepatic impairment: Dosage adjustment not required; use with caution in patients with liver disease. See notes in Precautions.

Adverse effects: Common Headache, gastrointestinal disturbances, skin rashes and lipoatrophy.

Uncommon Peripheral neuropathy, pancreatitis, fat redistribution (see Lipodystrophy below), lactic acidosis, severe hepatomegaly with steatosis, sleep disorders.

Rare Increased liver enzymes, rapidly progressive ascending neuromuscular weakness.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

* **Didanosine**: increased risk of adverse effects, i.e. increased risk of fatal and non-fatal lactic acidosis or pancreatitis.
* **Ribavirin**: may decrease stavudine levels, also increased risk of fatal and non-fatal lactic acidosis.
* **Zidovudine**: may inhibit effect of stavudine (avoid concomitant use).

Notes: Well tolerated.

Do not use stavudine with zidovudine (AZT) due to an antagonistic effect.

Can be given without regard to food.

Oral solution is well tolerated and palatable.

Powder for oral solution should be protected from excessive moisture in tightly closed containers at 25 °C.

Reconstituted solution requires refrigeration; discard any unused portion after 30 days.

Shake oral solution well prior to each use.

Capsules can be opened and mixed with a small amount of food or water.

References:
Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).
Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Zidovudine

ATC code: J05AF01

Capsule: 100 mg; 250 mg

Oral liquid: 10 mg/ml

Solution for IV infusion injection: 10 mg/ml in 20 ml vial

Tablet: 300 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as ZDV, AZT and azidothymidine.

NOTE The abbreviation AZT which has sometimes been used for zidovudine has also been used for azathioprine and aztreonam. Exercise extreme caution with abbreviations.

Indications: Treatment of HIV infection in combination with other antiretroviral drugs; prevention of mother-to-child HIV transmission.

Contraindications: Abnormally low neutrophil counts or haemoglobin; neonates either with hyperbilirubinaemia requiring treatment other than phototherapy or with raised transaminase; acute porphyria.

Precautions: Haematological toxicity, including vitamin B_{12} deficiency, anaemia and myelosuppression; renal impairment; chronic hepatitis B or C; hepatic disease (see below).

HEPATIC DISEASE Potentially life-threatening lactic acidosis and severe hepatomegaly with steatosis reported. Exercise caution in patients with hepatomegaly, hepatitis, liver enzyme abnormalities, or risk factors for liver disease and hepatic steatosis; discontinue if there is any rapid deterioration in liver function tests, symptomatic hyperlactataemia, progressive hepatomegaly or lactic acidosis.

Dose:

Prevention of mother-to-child transmission of HIV.

Oral:

Neonate or **Infant** 4 mg/kg every 12 hours starting within 12 hours after birth and continuing up to 1–6 weeks of age, depending on national recommendations.

IV:

Neonate or **Infant** 1.5 mg/kg infused over 30 minutes, every 6 hours until oral dosing is possible.

HIV infection, in combination with other antiretroviral drugs.

Oral:

Infant *over 6 weeks old* 180–240 mg/m^2 twice daily, maximum 300 mg twice daily.

Simplified dosing tables based on weight bands are designed around 60 mg tablets (not on the 2nd WHO Model List of Essential Medicines for Children).

Zidovudine: recommended dosing based on weight bands using 60 mg and 300 mg tablets

Weight range (kg)		Target dose	Dose (tablets)	
		180–240 mg/m^2 twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	60 mg tablet	1	1
4	4.9	60 mg tablet	1	1
5	5.9	60 mg tablet	1	1
6	6.9	60 mg tablet	2	1
7	7.9	60 mg tablet	2	1
8	8.9	60 mg tablet	2	1
9	9.9	60 mg tablet	2	1
10	10.9	60 mg tablet	2	2
11	11.9	60 mg tablet	2	2
12	13.9	60 mg tablet	2	2
14	16.9	60 mg tablet	3	2
17	19.9	60 mg tablet	3	2
20	24.9	60 mg tablet	3	3
25	29.9	300 mg tablet	1	1
30	34.9	300 mg tablet	1	1

Zidovudine: recommended dosing based on weight bands using oral liquid and 300 mg tablets

Weight range (kg)		Target dose Infants > 6 weeks old: 180–240 mg/m² twice daily Maximum dose 300 mg twice daily	Dose (ml or tablets)	
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	10 mg/ml syrup	6 ml	6 ml
4	4.9	10 mg/ml syrup	6 ml	6 ml
5	5.9	10 mg/ml syrup	6 ml	6 ml
6	6.9	10 mg/ml syrup	9 ml	9 ml
7	7.9	10 mg/ml syrup	9 ml	9 ml
8	8.9	10 mg/ml syrup	9 ml	9 ml
9	9.9	10 mg/ml syrup	9 ml	9 ml
10	10.9	10 mg/ml syrup	12 ml	12 ml
11	11.9	10 mg/ml syrup	12 ml	12 ml
12	13.9	10 mg/ml syrup	12 ml	12 ml
14	16.9	300 mg tablet	0.5	0.5
17	19.9	300 mg tablet	0.5	0.5
20	24.9	300 mg tablet	1	0.5
25	29.9	300 mg tablet	1	1
30	34.9	300 mg tablet	1	1

Renal impairment: Severe: reduce dose.

Hepatic impairment: Dosage adjustment may be required; accumulation may occur. Use with caution; monitor for haematological toxicities frequently.

Adverse effects: Common Haematological toxicity, including neutropenia, leukopenia and anaemia, severe headache, malaise, nausea, vomiting, anorexia.

Uncommon Myopathy (associated with prolonged use), myositis, liver toxicity, lactic acidosis, severe hepatomegaly with steatosis, fat redistribution (see Lipodystrophy, below), skin and nail pigmentation, neuropathy.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

NOTE Increased risk of toxicity with nephrotoxic and myelosuppressive drugs.

Fluconazole: increased plasma concentration of zidovudine (increased risk of toxicity).

Ganciclovir: increased risk of haematological toxicity.

* **Interferon alfa**: increased risk of hepatic and haematological toxicity.

Phenytoin: plasma phenytoin concentration increased or decreased by zidovudine.

Pyrimethamine: increased antifolate effect.

* **Ribavirin**: increased risk of hepatic and haematological toxicity.

Rifampicin: avoidance of rifampicin advised by manufacturer of zidovudine.

Stavudine: may inhibit effect of stavudine (avoid concomitant use).

Valproic acid: plasma concentration of zidovudine possibly increased (risk of toxicity).

Notes: Do not use stavudine with zidovudine due to an antagonistic effect.

Can be given without regard to food.

Capsules can be opened and dissolved in water. Administer immediately.

Tablets may be crushed and combined with a small amount of food and administered immediately.

Store oral liquid at room temperature and protect from light.

For intermittent intravenous infusion, dilute to concentration 2 mg/ml or 4 mg/ml with glucose 5% and give over 1 hour, or 30 minutes in neonates.

Do not administer by intramuscular injection, intravenous push or rapid infusion.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine,* 2009, 10(10):591–613.
Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

6.4.2.2 Non-nucleoside reverse transcriptase inhibitors

Efavirenz

ATC code: J05AG03

Capsule: 50 mg; 100 mg; 200 mg

Oral liquid: 30 mg/ml

Tablet: 600 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection infants and children: towards universal access. Recommendations for a public health approach)*. At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as EFV or EFZ.

WHO age/weight restriction: > 3 years or > 10 kg weight.

Indications: HIV infection in combination with other antiretroviral drugs.

Contraindications: Pregnancy (substitute nevirapine for efavirenz in pregnant women or women for whom effective contraception cannot be assured).

PATIENT ADVICE Women of childbearing potential should undergo pregnancy testing as well as counselling about the risk to the fetus and the need to avoid pregnancy before initiating efavirenz therapy and for 12 weeks after stopping therapy. Barrier methods in combination with other (hormonal) methods of contraception should be used, as efavirenz may decrease the effectiveness of the oral contraceptive pill. (See Interactions.)

Precautions: Chronic hepatitis B or C; hepatic impairment; severe renal impairment; history of mental illness or seizures.

RASH Rash, usually occurring in the first 2 weeks, is the most common adverse effect; discontinue if severe rash with blistering, desquamation, mucosal involvement or fever; if rash is mild or moderate, may continue without interruption (rash usually resolves within 1 month). Rash is the principal side-effect seen in children, experienced by up to 40% of patients. Antihistamines may be useful for treatment and prophylaxis.

PSYCHIATRIC DISORDERS Patients should be advised to seek medical attention if severe depression, psychosis or suicidal ideation occurs.

Dose:

NOTE The bioavailability of efavirenz 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.

HIV infection in combination with other antiretroviral drugs, using oral liquid.

Oral:

Infants ***over 3 months or 10 kg*** or **Child** 19.5 mg/kg once daily. Dosing with capsules or tablets is preferred due to better bioavailability.

HIV infection in combination with other antiretroviral drugs, using tablets or capsules.

Oral:

Infants ***over 3 months or 10 kg*** or **Child** 15 mg/kg once daily.

Simplified dosing tables based on weight bands are designed around 100 mg capsules.

NOTE Where half capsules are called for, 50 mg capsules should be substituted, where available.

Efavirenz: recommended maintenance dosing based on weight bands

Weight range (kg)		Target dose	Dose (capsules)
		15 mg/kg once daily (capsule)	
		Weight > 40 kg: 600 mg once daily	
Bottom	**Top**	**Formulation (capsule)**	**Once daily**
10	10.9	100 mg	2
11	11.9	100 mg	2
12	13.9	100 mg	2
14	16.9	100 mg	2.5
17	19.9	100 mg	2.5
20	24.9	100 mg	3
25	29.9	100 mg	3.5
30	34.9	100 mg	4 (may be substituted with 2 capsules of 200 mg)

Renal impairment: Severe: avoid use.

Hepatic impairment: Mild to moderate: monitor for dose-related adverse effects (for example central nervous system effects) and monitor liver function.

Severe: avoid use.

Therapeutic drug monitoring is possible and may assist in dosing hepatically impaired patients.

Adverse effects: Common Rash (up to 40%, see note in Precautions), abdominal pain, nausea, diarrhoea, increased transaminase levels, neurological side effects (see below).

NEUROLOGICAL SIDE-EFFECTS Include somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, euphoria; neurological side-effects occur more commonly in adults than in children.

Uncommon Hepatitis, pancreatitis, psychosis, mania, seizures.

Rare Depression, suicidal ideation. Possible congenital abnormalities in infants exposed *in utero* during the first trimester.

Interactions with other medicines (* indicates severe):

Contraceptives, oral: efficacy of estrogen containing oral contraceptives possibly reduced.

* **Ergometrine**: increased risk of ergotism (avoid concomitant use).

Grapefruit juice: plasma concentration of efavirenz possibly increased.

Indinavir: efavirenz reduces plasma concentration of indinavir.

Lopinavir: plasma concentration of lopinavir reduced.

* **Midazolam**: increased midazolam toxicity (avoid concomitant use).

Nevirapine: plasma efavirenz concentration reduced.

Rifampicin: reduced plasma concentration of efavirenz (increase efavirenz dose).

Ritonavir: increased risk of toxicity (monitor liver function tests).

Saquinavir: efavirenz significantly reduces plasma concentration of saquinavir.

* **St John's wort *(Hypericum)***: decreased efavirenz concentration and treatment failure.

* **Voriconazole**: decreased voriconazole levels and increased efavirenz levels; consult specialist texts for management advice if this combination is necessary.

Notes: Take on an empty stomach, preferably at bedtime. Food, particularly high fat food, increases absorption by 50%. Safety of increased levels not assessed.

Capsules may be opened and added to liquids or small amounts of food to disguise their peppery taste.

Bedtime dosing is recommended, particularly during the first 2–4 weeks of therapy, to improve tolerability of central nervous system side-effects.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Nevirapine

ATC code: J05AG01

Oral liquid: 10 mg/ml

Tablet: 200 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection in infants and children: towards universal access. Recommendations for a public health approach)*. At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as NVP.

Indications: Progressive or advanced HIV infection, in combination with at least two other antiretroviral drugs; prevention of mother-to-child transmission.

Contraindications: Moderate or severe hepatic impairment; post-exposure prophylaxis.

Precautions: Hepatic impairment (see below); rash (see below); chronic hepatitis B or C; high CD4 cell count (preferably avoid in women with CD4 cell count greater then 250 cells/mm^3 or in men with CD4 cell count greater than 400 cells/mm^3).

HEPATIC DISEASE Potentially life-threatening hepatotoxicity including fatal fulminant hepatitis reported usually in the first 6 weeks; close monitoring required during first 18 weeks; assess liver function before treatment then every 2 weeks for 2 months, then after 1 month and then regularly; discontinue permanently if liver abnormalities accompanied by hypersensitivity reaction (rash, fever, arthralgia, myalgia, lymphadenopathy, hepatitis, renal impairment, eosinophilia, granulocytopenia); suspend if severe liver abnormalities but no hypersensitivity reaction; discontinue permanently if significant liver function abnormalities recur; monitor patient closely if mild to moderate liver abnormalities 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.

PATIENT ADVICE Patients and/or caregivers should be told how to recognize hypersensitivity reactions and advised to discontinue treatment and seek immediate medical attention if symptoms of hepatitis, severe skin reaction or hypersensitivity reactions develop.

Dose:

Progressive or advanced HIV infection, in combination with other antiretroviral drugs.

Oral:

Neonate, Infant or **Child** initially 160–200 mg/m^2 (maximum 200 mg) once daily for the first 14 days, increasing to twice daily after 14 days in the absence of nevirapine-induced rash (see Special considerations on dosing, below).

SPECIAL CONSIDERATIONS ON DOSING

a) Induction dose: once daily for first 14 days; it is generally half the daily maintenance dose given once daily except where the maintenance dose is divided unequally between a.m. and p.m.

b) Maintenance dose: target dose is 160–200 mg/m^2 given twice daily and adjusted for more aggressive dosing in the younger age group.

c) If a mild rash occurs during the first 14 days of induction dosing, continue once daily dosing and only escalate dose once the rash has subsided and the dose is well tolerated. If a severe rash occurs (especially if accompanied by fever, blistering or mucosal ulcerations), discontinue drug.

NOTE If treatment interrupted for more than 7 days, reintroduce with lowest dose and increase dose cautiously.

Simplified dosing tables based on weight bands are designed around 50 mg tablets (not on the 2nd WHO Model List of Essential Medicines for Children).

Nevirapine: recommended maintenance dosing based on weight bands using 50 mg and 200 mg tablets

Weight range (kg)		Target dose	Dose (tablets)	
		Maintenance dose after 2 week induction: 160–200 mg/m^2 to maximum 200 mg twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	50 mg tablet	1	1
4	4.9	50 mg tablet	1	1
5	5.9	50 mg tablet	1	1
6	6.9	50 mg tablet	2	1
7	7.9	50 mg tablet	2	1
8	8.9	50 mg tablet	2	1
9	9.9	50 mg tablet	2	1
10	10.9	50 mg tablet	2	2
11	11.9	50 mg tablet	2	2
12	13.9	50 mg tablet	2	2
14	16.9	50 mg tablet	3	2
17	19.9	50 mg tablet	3	2
20	24.9	50 mg tablet	3	3
25	29.9	200 mg tablet	1	1
30	34.9	200 mg tablet	1	1

Nevirapine: recommended maintenance dosing based on weight bands using 10 mg/ml syrup and 200 mg tablets

Weight range (kg)		Target dose	Dose (ml or tablets)	
		Maintenance dose after 2 week induction: 160–200 mg/m² to maximum 200 mg twice daily		
Bottom	Top	Formulation	a.m.	p.m.
3	3.9	10 mg/ml syrup	5 ml	5 ml
4	4.9	10 mg/ml syrup	5 ml	5 ml
5	5.9	10 mg/ml syrup	5 ml	5 ml
6	6.9	10 mg/ml syrup	8 ml	8 ml
7	7.9	10 mg/ml syrup	8 ml	8 ml
8	8.9	10 mg/ml syrup	8 ml	8 ml
9	9.9	10 mg/ml syrup	8 ml	8 ml
10	10.9	10 mg/ml syrup	10 ml	10 ml
11	11.9	10 mg/ml syrup	10 ml	10 ml
12	13.9	10 mg/ml syrup	10 ml	10 ml
14	16.9	200 mg tablet	1	0.5
17	19.9	200 mg tablet	1	0.5
20	24.9	200 mg tablet	1	0.5
25	29.9	200 mg tablet	1	1
30	34.9	200 mg tablet	1	1

Prevention of mother-to-child transmission (MTCT) of HIV infection.

Oral:

Neonate or **Infant** ***birth to 6 weeks, under 2500 g*** 10 mg daily;
over 2500 g 15 mg daily.
Infant ***6 weeks–6 months*** 20 mg daily;
6 months–9 months 30 mg daily;
9 months to end of breastfeeding 40 mg daily.

NOTE Give first dose as early as possible after delivery, preferably within the first 6 hours. If the infant weight is not available, administer 1 ml of 10 mg/ml oral suspension and thereafter follow national MTCT dosing recommendations.

Renal impairment: Mild and moderate: no dosage adjustment required.

Severe: use with caution.

Hepatic impairment: See note in Precautions.

Mild: use with caution.

Moderate to severe: avoid.

Adverse effects: Common Rash (including Stevens-Johnson syndrome which occurs in 0.3% of patients), nausea, headache, fever, abnormal hepatic transaminases.

Uncommon Hepatotoxicity (can be severe, life threatening and possibly fatal), vomiting, abdominal pain, fatigue, myalgia.

Rare Toxic epidermal necrolysis, diarrhoea, angioedema, hypersensitivity reactions, arthralgia, anaemia and granulocytopenia.

Interactions with other medicines (* indicates severe):

* **Contraceptives, oral**: accelerated metabolism of estrogens and progestogens (reduced contraceptive effect).

Efavirenz: plasma efavirenz concentration reduced.

* **Fluconazole**: increased plasma concentration of nevirapine.

Indinavir: nevirapine reduces plasma concentration of indinavir.

* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).

Lopinavir: plasma concentration of lopinavir possibly reduced.

* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).
* **Rifampicin**: reduced plasma concentration of nevirapine (avoid concomitant use).

Saquinavir: plasma concentration of saquinavir reduced.

* **St John's wort *(Hypericum)***: reduced plasma concentration of nevirapine (avoid concomitant use).
* **Voriconazole**: increased plasma concentration of nevirapine and reduced concentration of voriconazole.
* **Warfarin**: enhanced or reduced anticoagulant effect.

Notes: Can be given without regard to food.

Oral suspension must be shaken well; store at room temperature. Discard 6 months after opening.

Tablets are scored and can be divided into two equal parts to give a 100 mg dose.

Tablets can be crushed and combined with a small amount of water or food and immediately administered.

Nevirapine is preferred NNRTI for children under 3 years.

Monitor liver function prior to commencing nevirapine and then at frequent intervals (see note in Precautions).

A two week half dose lead-in is required to reduce the risk of serious rash, fulminant hepatitis and Stevens-Johnson syndrome. If a rash occurs during lead-in, do not increase the dose until the rash has resolved. Permanently cease nevirapine in children who experience severe rash. Warn parents and carers about a potential severe, life-threatening rash during the 14 day lead-in period.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine,* 2009, 10(10):591–613.

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection: Supplement I: pediatric antiretroviral drug information.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

6.4.2.3 Protease inhibitors

Fixed-dose combinations

Atazanavir

ATC code: J05AE08

Solid oral dosage form: 100 mg; 150 mg; 300 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

Special Notes: Also referred to as ATV.

WHO age/weight restriction: > 25 kg weight.

Indications: HIV infection, in combination with other antiretroviral drugs and usually with low dose ritonavir booster.

Contraindications: Hepatic impairment; treatment with rifampicin or St John's wort; porphyria.

Precautions: Cardiac conduction abnormalities; risk factors for QT prolongation; decreased gastric acidity; haemophilia; diabetes mellitus.

Dose:

NOTE The 2nd WHO Model List of Essential Medicines for Children (2009) has a weight restriction of > 25 kg for atazanavir. However, current recommendations differ.

HIV infection, in combination with other antiretroviral drugs, where other antiretroviral therapy has failed.

Oral:

Target dose

Child *over 6 years 15 kg up to 25 kg* 150 mg atazanavir and 80 mg ritonavir once daily;
25–30 kg 200 mg atazanavir and 100 mg ritonavir once daily;
30 kg and over 300 mg atazanavir and 100 mg ritonavir once daily (maximum dose).

NOTE To be used in combination with ritonavir (as above) and other antiretrovirals.

Recommended for patients from 6 years of age. Currently insufficient data for patients less than 6 years of age.

Renal impairment: No dosage adjustment required.

Hepatic impairment: Avoid use.

Adverse effects: Common Rash (see below), elevated total bilirubin (asymptomatic unconjugated hyperbilirubinaemia associated with scleral icterus or visible jaundice), jaundice, headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhoea, paraesthesias, prolongation of the PR interval.

Uncommon Asymptomatic first-degree heart block, hepatitis, lactic acidosis, fat redistribution and lipid abnormalities (see Lipodystrophy, below).

Rare Second-degree heart block, nephrolithiasis, prolonged QT interval, Stevens-Johnson syndrome.

RASH Rash is common and median onset is 7 weeks. Continue treatment if rash is mild to moderate (usually resolves in 1–2 weeks); discontinue therapy in the case of a severe rash.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

NOTE Atazanavir is extensively metabolized by hepatic CYP450 and is a potent CYP3A4 inhibitor and therefore interacts with numerous drugs. Consult specialist texts for details and advice on management.

Atazanavir may prolong the PR interval. Use with caution in patients taking other medications which affect AV conduction.

When used in combination with ritonavir, see also ritonavir drug interactions.

Antacids: reduced absorption. Administer atazanavir 2 hours before or 1 hour after antacids.

* **Contraceptives, oral**: increased concentration and possible toxicity. If used with ritonavir, efficacy of estrogen containing oral contraceptives possibly reduced. Consider non-hormonal contraceptive methods.

* **Didanosine**: buffered formulations of didanosine reduce atazanavir absorption. Administer atazanavir 2 hours before or 1 hour after didanosine.

Efavirenz: reduced atazanavir concentration. Use with ritonavir. Dose adjustment may be required.

* **Ergot derivatives**: increased risk of ergot toxicity.

* **Midazolam**: increased plasma levels of midazolam. Avoid combination.

Nevirapine: reduced atazanavir concentration. Avoid combination.

* **Omeprazole**: decreased atazanavir concentration and therapeutic effect. Dose adjustment required; consult product literature.

* **Ranitidine**: reduced absorption. Dose adjustment or careful dose scheduling required. Consult product literature.

* **Rifampicin**: decreased atazanavir concentrations. Avoid combination.

Ritonavir: plasma concentration possibly increased by ritonavir. This interaction is beneficial and ritonavir is used at low doses to increase the serum concentration of other protease inhibitors.

St John's wort: substantially reduced atazanavir concentration. Avoid combination.

Tenofovir: reduced atazanavir concentration. Use with ritonavir booster and give with food. Increased tenofovir concentration; care with toxicity.

Notes: Give with food to enhance absorption. Swallow capsules whole, do not open.

Advantage of once daily dosing over other protease inhibitors.

Should be used in combination with ritonavir to optimize drug levels.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
PENTA Steering Committee. PENTA 2009 guidelines for the use of antiretroviral therapy in paediatric HIV-1 infection. *HIV Medicine,* 2009, 10(10):591–613.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
The Liverpool Pharmacology Group. *Drug interaction charts.* The University of Liverpool, ©1999–2010 (http://www.hiv-druginteractions.org, accessed 10 February 2010).
Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Lopinavir + Ritonavir

ATC code: J05AE03; J05AE06

Capsule: 133.3 mg + 33.3 mg

Oral liquid: 80 mg + 20 mg/ml

Tablet (heat stable): 100 mg + 25 mg; 200 mg + 50 mg

ANTIRETROVIRAL DOSING The doses of antiretroviral drugs included in this formulary are based on the WHO guidelines for treatment of paediatric HIV *(Antiretroviral therapy of HIV infection infants and children: towards universal access. Recommendations for a public health approach).* At the time of printing, these guidelines were under review. Prescribers are encouraged to consult the latest guidelines as they are continually updated as further data or newer formulations become available.

The dosing guidance for antiretroviral drugs provided in this formulary has been simplified and includes weight-based tables, as the calculation and administration of exact doses based on body surface area may be impractical in resource-limited settings. The target doses for each drug are included in the tables; however in many cases the dose achieved for a particular patient weight may be significantly higher or slightly lower than the target dose. Decisions about dosing were based upon manufacturer's information, the antiretroviral drug formulation choices, available data from clinical studies, and expert paediatric pharmacology consultation, and were directed towards what could be considered the "optimal" dose for a particular weight band, given the limitations imposed by currently available drug formulations and the public health advantages of simplified dosing tables.

Situations that are frequently encountered in resource-limited settings, including the possible lack of refrigeration and the lack of syrup or liquid forms for small children are taken into consideration. Some of the formulations used to create these simplified dosing guidelines are not included on the 2nd WHO Model List of Essential Medicines for Children but may be available locally.

Prescribers are urged to consider if the dosing guidelines are appropriate for adoption given the antiretroviral drugs and formulations available locally.

Special Notes: Also referred to as LPV/r or LPV/RTV.

NOTE 5 ml oral solution is equivalent to 3 capsules; where appropriate, capsules may be used instead of oral solution; oral solution excipients include propylene glycol and alcohol 42%.

Indications: HIV infection, in combination with other antiretroviral drugs.

NOTE Ritonavir increases effect of lopinavir; the low doses of ritonavir used for this purpose do not have intrinsic antiviral activity.

Contraindications: Severe hepatic impairment; severe renal impairment; porphyria.

Precautions: Chronic hepatitis B or C (increased risk of hepatotoxicity); hepatic impairment; renal impairment; haemophilia; pancreatitis (see below); diabetes mellitus; cardiac conduction disorders; structural heart disease; concomitant use with drugs that prolong QT interval; oral solution contains propylene glycol: increased susceptibility to propylene glycol toxicity in slow metabolizers.

PANCREATITIS Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated; discontinue if pancreatitis diagnosed.

Dose:

HIV infection, in combination with other antiretroviral drugs.

Lopinavir + Ritonavir: recommended dosing based on weight bands for oral liquid

Weight range (kg)		Target dose	Dose (ml)	
		Lopinavir target doses: **5–7.9 kg: 16 mg/kg twice daily** **8–9.9 kg: 14 mg/kg twice daily** **10–13.9 kg: 12 mg/kg twice daily** **14–39.9 kg: 10 mg/kg twice daily**		
		Ritonavir target doses: **7–15 kg: 3 mg/kg twice daily** **15–40 kg: 2.5 mg/kg twice daily**		
		Maximum dose: **400 mg lopinavir + 100 mg ritonavir twice daily**		
Bottom	**Top**	**Formulation (per ml solution)**	**a.m.**	**p.m.**
3	3.9	80 mg lopinavir/ 20 mg ritonavir	1	1
4	4.9	80 mg lopinavir/ 20 mg ritonavir	1	1
5	5.9	80 mg lopinavir/ 20 mg ritonavir	1	1
6	6.9	80 mg lopinavir/ 20 mg ritonavir	1.5	1.5
7	7.9	80 mg lopinavir/ 20 mg ritonavir	1.5	1.5
8	8.9	80 mg lopinavir/ 20 mg ritonavir	1.5	1.5
9	9.9	80 mg lopinavir/ 20 mg ritonavir	1.5	1.5
10	10.9	80 mg lopinavir/ 20 mg ritonavir	2	2
11	11.9	80 mg lopinavir/ 20 mg ritonavir	2	2
12	13.9	80 mg lopinavir/ 20 mg ritonavir	2	2
14	16.9	80 mg lopinavir/ 20 mg ritonavir	2.5	2.5
17	19.9	80 mg lopinavir/ 20 mg ritonavir	2.5	2.5
20	24.9	80 mg lopinavir/ 20 mg ritonavir	3	3
25	29.9	80 mg lopinavir/ 20 mg ritonavir	3.5	4
30	34.9	80 mg lopinavir/ 20 mg ritonavir	4	4

or

Lopinavir + Ritonavir: recommended dosing based on weight bands for tablets

Weight range (kg)		Target dose	Dose (tablets)	
		Lopinavir target doses: **5–7.9 kg: 16 mg/kg twice daily** **8–9.9 kg: 14 mg/kg twice daily** **10–13.9 kg: 12 mg/kg twice daily** **14–39.9 kg: 10 mg/kg twice daily**		
		Ritonavir target doses: **7–15 kg: 3 mg/kg twice daily** **15–40 kg: 2.5 mg/kg twice daily**		
		Maximum dose: **400 mg lopinavir + 100 mg ritonavir twice daily**		
Bottom	**Top**	**Formulation (tablet)**	**a.m.**	**p.m.**
10	10.9	100 mg lopinavir/ 25 mg ritonavir	2	1
11	11.9	100 mg lopinavir/ 25 mg ritonavir	2	1
12	13.9	100 mg lopinavir/ 25 mg ritonavir	2	1
14	16.9	100 mg lopinavir/ 25 mg ritonavir	2	2
17	19.9	100 mg lopinavir/ 25 mg ritonavir	2	2
20	24.9	100 mg lopinavir/ 25 mg ritonavir	3	2
25	29.9	100 mg lopinavir/ 25 mg ritonavir	3	3
30	34.9	100 mg lopinavir/ 25 mg ritonavir	3	3

Renal impairment: Use with caution. Avoid oral solution (contains propylene glycol) in severe impairment. Use tablets with caution in severe impairment.

Hepatic impairment: Mild to moderate: avoid use of oral solution due to propylene glycol content. Use tablets and capsules with caution.

Severe: avoid use.

Adverse effects: Common Diarrhoea, headache, nausea, vomiting, rash, lipid abnormalities, asthenia, hypertension, insomnia, depression, amenorrhoea, raised hepatic enzymes. Tablets have less gastrointestinal side-effects than capsules.

Uncommon Pancreatitis, fat redistribution (lipoatrophy of peripheral fat and accumulation of central fat; see Lipodystrophy, below).

Rare Hepatitis, Stevens-Johnson syndrome, hyperglycaemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, haemolytic anaemia, spontaneous bleeding in haemophiliacs, prolonged PR interval.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

NOTE Lopinavir and ritonavir are extensively metabolized by hepatic CYP450 and are potent CYP3A inhibitors and therefore interact with numerous drugs. Consult specialist texts for details and advice on management.

In combination with ritonavir, see also Ritonavir.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.
* **Carbamazepine**: possibly reduced plasma lopinavir concentration.
* **Dexamethasone**: possibly reduced plasma lopinavir concentration.
* **Efavirenz**: plasma concentration of lopinavir reduced.
* **Ergot derivatives**: increased risk of ergot toxicity.

* **Garlic**: concurrent use of garlic and protease inhibitors can lead to reduced plasma levels and treatment failure.

  Lidocaine: possibly increased plasma concentration of lidocaine.

  Nelfinavir: plasma concentration of lopinavir reduced; plasma concentration of active metabolite of nelfinavir increased.

  Nevirapine: plasma concentration of lopinavir possibly reduced.

* **Phenobarbital**: plasma concentration of lopinavir possibly reduced.

  Phenytoin: plasma lopinavir concentration possibly reduced.

* **Rifampicin**: reduced plasma concentration of lopinavir (avoid concomitant use).

  Saquinavir: increased plasma concentration of saquinavir.

* **Simvastatin**: increased risk of myopathy.

* **Tenofovir**: plasma concentration of tenofovir increased.

Notes: Tablets can be given without regard to food. Oral solution and capsules should be given with food to increase absorption.

Once daily dosing is currently not recommended.

Heat stable tablets cannot be broken or crushed as bioavailability is lost.

Capsules should not be crushed or opened. Must be swallowed whole.

Liquid has a low volume for each dose but a very bitter taste.

If co-administered with didanosine, give didanosine 1 hour before or 2 hours after lopinavir + ritonavir.

Capsules and liquid should be refrigerated or stored at up to 25 °C with reduced 2 month expiry.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

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Working group on antiretroviral therapy and medical management of HIV-infected children. *Guidelines for the use of antiretroviral agents in pediatric HIV infection.* 23 February 2009:1–139 (http://aidsinfo.nih.gov/contentfiles/pediatricguidelines.pdf, accessed 10 February 2010).

Ritonavir

ATC code: J05AE03

Oral liquid: 80 mg/ml

Solid oral dosage form: 100 mg

Tablet (heat stable): 25 mg; 100 mg

Special Notes: Also referred to as r or RTV.

Ritonavir is recommended for use in combination as a pharmacological booster, and not as an antiretroviral in its own right.

Indications: HIV infection, as a pharmacological booster to increase other protease inhibitors, in combination with other antiretroviral drugs.

Contraindications: Severe hepatic impairment; porphyria.

Precautions: Chronic hepatitis B or C (increased risk of hepatotoxicity); hepatic impairment; diabetes mellitus; hyperglycaemia; haemophilia; cardiac conduction abnormalities; structural heart disease; pancreatitis (see below).

PANCREATITIS Signs and symptoms suggestive of pancreatitis (including raised serum amylase and lipase) should be evaluated; discontinue if pancreatitis diagnosed.

Dose:

HIV infection, as a pharmacological booster to increase other protease inhibitors, in combination with other antiretroviral drugs.
Oral:
Child *7–14.9 kg* 3 mg/kg twice daily;
15–40 kg 2.5 mg/kg twice daily (maximum 100 mg twice daily).

Renal impairment: No dosage adjustment necessary (renal clearance is negligible).

Hepatic impairment: Mild to moderate: no dosage adjustment recommended.

Severe: avoid in severe hepatic impairment; if no alternative, use with extreme caution.

Adverse effects: Common Nausea, vomiting, diarrhoea (may impair absorption; close monitoring required), headache, abdominal pain, taste disturbances, dyspepsia, anorexia, circumoral and peripheral paraesthesia, lipid abnormalities.

Uncommon Vasodilatation, hypotension, syncope, dizziness, dehydration, renal insufficiency, fat redistribution (see Lipodystrophy, below), exacerbation of liver disease.

Rare Hyperglycaemia, new onset diabetes mellitus, exacerbation of existing diabetes mellitus, spontaneous bleeding in haemophiliacs, pancreatitis, hepatitis, menorrhagia, seizures, prolongation of PR interval, atrioventricular block.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

NOTE Ritonavir is extensively metabolized by hepatic CYP450 and is a potent CYP3A inhibitor and therefore interacts with numerous drugs. Consult specialist texts for details and advice on management.

* **Amitriptyline**: plasma concentration possibly increased by ritonavir.
* **Amiodarone**: increased risk of cardiac toxicity and arrhythmias. Avoid combination.
* **Amlodipine**: possibly increased plasma concentration of amlodipine.
* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoidance of concomitant use.

  Azithromycin: plasma concentration of azithromycin possibly increased.
* **Carbamazepine**: plasma concentration possibly increased by ritonavir.
* **Chlorpromazine**: plasma concentration possibly increased by ritonavir.
* **Ciclosporin**: plasma concentration possibly increased by ritonavir.
* **Clomipramine**: plasma concentration possibly increased by ritonavir.
* **Codeine**: ritonavir possibly increases plasma concentration of codeine.
* **Contraceptives, oral**: accelerated metabolism of estrogens (reduced contraceptive effect).

  Dexamethasone: plasma concentration possibly increased by ritonavir.

* **Diazepam**: plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression; avoid concomitant use).
* **Didanosine**: simultaneous administration can inactivate both drugs. Give didanosine 1 hour before or 2 hours after ritonavir.

  Efavirenz: increased risk of toxicity (monitor liver function tests).
* **Ergot derivatives**: increased risk of ergot toxicity.

  Erythromycin: plasma concentration possibly increased by ritonavir.

  Fluconazole: plasma concentration increased by ritonavir.
* **Fluoxetine**: plasma concentration of fluoxetine possibly increased.
* **Fluphenazine**: plasma concentration possibly increased by ritonavir.
* **Garlic**: concurrent use of garlic and protease inhibitors can lead to reduced plasma levels and treatment failure.
* **Haloperidol**: plasma concentration possibly increased by ritonavir.

  Hydrocortisone: plasma concentration possibly increased by ritonavir.

  Ibuprofen: plasma concentration possibly increased by ritonavir.
* **Levonorgestrel**: accelerated metabolism of levonorgestrel (reduced contraceptive effect).
* **Medroxyprogesterone**: accelerated metabolism of medroxyprogesterone (does not apply to injectable medroxyprogesterone acetate for contraception).
* **Morphine**: ritonavir possibly increases plasma concentration of morphine.
* **Nifedipine**: plasma concentration possibly increased by ritonavir.
* **Norethisterone**: accelerated metabolism of norethisterone (reduced contraceptive effect).

  Prednisolone: plasma concentration possibly increased by ritonavir.
* **Quinidine**: increased plasma quinidine concentration (increased risk of ventricular arrhythmias; avoid concomitant use).
* **Rifampicin**: plasma concentration possibly increased by ritonavir.

  Saquinavir: ritonavir increases plasma concentration of saquinavir. This interaction is beneficial and ritonavir is used at low doses to increase the serum concentration of other protease inhibitors.
* **Simvastatin**: increased risk of myopathy.
* **St John's wort *(Hypericum)***: reduced ritonavir concentration and possible loss of efficacy.
* **Verapamil**: plasma concentration possibly increased by ritonavir.
* **Voriconazole**: reduced voriconazole concentration and possible treatment failure.
* **Warfarin**: plasma concentration possibly increased by ritonavir.

Notes: Unpleasant/foul taste may require special techniques to increase tolerance in children.

Should be taken with food.

Oral solution can be mixed with milk, chocolate pudding or ice cream. Do not mix with other liquids or water.

Administer strong flavoured foods, such as maple syrup, cheese or jam, immediately after dose.

Oral solution should be stored at room temperature. Do not refrigerate. Shake well before use.

Store soft gelatin capsules in fridge until dispensed. Patient can store in fridge or store at room temperature (use within 30 days).

Give with food to increase absorption and reduce gastrointestinal adverse effects.

If prescribed with didanosine, separate drugs by 2 hours.

Capsules and liquid formulations contain alcohol as a major excipient.

References:
Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Saquinavir

ATC code: J05AE01

Solid oral dosage form: 200 mg

Special Notes: Also referred to as SQV.

WHO age/weight restriction: > 25 kg weight.

Indications: HIV infection, in combination with at least two other antiretroviral drugs and usually with low-dose ritonavir booster.

Contraindications: Severe hepatic impairment; porphyria.

Precautions: Chronic hepatitis B or C; hepatic impairment; renal impairment; diabetes mellitus; haemophilia; concomitant use of garlic (reduces plasma saquinavir concentration); pancreatitis.

Dose:

Should not be taken as the sole protease inhibitor.

There is limited information available on the appropriate dose of saquinavir in children.

HIV infection, in combination with other antiretroviral drugs and usually with low-dose ritonavir booster.
Oral:
Child *over 25 kg* some studies reported using 33 mg/kg three times daily.

Renal impairment: Severe: dose adjustment possibly required in severe impairment.

Hepatic impairment: Manufacturer advises caution in moderate hepatic impairment; avoid in severe impairment.

Adverse effects: Common Diarrhoea, abdominal discomfort, nausea, vomiting, headache, lipid abnormalities, paraesthesia, photosensitivity, acne, pruritus.

Uncommon Exacerbation of chronic liver disease, fat redistribution (see Lipodystrophy, below), fever, rash, hypersensitivity reactions.

Rare New onset diabetes mellitus, exacerbation of diabetes mellitus, hyperglycaemia, hypoglycaemia, ketoacidosis, spontaneous bleeding in haemophiliacs, pancreatitis, buccal and mucosal ulceration, Stevens-Johnson syndrome, nephrolithiasis, thrombocytopenia, liver damage, elevation in serum transaminases.

LIPODYSTROPHY Lipodystrophy has been observed in patients taking antiretroviral agents, but a direct causal relationship has not been established.

Interactions with other medicines (* indicates severe):

NOTE Saquinavir is extensively metabolized by hepatic CYP450 and is a potent CYP3A inhibitor and therefore interacts with numerous drugs. Consult specialist texts for details and advice on management.

* **Amiodarone**: increased risk of cardiac toxicity and arrhythmias. Avoid combination.
* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use; possibly due to enzyme inhibition.

Carbamazepine: possibly reduced plasma saquinavir concentration.

* **Ciclosporin**: plasma concentration of both ciclosporin and saquinavir increased.

Dexamethasone: possibly reduced plasma saquinavir concentration.

Efavirenz: efavirenz significantly reduces plasma concentration of saquinavir.

* **Ergot derivatives**: increased risk of ergot toxicity; avoid combination.

Fluconazole: plasma concentration of saquinavir possibly increased.

* **Garlic**: concurrent use of garlic and protease inhibitors can lead to reduced plasma levels and treatment failure.

Indinavir: indinavir increases plasma concentration of saquinavir.

Lopinavir: increased plasma concentration of saquinavir.

* **Midazolam**: increased midazolam toxicity; avoid combination.

Nelfinavir: combination may lead to increased plasma concentration of either drug (or both).

Nevirapine: plasma concentration of saquinavir reduced.

* **Phenobarbital**: plasma concentration of saquinavir possibly reduced.

Phenytoin: plasma saquinavir concentration possibly reduced.

* **Rifampicin**: plasma concentration of saquinavir significantly reduced; avoid concomitant use.
* **Ritonavir**: ritonavir increases plasma concentration of saquinavir. This interaction is beneficial and ritonavir is used at low doses to increase the serum concentration of other protease inhibitors.
* **Simvastatin**: increased risk of myopathy.

Warfarin: possibly enhanced anticoagulant effect.

Notes: Give with or after food. Should be taken within 2 hours after food to increase absorption.

Safety and effectiveness not well established in children less than 16 years.

Must be taken with ritonavir (never unboosted).

Sun exposure may cause photosensitivity; sunscreen and protective clothing recommended.

References:

Antiretroviral therapy of HIV infection in infants and children: towards universal access: Recommendations for a public health approach. Geneva, World Health Organization, 2006 (http://www.who.int/hiv/pub/guidelines/paediatric020907.pdf, accessed 10 February 2010).

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

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6.4.3 Other antivirals

Ribavirin is listed as an essential medication in children for treatment of viral haemorrhagic fevers only. In particular it is indicated for treatment of Lassa fever, Argentine haemorrhagic fever, Crimean–Congo haemorrhagic fever and haemorrhagic fever with renal syndrome (HFRS).

Ribavirin

ATC code: J05AB04

Injection for intravenous administration: 800 mg/10 ml and 1 g/10 ml phosphate buffer solution

Solid oral dosage form: 200 mg; 400 mg; 600 mg

Ribavirin is potentially mutagenic, tumour promoting and gonadotoxic. May cause birth defects and/or death of the exposed fetus.

Both males and females should avoid pregnancy during treatment and for at least 6 months after treatment has ceased.

Special Notes: Also referred to as tribavirin.

Indications: Treatment of haemorrhagic fever, including Lassa fever, Argentine haemorrhagic fever and Crimean-Congo haemorrhagic fever; haemorrhagic fever with renal syndrome (Hantavirus).

Contraindications: Pregnancy (see below); breastfeeding; severe cardiac disease, including unstable or uncontrolled cardiac disease in previous 6 months; haemoglobinopathies (including thalassemia or sickle-cell anaemia); haemoglobin levels less than 8 g/dl; severe debilitating medical conditions; severe hepatic dysfunction or decompensated cirrhosis of the liver; autoimmune disease (including autoimmune hepatitis); renal impairment.

PREGNANCY Teratogenic risk; risk of serious fetal abnormalities exists when ribavirin is used during pregnancy, but because of the high risk of mortality from haemorrhagic fevers for both pregnant women and the fetus, maternal benefit should be considered. Lassa fever is especially severe late in pregnancy, with maternal death or fetal loss occurring in more than 80% of cases during the third trimester.

Precautions: For both males and females: contraception essential during and for at least 6 months after treatment has ceased, condoms must be used if the partner of the male patient is pregnant (as ribavirin is excreted in semen); monitor blood counts at least weekly; pregnant health-care workers should not administer ribavirin.

Dose:

Haemorrhagic fevers.

Oral:

Child *all ages* initially 30 mg/kg (maximum 2 g) then 15 mg/kg (maximum 1 g) every 6 hours for 4 days, then 7 mg/kg (maximum 500 mg) every 6 hours for 6 days.

Slow IV infusion:

Child *all ages* 17 mg/kg every 6 hours for 4 days, then 7 mg/kg every 8 hours for 6 days.

Haemorrhagic fever with renal syndrome.

Slow IV infusion: No paediatric dose.

Adult initially 33 mg/kg (maximum 1 g) as a single dose, then 16 mg/kg (maximum 1 g) every 6 hours for 4 days, then 8 mg/kg (maximum 500 mg) every 8 hours for 6 days.

Renal impairment: Avoid use in all degrees of renal impairment.

Hepatic impairment: Dose reduction not necessary; avoid in severe hepatic dysfunction or decompensated cirrhosis.

Adverse effects: Common Rash, pruritus, anorexia, dyspnoea, cough, anaemia, haemolytic anemia (patients with pre-existing cardiac disease are at increased risk), increase in uric acid concentration.

Uncommon Dizziness, insomnia, irritability, fatigue, depression, suicidal ideation (in combination with peginterferon alfa treatment (more frequent in children)), thrombotic thrombocytopenic purpura, increases in serum bilirubin and liver enzymes, particularly AST and ALT.

Rare Reticulocytosis, myocardial infarction, arrhythmias, interstitial pneumonitis, pancreatitis, hypersensitivity.

OTHER ADVERSE EFFECTS Neutropenia, aplastic anaemia, nausea, vomiting, diarrhoea, colitis, fever, rigors, myalgia, arthralgia, headache, impaired concentration, anxiety, autoimmune disorders, diabetes, hypothyroidism, hyperthyroidism, retinal haemorrhage, retinal thrombosis, alopecia.

Interactions with other medicines (* indicates severe):

Ribavirin causes anaemia; treatment with other drugs which also have this effect may worsen this; avoid combinations or monitor closely.

Drug interactions with ribavirin may occur for up to 2 months after stopping ribavirin due to its long half-life.

Azathioprine: increased risk of azathioprine induced myelotoxicity.

Didanosine: ribavirin with didanosine has resulted in didanosine toxicity, e.g. pancreatitis, lactic acidosis; avoid combination.

Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs): ribavirin may inhibit activation of NRTIs (lamivudine, stavudine and zidovudine appear unaffected); monitor HIV RNA level closely and review NRTI treatment if this increases, seek specialist advice. Monitor closely for NRTI toxicity.

Warfarin: ribavirin may decrease warfarin's anticoagulant effect; monitor INR and increase warfarin dose if needed.

Notes: Oral ribavirin should be taken with food.

ADMINISTRATION Give by slow intravenous infusion (over 10–15 minutes).

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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6.5 Antiprotozoal medicines

6.5.1 Antiamoebic and antigiardiasis medicines

Amoebiasis

Amoebic dysentery is caused by *Entamoeba histolytica*. It is transmitted by the faeco-oral route and infection is usually caused by ingestion of cysts from contaminated food and drink. Asymptomatic carriers are common in endemic areas. In non-endemic areas, asymptomatic carriers should be treated to reduce the risk of transmission and protect the patient from invasive amoebiasis.

Symptomatic (invasive) amoebiasis may be classified as either intestinal or extra-intestinal. Intestinal forms of amoebiasis include amoebic dysentery and non-dysenteric amoebic colitis. Extra-intestinal amoebiasis most commonly involves the liver, but in some cases may involve the skin, the genito-urinary tract, the lung and the brain. Invasive amoebiasis is more likely in malnutrition and immunosuppression, and requires treatment.

Giardiasis

Giardiasis is acquired by oral ingestion of *Giardia* cysts. Treatment should be offered to all infected patients. Larger epidemics are difficult to eradicate because of the high proportion of symptomless carriers and because excreted cysts can survive for long periods outside the human host. Treatment of asymptomatic carriers is generally not recommended, except possibly in households with immunocompromised patients.

Diloxanide

ATC code: P01AC01

Tablet: 500 mg (furoate)

Special Notes: WHO age/weight restriction: > 25 kg weight.

Indications: Amoebiasis (asymptomatic carriers in non-endemic areas; eradication of residual luminal amoebae after treatment of invasive disease with other drugs).

Contraindications: Pregnancy (defer treatment until after first trimester).

Dose:

Amoebiasis.

Oral:

Child *over 25 kg* 7 mg/kg (maximum 500 mg) three times daily for 10 days. The course of treatment may be repeated if necessary.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Flatulence.

Uncommon Vomiting, pruritus and urticaria.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Diloxanide 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.

Treatment with diloxanide is regarded as successful if stools are free of *Entamoeba histolytica* for 1 month. Several stool specimens should be examined when evaluating response to treatment.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Metronidazole

ATC code: P01AB01

Injection: 500 mg in 100 ml vial

Oral liquid: 40 mg (as benzoate)/ml

Tablet: 200 mg to 500 mg

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Invasive amoebiasis and giardiasis.

Precautions: Hepatic impairment; disulfiram-like reaction with alcohol consumption; clinical and laboratory monitoring (including full blood count and hepatic function tests) in courses lasting longer than 10 days.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Invasive amoebiasis.
Oral or *IV:*
Infant or **Child** 10 mg/kg three times daily for 8–10 days.
The IV route should only be used if oral administration is not possible and only until the patient can complete the course orally.

Giardiasis.
Oral:
Infant or **Child** 10 mg/kg three times daily for 3–7 days.

NOTE In amoebiasis and giardiasis, various dosage regimens are used and definitive recommendations should be based on local experience. Eradication may take re-treatment and longer courses.

Renal impairment: Metabolites may accumulate in severe impairment possibly causing adverse effects. Dose adjustment is not usually necessary.

Hepatic impairment: Severe impairment: reduce total daily dose to one third and give once daily.

Use with caution in hepatic encephalopathy.

Adverse effects: Common Gastrointestinal intolerance (nausea, abdominal pain, vomiting, diarrhoea), anorexia, metallic taste, central nervous system effects (e.g. dizziness, headache), thrombophlebitis (if administered intravenously).

Uncommon Furry tongue, glossitis, stomatitis, paraesthesia.

Rare Pancreatitis, abnormal liver function tests, jaundice, hepatitis, optic neuritis, thrombocytopenia, *Clostridium difficile*-associated disease, hypersensitivity reactions (e.g. rash, itch, flushing, fever), anaphylaxis, angioedema, erythema multiforme, Stevens-Johnson syndrome, leukopenia, peripheral neuropathy, seizures, darkening of the urine.

HIGH-DOSE AND/OR PROLONGED TREATMENT Leukopenia is reversible and usually only occurs after prolonged treatment; peripheral neuropathy (usually reversible) and/or central nervous system toxicity (including seizures) may occur.

Interactions with other medicines (* indicates severe):

Contraceptives, oral: contraceptive effect of estrogens possibly reduced (risk probably small).

Ethanol: disulfiram-like reaction.

Fluorouracil: metabolism of fluorouracil inhibited (increased toxicity).

Lithium: increased lithium toxicity reported.

Mebendazole: increased levels/effect of metronidazole.

Phenobarbital: metabolism of metronidazole accelerated (reduced plasma concentration).

* **Phenytoin**: metabolism of phenytoin inhibited (increased plasma phenytoin concentration).

Typhoid vaccine: reduced effectiveness of vaccine.

* **Warfarin**: enhanced anticoagulant effect.

Notes: Well absorbed orally and the intravenous route is normally reserved for severe infections or those unable to take or tolerate oral medication.

Oral absorption from the suspension is lower than from the tablets.

PATIENT ADVICE Metronidazole tablets should be swallowed whole with water, during or after a meal; metronidazole suspension should be taken 1 hour before a meal.

ADMINISTRATION For intravenous infusion, infuse over 20–30 minutes.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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6.5.2 Antileishmaniasis medicines

The incidence of leishmania infection is increasing, and children account for a significant proportion of those with visceral leishmaniasis in disease endemic areas. Morbidity and mortality related to this infection is substantial.

Leishmaniasis is caused by the parasitic protozoa, *Leishmania*, and is usually categorized as visceral, cutaneous or mucocutaneous. It may manifest as a self-limiting localized skin lesion, but can progress from this to mucosal involvement, to disseminated progressive disease (cutaneous form) or, without treatment, to a fatal disease (visceral form). Humans are the incidental hosts of infection, and mammals, such as rodents and canids, are the reservoir hosts. The parasites are transmitted by sandflies.

Visceral leishmaniasis

Visceral leishmaniasis (kala-azar) is caused by *Leishmania donovani* and *L. infantum* ("Old World" species), and by *L. chagasi* ("New World" species). It is usually responsive, at least initially, to the pentavalent antimony compounds meglumine antimoniate or sodium stibogluconate. Patients are considered to be parasitologically cured when no parasites are detected in splenic or bone marrow aspirates.

In some areas, resistance to antimonials is widespread. **Amphotericin B** or parenteral **paromomycin** may be useful in resistant cases.

Cutaneous leishmaniasis

Cutaneous leishmaniasis comprises two conditions. The Old World variety is caused by *L. tropica, L. major, L. infantum* or *L. aethiopica*. The New World variety is caused by *L. amazonensis, L. mexicana, L. peruviana, L. guyanensis, L. panamensis* or *L. braziliensis*. The New World variety tends to be more severe and slower to heal. Infections caused by *L. major, L. mexicana, L. tropica* or *L. peruviana* are responsive to intralesional injections of **antimonial compounds.** Mild lesions can often be left to heal spontaneously. However, it is preferable to treat *L. tropica* infections with a view to reducing transmission, since humans seem to be the only host.

Mucocutaneous leishmaniasis

Mucocutaneous leishmaniasis is caused by *L. braziliensis* or *L. panamensis*. In this form of the disease, the primary lesions do not heal, and spread to the mucosa may occur. It usually responds to **antimonials** and, when relapses occur, further extended courses of treatment are often successful.

Emergency use of **corticosteroids** may be needed to control pharyngeal or tracheal oedema produced by severe inflammation resulting from antigens liberated from dead parasites during the early phase of treatment. **Antibiotics** may also be needed to treat secondary infections. Plastic surgery offers the only means of ameliorating disfiguring scars.

Diffuse cutaneous leishmaniasis

Diffuse cutaneous leishmaniasis usually occurs following infection with *L. amazonensis, L. aethiopica* or *L. mexicana* and should be treated. Relapse is common and repeated courses may be required.

Amphotericin B

ATC code: J02AA01

Powder for injection: 50 mg in vial as deoxycholate or liposomal

> Amphotericin B is available as deoxycholate and as several lipid forms including a liposomal form; these should not be considered interchangeable and care should be taken to ensure that the form and dose are correct.
>
> Large overdoses have occurred when conventional formulations were dispensed inadvertently for lipid based or liposomal products. Single daily doses of conventional amphotericin B formulation never exceed 1.5 mg/kg.
>
> Anaphylaxis has been reported with amphotericin B; facilities for cardiopulmonary resuscitation should be available during administration due to the possibility of anaphylactic reaction.

Special Notes: Also referred to as amphotericin.

Amphotericin B is available as the conventional deoxycholate complex and liposomal forms. Other lipid forms are also available (not included in the Second WHO Model List of Essential Medicines for Children).

Indications: Visceral, mucocutaneous and cutaneous leishmaniasis unresponsive to pentavalent antimony compounds.

Precautions: Close medical supervision throughout treatment and initial test dose required (see Test dose, below); renal impairment; monitor hepatic and renal function tests; blood counts and plasma electrolyte (including potassium and magnesium concentration) monitoring required; avoid rapid infusion (risk of arrhythmias). Liposomal amphotericin B: diabetes as each 50 mg vial of liposomal amphotericin B contains 900 mg of sucrose.

TEST DOSE **Amphotericin B deoxycholate** A test dose of 1 mg, given by infusion, is recommended followed by a full dose 4–6 hours later. The patient should be observed for at least 30 minutes after the test dose.

Liposomal amphotericin B Initial test dose 100 mcg/kg (maximum 1 mg) infused intravenously over 10 minutes.

Dose:

CONVENTIONAL AMPHOTERICIN B (AS DEOXYCHOLATE)

Visceral leishmaniasis by *L. donovani.*
IV:
Child *all ages* 0.75-1 mg/kg/day, daily or on alternate days for 15–20 doses.

Visceral leishmaniasis by *L. infantum.*
IV:
Child *all ages* 0.75–1 mg/kg/day, daily or on alternate days for 20–30 doses.

For New World cutaneous leishmaniasis by *L. braziliensis* and for relapse treatment by *L. amazonensis, L. peruviana* and *L. venezuelensis.*
IV:
Child *all ages* 0.7 mg/kg/day for 25–30 doses.

For New World mucocutaneous leishmaniasis (by all parasite species).
IV:
Child *all ages* 0.7–1 mg/kg on alternate days up to 25–45 doses.

LIPOSOMAL AMPHOTERICIN B

Visceral leishmaniasis by *L. donovani* in the Indian subcontinent.
IV:
Child *all ages* 3-5 mg/kg over 3–5 days, up to a total cumulative dose of 15 mg/kg or 10 mg/kg single dose.

Visceral leishmaniasis by *L. donovani* in East Africa.
IV:
Child *all ages* 3–5 mg/kg/day over 6–10 days, up to 30 mg/kg total cumulative dose.

Visceral leishmaniasis by *L. infantum.*
IV:
Child *all ages* 3–5 mg/kg/day over 3–6 days, up to 18–21 mg/kg total cumulative dose.

Visceral leishmaniasis in HIV coinfected patients.
IV:
Child *all ages* 3–5 mg/kg daily or intermittently for 10 doses (days 1–5, 10, 17, 24, 31 and 38), up to a 40 mg/kg total cumulative dose.

For New World cutaneous leishmaniasis by *L. braziliensis* and for relapse treatment by *L. amazonensis, L. peruviana* and *L. venezuelensis.*
IV:
Child *all ages* 2–3 mg/kg/day over 6–10 days, up to 30 mg/kg total cumulative dose.

For New World mucocutaneous leishmaniasis (by all parasite species).
IV:
Child *all ages* 2–3 mg/kg/day, up to 40–60 mg/kg total cumulative dose.

Renal impairment: Mild: use only if no alternative. No dosage reduction is necessary, but further impairment is likely with conventional (as deoxycholate) amphotericin B. Nephrotoxicity may be reduced with use of liposomal formulations.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Adverse effects are similar for all amphotericin B formulations; the rates depend on the formulation used; the liposomal formulation is generally better tolerated.

Common Fever, headache, nausea and vomiting, anorexia, diarrhoea, epigastric pain, muscle and joint pain, infusion reactions (see below), thrombophlebitis, anaemia, nephrotoxicity (see below).

Uncommon Hypotension or hypertension, hypokalaemia, hypomagnesaemia, cardiac arrest, arrhythmias (rapid infusion of conventional amphotericin B), blood dyscrasias, gastrointestinal bleeding, elevated liver enzymes, hepatotoxicity, rash, neurological effects (e.g. seizures, confusion, blurred vision, hearing loss, tinnitus).

Rare Anaphylactoid reactions, hyperkalaemia (especially in renal impairment), cardiovascular toxicity (including arrhythmias, ECG changes).

NEPHROTOXICITY Conventional (as deoxycholate) amphotericin B affects renal function in all patients; changes are dose related and generally reversible (except with cumulative doses > 3–5 g). Distal tubular damage may lead to loss of concentrating ability, renal tubular acidosis, nephrocalcinosis, hypokalaemia and hypomagnesaemia. Anuria or oliguria may occur. Risk is greater in those with renal impairment or when used with other nephrotoxic drugs. Nephrotoxicity may be associated with sodium depletion.

Liposomal amphotericin B is less nephrotoxic than conventional (deoxycholate) amphotericin B.

INFUSION REACTIONS Include fever, chills, hypotension, anorexia, nausea, vomiting, headache, malaise, muscle and joint pain; usually lessen with continued treatment.

Continuous infusion of conventional (as deoxycholate) amphotericin B reduces infusion reactions.

With liposomal amphotericin B, one or more acute infusion reactions (chest pain, hypoxia, dyspnoea, severe abdominal, flank or leg pain, flushing and urticaria) may occur; these may be related to the liposomal component; frequency is very variable.

Interactions with other medicines (* indicates severe):

Amikacin: increased risk of nephrotoxicity.

* **Ciclosporin**: increased risk of nephrotoxicity.

* **Dexamethasone**: increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions).

* **Digoxin**: hypokalaemia caused by amphotericin B increases cardiac toxicity of digoxin.

Fluconazole: possible antagonism of effect of amphotericin B.

Flucytosine: renal excretion of flucytosine decreased and cellular uptake increased (flucytosine toxicity possibly increased).

Furosemide: increased risk of hypokalaemia.

Gentamicin: increased risk of nephrotoxicity.

Hydrochlorothiazide: increased risk of hypokalaemia.

* **Hydrocortisone**: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

Miconazole: possible antagonism of effects of amphotericin B.

Paromomycin: possible increased risk of nephrotoxicity.

Pentamidine: possible increased risk of nephrotoxicity.

* **Prednisolone**: increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions).

Streptomycin: increased risk of nephrotoxicity.

Vancomycin: possible increased risk of nephrotoxicity.

Notes: Check renal function before starting treatment; monitor renal function and electrolytes (especially potassium, magnesium and sodium) at least three times weekly and complete blood picture and hepatic function twice weekly during treatment and until stable after treatment stops.

Prophylactic antipyretics or hydrocortisone should only be used in patients who have previously experienced acute adverse reactions (in whom continued treatment with amphotericin B is essential).

Proper hydration and potassium supplementation are important. Treatment should always be given in hospital to enable continuous monitoring of patients.

ADMINISTRATION ADVICE Incompatible with sodium chloride solutions, flush existing line with glucose 5% or use a separate line.

Do not mix with any other drugs.

After initial reconstitution, do not administer without further dilution.

Conventional amphotericin B (as deoxycholate) Reduce risk of thrombophlebitis by using large peripheral veins or a central venous catheter, changing venous access sites frequently, and infusing over longer periods.

Reconstitute as per product instructions including further dilution with glucose 5% to produce a final concentration of 0.1 mg/ml (in fluid restricted children up to 0.4 mg/ml if given via a central line).

Initial test dose should be given over 20–30 minutes. To minimize infusion-related reactions, infuse the initial treatment dose slowly over 4–6 hours or continuously over 24 hours; tolerance to infusion reactions increases with subsequent doses, which may allow a shorter infusion, however, do not give over less than 2 hours.

Liposomal amphotericin B Reconstitute as per product instructions including filtering through a 5 micron filter and further dilute with glucose 5% to produce a final concentration of 0.2–2 mg/ml.

Initial test dose should be given over 10 minutes. Then infuse subsequent doses over 30–60 minutes.

References:

González U et al. Interventions for American cutaneous and mucocutaneous leishmaniasis. *Cochrane Database of Systematic Reviews,* 2009, 2 (Art. No.: CD004834. DOI: 10.1002/14651858.CD004834.pub2).
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WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Paromomycin

ATC code: A07AA06

Solution for intramuscular injection: 750 mg of paromomycin base present as the sulfate

Indications: Visceral leishmaniasis.

Contraindications: Intestinal obstruction; hypersensitivity to aminoglycosides; previous course of paromomycin treatment in preceding 3 months; concurrent administration with nephrotoxic or ototoxic drugs including aminoglycosides.

Precautions: Impaired gastrointestinal motility; possible or proven bowel lesions; impaired renal function.

Dose:

All doses are in terms of paromomycin base.

Visceral leishmaniasis in the Indian subcontinent.
IM:
Child *over 5 kg* 11 mg/kg daily for 21 days.

Visceral leishmaniasis in East Africa.
Only use in combination with pentavalent antimonials.
IM:
Child *over 5 kg* 11 mg/kg daily for 17 days.

Renal impairment: Mild: avoid or use with caution; nephrotoxic.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Nausea, vomiting, diarrhoea, abdominal cramps, allergic reaction, injection site pain, fever, reversible ototoxicity.

Uncommon Rash, headache, dizziness, anorexia, hypocholesterolaemic and malabsorptive effects, e.g. of xylose and sucrose, steatorrhoea and precipitation of bile salts, raised liver enzymes, renal toxicity, tetany.

Interactions with other medicines (* indicates severe):

Amphotericin B: possible increased risk of nephrotoxicity.

Cisplatin: increased risk of ototoxicity.

Digoxin: reduced digoxin absorption and subsequent reduced digoxin serum concentrations and efficacy.

Furosemide: increased risk of ototoxicity.

Methotrexate: may reduce gastrointestinal absorption of methotrexate.

* **Neostigmine**: possible antagonism of neostigmine.

* **Pyridostigmine**: possible antagonism of pyridostigmine.

* **Suxamethonium**: possible enhanced effects of suxamethonium.

Vancomycin: increased risk of ototoxicity.

References:

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Sodium stibogluconate or Meglumine antimoniate

ATC code: P01CB01; P01CB02

Sodium stibogluconate IV/IM injection: 100 mg of pentavalent antimony per ml

Meglumine antimoniate IV/IM injection: 81 mg of pentavalent antimony per ml

> Sodium stibogluconate and meglumine antimoniate are not the same compound. Please ensure doses are calculated on the compound available.

Special Notes: Meglumine antimoniate and sodium stibogluconate are the pentavalent antimony compounds used to treat all forms of leishmaniasis. Both agents are similarly effective in leishmaniasis and their pharmacokinetics are similar.

Please be aware that the two compounds do not contain equivalent amounts of pentavalent antimony.

Meglumine antimoniate is also referred to as meglumine antimonate.

Indications: Visceral, cutaneous, mucocutaneous and post-kala-azar dermal leishmaniasis.

Contraindications: Pre-existing severe cardiac, liver, renal, pancreas or haematological morbidities; pregnancy.

Precautions: Renal impairment; hepatic impairment.

MUCOCUTANEOUS DISEASE Successful treatment of mucocutaneous leishmaniasis may induce severe inflammation around lesions (may be life threatening if pharyngeal or tracheal involvement), may require systemic corticosteroids.

Dose:

Doses are expressed in terms of pentavalent antimony.

Sodium stibogluconate IV/IM injection contains 100 mg of pentavalent antimony per ml.

Meglumine antimoniate IV/IM injection contains 81 mg of pentavalent antimony per ml.

Visceral leishmaniasis.

IV/IM:

Child *all ages* 20 mg/kg (minimum 200 mg) daily for 28 days in *L. infantum* infections and for 30 days in *L. donovani* infections.

Post-kala-azar dermal leishmaniasis.

IV/IM:

Child *all ages* 20 mg/kg (minimum 200 mg) daily for 30–60 days.

Cutaneous leishmaniasis.

Intralesional:

Child *all ages* 1–5 ml per session, every 3–7 days (1–5 infiltrations).

Systemic treatment is acceptable if the patient suffers from numerous lesions (typically greater than four), face-disfiguring or complicated lesion(s), if the size or localization of the lesion makes local therapy impossible, or if local therapy has been tried and failed. For diffuse cutaneous forms by *L. aethiopica*, the addition of paromomycin may be necessary.

IV/IM:

Child *all ages* 20 mg/kg daily for 10–20 days.

Mucocutaneous leishmaniasis.

IM/IV:

Child *all ages* 20 mg/kg daily for 30 days.

Renal impairment: Moderate: increased adverse effects.

Severe: contraindicated.

Hepatic impairment: Mild to moderate impairment: use with caution; increased risk of liver damage and hepatic failure.

Adverse effects: Common Anorexia, vomiting, nausea, abdominal pain, malaise, myalgia, arthralgia, headache, metallic taste, lethargy, elevated pancreatic and liver enzymes, leukopenia, anaemia, thrombocytopenia.

Rare Cardiotoxicity and sudden death (see below), hepatotoxicity, pancreatitis, flushing, bleeding from nose or gum, vertigo, fever, sweating, rash, anaphylaxis, pain and thrombosis on intravenous administration, pain on intramuscular injection, renal impairment and/or damage, peripheral neuropathy, substernal pain or cough.

CARDIOTOXICITY Electrocardiographic changes are dependent on dose and duration of treatment, the most common being T-wave inversion, prolonged QT interval and arrhythmias. Cardiotoxicity and sudden deaths are serious but uncommon side-effects. Prolongation of corrected QT interval (greater than 0.5 seconds) signals the likely onset of serious and potentially fatal cardiac arrhythmias or death.

Interactions with other medicines (* indicates severe):

Furosemide: increased risk of toxicity.

Vancomycin: increased risk of toxicity.

Cisplatin: increased risk of toxicity.

Amphotericin B: possibly increased risk of nephrotoxicity.

* **Pyridostigmine**: possible antagonism.
* **Neostigmine**: possible antagonism.
* **Suxamethonium**: possibly enhanced effects of suxamethonium.

Notes: Monitoring of patients with serum chemistry, complete blood count and electrocardiography should be done. The quality of pentavalent antimonials should be assured. Substandard drugs are known to cause severe toxicity and death. If serious side-effects arise (in most cases related to hepato- and cardiotoxicity), the treatment should be changed to another drug.

Ampoules should be stored in well-closed containers, protected from light. It should be noted that antimonial compounds are polymers that may deteriorate with age.

ADMINISTRATION The injection should be filtered immediately before administration using a 5 micron or less filter. Intravenous injection should be given either by infusion (over 5–10 minutes) or slow injection through a fine needle (23–25 gauge; 0.6–0.5 mm) to avoid any risk of subsequent thrombosis. Intramuscular injection should be given deep into the muscle. If the volume of injection exceeds a suitable size for the patient, it should be divided into two doses; one in each buttock or thigh. Infusions should be ceased if coughing or substernal pain occurs.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Glucantime Product Information. Sanofi-Aventis Farmacêutica, Brazil (accessed April 14 2010).
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6.5.3 Antimalarial medicines

6.5.3.1 For curative treatment

Malaria, which is transmitted by anopheline mosquitoes, is caused by four species of plasmodial parasites. *Plasmodium vivax* is extensively distributed. *P. falciparum* is also widespread, and causes the most severe infections, which are responsible for nearly all malaria-related deaths. *P. ovale* is mainly confined to Africa and is less prevalent, while *P. malariae*, which causes the least severe but most persistent infections, also occurs widely.

Certain tissue forms of *P. vivax* and *P. ovale*, which can persist in the liver for many months, and sometimes years, are responsible for relapses. Such latent forms are not generated by *P. falciparum* or *P. malariae*. Recrudescence of these infections results from persistent blood forms in inadequately treated or untreated patients.

The following recent key recommendations regarding antimalarial therapy have been endorsed:

First-line treatment for malaria should be with combinations of medicines rather than single drug therapy.

- Artemisinin-containing combination therapy (ACT) is recommended as first-line curative treatment for uncomplicated malaria.

Treatment of *severe* falciparum malaria requires parenteral therapy. Parenteral antimalarials are also used to initiate treatment in patients unable to take oral treatment.

Amodiaquine

ATC code: P01BA06

Tablet: 153 mg or 200 mg (as hydrochloride)

Special Notes: Recommended for children over 5 months only.

Occasionally abbreviated to AQ.

Indications: Treatment of uncomplicated malaria caused by *P. falciparum.* To be used (a) in combination with artesunate or (b) may be used alone for the treatment of *P. vivax, P. ovale* and *P. malariae* infections.

Contraindications: Hepatic impairment; blood disorders; retinopathy.

Precautions: G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs.

Dose:

Treatment of uncomplicated falciparum malaria.
Oral:
Infant or **Child *over 5 months*** 10 mg/kg daily for 3 days.

Renal impairment: No information available.

Hepatic impairment: Avoid use.

Adverse effects: Blood disorders including leukopenia and agranulocytosis, hepatitis, gastrointestinal disturbances, visual disturbances (retinopathy associated with long-term, high-dose therapy), rarely, rash, pruritus, skin pigmentation, neuromyopathy.

PATIENT ADVICE Patients and their carers should be told how to recognize the signs of blood disorders and advised to seek medical attention as soon as possible if symptoms such as fever, sore throat, rash, mouth ulcers, purpura, bruising or bleeding develop. They should also be told how to recognize signs of hepatitis and advised to seek medical attention if symptoms such as anorexia, abnormal weight loss, asthenia, abdominal pains, fever, nausea or vomiting develop.

Interactions with other medicines (* indicates severe):

Chlorpromazine: plasma concentration of chlorpromazine increased (consider reducing chlorpromazine dose).

Notes: Concern has been expressed about higher rates of neutropenia in children and the drug has twice been removed from the adult formulary because of safety concerns but has since been reinstated (1988).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Artemether

ATC code: P01BE02

Oily injection: 80 mg/ml in 1 ml ampoule

Indications: Management of severe malaria. Treatment of severe *P. falciparum* malaria in areas where quinine is ineffective.

Contraindications: First trimester of pregnancy.

Precautions: SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Treatment of severe *P. falciparum* malaria in areas of quinine resistance.
Intramuscular injection:
Infant or **Child *over 6 months*** loading dose of 3.2 mg/kg, then 1.6 mg/kg daily until patient can tolerate oral medication or to maximum of 7 days; this is followed by a complete treatment course of an effective artemisinin-based combination therapy to effect a radical cure.

Renal impairment: Caution in severe impairment; monitor ECG and plasma potassium.

Hepatic impairment: Caution in severe impairment; monitor ECG and plasma potassium.

Adverse effects: Common Headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus.

Uncommon Neutropenia, elevated liver enzyme values.

Rare Cardiotoxicity (after high doses), neurotoxicity in animal studies.

Interactions with other medicines (* indicates severe):

* **Amitriptyline**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Azithromycin**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Chloroquine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Chlorpromazine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Ciprofloxacin**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Erythromycin**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Fluconazole**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Fluoxetine**: avoid concomitant use.
* **Grapefruit juice**: metabolism of artemether and lumefantrine may be inhibited (avoid concomitant use).

Haloperidol: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Lopinavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Mefloquine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Ofloxacin: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Primaquine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Proguanil: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Pyrimethamine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Quinine: risk of ventricular arrhythmias (manufacturer of artemether with lumefantrine advises avoid concomitant use).

Ritonavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Saquinavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Sulfadoxine + pyrimethamine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Notes: ADMINISTRATION Since small volumes are required for children, a 1 ml syringe should be used to ensure correct dosage.

Oily injection currently formulated in arachis (peanut) oil. Care should be taken in patients with known peanut allergy.

References:

Guidelines for the treatment of malaria. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546948_eng.pdf, accessed 10 February 2010).

Artemether + Lumefantrine

ATC code: P01BE52

Tablet: 20 mg/120 mg

Dispersible tablet: 20 mg/120 mg

Special Notes: Not for use in children under 5 kg.

Indications: Treatment of uncomplicated malaria caused by *P. falciparum* alone or with other Plasmodium spp. in areas with significant drug resistance.

Contraindications: First trimester of pregnancy; history of arrhythmias; history of clinically relevant bradycardia; history of congestive heart failure accompanied by reduced left ventricular ejection fraction; family history of sudden death or of congenital prolongation of QTc interval (also see Precautions).

Precautions: Electrolyte disturbances; concomitant administration of drugs that prolong QT interval; monitor patients unable to take food (greater risk of recrudescence); severe renal impairment or hepatic impairment.

Dose:

Treatment of uncomplicated *P. falciparum* and other Plasmodium malaria.

Oral:

Infant or **Child *5–14 kg*** initially 1 tablet followed by 5 further doses of 1 tablet each at 8, 24, 36, 48 and 60 hours (total 6 tablets over 60 hours);

15–24 kg initially 2 tablets followed by 5 further doses of 2 tablets each at 8, 24, 36, 48 and 60 hours (total 12 tablets over 60 hours);

25–34 kg initially 3 tablets followed by 5 further doses of 3 tablets each at 8, 24, 36, 48 and 60 hours (total 18 tablets over 60 hours);

over 34 kg initially 4 tablets followed by 5 further doses of 4 tablets each at 8, 24, 36, 48 and 60 hours (total 24 tablets over 60 hours).

Renal impairment: Severe: caution; monitor ECG and plasma potassium.

Hepatic impairment: Severe: caution; monitor ECG and plasma potassium.

Adverse effects: Common Abdominal pain, anorexia, diarrhoea, nausea and vomiting, headache, dizziness, sleep disorders, palpitation, arthralgia, myalgia, cough, asthenia, fatigue, pruritus, rash.

Infrequent Paraesthesia, ataxia.

Rare Hepatitis, hypersensitivity.

Interactions with other medicines (* indicates severe):

* **Amitriptyline**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Azithromycin**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Chloroquine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Chlorpromazine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Ciprofloxacin**: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Erythromycin: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Fluconazole: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Fluoxetine: avoid concomitant use.

Grapefruit juice: metabolism of artemether and lumefantrine may be inhibited (avoid concomitant use).

Haloperidol: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Levofloxacin: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Lopinavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Mefloquine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Ofloxacin: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Primaquine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Proguanil: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Pyrimethamine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Quinine: risk of ventricular arrhythmias (manufacturer of artemether with lumefantrine advises avoid concomitant use).

Ritonavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Saquinavir: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Sulfadoxine + pyrimethamine: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Notes: Non-dispersible tablets may be crushed.

If the dose is vomited within 1 hour of taking, the dose should be repeated; this is a particular risk in children.

References:

Guidelines for treatment of malaria in the United States. Atlanta, Centers for Disease Control and Prevention, 2009 (http://www.cdc.gov/malaria/, accessed 10 February 2010).

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Joint formulary committee, British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary 2008. 55th ed.* London, BMJ Group RBS Publishing, 2008.

Artesunate

ATC code: P01BE03

Injection: ampoules, containing 60 mg anhydrous artesunic acid with a separate ampoule of 5% sodium bicarbonate solution

Tablet: 50 mg

Rectal capsules: 50 mg and 200 mg

Indications: Oral treatment of uncomplicated malaria caused by *P. falciparum*, in combination with other antimalarials.

Intravenous treatment of severe malaria.

Rectal pre-referral emergency treatment of suspected severe malaria.

Contraindications: First trimester of pregnancy.

Precautions: Risk of recurrence if used as oral monotherapy in non-immune patients.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example, riding a bike or operating machinery, for 24 hours.

Dose:

Treatment of uncomplicated malaria caused by *P. falciparum.*
Oral:
Infant or **Child *over 5 months*** 4 mg/kg daily for 3 days. Not recommended as monotherapy and should be used in combination with either amodiaquine, mefloquine or sulfadoxine + pyrimethamine.

Treatment of severe *P. falciparum* malaria in areas of multiple drug resistance.
IV or *IM:*
Child 2.4 mg/kg given at 0, 12, 24 hours then once daily until oral treatment is possible.

Give a full course of artemisinin-based combination therapy (see artemether + lumefantrine) or oral quinine after initial parenteral artesunate.

Pre-referral treatment of severe malaria only (patients should be taken to an appropriate health facility for follow-up care).
Rectal:
Child *all ages* approximately 10 mg/kg.
Using available suppositories:
Neonate–Child *1 year (5–8 kg)* 50 mg;
13–42 months (9–19 kg) 100 mg;
43–60 months (20–29 kg) 200 mg;
6–12 years (30–39 kg) 300 mg.

Give a full course of artemisinin-based combination therapy (see artemether + lumefantrine) or oral quinine after initial rectal artesunate.

Renal impairment: No information available.

Hepatic impairment: No information available.

Adverse effects: Common Headache, nausea, vomiting, abdominal pain, diarrhoea, dizziness, tinnitus.

Uncommon Neutropenia, elevated liver enzyme values.

Rare ECG abnormalities, including prolongation of QT interval, temporary suppression of reticulocyte response and induction of blackwater fever reported, neurotoxicity in animal studies.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Artesunate monotherapy is not recommended for uncomplicated malaria due to the risk of developing drug resistance.

RECONSTITUTION OF PARENTERAL FORMS Artesunic acid should be dissolved in 1 ml of sodium bicarbonate 5% solution for injection (to form sodium artesunate). This can be administered intramuscularly or then further diluted in 5 ml of glucose 5% solution for injection before intravenous administration by bolus injection. Solutions should be freshly prepared prior to administration; consult manufacturer's literature.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Chloroquine

ATC code: P01BA01

Oral liquid: 10 mg base (as phosphate or sulfate)/ml

Tablet: 100 mg; 150 mg base (as phosphate or sulfate)

Indications: Only for use in the treatment of *P. vivax* infection from areas where the parasite remains sensitive.

Contraindications: Retinal damage or impaired visual field.

Precautions: If patient continues to deteriorate after chloroquine, suspect resistance and administer quinine intravenously as emergency measure; may exacerbate psoriasis; neurological disorders (avoid for prophylaxis if history of epilepsy); may aggravate myasthenia gravis; severe gastrointestinal disorders; G6PD deficiency; avoid concurrent therapy with hepatotoxic drugs.

Dose:

Treatment of *P. vivax* malaria.

Oral:

Child 10 mg/kg (maximum 600 mg) followed by 5 mg/kg (maximum 300 mg) 6–8 hours later; then 5 mg/kg daily on next 2 days. Alternatively, 10 mg/kg for 2 days, followed by 5 mg/kg daily on day 3. Total dose 25 mg/kg over 3 days.

NOTE Doses expressed as base.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Extensively liver metabolized; use with caution in liver impairment; monitor liver function tests.

Avoid concurrent therapy with hepatotoxic drugs.

Adverse effects: Common Headache, gastrointestinal disturbances, skin reactions and itch which can be severe enough to affect compliance.

Uncommon Psychotic episodes, anxiety, personality changes, reversible corneal opacities, visual disturbances (retinopathy associated with long-term, high-dose therapy or inappropriate self-medication), seizures.

Rare Depigmentation or loss of hair, bone marrow suppression, hypersensitivity reactions such as urticaria and angioedema, atrioventricular block (may be result of inappropriate self-medication), porphyria and psoriasis in susceptible individuals, tinnitus, hearing loss, blue-black pigmentation of mucous membranes and skin, photosensitivity.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of chloroquine.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Carbamazepine: possible increased risk of convulsions.

* **Ciclosporin**: increased plasma ciclosporin concentration (increased risk of toxicity).

* **Digoxin**: plasma digoxin concentration possibly increased.

Ethosuximide: possible increased risk of convulsions.

* **Mefloquine**: increased risk of convulsions.

Neostigmine: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine.

Phenytoin: possible increased risk of convulsions.

Praziquantel: plasma concentration of praziquantel possibly reduced.

Pyridostigmine: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine.

Quinine: increased risk of ventricular arrhythmias.

Valproic acid: possible increased risk of convulsions.

Notes: To eliminate liver forms of *P. vivax*, follow with primaquine oral treatment.

PATIENT ADVICE Take with food to reduce GI side effects. If vomiting occurs within 1 hour of taking dose, dose may be repeated.

References:

Guidelines for the treatment of malaria. Geneva, World Health Organization, 2006 (http://whqlibdoc.who.int/publications/2006/9241546948_eng.pdf, accessed 10 February 2010).
Guidelines for treatment of malaria in the United States. Atlanta, Centers for Disease Control and Prevention, 2009 (http://www.cdc.gov/malaria/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Joint formulary committee, British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary 2008. 55th ed.* London, BMJ Group RBS Publishing, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

Doxycycline

ATC code: J01AA02

Capsule: 100 mg (as hydrochloride)

Tablet (dispersible): 100 mg (as monohydrate)

Indications: Supplement to quinine or artesunate treatment for multiple drug-resistant *P. falciparum* malaria.

Contraindications: Pregnancy; porphyria; systemic lupus erythematosus.

Precautions: Avoid exposure to sunlight or sunlamps; photosensitivity reported.

Dose:

Supplement to quinine or artesunate treatment for multiple drug-resistant malaria.
Oral:
Child *over 8 years* 2 mg/kg (maximum 100 mg) twice daily for 7–10 days.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Avoid (or use with caution).

Adverse effects: Common Gastrointestinal disturbances, nausea, vomiting, diarrhoea, anorexia, flushing, tinnitus, photosensitivity.

Uncommon Rash, stomatitis, bone deformity, fungal overgrowth.

Rare Photo-onycholysis, nail discoloration, oesophageal ulcers (due to partly swallowed tablets), *Clostridium difficile* infection, hepatitis, fatty liver degeneration, headache and visual disturbances which may indicate benign intracranial hypertension, hypersensitivity reactions including Stevens-Johnson syndrome.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of doxycycline.

Carbamazepine: accelerated metabolism of doxycycline (reduced effect).

* **Ciclosporin**: possibly increased plasma ciclosporin concentration.

Ferrous salts: absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts.

Methotrexate: increased risk of methotrexate toxicity.

Phenobarbital: metabolism of doxycycline accelerated (reduced plasma concentration).

Phenytoin: increased metabolism of doxycycline (reduced plasma concentration).

Rifampicin: plasma doxycycline concentration possibly reduced.

* **Warfarin**: anticoagulant effect possibly enhanced.

Notes: PATIENT ADVICE Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. Should be given with food or milk, to counter gastric irritation.

For use only in combination with quinine or artesunate.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Guidelines for treatment of malaria in the United States. Atlanta, Centers for Disease Control and Prevention, 2009 (http://www.cdc.gov/malaria/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Mefloquine

ATC code: P01BC02

Tablet: 250 mg (as hydrochloride)

Indications: Used in combination with artesunate for the treatment of uncomplicated falciparum malaria.

Contraindications: History of neuropsychiatric disorders including depression or convulsions; hypersensitivity to quinine.

Precautions: Avoid use in cardiac conduction disorders; epilepsy.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Treatment of uncomplicated *P. falciparum* malaria in combination with artesunate.

Oral:

Child *over 3 months or 5 kg* 25 mg/kg usually given over 2–3 days. Round to the nearest quarter of a tablet.

NOTE Doses expressed as salt.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Mefloquine is metabolized by the liver and eliminated by the biliary system. It should be used in caution in patients with disorders of the biliary system who may not be able to clear the drug.

Adverse effects: Common Nausea, vomiting, diarrhoea, abdominal pain, anorexia, headache, dizziness (can be severe), loss of balance, somnolence, insomnia and abnormal dreams.

Uncommon Circulatory disorders, tachycardia, bradycardia, cardiac conduction disorders, muscle weakness, myalgia, arthralgia, rash, urticaria, pruritus, alopecia, disturbances in liver function tests, visual disturbances, tinnitus, vestibular disorders, seizures.

Neuropsychiatric disorders occur in at least 1:10 000 patients treated with mefloquine and the incidence is thought to be up to 1:1000 when used at treatment doses. These include sensory and motor neuropathies, tremor, ataxia, anxiety, depression, suicidal ideation, confusion, hallucinations, panic attacks, emotional instability, aggression, agitation and psychoses.

Rare Hyperpyrexia, leukopenia, leukocytosis, thrombocytopenia, Stevens-Johnson syndrome, atrioventricular block and encephalopathy.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.

  Atenolol: increased risk of bradycardia.

* **Carbamazepine**: antagonism of anticonvulsant effect.

* **Chloroquine**: increased risk of convulsions.

  Digoxin: possibly increased risk of bradycardia.

* **Ethosuximide**: antagonism of anticonvulsant effect.

  Phenytoin: antagonism of anticonvulsant effect.

  Propranolol: increased risk of bradycardia.

* **Quinidine**: increased risk of ventricular arrhythmias.

* **Quinine**: increased risk of convulsions, but should not prevent the use of intravenous quinine in severe cases.

* **Valproic acid**: antagonism of anticonvulsant effect.

Notes: Mefloquine monotherapy is no longer recommended as this is likely to result in increasing levels of parasite resistance to this drug.

Because of the high incidence of neuropsychiatric disorders other drugs should be used in preference to mefloquine where possible.

Mefloquine should not be used for treatment if it was used for prophylaxis and failed to prevent infection.

Tablets may be crushed and mixed with food such as jam or honey just before administration.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

Primaquine

ATC code: P01BA03

Tablet: 7.5 mg; 15 mg (as diphosphate)

Indications: Only for use to achieve radical cure of *P. vivax* and *P. ovale* infections.

Contraindications: Conditions that predispose to granulocytopenia including active rheumatoid arthritis and lupus erythematosus; severe G6PD deficiency.

Precautions: Monitor blood count; if methaemoglobinaemia or haemolysis occur, withdraw treatment and consult physician; mild to moderate G6PD deficiency.

Dose:

Radical cure of *P. vivax* and *P. ovale* infections after standard chloroquine or artemisinin-based combination therapy.
Oral:
Child 250 micrograms/kg daily for 14 days.
In mild to moderate G6PD deficiency use 500–750 micrograms/kg once a week for 8 weeks.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Primaquine is metabolized by the liver; use with caution in patients with liver impairment and monitor liver function tests.

Adverse effects: Common Anorexia, nausea and vomiting, abdominal pain, dizziness, headache.

Infrequent Acute haemolytic anaemia (frequently in G6PD deficiency).

Rare Hypertension, methaemoglobinaemia, haemoglobinuria, agranulocytosis, granulocytopenia and leukopenia.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Guidelines for treatment of malaria in the United States. Atlanta, Centers for Disease Control and Prevention, 2009 (http://www.cdc.gov/malaria/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Joint formulary committee, British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary 2008. 55th ed.* London, BMJ Group RBS Publishing, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

Quinine

ATC code: P01BC01

Injection: 300 mg quinine hydrochloride/ml in 2 ml ampoule

Tablet: 300 mg (quinine sulfate) or 300 mg (quinine bisulfate)

Indications: Multiple drug-resistant *P. falciparum* malaria.

Contraindications: Haemoglobinuria; optic neuritis; tinnitus; myasthenia gravis.

Precautions: Atrial fibrillation; conduction defects; heart block; monitor for signs of cardiac toxicity and hypoglycaemia during intravenous use; renal impairment; G6PD deficiency.

Dose:

Treatment of multiple drug-resistant *P. falciparum* malaria.

Oral:

Child 10 mg/kg (quinine sulfate) every 8 hours for 3, 7 or 10 days. The duration of treatment is dependent on local susceptibility of *P. falciparum* and whether or not additional antimalarials are being or have been used.

IV (only in patients unable to take quinine by mouth):

Child 20 mg/kg (quinine dihydrochloride) followed by 10 mg/kg (quinine hydrochloride) every 12 hours. The initial dose should be halved in patients who have received quinine, quinidine or mefloquine during the previous 12–24 hours.

Renal impairment: Reduce parenteral maintenance dose for malaria treatment.

Give a lower dose at increased intervals with oral therapy. Mild impairment: administer every 8 hours; moderate impairment: administer every 12 hours; severe impairment: administer every 24 hours.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Cinchonism (tinnitus, headache, blurred vision, temporary blindness, altered auditory acuity, nausea, diarrhoea, hot and flushed skin, rashes, confusion), hypersensitivity reactions, gastrointestinal disturbances, CNS disturbances.

Uncommon Hypoglycaemia, especially after parenteral administration, caused by increased insulin release (also associated with severe malaria and therefore a poor prognostic sign), asthma.

Rare Haemorrhage and renal damage (culminating in acute renal failure and anuria), blood disorders, prolonged QT interval, angioedema.

NOTE Very toxic in overdosage; immediate medical attention required.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: risk of ventricular arrhythmias (manufacturer of artemether with lumefantrine advises to avoid concomitant use).

  Chloroquine: increased risk of ventricular arrhythmias.

* **Digoxin**: plasma concentration of digoxin increased.

* **Mefloquine**: increased risk of convulsions, but should not prevent the use of intravenous quinine in severe cases.

  Suxamethonium: possibly enhanced effects of suxamethonium.

Notes: Use only in the management of severe malaria. To avoid resistance, quinine should always be used in combination with either doxycycline (not in children under 8 years), clindamycin or sulfadoxine/pyrimethamine (SP) where there is no SP resistance. Clindamycin dose for combination therapy: 7–13 mg/kg (maximum 450 mg) every 8 hours for 7 days.

PATIENT ADVICE If all or part of a dose is vomited within 1 hour, the same amount must be re-administered immediately.

IV administration: give by slow intravenous infusion over 4 hours.

Quinine (anhydrous base) 100 mg ≡ quinine bisulfate 169 mg ≡ quinine dihydrochloride 122 mg ≡ quinine sulfate 121 mg.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Guidelines for treatment of malaria in the United States. Atlanta, Centers for Disease Control and Prevention, 2009 (http://www.cdc.gov/malaria/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Joint formulary committee, British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary 2008. 55th ed.* London, BMJ Group RBS Publishing, 2008.

Sulfadoxine + Pyrimethamine

ATC code: P01BD51

Tablet: 500 mg + 25 mg

Indications: Treatment of *P. falciparum* malaria in combination with artesunate.

Contraindications: Hypersensitivity to sulfonamides or pyrimethamine; severe hepatic or renal impairment (except where no alternative treatment available).

Precautions: Avoid in blood disorders unless under specialist supervision; discontinue immediately if blood disorder occurs; rash; sore throat; mouth ulcers or shortness of breath; G6PD deficiency; predisposition to folate deficiency.

Dose:

Treatment of *P. falciparum* malaria in combination with other antimalarials.

Oral:

Child *5–10 kg* half a tablet;
11–20 kg 1 tablet as a single dose;
21–30 kg 1½ tablets as a single dose;
31–45 kg 2 tablets as a single dose.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: No information available.

Adverse effects: Common Rashes, pruritus, slight hair loss, gastrointestinal disturbances including nausea, vomiting, stomatitis, fatigue, headache, fever, polyneuritis.

Rare Pulmonary infiltrates such as eosinophilic or allergic alveolitis (if symptoms of cough or shortness of breath, withdraw treatment), rarely erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis, hepatitis, leukopenia, thrombocytopenia, megaloblastic anaemia and purpura.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.
* **Ciclosporin**: increased risk of nephrotoxicity.
* **Folate/folic acid**: concurrent use should be avoided as folate may antagonize the effect of sulfadoxine + pyrimethamine.
* **Methotrexate**: antifolate effect of methotrexate increased; risk of methotrexate toxicity increased.
* **Phenytoin**: plasma phenytoin concentration possibly increased; increased antifolate effect.
* **Sulfadiazine**: increased antifolate effect.
* **Sulfamethoxazole + trimethoprim**: increased antifolate effect.

  Thiopental: enhanced effects of thiopental.
* **Trimethoprim**: increased antifolate effect.
* **Warfarin**: enhanced anticoagulant effect.

Notes: Sulfadoxine + pyrimethamine monotherapy is no longer recommended as this is likely to result in increasing levels of parasite resistance to this drug.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Joint formulary committee, British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary 2008. 55th ed.* London, BMJ Group RBS Publishing, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

6.5.3.2 For prophylaxis

No drug regimen gives assured protection to everybody, and indiscriminate use of antimalarials can increase the risk of inducing resistance. Avoidance of mosquito bites using insect repellents, mosquito nets (preferably impregnated with an insecticide), long pants and long-sleeved shirts, and door and window screens are important preventative strategies.

Current guidelines should be consulted to inform management of malaria, for example, the *WHO guidelines for the treatment of malaria*.

Chloroquine

ATC code: P01BA01

Oral liquid: 10 mg (as phosphate or sulfate)/ml

Tablet: 150 mg (as phosphate or sulfate)

Indications: Only for use in the prophylaxis of *P. vivax* infection from areas where the parasite remains sensitive.

Contraindications: Not for prophylaxis of *P. falciparum.*

Precautions: Chloroquine resistance is now widespread in Africa, Asia and the Pacific so is no longer the prophylaxis drug of choice.

Dose:

Prophylaxis for *P. vivax* in central American regions.

Oral:

Child *up to 12 weeks and under 6 kg* 37.5 mg once weekly;
12 weeks–1 year, 6–10 kg 75 mg once weekly;
1–4 years, 10–16 kg 112.5 mg once weekly;
4–8 years, 16–25 kg 150 mg once weekly;
8–13 years, 25–45 kg 225 mg once weekly;
over 13 years and 45 kg 310 mg once weekly.

Dose expressed as chloroquine base and should be started 1 week before entering endemic area and continued for 4 weeks after leaving.

Renal impairment: Severe renal impairment GFR < 10 ml/minute: reduce dose by half.

Hepatic impairment: No information available.

Adverse effects: Common Headache, gastrointestinal disturbances, skin reactions and itch which can be severe enough to affect compliance.

Uncommon Psychotic episodes, anxiety, personality changes, reversible corneal opacities, visual disturbances (retinopathy associated with long-term, high-dose therapy or inappropriate self-medication), seizures.

Rare Depigmentation or loss of hair, bone marrow suppression, hypersensitivity reactions such as urticaria and angioedema, atrioventricular block (may be result of inappropriate self-medication), porphyria and psoriasis in susceptible individuals, tinnitus, hearing loss, blue-black pigmentation of mucous membranes and skin, photosensitivity.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of chloroquine.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.

Carbamazepine: possible increased risk of convulsions.

* **Ciclosporin**: increased plasma ciclosporin concentration (increased risk of toxicity).

* **Digoxin**: plasma digoxin concentration possibly increased.

Ethosuximide: possible increased risk of convulsions.

* **Mefloquine**: increased risk of convulsions.

Neostigmine: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine.

Phenytoin: possible increased risk of convulsions.

Praziquantel: plasma concentration of praziquantel possibly reduced.

Pyridostigmine: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine.

Quinine: increased risk of ventricular arrhythmias.

Valproic acid: possible increased risk of convulsions.

Notes: PATIENT ADVICE Oral chloroquine should be taken after meals to minimize nausea and vomiting; if part or all of a dose is vomited, the same amount must be immediately re-administered.

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.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

Doxycycline

ATC code: J01AA02

Solid dosage form: 100 mg (as hydrochloride)

Special Notes: WHO age/weight restriction: > 8 years.

Should not be used in children under 8 years: deposition of tetracyclines in growing bones and teeth (by binding to calcium) causes staining and occasionally dental hypoplasia.

Indications: Short-term prophylaxis of multiple drug-resistant *P. falciparum* malaria.

Contraindications: Pregnancy; porphyria; systemic lupus erythematosus.

Precautions: Avoid exposure to sunlight or sunlamps; photosensitivity reported.

Dose:

Short-term prophylaxis of multiple drug-resistant *P. falciparum* malaria.

Oral:

Child *over 8 years* 2 mg/kg (maximum 100 mg) daily for up to 8 weeks; doxycycline should be started on the day before exposure and continued for 4 weeks after last risk of exposure.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Avoid (or use with caution).

Adverse effects: Common Gastrointestinal disturbance, nausea, vomiting, diarrhoea, anorexia, flushing, tinnitus, photosensitivity.

Uncommon Rash, stomatitis, bone deformity, fungal overgrowth.

Rare Photo-onycholysis, nail discoloration, oesophageal ulcers (due to partly swallowed tablets), *Clostridium difficile* infection, hepatitis, fatty liver degeneration, headache and visual disturbances which may indicate benign intracranial hypertension, hypersensitivity reactions including Stevens-Johnson syndrome.

Interactions with other medicines (* indicates severe):

Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of doxycycline.

Carbamazepine: accelerated metabolism of doxycycline (reduced effect).

* **Ciclosporin**: possibly increased plasma ciclosporin concentration.

Ferrous salts: absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts.

Methotrexate: increased risk of methotrexate toxicity.

Phenobarbital: metabolism of doxycycline accelerated (reduced plasma concentration).

Phenytoin: increased metabolism of doxycycline (reduced plasma concentration).

Rifampicin: plasma doxycycline concentration possibly reduced.

* **Warfarin**: anticoagulant effect possibly enhanced.

Notes: PATIENT ADVICE Capsules should be swallowed whole with plenty of fluid while sitting or standing to prevent oesophageal irritation. May be given with food or milk, to counter gastric irritation.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Centers for Disease Control and Prevention. *CDC health information for international travel 2010.* Atlanta, U.S. Department of Health and Human Services, Public Health Service, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Mefloquine

ATC code: P01BC02

Tablet: 250 mg (as hydrochloride)

Special Notes: WHO age/weight restriction: > 5 kg or > 3 months.

Indications: Prophylaxis of malaria for travellers to areas with high risk of multiple resistant *P. falciparum*.

Contraindications: History of neuropsychiatric disorders including depression or convulsions; hypersensitivity to quinine.

Precautions: Avoid use in cardiac conduction disorders and in epilepsy.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Prophylaxis of malaria for travellers to areas with high risk of multiple resistant *P. falciparum*.
Oral:
Child *over 3 months or 5 kg* 5 mg/kg (maximum 250 mg) once a week; prophylaxis should start 1–3 weeks before departure and continue for 4 weeks after last exposure. Round dose to the nearest quarter of a tablet.

Renal impairment: Use with caution in severe renal impairment, otherwise dose reduction not needed.

Hepatic impairment: Mefloquine is metabolized by the liver and eliminated by the biliary system. It should be used with caution in patients with disorders of the biliary system who may not be able to clear the drug.

Avoid use for prophylaxis in severe liver disease.

Adverse effects: Common Nausea, vomiting, diarrhoea, abdominal pain, anorexia, headache, dizziness (can be severe), loss of balance, somnolence, insomnia and abnormal dreams.

Uncommon Circulatory disorders, tachycardia, bradycardia, cardiac conduction disorders, muscle weakness, myalgia, arthralgia, rash, urticaria, pruritus, alopecia, disturbances in liver function tests, visual disturbances, tinnitus, vestibular disorders, seizures.

Neuropsychiatric disorders occur in at least 1:10 000 patients treated with mefloquine and the incidence is thought to be up to 1:1000 when used at treatment doses. These include sensory and motor neuropathies, tremor, ataxia, anxiety, depression, suicidal ideation, confusion, hallucinations, panic attacks, emotional instability, aggression, agitation and psychoses.

Rare Hyperpyrexia, leukopenia, leukocytosis, thrombocytopenia, Stevens-Johnson syndrome, atrioventricular block and encephalopathy.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

  Atenolol: increased risk of bradycardia.

* **Carbamazepine**: antagonism of anticonvulsant effect.

* **Chloroquine**: increased risk of convulsions.

  Digoxin: possibly increased risk of bradycardia.

* **Ethosuximide**: antagonism of anticonvulsant effect.

  Phenytoin: antagonism of anticonvulsant effect.

  Propranolol: increased risk of bradycardia.

* **Quinidine**: increased risk of ventricular arrhythmias.

* **Quinine**: increased risk of convulsions, but should not prevent the use of intravenous quinine in severe cases.
* **Valproic acid**: antagonism of anticonvulsant effect.

Notes: PATIENT ADVICE Warn travellers about the importance of avoiding mosquito bites, importance of taking prophylaxis regularly, and importance of an immediate visit to doctor if ill within 1 year and especially within 3 months of potential exposure.

Patients should be informed about adverse effects associated with mefloquine and if they occur, advised to seek medical advice on alternative antimalarials.

Mefloquine tablets may be crushed and mixed with food such as jam or honey just before administration.

1 tablet = 228 mg base (250 mg salt).

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Proguanil

ATC code: P01BB01

Tablet: 100 mg (hydrochloride)

Indications: Prophylaxis of malaria in areas of low resistance in combination with chloroquine.

Dose:

Prophylaxis of malaria in areas of low resistance in combination with chloroquine.
Oral:
Child *under 1 year* 25 mg daily;
1–4 years 50 mg daily;
5–8 years 100 mg daily;
9–12 years 150 mg daily.
Start taking 1–2 days before entering and continue for 4 weeks after leaving an endemic area.

Renal impairment: Mild: half dose.

Moderate: quarter dose every 48 hours.

Severe: quarter dose once weekly.

Hepatic impairment: Metabolized by the liver to the active metabolite so unlikely to be effective in patients with severe liver impairment.

Adverse effects: Common Mild gastric intolerance, diarrhoea, constipation, nausea, vomiting, stomatitis.

Infrequent Mouth ulcers, vertigo, reversible alopecia, skin reactions.

Rare Megaloblastic anaemia and pancytopenia (more likely with renal impairment), cholestasis, vasculitis, hepatitis, seizures, psychosis, hypersensitivity reactions such as urticaria and angioedema.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

  Pyrimethamine: increased antifolate effect.

  Warfarin: isolated reports of enhanced anticoagulant effect.

Notes: PATIENT ADVICE Warn travellers about the 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.

Approximately 3% of Caucasians cannot metabolize proguanil to cycloguanil, the active metabolite, and these people are effectively only receiving the chloroquine component of their therapy. These patients also have an increased risk of adverse effects, especially GI side effects.

Tablets may be crushed and mixed with food such as milk, jam or honey just before administration.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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6.5.4 Antipneumocystosis and antitoxoplasmosis medicines

Pneumocystosis

Pneumocystis jiroveci (Pneumocystis carinii) is classified as a protozoan which in otherwise healthy people rarely produces signs of infection. However, it is a frequent cause of opportunistic infection in immunosuppressed, debilitated or malnourished patients. *P. jiroveci (P. carinii)* is a common cause of pneumonia in people with AIDS, and the most frequent immediate cause of death in these patients.

Sulfamethoxazole + trimethoprim (co-trimoxazole) is the treatment of choice for *P. jiroveci (P. carinii)* pneumonia; it is also used for prophylaxis in HIV-infected, HIV-exposed and other immunocompromised children. Refer to the WHO guidelines *Co-trimoxazole prophylaxis for HIV-exposed and HIV-infected infants and children* (available from https://www.who.int/hiv/pub/paediatric/en/).

Toxoplasmosis

Toxoplasmosis is caused by infection with the protozoan parasite, *Toxoplasma gondii*. Most infections are self-limiting and do not require treatment. However, in immunodeficiency, primary infection may result in encephalitis, myocarditis or pneumonitis. Impairment of immunity (e.g. in people with AIDS) in a previously infected person may cause reactivation, resulting in encephalitis or meningoencephalitis.

The treatment of choice for toxoplasmosis is a combination of **pyrimethamine** and **sulfadiazine**; a **folate** supplement is also given to counteract the inhibition of folate synthesis associated with these drugs.

Pyrimethamine

ATC code: P01BD01

Tablet: 25 mg

Indications: Treatment and prophylaxis of toxoplasmosis; prophylaxis of *Pneumocystis jiroveci (Pneumocystis carinii)* pneumonia.

Local antimicrobial sensitivity patterns need to be taken into account. Expert advice essential.

Contraindications: Megaloblastic anaemia.

Precautions: Folate deficiency; blood counts required with prolonged treatment; supplement folate throughout treatment to prevent haematological toxicity; history of seizures (avoid large loading doses); renal impairment; hepatic impairment.

Dose:

NOTE Calcium folinate must always be administered with pyrimethamine to prevent haematological toxicity. Due to the long half-life of pyrimethamine, calcium folinate administration should be continued for 1 week after pyrimethamine has been discontinued.

Treatment of congenital toxoplasmosis (in combination with sulfadiazine and calcium folinate).

Oral:

Neonate 1 mg/kg twice daily for 2 days, then 1 mg/kg once daily for 6 months, then 1 mg/kg three times weekly for a further 6 months. Duration of treatment depends on whether the neonate has overt disease. If without overt disease but born to mother infected during pregnancy, treat for 4 weeks, followed by further courses if infection confirmed.

Treatment of toxoplasmosis (in combination with sulfadiazine and calcium folinate).

Oral:

Child *over 1 month* 1 mg/kg (maximum 25 mg/dose) twice daily for 3 days, then 1 mg/kg (maximum 25 mg) once daily for at least 6 weeks.

Primary prophylaxis of toxoplasmosis (in combination with dapsone (not on EMLc for this indication) and calcium folinate).

Oral:

Child *over 1 month* 1 mg/kg once daily. Maximum 25 mg daily.

Secondary prophylaxis of toxoplasmosis in addition to prophylaxis of *Pneumocystis jiroveci (Pneumocystis carinii)* pneumonia (in combination with sulfadiazine and calcium folinate).

Oral:

Infant or **Child** 1 mg/kg once daily. Maximum 50 mg daily.

NOTE Clindamycin (not on the EMLc for this indication) may be used instead of sulfadiazine in patients intolerant of sulfonamides.

Renal impairment: Use with caution. Dosage adjustment not considered to be necessary in renal impairment.

Hepatic impairment: Use with caution in patients with hepatic impairment.

Adverse effects: Depression of haematopoiesis (with high doses), megaloblastic anaemia, rashes, insomnia, gastrointestinal disturbances.

Interactions with other medicines (* indicates severe):

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises avoid concomitant use.
* **Methotrexate**: antifolate effect of methotrexate increased.
* **Phenytoin**: antagonism of anticonvulsant effect; increased antifolate effect.

  Proguanil: increased antifolate effect.
* **Silver sulfadiazine**: increased antifolate effect.
* **Sulfadiazine**: increased antifolate effect.
* **Sulfamethoxazole + trimethoprim**: increased antifolate effect.
* **Trimethoprim**: increased antifolate effect.

  Zidovudine: increased antifolate effect.

Notes: Pyrimethamine-associated reversible bone marrow suppression warrants that a complete blood count be performed at least weekly while the patient is on daily pyrimethamine and at least monthly while on less than daily dosing. It is also important that calcium folinate be always administered with pyrimethamine and increased doses of calcium folinate may be necessary if marrow suppression occurs.

Administer pyrimethamine with food to minimize vomiting.

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Sulfadiazine

ATC code: J01EC02

Tablet: 500 mg

Indications: Toxoplasmosis in combination with pyrimethamine; prophylaxis of *Pneumocystis jiroveci (Pneumocystis carinii)* pneumonia in combination with pyrimethamine.

Local antimicrobial sensitivity patterns need to be taken into account. Expert advice essential.

Contraindications: Hypersensitivity to any sulfa drug; porphyria.

Precautions: Renal impairment; hepatic impairment; G6PD deficiency; urinary obstruction; blood dyscrasia.

Dose:

Treatment of congenital toxoplasmosis (in combination with pyrimethamine and calcium folinate).
Oral:
Neonate 50 mg/kg twice daily for 12 months.

Treatment of toxoplasmosis (in combination with pyrimethamine and calcium folinate).
Oral:
Child *all ages* 25–50 mg/kg (maximum 1–1.5 g per dose) four times daily, followed by secondary prophylaxis therapy.

Secondary prophylaxis of toxoplasmosis in addition to prophylaxis of *Pneumocystis jiroveci (Pneumocystis carinii)* pneumonia (in combination with pyrimethamine and calcium folinate).
Oral:
Child *all ages* 85–120 mg/kg daily in 2–4 divided doses.

NOTE Clindamycin (not on the EMLc for this indication) may be used instead of sulfadiazine in patients intolerant of sulfonamides.

Renal impairment: Use with caution in renal impairment.

Severe renal impairment: avoid; high risk of crystalluria.

Hepatic impairment: Use with caution.

Adverse effects: Common Nausea.

Uncommon Vomiting, rash, abdominal pain.

Rare Hepatitis, pancreatitis, Stevens-Johnson syndrome, crystalluria, blood dyscrasias.

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: plasma ciclosporin concentration possibly reduced; increased risk of nephrotoxicity.

Methotrexate: risk of methotrexate toxicity increased.

Phenytoin: plasma phenytoin concentration possibly increased.

* **Pyrimethamine**: increased antifolate effect.

* **Sulfadoxine + pyrimethamine**: increased antifolate effect.

Thiopental: enhanced effects of thiopental.

* **Warfarin**: enhanced anticoagulant effect.

References:
American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Sulfamethoxazole + Trimethoprim

ATC code: J01EE01

Injection: 80 mg + 16 mg/ml in 5 ml ampoule; 80 mg + 16 mg/ml in 10 ml ampoule

Oral liquid: 40 mg + 8 mg/ml

Tablet: 100 mg + 20 mg; 400 mg + 80 mg

Special Notes: Also referred to as co-trimoxazole.

Indications: Treatment and prophylaxis of *Pneumocystis jiroveci (Pneumocystis carinii)* pneumonia.

Local antimicrobial patterns need to be taken into account.

Contraindications: Hypersensitivity to sulfonamides or trimethoprim; porphyria; megaloblastic anaemia; severe renal impairment; severe hepatic impairment.

Precautions: Mild to moderate renal impairment; maintain adequate fluid intake (to avoid crystalluria); avoid in blood disorders (unless under specialist supervision); monitor blood counts on prolonged treatment; discontinue immediately if blood disorder develops; rash (discontinue immediately); predisposition to folate deficiency; asthma; G6PD deficiency; jaundiced neonates.

Dose:

Doses are expressed in terms of the trimethoprim component.

Treatment of *P. jiroveci (P. carinii)* infections.
Oral or *IV:*
Infant or **Child** ***over 1 month*** 10 mg/kg every 12 hours for 14–21 days. Total daily dose may alternatively be given in 3–4 divided doses. The IV route is preferred.

Prophylaxis for *P. jiroveci (P. carinii)* infections.
Oral:
Infant or **Child** ***under 6 months*** 20 mg once daily;
6 months–5 years 40 mg once daily;
6–12 years 80 mg once daily.

Renal impairment: Severe impairment: avoid use.

Moderate impairment: use half normal dose.

Plasma monitoring may be required with high doses in renal impairment; seek expert advice.

Hepatic impairment: Severe impairment: avoid use.

Adverse effects: Some adverse effects may be hypersensitivity reactions (see below).

Incidence of some adverse effects (rash, fever, nausea, neutropenia, thrombocytopenia, raised hepatic aminotransferases) is substantially higher in patients with AIDS.

Common Fever, nausea, vomiting, diarrhoea, anorexia, rash, itch, stomatitis, hyperkalaemia, thrombocytopenia, photosensitivity.

Uncommon Headache, drowsiness, blood disorders (including neutropenia, leukopenia, thrombocytopenia, eosinophilia, megaloblastic anaemia, methaemoglobinaemia).

Rare Erythema, vasculitis, hyponatraemia, hypoglycaemia, pancreatitis, hepatitis, jaundice, hepatic necrosis, crystalluria, urinary obstruction with anuria/oliguria, lowered mental acuity, depression, tremor, ataxia (after IV use in HIV patients), antibiotic-associated colitis, *Clostridium difficile*-associated disease, aseptic meningitis.

HYPERSENSITIVITY May present with fever, dyspnoea, cough, rash, eosinophilia; the most serious effects include anaphylaxis, Stevens-Johnson syndrome, toxic epidermal necrolysis, serum sickness-like syndrome, lupus-like syndrome, pneumonitis, hepatitis, interstitial nephritis, systemic vasculitis and pancytopenia.

Interactions with other medicines (* indicates severe):

Trimethoprim is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g. pyrimethamine.

Trimethoprim can cause hyperkalaemia; administration with potassium supplements or other drugs which also cause potassium retention can further increase potassium concentration.

Trimethoprim with sulfamethoxazole can cause nephrotoxicity; giving with other nephrotoxic drugs may cause additional renal adverse effects.

* **Azathioprine**: increased risk of haematological toxicity.
* **Ciclosporin**: increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim.
* **Dapsone**: plasma concentration of both dapsone and trimethoprim may increase with concomitant use.

Digoxin: plasma concentration of digoxin possibly increased.

Lamivudine: plasma concentration of lamivudine increased (avoid concomitant use of high-dose sulfamethoxazole + trimethoprim).

* **Mercaptopurine**: increased risk of haematological toxicity.
* **Methotrexate**: antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased.
* **Phenytoin**: antifolate effect and plasma phenytoin concentration increased.

Procainamide: increased plasma procainamide concentration.

* **Pyrimethamine**: increased antifolate effect.
* **Sulfadoxine + pyrimethamine**: increased antifolate effect.

Thiopental: enhanced effects of thiopental.

* **Warfarin**: enhanced anticoagulant effect.

Notes: Oral dose is best given with or after food.

Attention should be paid to the folate status of the patient should treatment be prolonged or high dose.

DILUTION AND ADMINISTRATION For intermittent intravenous infusion may be further diluted in glucose 5% and 10% or sodium chloride 0.9% or Ringer's intravenous solution. Must be further diluted; dilute each 5 ml of injection solution to 125 ml. Infuse over 60–90 minutes (but may be adjusted according to fluid requirements). If fluid restriction necessary, 5 ml may be diluted with 75 ml of glucose 5% and the required dose infused over a maximum of 60 minutes. Check container for haze or precipitant during administration. In severe fluid restriction may be given undiluted via a central venous line.

References:

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6.5.5 Antitrypanosomal medicines

6.5.5.1 African trypanosomiasis

African trypanosomiasis, or sleeping sickness, is a protozoan infection which is transmitted by *Glossina* spp. (tsetse flies). Two subspecies of *Trypanosoma brucei* (*T. brucei gambiense* and *T. brucei rhodesiense)* produce distinctive clinical forms of the disease. *T. brucei gambiense* infection constitutes 95% of all human African trypanosomiasis cases. The early stage of African trypanosomiasis results from infection of the blood stream and lymph nodes. The second meningoencephalitic stage results from infection of the central nervous system. Signs of the later stage develop within a few weeks in *T. brucei rhodesiense* infection but only after several months or years in *T. brucei gambiense* infection.

First-stage disease

Treatment of early-stage infections of *T. brucei rhodesiense* with **suramin sodium** and *T. brucei gambiense* with **pentamidine** can be curative if started before the central nervous system has become involved.

Second-stage disease

Eflornithine and **melarsoprol** are used for the treatment of second-stage (neurological) trypanosomal infections, since both medications reach therapeutic levels in the central nervous system.

Following treatment of African trypanosomiasis, patients should be followed up at 6-monthly intervals for 24 months. Monitoring of leukocytes, total protein content and trypanosome presence in cerebrospinal fluid is recommended in order to evaluate treatment efficacy.

Eflornithine

ATC code: P01CX03

Injection: 200 mg (hydrochloride)/ml in 100 ml bottle

Iatrogenic mortality from 0.7–2%.

Reactions requiring immediate corrective measures and withdrawal of treatment include severe anaemia (8 g/dl), leukopenia (< 1000 cells/mm^3), thrombocytopenia (< 20 000 cells/mm^3).

Eflornithine is a toxic drug. Adverse effects occur frequently during its use, and are sometimes fatal. Eflornithine should therefore be used only for approved indications where close observation can be maintained.

Special Notes: Also referred to as (alpha)-difluoromethylornithine and DFMO.

Medicine for the treatment of second-stage African trypanosomiasis.

Indications: Treatment of second-stage *Trypanosoma brucei gambiense* infection.

Contraindications: Ineffective in the treatment of *Trypanosoma brucei rhodesiense* human African trypanosomiasis.

Precautions: Hospitalization and close supervision throughout treatment; renal impairment; monitor complete blood and platelet counts for bone marrow suppression (severe anaemia, leukopenia or thrombocytopenia requires an interruption in treatment until there is evidence of bone marrow recovery); concurrent bacterial infections.

Dose:

Treatment of second-stage *Trypanosoma brucei gambiense* infection.
Slow IV infusion:
Child *under 35 kg* 150 mg/kg over 2 hours every 6 hours for 14 days;
over 35 kg 100 mg/kg over 2 hours every 6 hours for 14 days.

NOTE These doses are based on clinical experience and limited evidence.

Renal impairment: Dosage adjustment may be required in all degrees of renal impairment. Eflornithine is 80% renally excreted.

Adverse effects: Common Diarrhoea, nausea, vomiting, abdominal pain, tremor, dizziness, confusion, seizures, injection site reaction, anaemia, leukopenia, thrombocytopenia.

Uncommon Anorexia, headache, oedema, bacterial infection at the catheter site with risk of phlebitis, cellulitis, pyomyositis and generalized sepsis, death.

Rare Alopecia, pruritus, muscle pain, eosinophilia, impaired hearing (usually with longer courses used for cancer treatment).

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concurrent use.

Notes: Eflornithine hydrochloride concentrate for injection is hypertonic and must be diluted with sterile water for injection before infusion.

After dilution with sterile water for injection, eflornithine must be used within 24 hours. Bags containing diluted eflornithine should be stored at 4 °C (39 °F) to minimize the risk of microbial proliferation.

Strict aseptic technique should be used when administering, with frequent replacement of IV cannulas (at least every 2 days).

Monitoring should continue for up to 4 weeks after finishing treatment.

Eflornithine in combination with nifurtimox has been recently introduced to reduce duration and workload of eflornithine monotherapy and may delay the appearance of drug resistance. Currently, there is a multicentre trial being conducted which includes assessing the safety and efficacy in children at the same dose as adults.

References:

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Melarsoprol

ATC code: P01CD01

Injection: 36 mg/ml (3.6%) solution, 5 ml ampoule (180 mg of active compound)

Melarsoprol is very toxic with a 3–10% lethality. It should therefore be used only for the approved indications where close observation can be maintained and it can be administered by experienced personnel. Melarsoprol is strictly for intravenous use only.

Special Notes: Also referred to as Mel B or Melarsen Oxide-BAL.

Treatment of second-stage African trypanosomiasis.

Indications: Treatment of second-stage *Trypanosoma brucei rhodesiense* or *Trypanosoma brucei gambiense* infection.

Contraindications: Ingestion of alcohol during treatment.

Precautions: Hospitalization and close medical supervision required throughout treatment; reactive encephalopathy (immediate treatment suspension essential); treat intercurrent infections such as pneumonia and malaria before melarsoprol administration; malnutrition (if possible, correct with protein-rich diet); G6PD deficiency; leprosy (may precipitate erythema nodosum); fever; avoid use during influenza epidemics (increased risk of reactive encephalopathy in febrile patients); avoid extravasation.

Dose:

Treatment of second-stage *Trypanosoma brucei rhodesiense* infection.
Slow IV infusion:
Child *all ages* dose gradually increased from 1.2 mg/kg to maximum of 3.6 mg/kg daily in courses of 3–4 days with intervals of 7–10 days between courses.

Treatment of second-stage *Trypanosoma brucei gambiense* infection.
Slow IV infusion:
Child *all ages* 2.2 mg/kg daily for 10 days.

NOTE Prednisolone 1 mg/kg once daily should be administered concurrently to all patients for the duration of melarsoprol therapy.

Adverse effects: Common Fatal reactive encephalopathy (see below), peripheral neuropathy, Jarisch-Herxheimer reaction (fever and chills may also occur, resulting from trypanosome destruction), headache, diarrhoea, vomiting, arthralgia, fever, skin reactions, thrombophlebitis.

Reactive encephalopathy appears to be more frequent in children.

Uncommon Myocardial damage, albuminuria, hypertension, hyperthermia, urticaria.

Rare Agranulocytosis, aplastic anaemia, thrombocytopenia, hypersensitivity reactions (especially on second or subsequent doses), haemorrhagic encephalopathy, exfoliative dermatitis.

FATAL REACTIVE ENCEPHALOPATHY Also known as "arsenical encephalopathy", is characterized by fever, headache, tremor, slurred speech, seizures and ultimately coma (occurs in 3–10% of patients treated with melarsoprol, and is fatal in approximately 50% of those who experience it).

Interactions with other medicines (* indicates severe):

Alcohol: combination contraindicated as increases toxicity of melarsoprol.

Notes: Relapse has been reported in up to 20–30% of late-stage trypanosomiasis patients after treatment with melarsoprol. This appears related to resistance, although reinfection or inadequate CSF concentrations of the drug may be responsible in some cases. Re-treatment with melarsoprol in these patients has not been consistently effective and is not recommended. Eflornithine therapy should be considered.

Patients should remain supine and fasting for at least 2 hours after injection to reduce gastrointestinal side-effects.

ADMINISTRATION Melarsoprol should be administered by slow intravenous injection as a 3.6% solution in propylene glycol. Because melarsoprol injection is intensely irritating due to its propylene glycol content, care should be taken to avoid leakage into the surrounding tissues. Extravasation during intravenous administration may result in extreme local tissue damage and destruction.

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Pentamidine

ATC code: P01CX01

Powder for injection: 300 mg (pentamidine isetionate) in vial

Pentamidine isetionate is toxic and personnel should be adequately protected during handling and administration; consult product literature.

Severe, sometimes fatal, hypotension, hypoglycaemia, pancreatitis and cardiac arrhythmias have been reported. Other life-threatening reactions requiring immediate corrective measures and withdrawal of treatment have included leukopenia (< 1000 cells/mm^3), thrombocytopenia (< 20 000 cells/mm^3), acute renal failure, hypocalcaemia and ventricular tachycardia.

Fatalities have been documented following pentamidine administration. The ratio of therapeutic to toxic dose of pentamidine is very low and adverse effects, some of which may be life threatening, occur frequently during its use. Pentamidine should, therefore, be used only for the approved indications where close observation can be maintained.

Special Notes: Medicine for the treatment of first-stage African trypanosomiasis.

The WHO Model List of Essential Medicines for Children 2009 has the 200 mg vial listed. This strength is no longer in production and a 300 mg vial is available.

Indications: Treatment of first-stage *Trypanosoma brucei gambiense* infection.

Precautions: Cerebrospinal fluid examination before treatment (pentamidine not likely to be effective if leukocyte count greater than 5–10 cells/mm^3, or trypanosomes detected in cerebrospinal fluid); risk of severe hypotension following administration; hypotension or hypertension; hepatic impairment; hypoglycaemia or hyperglycaemia; leukopenia; thrombocytopenia; anaemia; immunodeficiency (if acute deterioration in bone marrow, renal or pancreatic function, interrupt or discontinue treatment); renal impairment.

Dose:

Treatment of first-stage *T. brucei gambiense* infection.
IM:
Infant or **Child** 4 mg/kg daily for 7 days.

Renal impairment: Severe impairment: reduce dose interval (e.g. every alternate day).

Hepatic impairment: Use with caution.

Adverse effects: Common Pain at injection site.

Rare Diarrhoea, nausea, nephrotoxicity, acute hypotension, hypoglycaemia (may be followed by hyperglycaemia and type I diabetes mellitus), pancreatitis; also hypocalcaemia, gastrointestinal disturbances, confusion, hallucinations, arrhythmias, thrombocytopenia, leukopenia, abnormal liver function tests, anaemia, hyperkalaemia, rash, Stevens-Johnson syndrome; pain, local induration, sterile abscess and muscle necrosis at injection site.

Interactions with other medicines (* indicates severe):

Amphotericin B: possibly increased risk of nephrotoxicity.

Artemether: increased level and toxicity of pentamidine. Avoid concomitant use.

Quinine: increased level and toxicity of pentamidine and quinine. Avoid concomitant use.

Typhoid vaccine: pentamidine may decrease the effect of typhoid vaccine.

Notes: A cerebrospinal fluid examination before treatment is required as pentamidine is not effective if trypanosomes are detected in the cerebrospinal fluid or the leukocyte count is above 5–10 cells/mm^3.

Before administration, establish baseline blood pressure and administer with patient lying down; they should remain lying for 1–2 hours after administration.

Monitor blood pressure and cardiac rhythm during administration and treatment period.

Hypoglycaemia post-administration is easily prevented by administering oral sugar, in tea or similar, half an hour before administration.

Periodic ECG is desirable.

Extreme care should be taken to ensure aseptic technique when administering to avoid the risk of abscess or necrosis at the injection site.

RECONSTITUTION AND ADMINISTRATION Reconstitute vial with water for injection to a final concentration of 100 mg/ml. Administer by deep intramuscular injection and preferably into the buttock. Pentamidine isetionate is toxic; care is required to protect personnel during handling and administration.

References:

Doua F. The efficacy of pentamidine in the treatment of early-late stage *Trypanosoma brucei gambiense* trypanosomiasis. *American Journal of Tropical Medicine and Hygiene,* 1996, 55(6):586–588.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

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Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

WHO expert committee on the control and surveillance of African trypanosomiasis. Control and surveillance of African trypanosomiasis. *WHO Technical Report Series*, 1998, 881:1–114.

Suramin sodium

ATC code: P01CX02

Powder for injection: 1 g in vial

A potentially fatal immediate hypersensitivity reaction is estimated to occur in 1 per 20 000 patients; a test dose is recommended before starting treatment. Suramin sodium should only be administered by experienced staff.

Special Notes: Medicine for the treatment of first-stage African trypanosomiasis.

Indications: Treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Contraindications: Previous anaphylaxis or suramin sensitivity; severe liver impairment; severe renal impairment.

Precautions: Debilitated or malnourished patients; albuminuria; onchocerciasis.

Dose:

Treatment of the initial phase of *Trypanosoma brucei rhodesiense* infection.

Slow IV injection:

Child *all ages* 5 mg/kg on day 1 (as a test dose) followed by 20 mg/kg on day 3, 10, 17, 24 and 31.

FIRST (TEST) DOSE Administer first dose with particular caution; wait at least 1 minute after injecting the first few microlitres; inject next 0.5 ml over 30 seconds and wait 1 minute; inject the remainder over several minutes.

Renal impairment: Mild to moderate impairment: use with caution.

Severe impairment: avoid use.

Suramin is excreted renally at a slow rate due to extensive protein binding. Drug can be excreted in the urine unchanged for 3 months following doses of suramin.

Hepatic impairment: Severe impairment: avoid use. Administration of suramin in individuals with significant hepatic dysfunction, in whom serum albumin levels may be reduced, may result in toxic serum suramin levels due to an increased free fraction of the drug in the plasma.

Adverse effects: Common Fever, rash, vomiting, nausea and metallic taste, thrombocytopenia, peripheral neuropathy, transient hyperbilirubinaemia, mild proteinuria.

Rare Immediate and potentially fatal allergic reaction with nausea, vomiting, shock and loss of consciousness during first dose (see First (test) dose), albuminuria, abdominal pain, severe diarrhoea, stomal ulceration, exfoliative dermatitis, tiredness, anorexia, malaise, polyuria, thirst, raised liver enzyme values, paraesthesia and hyperaesthesia of palms and soles.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concurrent use.

Notes: Suramin is only effective in the early stages of the illness, in which no CNS involvement has occurred. Suramin crosses the blood-brain barrier poorly, and in later stages where the organism has penetrated the CNS, other agents must be used.

Cerebrospinal fluid examination should be conducted before treatment.

Administer only under close medical supervision in hospital and with general condition improved as far as possible before treatments.

Poor nutritional status increases frequency of adverse reactions, so correct with a protein-rich diet and maintain satisfactory food and fluid intake during treatment.

Conduct urine tests before treatment and weekly during treatment; reduce dose if moderate albuminuria, discontinue immediately if severe albuminuria or casts in urine.

RECONSTITUTION OF INJECTION Reconstitute in water for injections to produce a final concentration of 10%. The compound deteriorates quickly in air and so should be injected immediately after preparation.

References:
Abramowicz M. Drugs for parasitic infections. In: Abramowicz M, ed. *The Medical Letter on Drugs and Therapeutics.* New Rochelle, The Medical Letter, 2000:1–12.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Human African trypanosomiasis. Geneva, World Health Organization, 2010 (http://www.who.int/trypanosomiasis_african/drugs/en/index.html, accessed 10 February 2010).
Odero RO. African trypanosomiasis (sleeping sickness). *eMedicine.* New York, WebMD, 2009 (http://emedicine.medscape.com/article/228613-overview, accessed 10 February 2010).
Porter RS, ed. *Merck Manual Online.* Whitehouse Station, Merck Research Laboratories, ©2006–2008 (http://www.merck.com/mmpe/index.html, accessed 10 February 2010).
WHO expert committee on the control and surveillance of African trypanosomiasis. Control and surveillance of African trypanosomiasis. *WHO Technical Report Series*, 1998, 881:1–114.

6.5.5.2 American trypanosomiasis

Chagas disease is a disease caused by the parasite *T. cruzi*. It is transmitted to humans by insect vectors that are found only in the Americas (mainly in rural areas of Latin America where poverty is widespread).

Chagas disease has an acute and a chronic phase. If Chagas disease is not treated, infection is lifelong.

The acute illness (which occurs immediately after inoculation and lasts weeks to months) may be mild or asymptomatic. Symptoms include fever or swelling at the inoculation site.

After this, most people enter a chronic phase, during which most people are asymptomatic. Approximately 30% will develop serious complications including cardiac and gastrointestinal manifestations of the disease. In people with immunosuppresssion (e.g. HIV/AIDS), Chagas disease can reactivate and potentially cause severe disease.

Benznidazole

ATC code: P01CA02

Tablet: 100 mg

Indications: Treatment of Chagas disease (American trypanosomiasis).

Contraindications: Pregnancy.

Precautions: Hepatic impairment; renal impairment; haematological conditions; history of neurological clinical manifestations; allergic condition to imidazoles; monitor blood count, especially leukocytes, throughout treatment.

Dose:

Treatment of congenital acute phase or early chronic phase of Chagas disease (American trypanosomiasis).
Full-term neonate initially 5 mg/kg daily, increasing after 3 days to 10 mg/kg daily, if no leucopenia or thrombocytopenia. Dose must be given in 2–3 divided doses for 60 days.

Treatment of acute phase or early chronic phase of Chagas disease (American trypanosomiasis).
Oral:
Infant or **Child** ***under 40 kg*** 7.5 mg/kg daily in 2–3 divided doses for 60 days;
40 kg and over 5 mg/kg daily in 2–3 divided doses for 60 days.

NOTE Acute meningoencephalitis may require a dose of up to 25 mg/kg daily.

Treatment of chronic phase of Chagas disease (American trypanosomiasis).
Oral:
Infant or **Child** 5 mg/kg daily in 2–3 divided doses for 60 days.

NOTE The treating physician should determine the age limits and clinical suitability of this specific therapy.

Renal impairment: Avoid use in renal failure (limited data available).

Hepatic impairment: Avoid use in hepatic failure (limited data available).

Adverse effects: Common Rashes (discontinue treatment if severe and accompanied by fever and purpura), nausea, vomiting and abdominal pain, peripheral neuropathy.

Uncommon Paraesthesia, peripheral neuritis, leukopenia, arthralgia, myalgia.

Rare Agranulocytosis, bone marrow depression, headache, dizziness, fatigue.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kirchhoff LV. Chagas disease (American trypanosomiasis): treatment & medication. *eMedicine.* New York, WebMD, 2009 (http://emedicine.medscape.com/article/214581-treatment, accessed 10 February 2010).
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
WHO expert committee on the control of Chagas disease. Control of Chagas disease: second report of the WHO expert committee. *WHO Technical Report Series,* 2002, 905 (http://whqlibdoc.who.int/trs/WHO_TRS_905.pdf).

Nifurtimox

ATC code: P01CC01

Tablet: 30 mg; 120 mg; 250 mg

Special Notes: Not all tablet strengths listed may be commercially available.

Indications: Treatment of Chagas disease (American trypanosomiasis).

Contraindications: Pregnancy; porphyria; hypersensitivity to hydantoin; allergic afflictions (particularly those involving skin manifestations).

Precautions: Close medical supervision required in patients with history of cerebral damage or predisposition to seizures, psychosis or serious behavioural alterations; co-administer aluminium hydroxide to reduce gastrointestinal irritation; renal impairment; hepatic impairment.

Dose:

Treatment of acute phase or early chronic phase of Chagas disease (American trypanosomiasis).

Oral:

Neonate, Infant or **Child *under 40 kg*** 15–20 mg/kg daily in three divided doses for 60 days. Administer every 8 hours after meals.

Child *40 kg or over* 12.5–15 mg/kg daily in three divided doses for 60 days. Administer every 8 hours after meals.

Treatment of chronic phase of Chagas disease (American trypanosomiasis).

Oral:

Infant or **Child** 8–10 mg/kg daily in three divided doses for 60 days. Administer every 8 hours after meals.

NOTE The treating physician should determine the age limits and clinical suitability of this specific therapy.

Renal impairment: Mild and moderate impairment: dosage adjustment may be required due to increased serum levels and toxicity of nifurtimox.

Severe impairment/failure: avoid use (limited data available).

Hepatic impairment: Hepatic function impairment may increase blood concentrations of this medication, increasing the risk of side-effects.

Adverse effects: Common Rash, anorexia, loss of weight, nausea, vomiting, gastric pain, headache, vertigo.

Uncommon Memory loss, sleep disturbances, excitability, myalgia, arthralgia, peripheral neuritis (may require discontinuation).

Rare Tremors, seizures, psychotic reactions, suicidality.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Nifurtimox is best taken with or after meals to minimize gastrointestinal irritation.

Tablets should be taken three times daily, preferably in the morning, at noon and at night, after meals.

Infants may take it crushed and mixed with a small amount of food. In this case it is convenient to give the medication before the full meal.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Kirchhoff LV. Chagas disease (American trypanosomiasis): treatment & medication. *eMedicine.* New York, WebMD, 2009 (http://emedicine.medscape.com/article/214581-treatment, accessed 10 February 2010).

Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

Lampit Product Information. Bayer, 1995 (http://www.drugs.com/mmx/lampit.html, accessed 10 February 2010).

WHO expert committee on the control of Chagas disease. Control of Chagas disease: second report of the WHO expert committee. *WHO Technical Report Series,* 2002, 905 (http://whqlibdoc.who.int/trs/WHO_TRS_905.pdf).

SECTION 7:
Antimigraine medicines

7 Antimigraine medicines

Migraine is the most common identifiable cause of recurrent or chronic headache in childhood. Prior to diagnosing migraine in a child, alternative causes of headache including raised intracranial pressure (e.g. due to a space-occupying lesion or meningitis) or systemic illness must also be considered. A careful history, examination and follow-up help guide the correct diagnosis.

In children, the presentation of migraine is influenced by the age of the child, but is characterized by periodic episodes of paroxysmal headache often accompanied by pallor, nausea, vomiting and relief with sleep. Migraines with aura or prolonged neurological symptoms are uncommon in young children. In adolescents, the presentation of migraine is often similar to that of adults.

The following features are suggestive of an alternative diagnosis or possible intracranial pathology warranting further investigation or referral:

- recurrent early morning headaches
- headaches that are prolonged and incapacitating
- progressive change in personality or behaviour
- abnormal neurological examination findings
- failure to respond to usual treatment measures.

Treatment of migraine in children consists of three components: general measures, acute measures, and, in some cases, preventive treatment. General measures include appropriate reassurance and avoidance of any identified trigger factors.

7.1 For treatment of acute attack

For treatment of an acute attack early use of simple analgesics are often effective.

Ibuprofen

ATC code: M01AE01

Tablet: 200 mg; 400 mg

Special Notes: WHO age/weight restriction: > 3 months.

Indications: Acute migraine attack.

Contraindications: Hypersensitivity (including asthma, angioedema, urticaria or rhinitis) to acetylsalicylic acid or any other NSAIM; active peptic ulceration or upper gastrointestinal bleeding; severe renal failure, hepatic failure or cardiac failure.

Precautions: Asthma; cardiac disease; volume depletion, such as in gastroenteritis or dehydration (increased risk of renal impairment); concomitant use of drugs that increase risk of bleeding; previous peptic ulceration; dehydration; coagulation defects; allergic disorders; renal impairment; hepatic impairment.

Dose:

Treatment of acute migraine attack.

Oral:

Infant or **Child** ***over 3 months*** 5–10 mg/kg three or four times daily with or after food. Maximum dose is 40 mg/kg/day.

Renal impairment: Mild and moderate impairment: use lowest effective dose and monitor renal function; sodium and water retention may occur, as may deterioration in renal function possibly leading to renal failure.

Severe impairment: avoid use.

Hepatic impairment: Use with caution; increased risk of gastrointestinal bleeding and can cause fluid retention; avoid in severe liver disease.

Adverse effects: Common Nausea, diarrhoea, dyspepsia, headache, dizziness, fluid retention, abdominal pain.

Uncommon Rash, urticaria, photosensitivity, renal impairment, raised blood pressure, gastrointestinal ulceration and bleeding.

Rare Angioedema, bronchospasm, hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), colitis, aseptic meningitis.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: avoid concomitant use (increased adverse effects).
* **Ciclosporin**: increased risk of nephrotoxicity.

  Dexamethasone: increased risk of gastrointestinal bleeding and ulceration.

  Digoxin: possible exacerbation of heart failure, reduced renal function and increased plasma digoxin concentration.

  Enalapril: antagonism of hypotensive effect, increased risk of renal impairment.
* **Fluoxetine**: increased risk of bleeding.

  Furosemide: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

  Heparin: possible increased risk of bleeding.

  Hydrocortisone: increased risk of gastrointestinal bleeding and ulceration.
* **Lithium**: reduced excretion of lithium (increased risk of toxicity).
* **Methotrexate**: excretion of methotrexate reduced (increased risk of toxicity).

  Penicillamine: possible increased risk of nephrotoxicity.
* **Phenytoin**: effect of phenytoin possibly enhanced.

  Prednisolone: increased risk of gastrointestinal bleeding and ulceration.

  Propranolol: antagonism of hypotensive effect.

  Ritonavir: plasma concentration possibly increased by ritonavir.

  Spironolactone: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possible increased risk of hyperkalaemia.
* **Warfarin**: anticoagulant effect possibly enhanced and risk of bleeding increased.

  Zidovudine: increased risk of haematological toxicity.

Notes: Give with or after food.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Paracetamol

ATC code: N02BE01

Oral liquid: 25 mg/ml

Tablet: 300 mg to 500 mg

Special Notes: Also referred to as acetaminophen.

Indications: Acute migraine attack.

Precautions: Hepatic impairment; overdosage.

Dose:

Treatment of acute migraine attack.
Oral:
Infant or **Child** 15 mg/kg, up to 1 g, every 4–6 hours as necessary. Maximum 60 mg/kg in 24 hours.

Hepatic impairment: Dose-related toxicity; avoid large doses.

Adverse effects: Rare Rash, hypersensitivity, neutropenia, thrombocytopenia, pancytopenia.

HEPATOTOXICITY Hepatotoxicity (and less frequently renal damage) can occur after paracetamol overdosage. Children who are malnourished, have a febrile illness, have not eaten for a few days or are taking liver enzyme-inducing drugs may be at an increased risk of liver damage from paracetamol overdosage. Refer to section 4.2 for more information on paracetamol toxicity.

Interactions with other medicines (* indicates severe):

Metoclopramide: increased absorption of paracetamol.

Warfarin: prolonged regular use of paracetamol possibly enhances anticoagulant effect.

Notes: Shake suspension well before use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

7.2 For prophylaxis

For frequent or severe migraine, preventive medications may be appropriate, with specialist consultation where possible. Prophylaxis can reduce the severity and frequency of attacks but does not eliminate them completely, so additional symptomatic treatment is still needed.

Propranolol

ATC code: C07AA05

Tablet: 20 mg; 40 mg (as hydrochloride)

Indications: Migraine prophylaxis.

Contraindications: Asthma; history of bronchospasm; uncontrolled heart failure; marked bradycardia; hypotension; sick sinus syndrome; second or third-degree atrioventricular block; cardiogenic shock; metabolic acidosis; severe peripheral arterial disease; phaeochromocytoma.

Precautions: Avoid abrupt withdrawal; first-degree atrioventricular block; portal hypertension; diabetes mellitus; history of obstructive airways disease; renal impairment; liver disease; myasthenia gravis; history of hypersensitivity (increased reaction to allergens, also reduced response to epinephrine (adrenaline)).

Dose:

Migraine prophylaxis.

Oral:

Child *over 2 years* 200–500 micrograms/kg three times daily; maximum 4 mg/kg daily. Usual dose 10–20 mg 2–3 times daily.

Renal impairment: Severe: start with small dose; higher plasma concentrations after oral administration; may reduce renal blood flow and adversely affect renal function.

Hepatic impairment: Reduce oral dose.

Adverse effects: Common Nausea, diarrhoea, fatigue, insomnia, nightmares, dyspnoea, bronchospasm, peripheral vasoconstriction, exacerbation of Raynaud syndrome, bradycardia, heart failure, hypotension, conduction disorders.

Uncommon Rash, exacerbation of psoriasis, muscle cramp, dry eyes.

Rare Hypersensitivity reaction, thrombocytopenic purpura, liver function abnormality, alopecia, cardiac arrest.

Interactions with other medicines (* indicates severe):

* **Bupivacaine**: increased risk of bupivacaine toxicity.

* **Chlorpromazine**: concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect.

Contraceptives, oral: antagonism of hypotensive effect by estrogens.

Dexamethasone: antagonism of hypotensive effect.

Diazepam: enhanced hypotensive effect.

Digoxin: increased risk of atrioventricular block and bradycardia.

Enalapril: enhanced hypotensive effect.

* **Epinephrine**: severe hypertension.

Furosemide: enhanced hypotensive effect.

Halothane: enhanced hypotensive effect.

Hydrochlorothiazide: enhanced hypotensive effect.

Hydrocortisone: antagonism of hypotensive effect.

Ibuprofen: antagonism of hypotensive effect.

Insulins: enhanced hypoglycaemic effect; propranolol may mask warning signs of hypoglycaemia such as tremor.

Ketamine: enhanced hypotensive effect.

* **Lidocaine**: increased myocardial depression; increased risk of lidocaine toxicity (interaction less likely when lidocaine used topically).

Mefloquine: increased risk of bradycardia.

Neostigmine: antagonism of effect of neostigmine.

* **Nifedipine**: enhanced hypotensive effect. Possible severe hypotension and heart failure.

Nitrous oxide: enhanced hypotensive effect.

Prednisolone: antagonism of hypotensive effect.

* **Procainamide**: increased myocardial depression.

Pyridostigmine: antagonism of effect of pyridostigmine.

* **Quinidine**: increased myocardial depression.

Rifampicin: metabolism of propranolol accelerated (significantly reduced plasma concentration of propranolol).

Sodium nitroprusside: enhanced hypotensive effect.

Spironolactone: enhanced hypotensive effect.

Suxamethonium: enhanced muscle relaxant effect.

Thiopental: enhanced hypotensive effect.

Vecuronium: enhanced muscle relaxant effect.

* **Verapamil**: asystole, severe hypotension and heart failure.

Notes: Advise patient or carer not to discontinue abruptly.

Give with food.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

SECTION 8:
Antineoplastic, immunosuppressives and medicines used in palliative care

8 Antineoplastic, immunosuppressives and medicines used in palliative care

8.1 Immunosuppressive medicines

NOTE. *WHO advises that this class of drugs is for use only when adequate resources and specialist care are available. Specific expertise, diagnostic precision, individualization of dosage and special equipment are required for their proper use.*

Immunosuppressive drugs are used in organ transplant recipients to suppress rejection; they are also used as second-line drugs in chronic inflammatory conditions. Treatment should only be initiated by a specialist. Careful monitoring of blood counts is required in patients receiving immunosuppressive drugs, and the dose should be adjusted to prevent bone marrow toxicity. Immunosuppressed patients are particularly prone to atypical infections.

Azathioprine

ATC code: L04AX01

Powder for injection: 100 mg (as sodium salt) in vial

Tablet: 50 mg

Special Notes: Also referred to as AZT (Note: this abbreviation is also used for zidovudine).

Indications: To prevent rejection in organ transplant recipients in combination with other medications.

Contraindications: Hypersensitivity to azathioprine or mercaptopurine.

Precautions: Liver disease; renal impairment. Monitor for toxicity throughout treatment; full blood counts necessary every week (or more frequently with higher doses and in renal or hepatic impairment) for first 4 weeks of treatment, and at least every 3 months thereafter.

Patients with genetic deficiency of the enzyme thiopurine methyltransferase (TPMT) which metabolizes azathioprine are at greater risk of myelosuppressive effects.

BONE MARROW SUPPRESSION Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, infection.

Dose:

Organ transplantation.
Oral or *IV:*
Child *1 month–12 years* initially 3–5 mg/kg once daily beginning at the time of transplant; maintenance 1–3 mg/kg once daily, adjusted according to response. Total daily dose may alternatively be given in two divided doses.

Renal impairment: Mild: dose as in normal renal function.

Moderate: 75–100% of normal dose.

Severe: 50–100% of normal dose.

Hepatic impairment: May need dose reduction.

Adverse effects: Common Leukopenia, thrombocytopenia, anaemia, increased susceptibility to infections due to immunosuppression, alopecia, diarrhoea, anorexia, nausea and vomiting, mouth ulcers, oesophagitis.

Uncommon Hepatitis, photosensitivity.

Rare Hepatic veno-occlusive disease, hypersensitivity reactions, malaise, dizziness, fever, muscular pains, arthralgia, rash, hypotension or interstitial nephritis call for immediate withdrawal, cholestatic jaundice, colitis in patients also receiving corticosteroids, pancreatitis, pneumonitis, increased incidence of malignancies and lymphoproliferative disorders.

Interactions with other medicines (* indicates severe):

* **Allopurinol**: effects of azathioprine enhanced and toxicity increased, reduce dose of azathioprine.

  Phenytoin: possibly reduced absorption of phenytoin.
* **Sulfamethoxazole + trimethoprim**: increased risk of haematological toxicity.
* **Trimethoprim**: increased risk of haematological toxicity.
* **Vaccine, live**: avoid use of live vaccines with azathioprine (impairment of immune response).
* **Warfarin**: anticoagulant effect possibly reduced.

Notes: Intravenous injection is alkaline and very irritant; the intravenous route should therefore only be used if oral administration is not possible. For intravenous injection give over at least 1 minute. For intravenous infusion dilute to a concentration of 0.25–2.5 mg/ml in glucose 5% or sodium chloride 0.9% or sodium chloride and glucose; give over 30–60 minutes.

PATIENT INFORMATION Patients should be warned to report immediately any signs or symptoms of bone marrow suppression, for example unexplained bruising or bleeding, infection.

Specific expertise, diagnostic precision, individualization of dosage or special equipment required for proper use.

HAZARDOUS AGENT Azathioprine is an immunosuppressive agent. Use appropriate precautions for handling and disposal.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Ciclosporin

ATC code: L04AA01

Capsule: 25 mg

Concentrate for injection: 50 mg/ml in 1 ml ampoule for organ transplantation

Special Notes: Also referred to as cyclosporine.

Indications: For use in organ transplant recipients in kidney, liver, heart or bone marrow transplantation, graft-versus-host disease and nephrotic syndrome.

Contraindications: Hypersensitivity to ciclosporin or any component of formulations (e.g. polyoxyl 35 castor oil in injection or polyoxyl 40 hydrogenated castor oil in capsules); breastfeeding.

Precautions: Monitor kidney function (dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction, exclude rejection if kidney transplant); monitor liver function (adjust dosage according to bilirubin and liver enzymes); monitor blood pressure (discontinue if hypertension cannot be controlled by antihypertensives); monitor serum potassium, particularly if marked renal impairment (risk of hyperkalaemia); monitor serum magnesium; hyperuricaemia; measure blood lipids before and during treatment; avoid in porphyria.

ADDITIONAL CAUTIONS IN NEPHROTIC SYNDROME Reduce dose by 25–50% if serum creatinine more than 30% above baseline at more than one measurement; perform renal biopsies at yearly intervals; contraindicated in uncontrolled infections and malignancy.

Dose:

NOTE Lower doses are required when ciclosporin is used with other immunosuppressants.

Serum level monitoring is required, a guide (based on adult recommendations) is provided in Notes, however, specialist transplant protocols should be consulted.

Solid organ transplantation.

Oral:

Child *over 3 months* 10–15 mg/kg 4–12 hours before surgery, then 10–15 mg/kg/day in 1–2 doses for 1–2 weeks, reducing to 2–6 mg/kg/day in 1–2 doses for maintenance (adjust dose according to blood ciclosporin concentration and kidney function).

IV:

Child *over 3 months* 3–5 mg/kg 4–12 hours before surgery, then 3–5 mg/kg/day in 1–2 doses for 1–2 weeks, reducing to 0.6–2 mg/kg/day for maintenance (adjust dose according to blood ciclosporin concentration and kidney function).

Bone marrow transplantation or graft-versus-host disease (GVHD).

Oral:

Child *over 3 months* 12.5–15 mg/kg daily for 2 weeks, starting on day before transplantation (or at the onset of GVHD), followed by 12.5 mg/kg/day in 1–2 doses for 3–6 months, then gradually tailed off (may take up to 1 year after transplant).

IV:

Child *over 3 months* 3–5 mg/kg/day in 1–2 doses for 2 weeks, starting on the day before transplantation (or at the onset of GVHD), followed by oral maintenance doses.

Nephrotic syndrome.

Oral:

Child *all ages* 3 mg/kg/dose twice daily. In renal impairment, initial dose should not exceed 2.5 mg/kg/day. For maintenance treatment, slowly reduce to lowest effective dose according to whole blood ciclosporin concentrations, proteinuria and serum creatinine measurements. Discontinue after 3 months if no improvement (after 6 months in membranous glomerulonephritis).

Renal impairment: Monitor kidney function, dose-dependent increase in serum creatinine and urea during first few weeks may necessitate dose reduction (exclude rejection if kidney transplant).

Hepatic impairment: May need dose adjustment based on bilirubin or liver enzyme levels.

Adverse effects: Common Nephrotoxicity (dose-related and reversible increases in serum creatinine and urea unrelated to tissue rejection), gingival hyperplasia, hirsutism, headache, tremor, burning sensation in hands and feet during initial therapy, electrolyte disturbances including hyperkalaemia, hypomagnesaemia, hepatic dysfunction, hyperuricaemia, hypercholesterolaemia, hyperglycaemia, hypertension (especially in heart transplant patients), increased incidence of malignancies and lymphoproliferative disorders, increased susceptibility to infections due to immunosuppression, increased insulin requirements, diabetes.

Uncommon Gastrointestinal disturbances, fatigue, myopathy or muscle weakness, gout.

Rare Confusion, coma, psychosis, allergic reactions, thrombocytopenia (sometimes with haemolytic uraemic syndrome), also mild anaemia, seizures, neuropathy, dysmenorrhoea or amenorrhoea, pancreatitis.

Interactions with other medicines (* indicates severe):

Aciclovir: increased risk of nephrotoxicity.

Allopurinol: plasma ciclosporin concentration possibly increased (risk of nephrotoxicity).

* **Amikacin**: increased risk of nephrotoxicity.
* **Amiloride**: increased risk of hyperkalaemia.
* **Amphotericin B**: increased risk of nephrotoxicity.

* **Azithromycin**: plasma concentration of ciclosporin possibly increased.
* **Carbamazepine**: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).
* **Chloramphenicol**: plasma concentration of ciclosporin possibly increased.
* **Chloroquine**: increased plasma ciclosporin concentration (increased risk of toxicity).
* **Ciprofloxacin**: increased risk of nephrotoxicity.
* **Contraceptives, oral**: plasma ciclosporin concentration increased by progestogens and possibly increased by estrogens.
* **Digoxin**: increased plasma concentration of digoxin (increased risk of toxicity).
* **Doxorubicin**: increased risk of neurotoxicity.
* **Doxycycline**: possibly increased plasma ciclosporin concentration.
* **Enalapril**: increased risk of hyperkalaemia.
* **Erythromycin**: increased plasma ciclosporin concentration (inhibition of metabolism of ciclosporin).

  Etoposide: possibly increased plasma concentration of etoposide (increased risk of toxicity).
* **Fluconazole**: metabolism of ciclosporin inhibited (increased plasma concentration).
* **Gentamicin**: increased risk of nephrotoxicity.
* **Grapefruit juice**: increased plasma ciclosporin concentration (risk of toxicity).

  Griseofulvin: plasma ciclosporin concentration possibly reduced.

  Hydrochlorothiazide: increased risk of nephrotoxicity and possibly hypermagnesaemia.
* **Ibuprofen**: increased risk of nephrotoxicity.
* **Levofloxacin**: increased risk of nephrotoxicity.
* **Levonorgestrel**: inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration).
* **Medroxyprogesterone**: inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration).
* **Methotrexate**: increased toxicity.
* **Metoclopramide**: plasma ciclosporin concentration increased.
* **Nelfinavir**: possibly increased plasma ciclosporin concentration.
* **Norethisterone**: inhibition of ciclosporin metabolism (increased plasma ciclosporin concentration).
* **Ofloxacin**: increased risk of nephrotoxicity.
* **Phenobarbital**: metabolism of ciclosporin accelerated (reduced effect).
* **Phenytoin**: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).
* **Potassium salts**: increased risk of hyperkalaemia.

  Prednisolone: increased plasma concentration of prednisolone.
* **Rifampicin**: accelerated metabolism of ciclosporin (reduced plasma ciclosporin concentration).
* **Ritonavir**: plasma concentration possibly increased by ritonavir.
* **Saquinavir**: plasma concentration of both ciclosporin and saquinavir increased.
* **Silver sulfadiazine**: increased risk of nephrotoxicity; possibly reduced plasma concentration of ciclosporin.
* **Simvastatin**: increased risk of myopathy.

  Spironolactone: increased risk of hyperkalaemia.

Streptomycin: increased risk of nephrotoxicity.

* **Sulfadiazine**: plasma ciclosporin concentration possibly reduced; increased risk of nephrotoxicity.
* **Sulfadoxine + pyrimethamine**: increased risk of nephrotoxicity.
* **Sulfamethoxazole + trimethoprim**: increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim.
* **Trimethoprim**: increased risk of nephrotoxicity; plasma ciclosporin concentration possibly reduced by intravenous trimethoprim.
* **Vaccine, live**: avoid use of live vaccines with ciclosporin (impairment of immune response).
* **Vancomycin**: increased risk of nephrotoxicity.
* **Verapamil**: increased plasma ciclosporin concentration.

Notes: CONVERSION Any conversion between brands should be undertaken very carefully, and the manufacturer's product information consulted for further advice.

NOTE Concentrate for infusion may contain polyethoxylated castor oil, which has been associated with anaphylaxis; observe patient for 30 minutes after starting infusion and then at frequent intervals.

SERUM CONCENTRATION MONITORING Draw blood for ciclosporin measurement by venepuncture, not from a central line.

Avoid using nonspecific assays which measure ciclosporin plus metabolites. Concentrations obtained from nonspecific assays are not interchangeable with the results from a specific assay.

The ciclosporin concentration 2 hours after a dose (C2) correlates better with area under the curve (AUC) than the 12 hour trough concentration (C0). There is evidence to suggest that C2 is a better indicator of adequate immunosuppression.

The following concentrations are a guide. They depend on assay technique, transplant type, time since transplant and use of other immunosuppressants. Aim for higher concentrations in the first 3 months after transplant and where rejection has occurred and lower concentrations where adverse effects are experienced.

Trough concentrations (C0) Whole blood specific assay, 100–300 micrograms/l.

C2 concentrations Collect sample 2 hours (± 15 minutes) after a dose of ciclosporin.

Recommended C2 whole blood concentrations for Neoral® brand in adults Liver transplant: 600–1000 micrograms/l.

Kidney transplant: 800–1500 micrograms/l.

Continuous IV infusion Whole blood specific assay, 300–500 micrograms/l.

Consult local protocols or specialist advice for use in children.

INTRAVENOUS ADMINISTRATION ADVICE Dilute injection to 1:20 to 1:100 in glucose 5% or sodium chloride 0.9%; infuse IV over 2–6 hours (more slowly if facial flushing occurs); use a glass bottle and non-PVC administration set to avoid phthalate stripping and use short giving sets to reduce amount adsorbed.

PATIENT INFORMATION Swallow capsules whole and take them 12 hours apart at the same times each day.

Clean your teeth and gums regularly.

HAZARDOUS AGENT Ciclosporin is an immunosuppressive agent. Use appropriate precautions for handling and disposal.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

8.2 Cytotoxic medicines

NOTE. *WHO advises that while cytotoxic medicines are essential for the treatment of malignancy in children, adequate resources and specialist supervision are a prerequisite for the introduction of this class of drugs. Specific expertise, diagnostic precision, individualization of dosage and special equipment are required for their proper use. There are many differences in the spectrum and management of childhood cancers, compared to adult cancers, and the treatment of malignancy in children with drugs, radiotherapy and surgery is complex and should only be undertaken by specialists in this field. For this reason, the following information is provided merely as a guide.*

Chemotherapy may be curative or used to alleviate symptoms or prolong life (palliative). When the condition can no longer be managed with cytotoxic therapy, alternative palliative treatment (section 8.4) should be considered.

For some tumours, single-drug chemotherapy may be adequate, but for most malignancies, a combination of drugs provides the best response; specialist literature should be consulted. Cytotoxic drugs are often combined with other classes of drugs in the treatment of malignant conditions. Such drugs include hormone agonists and antagonists, corticosteroids and immunosuppressant drugs (section 8.3). Combinations are, however, more toxic than single drugs.

Cytotoxic medications should be used with great care and close monitoring. Specific doses and details of contraindications, precautions and adverse effects for the individual cytotoxic drugs have been omitted in the following section since treatment should be undertaken by specialists using approved regimens; specialist literature should be consulted for further information.

Adverse effects

Cytotoxic drugs have a considerable potential to damage normal tissue. Specific adverse effects apply, but a number are common to all cytotoxics, such as bone marrow and immunological suppression. The concomitant use of immunosuppressive drugs will enhance susceptibility to infections. Fever associated with neutropenia requires immediate treatment with antibiotics.

Nausea and vomiting following administration of cytotoxic drugs and abdominal radiotherapy are often distressing and may compromise further treatment. Symptoms may be acute (occurring within 24 hours of treatment), delayed (first occurring more than 24 hours after treatment) or anticipatory (occurring before subsequent doses). Antiemetic medicines are further discussed in section 17.2.

Hyperuricaemia may complicate treatment of conditions such as non-Hodgkin lymphomas and leukaemia. Renal damage may result from the formation of uric acid crystals. Patients should be adequately hydrated, and hyperuricaemia may be managed with allopurinol.

Alopecia is common during treatment with cytotoxic drugs. There is no drug treatment, but the condition often reverses spontaneously once treatment has stopped.

Oral mucositis is common during cancer chemotherapy, particularly with fluorouracil, methotrexate and anthracyclines. Prevention of a sore mouth is important, because once it has developed treatment is much less effective. Brushing teeth with a soft brush two to three times daily and rinsing the mouth frequently are probably the most effective preventative measures. Treatment involves regular use of saline mouthwashes. Generally mucositis is self-limiting, but it can be a focus for blood-borne infection in the absence of good oral hygiene. Any pain caused by mucositis should be dealt with effectively.

Allopurinol

ATC code: M04AA01

Tablet: 100 mg to 300 mg

Indications: Prophylaxis of hyperuricaemia associated with cancer chemotherapy.

Contraindications: Acute gout; previous allopurinol-induced rash.

Precautions: Ensure adequate fluid intake; renal impairment; hepatic impairment; withdraw treatment if rash occurs (see below).

For hyperuricaemia associated with cancer therapy, allopurinol should be started before cancer therapy.

RASH Risk of skin rash may be increased in patients receiving amoxicillin or ampicillin. The risk of hypersensitivity may also be increased in patients receiving thiazides or ACE inhibitors. If a rash occurs, treatment should be stopped; treatment may be reintroduced if the rash is mild but discontinue immediately if it recurs.

Dose:

Prophylaxis of hyperuricaemia associated with cancer chemotherapy beginning 1–2 days before chemotherapy.

Oral:

Child *1 month–12 years* 10–20 mg/kg daily (maximum 400 mg) preferably after food. Doses > 300 mg should be administered as divided doses.

Renal impairment: Mild: no dosage reduction necessary.

Moderate: 50% of usual dose.

Severe: 30% of usual dose.

Hepatic impairment: Reduce dose and monitor liver function.

Adverse effects: Common Rash (see Precautions above), gastrointestinal intolerance.

Uncommon Hypertension, alopecia, hepatotoxicity, paraesthesia, neuropathy, gynaecomastia.

Rare Hypersensitivity reactions including fever, lymphadenopathy, arthralgia, eosinophilia, erythema multiforme (Stevens-Johnson syndrome) or toxic epidermal necrolysis, vasculitis, hepatitis, renal impairment, malaise, headache, vertigo, drowsiness, visual and taste disturbance.

Very rare Seizures, blood disorders (including leukopenia, thrombocytopenia, haemolytic anaemia and aplastic anaemia).

Interactions with other medicines (* indicates severe):

Amoxicillin: increased risk of rash and hypersensitivity.

Ampicillin: increased risk of rash and hypersensitivity.

* **Azathioprine**: effects of azathioprine enhanced and toxicity increased; reduce dose of azathioprine.

Ciclosporin: plasma ciclosporin concentration possibly increased (risk of nephrotoxicity).

* **Cyclophosphamide**: increased risk of cyclophosphamide toxicity.

* **Didanosine**: increased plasma concentration of didanosine leading to didanosine toxicity.

Enalapril: increased risk of hypersensitivity.

Hydrochlorothiazide: increased risk of hypersensitivity, especially in renal impairment.

* **Mercaptopurine**: effects of mercaptopurine enhanced and toxicity increased; reduce dose of mercaptopurine.

* **Theophylline**: increased risk of theophylline toxicity.

* **Warfarin**: anticoagulant effect possibly enhanced.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Asparaginase

ATC code: L01XX02

Powder for injection: 10 000 IU in vial

Allergic reactions to asparaginase are frequent and can be fatal. Risk factors include intravenous administration, large doses, prior exposure to asparaginase and intervals of even a few days between doses. An intradermal test dose may be administered (see Precautions).

Special Notes: Also referred to as crisantaspase, L-asparaginase and colaspase.

Different brands of asparaginase may not be interchangeable and the units may be expressed differently.

Indications: Acute lymphoblastic leukaemia; T-cell non-Hodgkin lymphoma.

Contraindications: Allergy to asparaginase; history of pancreatitis; history of thrombosis or haemorrhagic events with previous asparaginase therapy; pregnancy.

Precautions: Underlying coagulopathy; impaired renal function; pre-existing liver impairment; discontinue at the first sign of renal failure or pancreatitis; appropriate measures should be taken to prevent hyperuricaemia and uric acid nephropathy (consider allopurinol, hydration and urinary alkalinization); test dose recommended (see below).

TEST DOSE An intradermal test dose of 2 international units is often recommended prior to the first dose of asparaginase or prior to restarting therapy after a hiatus of several days. However, false negative rates of up to 80% are reported. Serious allergic reactions can occur; intradermal testing should only be done in a hospital setting with adequate monitoring and resuscitation facilities. Desensitization may be performed in patients who are found to be hypersensitive from the intradermal test dose; consult specialist texts for details.

Dose:

See specialist treatment protocols.

Renal impairment: Use with caution.

Hepatic impairment: Use with caution.

Adverse effects: Children appear to tolerate asparaginase better than adults.

Common Allergic reactions, nausea, vomiting, fatty changes in the liver, elevated transaminases and bilirubin, decreased albumin and calcium concentrations, reduced fibrinogen and clotting factors (resulting in prolonged clotting times), uraemia, pancreatitis.

Uncommon Transient proteinuria, hyperglycaemia (rarely leading to diabetic ketoacidosis), CNS effects including depression or hyperexcitability, chills and fever (possibly caused by bacterial endotoxins in the preparation), increased fibrin degradation products, increased blood ammonia.

Rare Intracranial haemorrhage or thrombosis, peripheral venous and arterial thrombosis, transient myelosuppression, acute renal failure, Parkinsonian-like syndrome, diarrhoea, oral mucositis.

Interactions with other medicines (* indicates severe):

Vaccines, live: avoid use of live vaccines with asparaginase (impairment of immune response).

Cytarabine: decreased antineoplastic effect if given prior to cytarabine.

Methotrexate: decreased antineoplastic effect if given prior to methotrexate.

Prednisolone: increased hyperglycaemic effect.

Notes: Can be produced by either *Erwinia chrysanthemi* or *Escherichia coli*. Children who are hypersensitive to asparaginase derived from one organism may tolerate asparaginase derived from another organism but cross-sensitivity occurs in 20–30% of individuals.

Asparaginase is a contact irritant. Care should be taken to avoid contact with skin or mucous membranes (especially eyes). If accidental contact occurs, the affected area should be flushed with water for at least 15 minutes.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Bleomycin

ATC code: L01DC01

Powder for injection: 15 mg (as sulfate) in vial

Handle as a cytotoxic.

Indications: Adjunct to surgery and radiotherapy in palliative treatment of Hodgkin and non-Hodgkin lymphomas; carcinomas of the head, neck, larynx, cervix, penis, skin, vulva, testicles and including embryonal cell carcinoma, choriocarcinoma and teratoma; malignant effusions; Kaposi sarcoma.

Contraindications: Acute pulmonary infection or significantly reduced lung function; allergy to bleomycin; pregnancy; breastfeeding.

Precautions: Renal impairment; pulmonary impairment.

Dose:

Maximum cumulative dose for adults is 300 000–400 000 international units.

Consult specialist protocols.

Renal impairment: Monitor plasma creatinine at baseline and before each cycle.

Mild: dose as in normal renal function.

Moderate: 75% of normal dose (100% for malignant effusions).

Severe: 50% of normal dose (100% for malignant effusions).

Hepatic impairment: Dosage reduction not necessary.

Adverse effects: Common Rash, erythema, itch, vesiculation, hyperkeratosis, hyperpigmentation (particularly of skin folds), nail changes, oral mucositis, alopecia, fever and chills (usually occur within 4–10 hours of a dose and last 4–12 hours or longer), hypersensitivity (see below), pulmonary toxicity (see below), nausea and vomiting.

Uncommon Raynaud phenomenon.

Rare Acute chest pain during infusion.

HYPERSENSITIVITY Occurs in about 1% of lymphoma patients but otherwise appears to be rare. Usually presents with hypotension, high fever, chills, confusion and wheezing. May be immediate or delayed and usually occurs with the first or second dose.

PULMONARY TOXICITY Occurs in approximately 10% of patients, initial symptoms include dyspnoea, cough and sometimes fever. Pneumonitis may progress to pulmonary fibrosis and death. Onset may be delayed for up to 6 months after the last dose. Risk factors include high cumulative dose, mediastinal radiotherapy, renal impairment, pre-exisiting lung disease and oxygen supplementation. Stop bleomycin if pneumonitis is suspected. Corticosteroids are used although evidence is limited.

Interactions with other medicines (* indicates severe):

* **Cisplatin**: increased pulmonary toxicity.
* **Oxygen**: serious pulmonary toxicity in patients exposed to conventional oxygen concentrations during anaesthesia.

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with bleomycin (impairment of immune response).

* **Vinblastine**: increased risk of cardiovascular toxicity.

Digoxin: bleomycin may decrease digoxin absorption.

Amphotericin B: concurrent bleomycin may increase nephrotoxicity and risk of hypotension and bronchospasm.

Notes: No single monitoring test reliably predicts bleomycin pulmonary toxicity, monitoring may include:

chest X-ray at baseline, then each week during and for 4 weeks after treatment;

pulmonary function tests (particularly total lung volume and forced vital capacity);

baseline and monthly evaluation of carbon monoxide diffusion capacity; stop treatment if it falls to < 30–35% of pretreatment value.

1500 international units of bleomycin are equivalent to 1.5 USP bleomycin units and approximately 1.5 mg (by potency) or 1 mg (by weight). Caution is required when converting from mg to international units as protocols or trials may state bleomycin doses in terms of mg-potency rather than mg-weight.

Irritant to tissues; needs to be administered with care.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Calcium folinate

ATC code: V03AF03

Injection: 3 mg/ml in 10 ml ampoule

Tablet: 15 mg

Special Notes: Also referred to as calcium leucovorin, folinic acid or leucovorin.

Indications: Reduction of methotrexate-induced toxicity associated with high-dose methotrexate therapy (folate rescue).

Contraindications: Intrathecal injection of calcium folinate is contraindicated.

Precautions: Not for use in patients with pernicious anaemia or other megaloblastic anaemias due to vitamin B_{12} deficiency.

Avoid simultaneous administration of methotrexate.

Dose:

Consult specialist protocols.

Usually started 24 hours after beginning the methotrexate infusion. Doses and length of treatment may be based on methotrexate concentration.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Allergic reactions, fever.

Rare Seizures, fainting.

Interactions with other medicines (* indicates severe):

Phenobarbital: plasma concentration of phenobarbital possibly reduced.

Phenytoin: plasma phenytoin concentration possibly reduced.

Fluorouracil: toxicity enhanced but used for this purpose intentionally.

Trimethoprim: reduced therapeutic effect.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Carboplatin

ATC code: L01XA02

Injection: 10 mg/ml solution 5 ml, 15 ml, 45 ml and 60 ml vials

Handle as a cytotoxic agent.

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: 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.

Contraindications: Hypersensitivity to carboplatin, cisplatin, other platinum containing compounds or mannitol; severe bone marrow suppression or excessive bleeding; pregnancy; breastfeeding.

Precautions: Renal impairment.

Dose:

See specialist treatment protocols.

Doses frequently calculated according to individual patient's renal function and ability to clear the drug.

Calvert formula for carboplatin dosing in adults:

Total dose (mg) = target AUC (mg.minute/ml) x [GFR (ml/minute) + 25].

Modified Calvert formula for children:

Total dose (mg) = [target AUC (mg.minute/ml)] x [GFR (ml/minute) + (0.36 x body weight in kilograms)].

Renal impairment: Renal function is often factored into dose calculations for carboplatin. If renally-adjusted doses are not being used and the patient is renally impaired, consider reducing dose and monitor haematological parameters and renal function; avoid if creatinine clearance less than 20 ml/minute.

Hepatic impairment: Dosage reduction not necessary.

Adverse effects: Common Myelosuppression (see below), nausea, vomiting, peripheral neuropathy, taste abnormality, fatigue, hypersensitivity reactions including anaphylaxis (risk increases with repeated exposure), reversible elevation of serum creatinine, mild and reversible electrolyte abnormalities (hyponatraemia, hypokalaemia, hypocalcaemia, hypomagnesaemia), mild elevations of ALP, liver transaminases and bilirubin, alopecia, myalgia, weakness.

Uncommon Ototoxicity, abdominal pain, diarrhoea, constipation, oral mucositis.

Rare Acute renal failure, haemolytic uraemic syndrome, loss of vision (at higher than usually recommended doses).

MYELOSUPPRESSION Major dose-limiting effect. Thrombocytopenia is more common and pronounced than leukopenia; it may be cumulative and sometimes requires platelet transfusion. Nadir of platelet and neutrophil counts occurs 14–28 days after a dose, with recovery usually within 28 days. Anaemia may be cumulative and require transfusion.

Interactions with other medicines (* indicates severe):

Aminoglycosides: increased ototoxicity and nephrotoxicity.

Nephrotoxic drugs: increased renal toxicity.

Phenytoin: decreased serum levels of phenytoin.

Digoxin: reduced absorption of digoxin.

Clozapine: increased risk of agranulocytosis.

Notes: Needle or intravenous administration sets containing aluminium parts should not be used in the administration or preparation of carboplatin as an interaction may cause precipitate formation and loss of potency.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Chlorambucil

ATC code: L01AA02

Tablet: 2 mg

Handle as a cytotoxic.

Indications: Non-Hodgkin lymphomas; Hodgkin disease; histiocytosis.

Contraindications: Hypersensitivity to chlorambucil or any component; cross-hypersensitivity (skin rash) may occur with other alkylating agents; pregnancy; breastfeeding.

Precautions: Severe hepatic impairment; renal impairment; seizure disorders; bone marrow suppression; effective contraception is advised in both men and women; affects fertility (see Adverse effects). Reduce initial dose if a patient has received radiation therapy, myelosuppressive drugs, or has reduced baseline leukocyte or platelet count within the previous 4 weeks.

Dose:

Consult specialist protocols.

Renal impairment: Moderate or severe: use with caution and monitor response; increased risk of myelosuppression. Dose reduction not usually necessary.

Hepatic impairment: Consider dose reduction in severe hepatic impairment.

Adverse effects: Common Rash, dose-limiting myelosuppression (nadir 14 days), transient elevations in liver enzymes.

Uncommon Abdominal discomfort, diarrhoea, oral mucositis.

Rare Hallucinations, seizures, sterile cystitis, hepatotoxicity, jaundice, severe pneumonitis, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug fever, irreversible bone marrow suppression, pulmonary fibrosis, tremor, peripheral neuropathy, sterility in pre-pubertal and pubertal males (less likely in females).

Interactions with other medicines (* indicates severe):

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with chlorambucil (impairment of immune response).

Phenobarbital: increased toxicity of chlorambucil.

Notes: Tablets should be swallowed whole on an empty stomach and not broken, chewed or crushed.

Avoid the need to cut tablets by using different doses on alternate days.

Store tablets at 2–8 °C (36–46 °F). Tablets may be stored at room temperatures up to 30 °C (86 °F) for up to 1 week.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Cyclophosphamide

ATC code: L01AA01

Powder for injection: 500 mg in vial

Tablet: 25 mg

Handle as a cytotoxic.

Indications: Acute lymphoblastic leukaemia, non-Hodgkin lymphoma, retinoblastoma, neuroblastoma, rhabdomyosarcoma, soft tissue sarcomas, Ewing tumour, neuroectodermal tumours (including medulloblastoma), infant brain tumours, ependymona; as part of high-dose conditioning therapy for bone marrow transplantation.

Contraindications: Haemorrhagic cystitis; pregnancy; breastfeeding.

Precautions: Renal impairment; hepatic impairment; bone marrow suppression. Avoid contact with skin. May cause infertility (see Adverse effects).

Dose:

See specialist treatment protocols.

Renal impairment: Reduce dose in moderate to severe impairment.

Mild: dose as in normal renal function.

Moderate: 75–100% of normal dose depending on clinical indication and local protocol.

Severe: 50–100% of normal dose depending on clinical indication and local protocol.

Hepatic impairment: Reduce dose.

Adverse effects: Common Alopecia, nausea, vomiting, anorexia, haemorrhagic cystitis (see below), nasal congestion (with rapid injection), leukopenia (nadir at 8–15 days), impairment of fertility (may be irreversible), gonadal suppression (amenorrhoea).

Uncommon Hyperpigmentation of skin and nails, metallic taste, loss of taste.

Rare Heart failure (acute onset days after high-dose treatment; more common in older adult patients and those previously exposed to anthracyclines, may be reversible), pulmonary fibrosis (with long-term treatment), hepatic veno-occlusive disease (high dose), water retention resembling syndrome of inappropriate antidiuretic hormone secretion (SIADH) resulting in hyponatraemia and seizures (more common in high doses).

HAEMORRHAGIC CYSTITIS Occurs as a result of accumulation of active metabolites in the bladder. Symptoms range from mild irritation on voiding to life-threatening haemorrhagic cystitis. Patients should be advised to drink plenty of fluids during therapy, void frequently, and avoid taking the drug at night. Intravenous hydration may be required. Mesna (not included on the 2nd WHO Model list of essential medicines for children) may be used. Toxicity is caused by the metabolite acrolein; mesna reacts specifically with acrolein in the urinary tract, preventing toxicity; mesna is given for the same duration as cyclophosphamide. It is generally given intravenously; the dose of mesna is equal to or greater than that of cyclophosphamide, often 125%.

Interactions with other medicines (* indicates severe):

* **Allopurinol**: increases the myelotoxicity of cyclophosphamide.

Carbamazepine: may increase conversion of cyclophosphamide to active metabolites.

* **Chloramphenicol**: reduced cyclophosphamide effectiveness.
* **Ciclosporin**: decreased ciclosporin concentration.
* **Hydrochlorothiazide**: increased myelotoxicity of cyclophosphamide.
* **Ondansetron**: reduced cyclophosphamide effectiveness.

Phenytoin: possibly reduced absorption of phenytoin.

Phenobarbital: may increase conversion of cyclophosphamide to active metabolites.

Suxamethonium: enhanced effect of suxamethonium.

Vaccines, live: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

* **Warfarin**: increased INR and increased risk of bleeding.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Cytarabine

ATC code: L01BC01

Powder for injection: 100 mg in vial

Handle as a cytotoxic.

Special Notes: Also referred to as Ara-C.

Indications: Acute lymphoblastic leukaemia; acute myeloid leukaemia; non-Hodgkin lymphoma; meningeal leukaemia; meningeal neoplasms.

Contraindications: Pregnancy; breastfeeding.

Precautions: Hepatic impairment; renal impairment.

Dose:

See specialist treatment protocols.

Renal impairment: For low-dose regimens dose reductions are not necessary.

For high-dose therapy the following information should be considered:

elevated baseline serum creatinine (> 106 micromol/l) is an independent risk factor for the development of neurotoxicity during treatment;

retrospective analysis implicates impaired renal function as an independent risk factor for high-dose cytarabine-induced cerebral and cerebellar toxicity;

the incidence of neurotoxicity is increased following administration of high-dose cytarabine to patients with even mildly impaired renal function.

Suggested dose reductions for high-dose therapy in patients with renal impairment.

Mild: 50–60% of normal dose.

Moderate or severe: avoid use of cytarabine high-dose.

Hepatic impairment: Reduce dose.

Adverse effects: Common Myelosuppression (see below), nausea, vomiting, diarrhoea, oral mucositis, rash, fever, elevated liver function tests, alopecia, ocular discomfort.

Uncommon Conjunctivitis, gastrointestinal haemorrhage, oesophagitis, jaundice, dizziness, cellulitis at injection site, chest pain, urinary retention, renal impairment, anaphylaxis.

Rare Palmar-plantar erythrodysaesthesia, severe spinal cord toxicity following intrathecal administration.

MYELOSUPPRESSION Major dose-limiting adverse effect, includes neutropenia, thrombocytopenia and anaemia, more severe after high doses or continuous infusions. Neutropenia is biphasic with a nadir 7–9 days after the dose and a more severe nadir at 15–24 days. Platelet nadir is 12–15 days after dose. Recovery generally occurs after a further 10 days.

HIGH-DOSE THERAPY Associated with severe and sometimes fatal gastrointestinal, neurological and pulmonary toxicity; adverse effects include peripheral neuropathy, cerebral and cerebellar dysfunction, cardiomyopathy, pulmonary oedema, gastrointestinal ulceration. Reversible corneal toxicity leading to haemorrhagic conjunctivitis or keratitis can occur (prophylactic corticosteroid or lubricant eye drops may help).

Interactions with other medicines (* indicates severe):

Digoxin: decreases digoxin oral tablet absorption.

Flucytosine: plasma flucytosine concentration possibly reduced.

Phenytoin: reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with cytarabine (impairment of immune response).

Notes: Based on weight or body surface area, children may tolerate higher doses of cytarabine than adults.

Conjunctivitis (which occurs more frequently in high-dose therapy) is preventable and treatable with a corticosteroid eye drop. As prophylaxis, eye drops should be started 6–12 hours before initiation of cytarabine and continued for 24 hours following the last dose.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Dacarbazine

ATC code: L01AX04

Powder for Injection: 100 mg in vial

Highly irritant to tissues, inject with care.

Handle as a cytotoxic.

Indications: Hodgkin disease; rhabdomyosarcoma; neuroblastoma; fibrosarcomas; soft tissue sarcomas; bone marrow transplant.

Contraindications: Pregnancy (avoid for 6 months after treatment completed in both male and female patients); breastfeeding.

Precautions: Renal and hepatic impairment; bone marrow depression; ensure adequate contraception during and for 6 months after treatment in men and women.

Dose:

Consult specialist protocols.

Renal impairment: Mild: 75–80% of dose.

Moderate to severe: 70% of dose; use with caution.

Hepatic impairment: Dose reduction may be required in mild to moderate liver disease; avoid if severe.

Adverse effects: Common Diarrhoea, flu-like syndrome (fever, myalgia, malaise), transient increases in hepatic transaminases and ALP, facial flushing, pain along injected vein, nausea and vomiting.

Uncommon Agranulocytosis, blurred vision, seizures, confusion, headache, alopecia, erythematous and maculopapular rash, photosensitivity, hypotension (infusion related).

Rare Intractable nausea and vomiting, hepatic vein thrombosis and hepatocellular necrosis, tissue damage due to extravasation.

Interactions with other medicines (* indicates severe):

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with dacarbazine (impairment of immune response).

Phenobarbital: may induce dacarbazine metabolism.

Notes: INTRAVENOUS INFUSION 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.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Dactinomycin

ATC code: L01DA01

Powder for injection: 500 micrograms in vial

Handle as a cytotoxic.
Highly irritant to tissues; inject with care.

Special Notes: Also referred to as actinomycin D.

Indications: Trophoblastic tumours; Wilms tumour; testicular tumours; Ewing sarcoma; rhabdomyosarcoma; other soft tissue sarcomas.

Contraindications: Pregnancy; breastfeeding.

Precautions: Hepatic or biliary impairment; concurrent or previous radiotherapy; vesicant (extravasation during intravenous use can cause severe tissue damage).

Dose:
Consult specialist protocols.

Renal impairment: No dose reductions necessary.

Hepatic impairment: Consider dose reduction if raised serum bilirubin or biliary obstruction.

Adverse effects: Common Myelosuppression (see below), nausea and vomiting, oral mucositis, oesophagitis, pharyngitis, diarrhoea, fever, malaise, myalgia, alopecia, rash, acne.

Rare Anaphylaxis, hepatotoxicity, hepatic veno-occlusive disease (common in Wilms tumour).

MYELOSUPPRESSION Affects mainly white cells and platelets; nadir of white cell and platelet count occurs 14–21 days after dose with recovery in 21–25 days.

Interactions with other medicines (* indicates severe):

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with dactinomycin (impairment of immune response).

Notes: Current radiotherapy: radiation effects (including skin, gastrointestinal and bone marrow toxicity) may be potentiated.

Previous radiotherapy: erythema and pigmentation may recur at site of previous radiation.

Children may experience increased risk of toxicity and are at greater risk of hepatic veno-occlusive disease.

Vesicant; avoid extravasation. Extremely damaging to soft tissue and will cause a severe local reaction if extravasation occurs. Administer slow intravenous push over 10–15 minutes. Do not give intramuscularly or subcutaneously.

Care should be taken with units: chemotherapy protocols can list dactinomycin doses in mg (e.g. mg/kg or mg/m^2), but medication orders are often written in micrograms.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Daunorubicin

ATC code: L01DB02

Powder for injection: 50 mg (as hydrochloride)

Handle as a cytotoxic.

Special Notes: Daunorubicin hydrochloride (conventional formulation) should not be confused with daunorubicin liposomal formulation.

Indications: Acute myelogenous leukaemia; acute lymphocytic leukaemia; neuroblastoma; rhabdomyosarcoma.

Contraindications: Pregnancy; breastfeeding; congestive heart failure, left ventricular ejection fraction < 30–40%; arrhythmias; pre-existing bone marrow suppression.

Precautions: Hepatic and renal impairment; cardiac disease; reduced cardiac reserve or treatment with other cardiotoxic drugs; highly irritant to tissues (inject with extreme care); previous treatment to maximum cumulative dose with another anthracycline.

Dose:

Consult specialist protocols.

Maximum cumulative dose (irreversible myocardial toxicity may occur as total dosage approaches):
Child *under 2 years* 10 mg/kg (300 mg/m^2);
over 2 years 300 mg/m^2.

Renal impairment: Mild to moderate: reduce dose.

Hepatic impairment: Reduce dose according to serum bilirubin concentration; see specialist protocols for details.

Adverse effects: Common Rash, itch, nausea, vomiting, diarrhoea, alopecia, oral mucositis, oesophagitis, myelosuppression (see below), cardiac toxicity (see below), fatigue, headache.

Rare Secondary malignancies.

MYELOSUPPRESSION Occurs commonly, affecting white cells and to a lesser degree, platelets and red cells. The white count nadir occurs about 10 days after a dose with recovery by about 21 days.

CARDIAC TOXICITY May be acute, chronic or delayed. Acute toxicity (ECG changes and arrhythmias) occurs during or immediately after a dose and is not dose related. It is usually transient but may rarely result in myopericarditis and cardiac failure.

Chronic toxicity usually occurs within a year of stopping treatment and is related to cumulative dose. Cardiomyopathy may result in heart failure.

Delayed toxicity occurs years to decades after treatment and is thought to be dose related. It may present as ventricular dysfunction, heart failure, conduction disturbances or arrhythmias.

Interactions with other medicines (* indicates severe):

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with daunorubicin (impairment of immune response).

Notes: Daunorubicin is a vesicant; severe local tissue necrosis will result if extravasation occurs. Do not give intramuscularly or subcutaneously.

Give by intravenous injection or short infusion into a side arm of a fast running infusion to reduce the risk of irritation or extravasation.

Monitor ECG and left ventricular ejection fraction at baseline and during treatment.

References:
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Doxorubicin

ATC code: L01DB01

Powder for injection: 10 mg, 50 mg (as hydrochloride) in vial

Handle as a cytotoxic.

Special Notes: Also referred to as adriamycin or ADR.

Doxorubicin hydrochloride (conventional formulation) should not be confused with doxorubicin liposomal formulation.

Indications: Malignancies including Ewing sarcoma, osteogenic sarcoma, Wilms tumour, neuroblastoma, retinoblastoma, some liver tumours, acute lymphoblastic leukaemia, Hodgkin lymphoma, non-Hodgkin lymphoma, germ cell tumours of the testis.

Contraindications: Pregnancy and breastfeeding; congestive heart failure, left ventricular ejection fraction < 30–40%; arrhythmias; pre-existing bone marrow suppression.

Precautions: Avoid extravasation (highly irritant to the tissues); previous treatment to maximum cumulative dose with another anthracycline; hepatic impairment; renal impairment; cardiac disease; treatment with other cardiotoxic drugs; previous mediastinal or pericardial irradiation.

Dose:

Consult specialist protocols.

Renal impairment: Mild to moderate: use with caution; avoid excessive doses.

Severe: use 75% of normal dose; use with caution.

Hepatic impairment: Reduce dose according to serum bilirubin concentration.

Do not use doxorubicin if bilirubin > 85 micromol/l.

Bilirubin 20–50 micromol/l: reduce dose by 50%.

Bilirubin > 50 micromol/l: reduce dose by 75%.

Adverse effects: Common Rash, itch, myelosuppression (see below), cardiac toxicity (see below), red coloured urine, nausea, vomiting, stomatitis, gastrointestinal ulceration.

Uncommon Conjunctivitis, lacrimation and facial flushing, hyperpigmentation of nails, buccal mucosa and skin folds, fever, chills, palmar-plantar erythrodysaesthesia.

Rare Secondary malignancies.

CARDIAC TOXICITY May be acute, chronic or delayed. Acute toxicity (ECG changes and arrhythmias) occurs during or immediately after a dose and is not dose related. It is usually transient but may rarely result in myopericarditis and cardiac failure.

Chronic toxicity usually occurs within a year of stopping treatment and is related to cumulative dose. Cardiomyopathy may result in heart failure.

Delayed toxicity occurs years to decades after treatment and is thought to be dose-related. It may present as ventricular dysfunction, heart failure, conduction disturbances or arrhythmias.

MYELOSUPPRESSION Occurs commonly, affecting white cells and, to a lesser degree, platelets and red cells. The white cell count nadir occurs about 10 days after a dose, with recovery by about 21 days.

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: increased risk of neurotoxicity.

Phenytoin: possibly reduced absorption of phenytoin.

Phenobarbital: increases elimination of doxorubicin.

Stavudine: doxorubicin may inhibit effect of stavudine.

Vaccines, live: avoid use of live vaccines with doxorubicin (impairment of immune response).

* **Warfarin**: increased INR and increased risk of bleeding.

Notes: Doxorubicin is a vesicant; severe local tissue necrosis will result if extravasation occurs. Do not give intramuscularly or subcutaneously.

Monitor ECG and left ventricular ejection fraction at baseline and during treatment.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Etoposide

ATC code: L01CB01

Capsule 100 mg

Injection 20 mg/ml in 5 ml ampoule

Handle as a cytotoxic.

Special Notes: Also known as VP-16.

This entry is for etoposide not etoposide phosphate which is not equivalent.

Indications: Stage 4 neuroblastoma; germ cell tumours; intracranial germ cell tumours; rhabdomyosarcoma; soft tissue sarcomas; neuroectodermal tumours (including medulloblastoma); relapsed Hodgkin disease; non-Hodgkin lymphoma; Ewing tumour; acute lymphoblastic leukaemia; acute myeloid leukaemia.

Contraindications: Pregnancy; breastfeeding; severe hepatic impairment; allergy to polysorbate 80, etoposide, benzyl alcohol; intrathecal administration.

Precautions: Hepatic and renal impairment.

Dose:

Consult specialist protocols.

Renal impairment: Consider dose reduction.

Mild impairment: 80–85% of normal dose.

Moderate to severe impairment: 50–75% of normal dose.

Hepatic impairment: Reduce dose according to serum bilirubin concentration.

Do not use etoposide in severe hepatic impairment or if bilirubin > 85 micromol/l.

Bilirubin 20–50 micromol/l: reduce dose by 50%.

Bilirubin > 50 micromol/l: reduce dose by 75%.

Adverse effects: Common Anorexia, constipation, abdominal pain, taste alteration, weakness, malaise, myelosuppression (see below), alopecia, nausea, vomiting, oral mucositis, diarrhoea, hypersensitivity reactions.

Uncommon Hypotension (with rapid infusion), peripheral neuropathy.

Rare Heart failure, cardiac arrest, radiation recall, dermatitis, Stevens-Johnson syndrome, secondary malignancies.

MYELOSUPPRESSION Major dose-limiting adverse effect. Mainly affects white cells but platelets and red cells are also affected. Neutrophil nadir occurs 7–14 days after administration. Recovery of bone marrow usually takes about 20 days.

Interactions with other medicines (* indicates severe):

Ciclosporin: possibly increased plasma concentration of etoposide (increased risk of toxicity).

Phenobarbital: possibly reduced plasma concentration of etoposide.

Phenytoin: possibly reduced absorption of phenytoin and possibly reduced plasma concentration of etoposide.

Vaccines, live: avoid use of live vaccines with etoposide (impairment of immune response).

* **Warfarin**: possibly enhanced anticoagulant effect.

Notes: For oral therapy it may be necessary to give different doses on different days in order to administer dose within whole capsule units. Capsules should be swallowed whole on an empty stomach.

ADMINISTRATION Do not administer by rapid intravenous injection. Administer by continuous intravenous infusion or by intravenous intermittent infusion via an in-line 0.22 micron filter over at least 60 minutes at a rate not to exceed 100 mg/m^2 per hour (or 3.3 mg/kg per hour) to minimize the risk of hypotensive reactions.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Fluorouracil

ATC code: L01BC02

Injection: 50 mg/ml 5 ml vial

Handle as a cytotoxic.

Special Notes: Also referred to as 5-fluorouracil or 5FU.

Indications: Treatment and palliation of solid tumours.

Contraindications: Pregnancy; breastfeeding; dihydropyrimidine dehydrogenase deficiency.

Precautions: Pre-existing cardiac disease; hepatic impairment.

Dose:

Consult specialist protocols.

Renal impairment: Dose reduction not required.

Hepatic impairment: Severe: not recommended.

Adverse effects: Adverse effects differ depending on whether fluorouracil is given as a bolus dose or by continuous infusion. Myelotoxicity is common with bolus doses but unusual with continuous infusions. Palmar-plantar erythrodysaesthesia is common with continuous infusion.

Common Myelosuppression (see below), gastrointestinal effects including nausea, vomiting, oral mucositis and diarrhoea (see below), alopecia, itch, maculopapular rash, ovarian failure, amenorrhoea.

Uncommon Oesophagitis, gastrointestinal ulceration and bleeding, proctitis, palmar-plantar erythrodysaesthesia, photosensitivity, confusion, ataxia, nystagmus, headache, acute cerebellar syndrome, lacrimation, visual changes, photophobia.

Rare Myocardial ischaemia, arrhythmias, anaphylaxis and allergic reactions, fever without signs of infection, vein pigmentation.

MYELOSUPPRESSION Includes neutropenia, thrombocytopenia and anaemia. Neutropenic nadir occurs 9–14 days, but may be as late as 25 days, after first course. Platelet nadir occurs about 7–17 days after a dose, with recovery after about a further 10 days.

DIARRHOEA May be dose limiting and is more severe if given with calcium folinate. Consider fluid and electrolyte replacement.

Interactions with other medicines (* indicates severe):

Metronidazole: metabolism of fluorouracil inhibited (increased toxicity).

Phenytoin: metabolism of phenytoin possibly inhibited (increased risk of toxicity).

Vaccines, live: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Warfarin**: anticoagulant effect possibly enhanced.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Mercaptopurine

ATC code: L01BB02

Tablet 50 mg

Handle as a cytotoxic.

Special Notes: Also known as 6-MP or 6-mercaptopurine.

Indications: Acute lymphoblastic leukaemia; lymphoblastic lymphomas.

Contraindications: Pregnancy; breastfeeding; severe liver disease; severe bone marrow suppression; patients whose disease showed prior resistance to mercaptopurine or thioguanine.

Precautions: Renal or hepatic failure; concurrent treatment with allopurinol (see Interactions).

Dose:

Consult specialist protocols.

Renal impairment: Moderate to severe: reduce dose.

Hepatic impairment: May need dose reduction; use with caution and monitor liver function tests.

Adverse effects: Common Oral mucositis, myelosuppression (dose-dependent), cholestatic jaundice (may be reversible, but may progress to hepatic necrosis with continued treatment; onset is more common with daily doses > 2.5 mg/kg).

Uncommon Anorexia, nausea, vomiting.

Rare Hypersensitivity syndrome (e.g. fever, pancreatitis, rash, arthralgia), gastrointestinal ulceration, alopecia, hyperpigmentation, secondary leukaemia or myelodysplasia.

Interactions with other medicines (* indicates severe):

* **Allopurinol**: effects of mercaptopurine enhanced and toxicity increased; reduce dose of mercaptopurine to 25%.
* **Azathioprine**: increased risk of myelosuppression, impaired renal function, and hepatotoxicity.
* **Mesalazine**: increased risk of myelosuppression.
* **Olsalazine**: increased risk of myelosuppression.

  Phenytoin: possibly reduced absorption of phenytoin.
* **Sulfamethoxazole + trimethoprim**: increased risk of haematological toxicity.
* **Sulfasalazine**: increased risk of myelosuppression.
* **Trimethoprim**: increased risk of haematological toxicity.

  Vaccines, live: avoid use of live vaccines with mercaptopurine (impairment of immune response).
* **Warfarin**: anticoagulant effect possibly reduced.

Notes: 1 in 300 patients lack functional thiopurine methyltransferase (TPMT) activity and are at risk of severe myelosuppression unless the dose is drastically reduced. These patients may tolerate doses one tenth of normal or less; TPMT genotyping is available on a limited basis.

Mercaptopurine is best taken in the evening on an empty stomach (1 hour before or 2 hours after a meal).

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Methotrexate

ATC code: L04AX03

Powder for injection: 50 mg (as sodium salt) in vial

Tablet: 2.5 mg (as sodium salt)

Handle as a cytotoxic.

Special Notes: Also referred to as MTX.

Indications: Maintenance and remission of acute lymphoblastic leukaemia, lymphoblastic lymphoma; treatment of early stage Burkitt lymphoma, non-Hodgkin lymphoma, osteogenic sarcoma, some neurological tumours including infant brain tumours, meningeal leukaemia; treatment and prevention of neurological involvement of leukaemia.

Contraindications: Pregnancy; breastfeeding; severe renal impairment; severe hepatic impairment.

Precautions: Monitor renal and hepatic function; peptic ulceration; ulcerative colitis; diarrhoea; ulcerative stomatitis; porphyria; pre-existing bone marrow suppression; concurrent use of other hepatotoxic drugs.

Dose:

Consult specialist protocols.

High-dose methotrexate requires specialist supportive care, such as alkalinization of the urine and calcium folinate rescue; consult specialist protocols.

Renal impairment: Accumulates; nephrotoxic.

Mild: 50–100% of normal dose.

Moderate: 50% of normal dose.

Severe: contraindicated.

Or refer to instructions in specialist protocols.

Hepatic impairment: Dose-related toxicity: avoid in severe hepatic impairment.

Adverse effects: Common Myelosuppression (see below), nausea and vomiting (more frequent with high doses), oral mucositis, pulmonary toxicity (see below), hepatotoxicity (see below), rash, itch, urticaria, photosensitivity, neurotoxicity (e.g. aseptic meningitis, encephalopathy, leukoencephalopathy) with high-dose or intrathecal use.

Uncommon Malaise, fatigue, chills, fever, headache, dizziness, tinnitus, blurred vision, alopecia, ocular irritation, oligospermia (transient).

Rare Anaphylactic/anaphylactoid reactions, severe skin reactions (e.g. Stevens-Johnson syndrome, toxic epidermal necrolysis), nephrotoxicity including renal failure, osteoporosis, skin and bone necrosis, macrocytic anaemia.

MYELOSUPPRESSION Includes neutropenia, thrombocytopenia and anaemia. Neutrophil and platelet nadirs occur about 5–13 days after a bolus dose with recovery between 14 and 28 days. Neutropenia may sometimes be biphasic with the first nadir 4–7 days after a dose and the second at 12–21 days. Pancytopenia may occur and is potentially fatal.

HEPATOTOXICITY Increased aminotransferases are common and usually transient and asymptomatic. Chronic hepatotoxicity (including necrosis, fatty change, periportal fibrosis or cirrhosis) generally occurs with long-term therapy and is also dependent on cumulative dose.

PULMONARY TOXICITY Can develop rapidly and may be fatal. Often occurs as fever, dyspnoea, chest pain and dry, non-productive cough. Lesions such as pneumonitis and pulmonary fibrosis can occur at all doses at any time during treatment. Pulmonary toxicity may not be fully reversible; corticosteroids may relieve symptoms. Also consider the possibility of infection.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: reduced excretion of methotrexate (increased toxicity).

Amoxicillin: reduced excretion of methotrexate (increased risk of toxicity).

Ampicillin: reduced excretion of methotrexate (increased risk of toxicity).

Benzylpenicillin: reduced excretion of methotrexate (increased risk of toxicity).

* **Ciclosporin**: increased toxicity.

* **Cisplatin**: risk of toxicity, particularly pulmonary.

* **Dexamethasone**: increased risk of haematological toxicity.

Doxycycline: increased risk of methotrexate toxicity.

* **Hydrocortisone**: increased risk of haematological toxicity.

* **Ibuprofen**: excretion of methotrexate reduced (increased risk of toxicity).

* **Nitrous oxide**: increased antifolate effect (avoid concomitant use).

Omeprazole: increased risk of methotrexate toxicity.

Phenoxymethylpenicillin: reduced excretion of methotrexate (increased risk of toxicity).

Phenytoin: reduced absorption of phenytoin; antifolate effect of methotrexate increased.

* **Prednisolone**: increased risk of haematological toxicity.

* **Pyrimethamine**: antifolate effect of methotrexate increased.

Silver sulfadiazine: increased risk of methotrexate toxicity.

Sulfadiazine: risk of methotrexate toxicity increased.

* **Sulfadoxine + pyrimethamine**: antifolate effect of methotrexate increased; risk of methotrexate toxicity increased.

* **Sulfamethoxazole + trimethoprim**: antifolate effect of methotrexate increased (avoid concomitant use); risk of methotrexate toxicity increased.
* **Trimethoprim**: antifolate effect of methotrexate increased (avoid concomitant use).

Vaccines, live: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Warfarin**: increased risk for elevated INR and subsequent bleeding.

Notes: High-dose methotrexate may cause precipitation of methotrexate or its metabolites in renal tubules. A high fluid throughput and alkalinization of urine, using sodium hydrogen carbonate if necessary, is recommended.

Patients or their carers should be advised to report 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 toxicity (e.g. dry cough, shortness of breath).

Advise patients to avoid sunlight; wear protective clothing, wide-brimmed hats, sunglasses and lip sunscreen.

Calcium folinate rescue is required for high-dose methotrexate doses; refer to specialist protocols.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Procarbazine

ATC code: L01XB01

Capsule: 50 mg (as hydrochloride)

Handle as a cytotoxic.

Indications: Hodgkin disease, gliomas, non-Hodgkin lymphoma.

Contraindications: Pregnancy; breastfeeding.

Precautions: Renal or hepatic impairment; may potentiate CNS depression if used with other sedating drugs.

Dose:

Consult specialist treatment protocols.

Renal impairment: Severe: avoid.

Hepatic impairment: Severe: avoid.

Adverse effects: Common Myelosuppression (see below), anorexia, neurotoxicity (e.g. somnolence, depression, confusion, headache, sleep disturbances, dizziness, hallucinations, ataxia, peripheral neuropathy), nausea, vomiting, infertility (see below).

Uncommon or rare Diarrhoea, oral mucositis, alopecia, skin reactions (e.g. rash, itch, hyperpigmentation), pulmonary fibrosis, pneumonitis, haemolysis, hepatic dysfunction, fever, myalgia, arthralgia, nystagmus, diplopia, orthostatic hypotension, tachycardia, secondary malignancies (see below).

MYELOSUPPRESSION Neutrophil and platelet nadirs occur about 28 days after a dose; recovery takes about 2 weeks. Anaemia is less common.

INFERTILITY Gonadal suppression resulting in amenorrhoea or azoospermia may not be reversible and is related to dose and duration of treatment. Consider measures to preserve fertility (even when used as an immunosuppressant).

SECONDARY MALIGNANCIES All alkylating agents, and particularly combinations of alkylating agents, have been associated with secondary malignancies. Myelodysplastic syndrome, a precursor of acute leukaemia, and acute myeloid leukaemia have been reported. Median time to development of acute leukaemia is 3–4 years after chemotherapy. Solid tumours have also been reported including ovarian, bladder and gastric cancers.

Interactions with other medicines (* indicates severe):

Amitriptyline: risk of serotonin syndrome (hypertensive crisis, tremor, excitation, cardiac palpitations, angina).

Epinephrine: risk of serotonin syndrome (hypertensive crisis, tremor, excitation, cardiac palpitations, angina).

Ethanol: disulfiram-like reaction.

Fluoxetine: risk of serotonin syndrome (hypertensive crisis, tremor, excitation, cardiac palpitations, angina).

Opioids: additive CNS depression.

Phenytoin: reduced absorption of phenytoin.

Phenobarbital: increases cytotoxic activity and CNS depression.

Selective serotonin reuptake inhibitors (SSRIs): risk of serotonin syndrome (hypertensive crisis, tremor, excitation, cardiac palpitations, angina).

Tricyclic antidepressants (TCAs): risk of serotonin syndrome (hypertensive crisis, tremor, excitation, cardiac palpitations, angina).

Vaccines, live: avoid use of live vaccines with procarbazine (impairment of immune response).

Notes: Procarbazine is a weak monoamine oxidase inhibitor; some references suggest dietary restrictions limiting foods with a high tyramine content such as cheese, tea, coffee, cola drinks, wine and bananas.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Vinblastine

ATC code: L01CA01

Powder for injection: 10 mg (sulfate) in vial

IMPORTANT Intrathecal injection is contraindicated.

For intravenous administration only. Inadvertent intrathecal injection causes severe neurotoxicity, which is usually fatal.

Handle as a cytotoxic.

Indications: Disseminated Hodgkin and non-Hodgkin lymphomas; advanced testicular carcinoma; palliative treatment of Kaposi sarcoma; trophoblastic tumours.

Contraindications: Pregnancy; breastfeeding.

Precautions: Recent exposure to radiotherapy; pre-existing neurotoxicity; pre-existing pulmonary disease; liver impairment; vesicant, avoid extravasation (see Adverse effects).

Dose:
Consult specialist treatment protocols.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction may be necessary. Reduce according to bilirubin concentration.

Adverse effects: Common Myelosuppression (see below), nausea, vomiting, oral mucositis, alopecia, constipation, abdominal pain, muscle pain.

Uncommon Gastrointestinal bleeding, paralytic ileus, neurotoxicity (see below).

Rare Acute shortness of breath and bronchospasm (may be progressive), myocardial infarction.

MYELOSUPPRESSION Common and major dose-limiting effect for vinblastine. Mainly affects neutrophils with the nadir occurring about 5–10 days after a dose and recovery after a further 7–14 days. Thrombocytopenia and anaemia are less frequent.

NEUROTOXICITY Less severe with vinblastine than other vinca alkaloids.

Related to both cumulative and individual doses. Includes peripheral neuropathy (e.g. loss of deep tendon reflexes, paraesthesia, paralysis) and autonomic neuropathy (e.g. constipation, abdominal pain, paralytic ileus, urinary retention, orthostatic hypotension). Motor function impairment may occur if severe. Vestibular and auditory nerve damage may result in dizziness, nystagmus, vertigo or deafness (may be temporary or permanent). Other adverse effects related to neurotoxicity may include malaise, weakness, headache, depression, jaw pain, ataxia, hoarseness, cortical blindness, seizures, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

EXTRAVASATION Extravasation may cause cellulitis, sloughing and necrosis. If extravasation is suspected, stop infusion/injection immediately, attempt to aspirate residual drug and start extravasation treatment according to local protocol.

Interactions with other medicines (* indicates severe):

* **Bleomycin**: increased risk of cardiovascular toxicity.
* **Erythromycin**: increased toxicity of vinblastine (avoid concomitant use).

Itraconazole: increased risk of neurotoxicity and paralytic ileus.

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with vinblastine (impairment of immune response).

Voriconazole: increased plasma concentration and toxicity of vinblastine.

Notes: For children over 10 years, dilute to at least 20 ml to avoid inadvertent intrathecal use.

Injections should be dispensed with the label "For intravenous use only; administration by any other route may be fatal".

Injections of vinblastine should not be in the same room when any intrathecal medication is to be administered.

Vinblastine vials should be stored under refrigeration and protected from light.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

Vincristine

ATC code: L01CA02

Powder for injection: 1 mg; 5 mg (sulfate) in vial

IMPORTANT Intrathecal injection is contraindicated.

For intravenous administration only. Inadvertent intrathecal injection causes severe neurotoxicity, which is usually fatal.

Handle as a cytotoxic.

Special Notes: Also known by the brand name Oncovin.

Indications: Acute leukaemias, lymphomas and paediatric solid tumours.

Contraindications: Pregnancy; breastfeeding; demyelinating Charcot-Marie-Tooth syndrome.

Precautions: Use with caution in patients with hepatic impairment; avoid extravasation.

Dose:

Consult specialist treatment protocols.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction may be necessary.

Adverse effects: Common Oral mucositis, alopecia, constipation, neurotoxicity (see below).

Rare Nausea, vomiting, acute shortness of breath and bronchospasm (may be progressive), anaphylaxis, chest pain, convulsions, paralytic ileus, myelosuppression.

NEUROTOXICITY Common and major dose-limiting effect for vincristine; related to both cumulative and individual doses. Includes peripheral neuropathy (e.g. loss of deep tendon reflexes, paraesthesia, paralysis) and autonomic neuropathy (e.g. constipation, abdominal pain, paralytic ileus, urinary retention, orthostatic hypotension). Motor function impairment may occur if severe. Vestibular and auditory nerve damage may result in dizziness, nystagmus, vertigo or deafness (may be temporary or permanent). Other adverse effects related to neurotoxicity may include malaise, weakness, headache, depression, jaw pain, ataxia, hoarseness, cortical blindness, seizures, syndrome of inappropriate antidiuretic hormone secretion (SIADH).

EXTRAVASATION Extravasation may cause cellulitis, sloughing and necrosis. If extravasation is suspected, stop infusion/injection immediately, attempt to aspirate residual drug and start extravasation treatment according to local protocol.

Interactions with other medicines (* indicates severe):

Asparaginase: may decrease vincristine clearance.

Itraconazole: increased plasma vincristine and risk of toxicity.

Nifedipine: possibly reduced metabolism of vincristine.

Phenytoin: possibly reduced absorption of phenytoin.

Vaccines, live: avoid use of live vaccines with vincristine (impairment of immune response).

Voriconazole: increased plasma vincristine and risk of toxicity.

* **Warfarin**: increased INR and risk of subsequent bleeding.

Notes: For children over 10 years, dilute to at least 20 ml to avoid inadvertent intrathecal use.

Injections should be dispensed with the label "For intravenous use only. Administration by any other route may be fatal".

Injections of vincristine should not be in the same room when any intrathecal medication is to be administered.

Many centres do not give vincristine and intrathecal medication on the same day, to minimize the risk of accidental intrathecal administration of vincristine.

Give prophylactic therapy for constipation (e.g. docusate with senna).

References:
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Solimando DA Jr., ed. *Lexi-Comp's drug information handbook for oncology. 4th ed.* Hudson, Lexi-Comp, 2004.

8.3 Hormones and antihormones

The corticosteroids **prednisolone**, **dexamethasone** and **hydrocortisone** are synthetic hormones which may be given at pharmacological doses for certain malignancies, particularly haematological malignancies. However, chronic use of steroids is associated with a range of side-effects which are covered in more detail in section 18.1.

Dexamethasone

ATC code: H02AB02

Oral liquid: 0.4 mg/ml

Injection: 4 mg dexamethasone phosphate (as disodium salt) in 1 ml ampoule

Immunosuppression may occur, patients may be more susceptible to infections, avoid exposure to chickenpox and measles. Corticosteroids may activate latent opportunistic infections or exacerbate systemic fungal infections. Acute myopathy may occur with high doses, elevated intraocular pressure may occur (especially with prolonged use), CNS effects ranging from euphoria to psychosis may occur.

Indications: Used with antineoplastic drugs for acute lymphoblastic leukaemias, Hodgkin disease and non-Hodgkin lymphomas; for inflammatory or allergic reactions including those to other antineoplastic drugs; pre- and post-chemotherapy as an antiemetic (see Section 17.2).

Contraindications: Untreated systemic infection (unless condition life threatening); administration of live virus vaccines.

Precautions: Abrupt withdrawal (see below); increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis, amoebiasis, strongyloidiasis; risk of severe chickenpox in non-immune patient (varicella zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension.

ABRUPT WITHDRAWAL Dexamethasone may cause suppression of hypothalamic-pituitary-adrenal (HPA) axis, especially in younger children or those on high doses for prolonged periods. Withdrawal and discontinuation of dexamethasone should be done slowly and carefully. Consult local protocols.

Dose:

See specialist treatment protocols.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Metabolized by the liver but also by other tissues; dose reduction not necessary.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short high-dose courses cause fewer adverse effects than prolonged courses of lower doses.

Common Adrenal suppression, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, dyslipidaemia, osteoporosis, fractures, increased appetite, dyspepsia, delayed wound healing, skin atrophy,

bruising, acne, hirsutism, growth retardation in children, myopathy, muscle weakness and wasting, fat redistribution (producing cushingoid appearance), weight gain, amenorrhoea, psychiatric effects (see below).

Uncommon Osteonecrosis, particularly of the femoral and humeral heads.

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions.

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration.

Albendazole: plasma albendazole concentration possibly increased.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless dexamethasone needed to control reactions).

Calcium salts: reduced absorption of calcium salts.

* **Carbamazepine**: accelerated metabolism of dexamethasone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of dexamethasone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of dexamethasone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

* **Lopinavir**: possibly reduced plasma lopinavir concentration.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

* **Phenobarbital**: metabolism of dexamethasone accelerated (reduced effect).

* **Phenytoin**: metabolism of dexamethasone accelerated (reduced effect).

Praziquantel: plasma praziquantel concentration reduced.

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of dexamethasone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Saquinavir: possibly reduced plasma saquinavir concentration.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of dexamethasone impair immune response.

Vaccine, live: high doses of dexamethasone impair immune response; avoid use of live vaccines.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect).

Notes: Monitor body weight, blood pressure, fluid and electrolyte balance and blood glucose concentration throughout treatment in order to detect serious side-effects early.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Hydrocortisone

ATC code: H02AB09

Powder for injection: 100 mg (as sodium succinate) in vial

Hypothalamic-pituitary-adrenal (HPA) suppression may occur, acute adrenal insufficiency (adrenal crisis) may occur with abrupt withdrawal after long-term therapy or with stress; withdrawal and discontinuation of steroids should be done carefully; patients with HPA axis suppression may require doses of systemic glucocorticosteroids prior to, during and after unusual stress (e.g. surgery). Immunosuppression may occur; patients may be more susceptible to infections; avoid exposure to chicken pox and measles. Corticosteroids may activate latent opportunistic infections or exacerbate systemic fungal infections. May cause osteoporosis (at any age) or inhibition of bone growth in paediatric patients. Acute myopathy may occur with high doses, elevated intraocular pressure may occur (especially with prolonged use), and CNS effects (ranging from euphoria to psychosis) may occur.

Indications: Synthetic hormone used as an adjuvant in treatment of malignancy.

Contraindications: Untreated systemic infection (unless condition life threatening); administration of live virus vaccines.

Precautions: Avoid using higher than recommended doses; suppression of HPA function, suppression of linear growth (i.e. reduction of growth velocity), reduced bone mineral density, hypercorticism (Cushing syndrome), hyperglycaemia or glycosuria may occur; titrate to lowest effective dose. Use with extreme caution in patients with respiratory tuberculosis or ocular herpes simplex; use with caution in patients with thyroid dysfunction, cirrhosis, nonspecific ulcerative colitis, hypertension, glaucoma, myasthenia gravis, diabetes.

Dose:

See specialist treatment protocols.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not needed.

Adverse effects: The incidence of adverse effects is related to dose and duration of treatment. Short high-dose courses cause fewer adverse effects than prolonged courses of lower doses.

Common Nausea, increased appetite, adrenal suppression, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, dyslipidaemia, osteoporosis, fractures, increased appetite, dyspepsia, delayed wound healing, skin atrophy, bruising, acne, hirsutism, growth retardation in children, myopathy, muscle weakness and wasting, fat redistribution (producing cushingoid appearance), weight gain, amenorrhoea, psychiatric effects (see below).

Uncommon Osteonecrosis, particularly of the femoral and humeral heads.

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions.

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

* **Carbamazepine**: accelerated metabolism of hydrocortisone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of hydrocortisone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

* **Phenobarbital**: metabolism of hydrocortisone accelerated (reduced effect).

* **Phenytoin**: metabolism of hydrocortisone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of hydrocortisone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of hydrocortisone impair immune response.

* **Vaccines, live**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).

Notes: Monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentration throughout treatment in order to detect serious side-effects early.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Prednisolone

ATC code: H02AB06

Tablet: 5 mg; 25 mg

Oral liquid: 5 mg/ml

Hypothalamic-pituitary-adrenal (HPA) suppression may occur, acute adrenal insufficiency (adrenal crisis) may occur with abrupt withdrawal after long-term therapy or with stress; withdrawal and discontinuation of steroids should be done carefully; patients with HPA axis suppression may require doses of systemic glucocorticosteroids prior to, during and after unusual stress (e.g. surgery). Immunosuppression may occur, patients may be more susceptible to infections, avoid exposure to chickenpox and measles. Corticosteroids may activate latent opportunistic infections or exacerbate systemic fungal infections. May cause osteoporosis (at any age) or inhibition of bone growth in paediatric patients. Acute myopathy may occur with high doses, elevated intraocular pressure may occur (especially with prolonged use) and CNS effects (ranging from euphoria to psychosis) may occur.

Indications: In conjunction with antineoplastic drugs for acute lymphoblastic and chronic lymphocytic leukaemias, Hodgkin disease and non-Hodgkin lymphomas.

Contraindications: Untreated systemic infection (unless condition life threatening); administration of live virus vaccines.

Precautions: Avoid using higher than recommended doses; suppression of HPA function, suppression of linear growth (i.e. reduction of growth velocity), reduced bone mineral density, hypercorticism (Cushing syndrome), hyperglycaemia or glycosuria may occur, titrate to lowest effective dose. Use with extreme caution in patients with respiratory tuberculosis or ocular herpes simplex; use with caution in patients with thyroid dysfunction, cirrhosis, non-specific ulcerative colitis, hypertension, glaucoma, myasthenia gravis, diabetes.

Dose:

Oral:

Child *less than 1 year* initially up to 25 mg, then 5–10 mg daily;
2–7 years initially up to 50 mg, then 10–20 mg daily;
8–12 years initially up to 75 mg, then 15–30 mg daily.
The above doses are only a guide and should only be used as part of a treatment protocol which includes other antineoplastic drugs and under specialist advice.

Renal impairment: Dose reduction not needed.

Hepatic impairment: Adverse effects more common.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short high-dose courses cause fewer adverse effects than prolonged courses of lower doses.

Common Adrenal suppression, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, dyslipidaemia, osteoporosis, fractures, increased appetite, dyspepsia, delayed wound healing, skin atrophy, bruising, acne, hirsutism, growth retardation in children, myopathy, muscle weakness and wasting, fat redistribution (producing cushingoid appearance), weight gain, amenorrhoea, psychiatric effects (see below).

Uncommon Osteonecrosis, particularly of the femoral and humeral heads.

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions.

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common.

Interactions with other medicines (* indicates severe):

Acetazolamide: increased risk of hypokalaemia; antagonism of diuretic effect.

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; prednisolone reduces plasma salicylate concentration.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless prednisolone needed to control reactions).

Atenolol: antagonism of hypotensive effect.

Calcium salts: reduced absorption of calcium salts.

* **Carbamazepine**: accelerated metabolism of prednisolone (reduced effect).

Ciclosporin: increased plasma concentration of prednisolone.

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of prednisolone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of prednisolone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

* **Phenobarbital**: metabolism of prednisolone accelerated (reduced effect).

* **Phenytoin**: metabolism of prednisolone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of prednisolone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with prednisolone.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of prednisolone impair immune response.

* **Vaccine, live**: high doses of prednisolone impair immune response; avoid use of live vaccines.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose prednisolone enhances anticoagulant effect).

Notes: Monitor body weight, blood pressure, fluid and electrolyte balance, and blood glucose concentration throughout treatment in order to detect serious side-effects early.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

8.4 Medicines used in palliative care

Access to appropriate medicines is needed to ensure adequate management of the most prevalent and distressing symptoms in children with life-threatening and life-limiting conditions.

Globally, malignancy and HIV/AIDS have been identified as the most common causes of childhood mortality requiring palliative care. Based on available data, the 10 most frequent symptoms or symptom clusters requiring pharmacological management for palliative care include fatigue and weakness, pain, anorexia and weight loss, delirium and agitation, breathlessness, nausea and vomiting, constipation, depression, excess respiratory tract secretions and anxiety.

A range of medications may be used to treat these symptom clusters. Systematic evidence for the safety and efficacy of these medicines in paediatric populations is often lacking. In the absence of randomized controlled trials in paediatric populations, recommendations have been based on current best available evidence which may be extrapolated from adult studies or, in some instances, based on expert opinion.

Amitriptyline

ATC code: N06AA09

Tablet: 10 mg; 25 mg

Indications: Neuropathic pain in palliative care.

Contraindications: Recent myocardial infarction, arrhythmias (especially heart block); manic phase in bipolar disorders; severe liver disease; porphyria.

Precautions: History of epilepsy; hepatic impairment; thyroid disease; phaeochromocytoma; history of mania; psychoses or depression (may aggravate psychotic or depressive symptoms); angle closure glaucoma; history of urinary retention; concurrent electroconvulsive therapy; avoid abrupt withdrawal; anaesthesia (increased risk of arrhythmias and hypotension).

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Neuropathic pain.

Oral:

Child *2–12 years* initially 200–500 micrograms/kg (maximum 25 mg) once daily at night, increased if necessary to a maximum of 1 mg/kg twice daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Sedative effects increased (avoid in severe liver disease}.

Adverse effects: Common Sedation, dry mouth, blurred vision (disturbance of accommodation, increased intraocular pressure), constipation, nausea, difficulty in micturition, cardiovascular adverse effects particularly with high dosage including ECG changes, arrhythmias, postural hypotension, tachycardia, syncope, sweating, tremor, rash and hypersensitivity reactions (urticaria, photosensitivity).

Uncommon Behavioural disturbances, hypomania or mania, confusion or delirium, headache, interference with sexual function, blood sugar changes, increased appetite and weight gain (occasional weight loss), endocrine adverse effects such as testicular enlargement, gynaecomastia and galactorrhoea, movement disorders and dyskinesias, dysarthria, paraesthesia, taste disturbances, tinnitus, fever, abnormal liver function tests.

Rare Blood dyscrasias including agranulocytosis, leukopenia, eosinophilia, purpura and thrombocytopenia, hepatitis, paralytic ileus, syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) with hyponatraemia, seizures, prolonged QT interval.

In overdose (high rate of fatality), excitement, restlessness, marked anticholinergic effects, severe symptoms including unconsciousness, convulsions, myoclonus, hyper-reflexia, hypotension, acidosis, respiratory and cardiac depression with arrhythmias.

Interactions with other medicines (* indicates severe):

* **Alcohol**: enhanced sedative effect.
* **Atemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

Atropine: increased antimuscarinic adverse effects.

* **Carbamazepine**: antagonism of anticonvulsant effect (convulsive threshold lowered); accelerated metabolism of amitriptyline (reduced plasma concentration; reduced antidepressant effect).

Chlorphenamine: increased antimuscarinic and sedative effects.

* **Chlorpromazine**: increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias.

Codeine: possibly increased sedation.

Contraceptives, oral: antagonism of antidepressant effect by estrogens but adverse effects of amitriptyline possibly increased due to increased plasma concentration of amitriptyline.

Diazepam: enhanced sedative effect.

* **Epinephrine**: increased risk of hypertension and arrhythmias (but local anaesthetics with epinephrine appear to be safe).
* **Ethosuximide**: antagonism of anticonvulsant effect (convulsive threshold lowered).
* **Fluphenazine**: increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias.

Furosemide: increased risk of postural hypotension.

Haloperidol: increased amitriptyline concentration; possibly increased risk of ventricular arrhythmias.

Halothane: increased risk of arrhythmias and hypotension.

Hydrochlorothiazide: increased risk of postural hypotension.

Isoniazid: increased plasma concentration of isoniazid.

Ketamine: increased risk of arrhythmias and hypotension.

Levothyroxine: enhanced effects of amitriptyline.

Morphine: possibly increased sedation.

Nitrous oxide: increased risk of arrhythmias and hypotension.

* **Phenobarbital**: antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of amitriptyline possibly accelerated (reduced plasma concentration).
* **Phenytoin**: antagonism of anticonvulsant effect (convulsive threshold lowered); possibly reduced plasma amitriptyline concentration.

Rifampicin: plasma concentration of amitriptyline possibly reduced.

* **Ritonavir**: plasma concentration possibly increased by ritonavir.

Spironolactone: increased risk of postural hypotension.

Thiopental: increased risk of arrhythmias and hypotension.

* **Valproic acid**: antagonism of anticonvulsant effect (convulsive threshold lowered).
* **Warfarin**: enhanced or reduced anticoagulant effect.

References:
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Cyclizine

ATC code: R06AE03

Injection: 50 mg/ml

Tablet: 50 mg

Indications: Nausea and vomiting in palliative care including after radiotherapy or chemotherapy.

Precautions: May counteract haemodynamic effects of opioids; porphyria; glaucoma; obstructive disease of the gastrointestinal tract; hepatic disease; epilepsy; severe heart failure (cyclizine may cause a fall in cardiac output associated with increases in heart rate, mean arterial pressure and pulmonary wedge pressure).

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Dose:

Oral or *IV injection:*
Infant or **Child *1 month–6 years*** 0.5–1 mg/kg up to three times daily, maximum single dose 25 mg;
6–12 years 25 mg up to three times daily.
Continuous intravenous or *subcutaneous infusion:*
Child *1 month–2 years* 3 mg/kg over 24 hours;
2–5 years 50 mg over 24 hours;
6–12 years 75 mg over 24 hours.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Causes sedation in liver impairment (avoid).

Adverse effects: Common Urticaria, rash, drowsiness, headache, dryness of the mouth, nose and throat, blurred vision, tachycardia, urinary retention, constipation, restlessness, nervousness, insomnia and auditory and visual hallucinations have been reported, particularly when dosage recommendations have been exceeded.

Rare Cholestatic jaundice has occurred in association with cyclizine. Rare reports of cholestatic hepatitis and hypersensitivity reactions, including anaphylaxis, angioedema, allergic skin reactions and bronchospasm, have been reported in association with cyclizine. Other central nervous system effects include dystonia, dyskinesia, extrapyramidal motor disturbances, tremor, twitching, muscle spasms, seizures, disorientation, dizziness, decreased consciousness, transient speech disorders, hypertension and paraesthesia. There have also been a few reports of fixed drug eruption, apnoea, generalized chorea, hypersensitivity hepatitis, hepatic dysfunction and agranulocytosis.

Interactions with other medicines (* indicates severe):

Alcohol: cyclizine may have additive effects with alcohol and other central nervous system depressants, e.g. hypnotics, tranquillizers, anaesthetics.

Pethidine: cyclizine enhances the soporific effect of pethidine.

Anticholinergic drugs: because of its anticholinergic activity, cyclizine may enhance the side-effects of other anticholinergic drugs.

Notes: For administration by mouth, tablets may be crushed.

There have been reports of abuse of cyclizine, either oral or intravenous, for its euphoric or hallucinatory effects. The concomitant misuse of cyclizine with large amounts of alcohol is particularly dangerous, since the antiemetic effect of cyclizine may increase the toxicity of alcohol.

Direct intravenous injection may be given over 3–5 minutes.

References:

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Valoid Product Information. GlaxoSmithKline, 2009 (http://emc.medicines.org.uk/document.aspx?documentId=14783, accessed 10 February 2010).

Dexamethasone

ATC code: H02AB02

Injection: 4 mg/ml

Tablet: 2 mg

Indications: Life-threatening cerebral oedema, cerebral oedema and nausea and vomiting (chemotherapy induced).

Contraindications: Untreated systemic infection (unless cerebral oedema is life-threatening).

Precautions: Consider the relevance of these listed precautions in palliative care.

Increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis, amoebiasis, strongyloidiasis; risk of severe chickenpox in non-immune patient (varicella zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; corneal perforation.

Dose:

Life-threatening cerebral oedema.
IV:
Child *under 35 kg* 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;
over 35 kg 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.

Cerebral oedema.
Oral, IM or *IV:*
1–2 mg/kg as a single dose, followed by a maintenance dose of 1–1.5 mg/kg (maximum 16 mg) daily in four to six divided doses.

Nausea and vomiting (chemotherapy induced).
Oral or *IV:*
Child *all ages* 10 mg/m^2 (maximum 20 mg) before chemotherapy, then 5 mg/m^2 every 6 hours.

NOTE If patients are unable to swallow tablets and the intravenous route is not suitable, dexamethasone may be administered subcutaneously as either a bolus or via a syringe driver as an infusion.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Consider relevance of adverse effects in palliative care.

Common Nausea, dyspepsia, malaise, hiccups, perineal irritation after intravenous administration, adrenal suppression, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, dyslipidaemia, osteoporosis, fractures, increased appetite, delayed wound healing, skin atrophy, bruising, acne, hirsutism, growth retardation in children, myopathy, muscle weakness and wasting, fat redistribution (producing cushingoid appearance), weight gain, amenorrhoea, psychiatric effects (see below).

Uncommon Osteonecrosis, particularly of the femoral and humeral heads.

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis.

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis is less common.

Interactions with other medicines (* indicates severe):

Consider the relevance of the listed interactions in palliative care.

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration.

Albendazole: plasma albendazole concentration possibly increased.

* **Amphotericin B**: increased risk of hypokalaemia.

Calcium salts: reduced absorption of calcium salts.

* **Carbamazepine**: accelerated metabolism of dexamethasone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of dexamethasone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of dexamethasone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

* **Lopinavir**: possibly reduced plasma lopinavir concentration.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

* **Phenobarbital**: metabolism of dexamethasone accelerated (reduced effect).

* **Phenytoin**: metabolism of dexamethasone accelerated (reduced effect).

Praziquantel: plasma praziquantel concentration reduced.

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of dexamethasone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Saquinavir: possibly reduced plasma saquinavir concentration.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of dexamethasone impair immune response.

* **Vaccine, live**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect).

Notes: When used in a syringe driver with other medications, special care is needed in preparation, particularly the order of addition, to avoid precipitation. Consult specialist references.

Tablets can be dissolved in water prior to administration.

When started for symptom control, cease treatment if no improvement seen after the first week.

References:
Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

Diazepam

ATC code: N05BA01

Injection: 5 mg/ml

Oral liquid: 0.4 mg/ml

Rectal solution: 2.5 mg; 5 mg; 10 mg (can be made as an extemporaneous product in countries where a commercial product is not available)

Tablet: 5 mg; 10 mg

Indications: Seizures, muscle spasm and anxiety.

Contraindications: Respiratory depression; acute pulmonary insufficiency; sleep apnoea; severe hepatic impairment; myasthenia gravis.

Precautions: Consider the relevance of these listed precautions in palliative care.

Respiratory disease; muscle weakness; history of alcohol or drug abuse; marked personality disorder; reduce dose in debilitated patients and in hepatic impairment (avoid if severe) and renal impairment; avoid prolonged use and abrupt withdrawal; when given intravenously, facilities for reversing respiratory depression with mechanical ventilation must be at hand (see below); porphyria.

PRECAUTIONS FOR INTRAVENOUS INFUSION Intravenous infusion of diazepam is potentially hazardous (especially if prolonged) calling for close and constant observation and it is best to be carried out in a specialist centre with intensive care facilities. Prolonged intravenous infusion may lead to accumulation and delay recovery.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Seizures.
IV:
Child *all ages* 0.3–0.4 mg/kg repeated once after 10 minutes if necessary.
PR:
Neonate 1.25–2.5 mg repeated once after 10 minutes if necessary.
Infant or **Child *1 month–2 years*** 5 mg repeated once after 10 minutes if necessary;
2–12 years 5–10 mg repeated once after 10 minutes if necessary.

Muscle spasm and anxiety.
IV:
Child *all ages* 0.1–0.3 mg/kg/dose repeated 1–4 hourly as required to a maximum of 0.6 mg/kg within 8 hours.
Oral:
Child *all ages* 0.05–0.3 mg/kg/dose 8–12 hourly.

Renal impairment: Start with small doses due to increased cerebral sensitivity.

Mild impairment: dosage reduction not necessary.

Moderate to severe impairment: use small doses and titrate to response.

Hepatic impairment: Can precipitate coma.

Low doses could be used but a shorter acting agent would be preferable.

Adverse effects: Consider relevance of adverse effects in palliative care.

Common Drowsiness and lightheadedness, confusion and ataxia, amnesia.

Uncommon Dependence, paradoxical increase in aggression, muscle weakness, occasionally headache, vertigo, salivation changes, gastrointestinal disturbances, skin reactions, visual disturbances, dysarthria, tremor, changes in libido, incontinence, urinary retention, hypotension and apnoea.

Rare Blood disorders and jaundice, pain and thrombophlebitis.

Interactions with other medicines (* indicates severe):

Consider the relevance of the listed interactions in palliative care.

Alcohol: enhanced sedative effect.

Amitriptyline: enhanced sedative effect.

Chlorphenamine: enhanced sedative effect.

Chlorpromazine: enhanced sedative effect.

Clomipramine: enhanced sedative effect.

Codeine: enhanced sedative effect.

Furosemide: enhanced hypotensive effect.

Haloperidol: enhanced sedative effect.

Halothane: enhanced sedative effect.

Hydrochlorothiazide: enhanced hypotensive effect.

Isoniazid: metabolism of diazepam inhibited.

Ketamine: enhanced sedative effect.

Morphine: enhanced sedative effect.

Nitrous oxide: enhanced sedative effect.

Phenytoin: plasma phenytoin concentrations possibly increased or decreased by diazepam.

Propranolol: enhanced hypotensive effect.

Rifampicin: metabolism of diazepam accelerated (reduced plasma concentration).

* **Ritonavir**: plasma concentration possibly increased by ritonavir (risk of extreme sedation and respiratory depression; avoid concomitant use).

Spironolactone: enhanced hypotensive effect.

Thiopental: enhanced sedative effect.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Docusate sodium

ATC code: A06AA02

Capsule: 100 mg

Oral liquid: 10 mg/ml

Indications: Constipation particularly when caused by opioid use.

Contraindications: Hypersensitivity; intestinal obstruction.

Precautions: Acute abdominal pain; nausea; vomiting; concomitant use of mineral oils (do not give with liquid paraffin).

Dose:

As a laxative.
Oral:
Infant or **Child** ***6 months–2 years*** 12.5 mg three times daily;
2–12 years 12.5–25 mg three times daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Rare Abdominal cramps, diarrhoea, nausea, rash, local throat irritation, intestinal obstruction.

Interactions with other medicines (* indicates severe):

Mineral oil: may increase absorption of mineral oil.

Acetylsalicylic acid: may increase the gastrointestinal toxicity of acetylsalicylic acid.

Notes: Oral preparations may take 1–2 days to act.

Take with plenty of fluid.

Oral liquid may be given with milk, fruit juice (not grapefruit) or infant formula to mask bitter taste.

References:

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Hyoscine hydrobromide

ATC code: A04AD01

Injection: 400 micrograms/ml; 600 micrograms/ml

Transdermal patches: 1 mg/72 hours

Indications: Excessive respiratory secretions.

Contraindications: Consider the relevance of these listed contraindications in palliative care.

Closed-angle glaucoma; urinary obstruction; myasthenia gravis.

Precautions: Consider the relevance of these listed precautions in palliative care.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Excessive respiratory secretions.
Oral or *sublingual* (injection solution can be used by these routes):
Child *2–12 years* 10 micrograms/kg; maximum 300 micrograms four times daily.
SC or *IV infusion:*
Child *all ages* 40–60 micrograms/kg daily as a continuous infusion.
Transdermal:
Infant or **Child *1 month–3 years*** 250 micrograms every 72 hours (quarter of a patch);
3–10 years 500 micrograms every 72 hours (half a patch);
10–12 years 1 mg every 72 hours (one patch).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Use with caution as central nervous system side-effects occur more often in patients with hepatic impairment.

Adverse effects: Consider the relevance of these listed adverse effects in palliative care.

Common Drowsiness, dizziness, blurred vision, difficulty in micturition.

Uncommon Tachycardia, arrhythmia, hallucinations, memory impairment, insomnia, confusion, dry and/or flushed skin.

Rare Fever due to anhidrosis, anaphylaxis.

Interactions with other medicines (* indicates severe):

Consider the relevance of these listed interactions in palliative care.

Atropine: may increase therapeutic effect and risk of side-effects.

Neostigmine: may antagonize anticholinergic effect.

Pyridostigmine: may antagonize anticholinergic effect.

Notes: Administration of the patch: apply to a hairless area of skin behind the ear. If less than whole patch is required, either cut with scissors along full thickness ensuring the membrane is not peeled away or cover portion to prevent contact with the skin.

Injection solution may be given orally.

Transdermal patch may contain metal; remove before MRI.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Ibuprofen

ATC code: M01AE01

Oral liquid: 20 mg/ml

Tablet: 200 mg; 400 mg; 600 mg

Special Notes: WHO age/weight restriction: > 3 months.

Indications: Specific use for management of bone pain.

Contraindications: Hypersensitivity to acetylsalicylic acid or any other NSAIM (including asthma, angioedema, urticaria or rhinitis); active peptic ulceration.

Precautions: Consider the relevance of listed precautions in palliative care.

Renal impairment; hepatic impairment; preferably avoid if history of peptic ulceration; cardiac disease; coagulation defects; allergic disorders.

Dose:

Treatment of bone pain.

Oral:

Infant or **Child** ***over 3 months*** 5–10 mg/kg three or four times daily with or after food. Maximum daily dose is 40 mg/kg/day.

Renal impairment: Mild impairment: use lowest effective dose and monitor for sodium and water retention; deterioration in renal function possibly leading to renal failure.

Moderate to severe impairment: avoid unless on dialysis.

Hepatic impairment: Severe impairment: not recommended.

Adverse effects: Consider relevance of adverse effects in palliative care.

Common Gastrointestinal disturbances including nausea, diarrhoea.

Uncommon Dyspepsia, ulceration and haemorrhage, hypersensitivity reactions including rash, angioedema and bronchospasm, haematuria, fluid retention, raised blood pressure, renal failure, headache, dizziness, vertigo, tinnitus.

Rare Hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), colitis, aseptic meningitis, nervousness, depression, drowsiness, insomnia, photosensitivity.

Interactions with other medicines (* indicates severe):

Consider the relevance of the listed interactions in palliative care.

* **Acetylsalicylic acid**: avoid concomitant use (increased adverse effects).
* **Ciclosporin**: increased risk of nephrotoxicity.
* **Ciprofloxacin**: possibly increased risk of seizures.

Dexamethasone: increased risk of gastrointestinal bleeding and ulceration.

Digoxin: possibly exacerbation of heart failure, reduced renal function, and increased plasma digoxin concentration.

Enalapril: antagonism of hypotensive effect, increased risk of renal impairment.

* **Fluoxetine**: increased risk of bleeding.

Furosemide: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

* **Glibenclamide**: possibly enhanced effect of glibenclamide.

Heparin: possibly increased risk of bleeding.

Hydrochlorothiazide: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

Hydrocortisone: increased risk of gastrointestinal bleeding and ulceration.

* **Methotrexate**: excretion of methotrexate reduced (increased risk of toxicity).
* **Ofloxacin**: possible increased risk of seizures.

Penicillamine: possible increased risk of nephrotoxicity.

* **Phenytoin**: effect of phenytoin possibly enhanced.

Prednisolone: increased risk of gastrointestinal bleeding and ulceration.

Propranolol: antagonism of hypotensive effect.

Ritonavir: plasma concentration possibly increased by ritonavir.

Spironolactone: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia.

* **Warfarin**: anticoagulant effect possibly enhanced.

Zidovudine: increased risk of haematological toxicity.

Notes: Advise patient or carer that ibuprofen should be taken after food or milk.

Oral suspension should be shaken before use.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Midazolam

ATC code: N05CD08

Injection: 1 mg/ml; 5 mg/ml

Indications: Palliative situations such as seizures, anxiety and agitation.

Contraindications: Consider the relevance of these listed contraindications in palliative care.

Acute or severe pulmonary insufficiency; sleep apnoea syndrome; severe liver disease; myasthenia gravis.

Dose:

For all indications in a palliative care setting.

SC or *IV injection:*

Child *all ages* 0.05–0.15 mg/kg every 1–2 hours.

Continuous SC or *IV infusion:*

Child *all ages* 10 micrograms/kg/hour by continuous SC or IV infusion, initially, and titrate to effect.

There is considerable variability in the dose required.

Oral:

Child *all ages* 0.3–0.5 mg/kg (maximum 15 mg) as a single dose. Use the parenteral form; bitter taste can be disguised in apple juice or chocolate sauce.

Buccal or *intranasal:*

Child *all ages* 0.2–0.5 mg/kg per dose (maximum 10 mg) as required. Use the parenteral form.

Renal impairment: Mild to moderate impairment: no dosage reduction necessary.

Severe impairment: use sparingly and titrate according to response. Bolus doses preferred.

Patients with renal impairment may be more susceptible to central nervous system side-effects.

Hepatic impairment: Central nervous system side-effects increased; avoid in severe impairment as can precipitate coma.

Adverse effects: Common Hypotension, hiccup, cough, apnoea or respiratory depression (particularly with IV administration).

Uncommon Erythema, rash, confusion.

Rare Arrhythmias, cardiorespiratory arrest, anaphylactic reactions.

Interactions with other medicines (* indicates severe):

Atazanavir: inhibits metabolism, prolonging sedation and respiratory depressant effects.

Carbamazepine: may increase midazolam's metabolism and decrease its effect.

Erythromycin: inhibits metabolism and prolongs sedation and respiratory depressant effects.

Fluconazole: inhibits the metabolism of midazolam, prolonging its sedative and respiratory depressant effects.

Lopinavir: inhibits metabolism, prolonging sedation and respiratory depressant effects.

Phenytoin: may increase metabolism, decreasing therapeutic effects.

Rifampicin: increases metabolism, decreasing therapeutic effects.

Ritonavir: inhibits metabolism, prolonging sedation and respiratory depressant effects.

Saquinavir: inhibits metabolism, prolonging sedation and respiratory depressant effects.

Notes: Midazolam injection can be administered orally, buccally or intranasally.

Onset of action: subcutaneous 5–10 minutes, oral 60 minutes, buccal within 15 minutes.

Compatible with most drugs commonly administered via syringe driver.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
Twycross R, Wilcock A, eds. *Palliative care formulary. 3rd ed.* Nottingham, palliativedrugs.com, 2007.

Morphine

ATC code: N02AA01

Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg

Injection: 10 mg/ml

Oral liquid: 2 mg/ml

Tablet (controlled release): 10 mg, 30 mg, 60 mg

Tablet (immediate release): 10 mg

Special Notes: Drug subject to international control under the Single Convention on Narcotic Drugs (1961).

Indications: Severe pain.

Contraindications: Consider the relevance of these listed contraindications in palliative care.

Avoid in acute respiratory depression; acute alcoholism and where risk of paralytic ileus; also avoid in raised intracranial pressure or head injury (affects pupillary responses vital for neurological assessment); avoid injection in phaeochromocytoma.

Precautions: Consider the relevance of these listed precautions in palliative care.

Renal and hepatic impairment; severe withdrawal symptoms if withdrawn abruptly; hypothyroidism; convulsive disorders; decreased respiratory reserve. Adjust dose according to response; due to physiological tolerance, increased doses will be required if using long-term.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for 24 hours.

Dose:

Severe pain.

SC injection:

Neonate initially 100 micrograms/kg every 6 hours, adjusted according to response.

Infant or **Child** ***1–6 months*** initially 100–200 micrograms/kg every 6 hours, adjusted according to response;

6 months–2 years initially 100–200 micrograms/kg every 4 hours, adjusted according to response;

2–12 years initially 200 micrograms/kg every 4 hours, adjusted according to response.

Continuous SC infusion:

Infant or **Child** ***1–3 months*** 10 micrograms/kg/hour;

3 months–12 years 20 micrograms/kg/hour.

IV injection:

Neonate initially 50 micrograms/kg every 6 hours, adjusted according to response.

Infant or **Child** ***1–6 months*** initially 100 micrograms/kg every 6 hours, adjusted according to response;

6 months–12 years initially 100 micrograms/kg every 4 hours, adjusted according to response.

IV infusion:
Neonate initially by intravenous injection (over at least 5 minutes) 25–100 micrograms/kg then by continuous intravenous infusion 10–30 micrograms/kg/hour, adjusted according to response.
Infant or **Child** ***1–6 months*** initially by intravenous injection (over at least 5 minutes) 100–200 micrograms/kg then by continuous infusion 10–30 micrograms/kg/hour, adjusted to response;
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.
Oral:
Infant or **Child** ***1–12 months*** initially 80–200 micrograms/kg every 4 hours, adjusted according to response;
1–2 years initially 200–400 micrograms/kg every 4 hours, adjusted according to response;
2–12 years initially 200–500 micrograms/kg (maximum 20 mg) every 4 hours, adjusted according to response.
Controlled release tablets may be used at a dose of 0.3–0.6 mg/kg/dose every 12 hours (all ages).

Renal impairment: Reduce dose or avoid; increased and prolonged effect; increased cerebral sensitivity.

Mild impairment: 75% of normal dose.

Moderate or severe impairment: use small doses and extended dosing intervals. Titrate to response.

Hepatic impairment: Avoid or reduce dose; may precipitate coma.

Adverse effects: Consider the relevance of these listed adverse effects in palliative care.

Common Nausea, vomiting (particularly in initial stages), constipation, miosis, drowsiness, also dry mouth, anorexia, spasm of urinary and biliary tract.

Uncommon Bradycardia, tachycardia, palpitation, euphoria, decreased libido, rash, urticaria, pruritus, sweating, headache, facial flushing, vertigo, postural hypotension, hypothermia, hallucinations, confusion, dependence, larger doses produce respiratory depression, hypotension and muscle rigidity.

Rare Syndrome of inappropriate antidiuretic hormone secretion, anaphylaxis, seizure.

Interactions with other medicines (* indicates severe):

Consider the relevance of these listed interactions in palliative care.

Alcohol: enhanced sedative and hypotensive effect.

Amitriptyline: possibly increased sedation.

Chlorpromazine: enhanced sedative and hypotensive effect.

Ciprofloxacin: manufacturer of ciprofloxacin advises to avoid premedication with morphine (reduced plasma ciprofloxacin concentration) when ciprofloxacin used for surgical prophylaxis.

Diazepam: enhanced sedative effect.

Haloperidol: enhanced sedative and hypotensive effect.

Metoclopramide: antagonism of effect of metoclopramide on gastrointestinal activity.

* **Ritonavir**: possibly increases plasma concentration of morphine.

Notes: When changing routes of administration in chronically treated patients, note the oral doses are approximately half as effective as parenteral doses.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Senna

ATC code: A06AB06

Oral liquid: 1.5 mg/ml

Indications: Constipation.

Contraindications: Intestinal obstruction; undiagnosed abdominal symptoms; inflammatory bowel disease.

Dose:

Oral:
Child *1 month–2 years* 2.25–4.5 mg at bedtime;
2–5 years 3.75–7.5 mg at bedtime;
6–12 years 7.5–15 mg at bedtime.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Abdominal discomfort, diarrhoea.

Uncommon Hypokalaemia (with prolonged use or overdosage), nausea, discoloration of urine.

Rare Melanosis coli (benign reversible, occurs with chronic use).

Interactions with other medicines (* indicates severe):

None known.

Notes: Useful in combination with docusate sodium.

May be mixed with water, milk or food.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

SECTION 9:
Antiparkinsonism medicines

9 Antiparkinsonism medicines

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

SECTION 10:
Medicines affecting the blood

10 Medicines affecting the blood

10.1 Antianaemia medicines

Anaemia occurs when the blood haemoglobin concentration falls below the reference range for the age and gender of the individual. Anaemia is a major global public health problem with major consequences for child health and development. The most significant contributor to the onset of anaemia is iron deficiency. The main risk factors for iron deficiency anaemia (IDA) in children include inadequate intake of iron-containing food, especially during periods of rapid growth when iron requirements are high, and parasitic infections (e.g. hookworm). Other contributing factors include malaria, micronutrient deficiencies (e.g. folate), haemoglobinopathies (e.g. sickle cell anemia or thalassemia), and anaemia of chronic disorders such as HIV infection or tuberculosis.

For detailed clinical guidelines regarding management of anaemia in children see the *WHO Pocket Book of Hospital Care for Children*, found at (http://www.who.int/child_adolescent_health/documents/9241546700/en/index.html).

For further details on prevention of anaemia see *Guidelines for the Use of Iron Supplements to Prevent and Treat Iron Deficiency Anaemia*, found at http://www.who.int/nutrition/publications/micronutrients/anaemia_iron_deficiency/1-57881-020-5/en/index.html.

Ferrous salt

ATC code: B03AA; B03AB

Oral liquid: equivalent to 25 mg of elemental iron (as sulfate)/ml

Tablet: equivalent to 60 mg 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. Adequate precautions including the use of child-resistant containers should be taken to store iron preparations to prevent such overdoses.

Indications: Used for iron deficiency anaemia or as nutritional supplement.

Contraindications: Haemosiderosis; haemochromatosis; any form of anaemia not caused by iron deficiency; patients receiving repeated blood transfusions; parenteral iron therapy.

Precautions: Should not be administered for longer than 6 months; peptic ulcer; regional enteritis; ulcerative colitis; intestinal strictures; diverticula; overdosage (see section 4.2).

Dose:

Treatment of iron deficiency anaemia.

Oral:

Neonate 2–4 mg/kg of elemental iron daily, given in 2–3 divided doses.

Infant and **Child** 3–6 mg/kg (maximum 200 mg) of elemental iron daily, given in 2–3 divided doses.

Prevention of iron deficiency anaemia (in those at particular risk).

Oral:

Child *under 5 years* 1–2 mg/kg (maximum 30 mg) of elemental iron daily;
over 5 years 30–60 mg of elemental iron daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Constipation, diarrhoea, dark stools, nausea, epigastric pain, gastrointestinal irritation.

Uncommon Long-term or excessive administration may cause haemosiderosis.

Interactions with other medicines (* indicates severe):

Calcium salts: reduced absorption of oral ferrous salts.

Ciprofloxacin: absorption of ciprofloxacin reduced by oral ferrous salts.

* **Dimercaprol**: avoid concomitant use.

Doxycycline: absorption of oral ferrous salts reduced by doxycycline; absorption of doxycycline reduced by oral ferrous salts.

Levodopa: absorption of levodopa may be reduced by oral ferrous salts.

Levofloxacin: absorption of levofloxacin reduced by oral ferrous salts.

Levothyroxine: absorption of levothyroxine reduced by oral ferrous salts (give at least 2 hours apart).

Methyldopa: oral ferrous salts reduce hypotensive effect of methyldopa.

Ofloxacin: absorption of ofloxacin reduced by oral ferrous salts.

Penicillamine: oral ferrous salts reduce absorption of penicillamine.

Zinc sulfate: absorption of zinc and of oral ferrous salts reduced.

Notes: Iron content in artificial formula feeds should be taken into account when considering iron supplementation.

1 mg elemental iron = approximately 3 mg dried ferrous sulfate = approximately 9 mg ferrous gluconate.

Compliance may be increased by giving the total daily dose as a single daily dose. However, gastrointestinal side-effects are increased and split daily doses may be better tolerated.

Although iron preparations are best absorbed on an empty stomach, they may be taken after food to reduce gastrointestinal adverse effects. They may discolour stools.

Liquid preparations containing iron salts should be well diluted with water. If possible, swallow through a drinking straw and brush teeth after administration to prevent discoloration of the teeth.

Temporary discoloration of the teeth can be minimized by brushing the teeth with baking soda.

Increase fibre in diet to minimize constipation.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Iron deficiency anaemia: assessment, prevention and control - a guide for programme managers. Geneva, World Health Organization, 2001 (http://whqlibdoc.who.int/hq/2001/WHO_NHD_01.3.pdf, accessed 10 February 2010).
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Folic acid

ATC code: B03BB01

Tablet: 1 mg; 5 mg

Indications: Treatment of folate deficiency, megaloblastic anaemia; prevention of folate deficiency in haemolytic anaemia.

Contraindications: Should never be given without vitamin B_{12} in undiagnosed megaloblastic anaemia or other vitamin B_{12} deficiency states because of risk of precipitating subacute combined degeneration of the spinal cord; folate-dependent malignant disease.

Dose:

Treatment of folate deficiency, megaloblastic anaemia.

Oral:

Neonate to **Child *1 year*** initially 500 micrograms/kg (maximum 5 mg) once daily for up to 4 months. Up to 10 mg once daily may be required in malabsorption states;
over 1 year 5 mg daily for 4 months. Up to 15 mg daily may be required in malabsorption states.

Haemolytic anaemia.

Oral:

Child *1 month–12 years* 2.5–5 mg once daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Rare Gastrointestinal disturbances, subacute combined degeneration of the spinal cord if given without vitamin B_{12} for vitamin B_{12} deficiency states.

Interactions with other medicines (* indicates severe):

* **Phenobarbital**: plasma concentration of phenobarbital possibly reduced.
* **Phenytoin**: plasma phenytoin concentration possibly reduced.

Sulfasalazine: possibly reduced absorption of folic acid.

* **Sulfadoxine + pyrimethamine**: possibly reduced efficacy of sulfadoxine + pyrimethamine.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Hydroxocobalamin

ATC code: B03BA03

Injection: 1 mg/1ml ampoule

Special Notes: Also referred to as vitamin B_{12}.

Indications: Used in the treatment of megaloblastic anaemia due to vitamin B_{12} deficiency (pernicious anaemia).

Precautions: Should not be given before diagnosis confirmed except in emergencies; monitor serum potassium levels (arrhythmias secondary to hypokalaemia in early therapy).

Dose:

Megaloblastic anaemia without neurological involvement.

IM:

Child *1 month–12 years* initially 250 micrograms–1 mg three times weekly for 2 weeks, then 250 micrograms once weekly until the blood count is normal, then 1 mg every 3 months if required.

Megaloblastic anaemia with neurological involvement.

IM:

Child *1 month–12 years* initially 1 mg on alternate days until no further improvement occurs, then 1 mg every 2 months.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, headache, dizziness, pain at injection site.

Uncommon Fever, chills, hot flushes, hypokalaemia during initial treatment.

Rare Hypersensitivity reactions including rash and pruritus, anaphylaxis, acneiform and bullous eruptions.

Interactions with other medicines (* indicates severe):

Chloramphenicol: response to hydroxocobalamin reduced.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

10.2 Medicines affecting coagulation

Anticoagulants are used to prevent thrombus (blood clot) formation, or extension of an existing thrombus, in the slower moving venous side of the circulation.

Thromboembolic disease is increasingly recognised in neonates and children. However, coagulation systems of children and adults are different, with important implications for use of anticoagulant medications in children. Anticoagulation in children should only be undertaken with specialist supervision and careful monitoring.

Phytomenadione

ATC code: B02BA01

Injection: 1 mg/1 ml, 10 mg/ml in 5 ml ampoule

Tablet 10 mg

Intravenous injections should be given very slowly (risk of vascular collapse).

Special Notes: Also referred to as vitamin K_1, phytonadione.

Indications: Antagonist to warfarin; prophylaxis against haemorrhagic disease of the newborn.

Precautions: Hepatic impairment; not an antidote to heparin.

Dose:

Prophylaxis of haemorrhagic disease of the newborn.

IM:

Neonate 0.5–1 mg as single dose at birth.

Oral:

Neonate 2 mg followed by a second dose after 4–7 days and, for breastfed babies, a third dose after 1 month.

IV:

Pre-term neonate 400 micrograms/kg (maximum 1 mg).

NOTE The IV route is preferred by some in pre-term neonates of very low birth weight, but it does not provide the prolonged protection of the IM injection; any babies receiving IV vitamin K should be given subsequent oral doses (as per oral dosing, above).

Treatment of haemorrhagic disease of the newborn.
IV:
Neonate 1 mg with further doses if necessary every 8 hours.

Warfarin-induced hypoprothrombinaemia with no or minor bleeding.
IV:
Child *1 month–12 years* 15–30 micrograms/kg (maximum 1 mg) as a single dose, repeated as necessary.

Warfarin-induced hypoprothrombinaemia: reversal of anticoagulation or if significant bleeding; treatment of haemorrhage associated with vitamin K deficiency.
IV:
Child *1 month–12 years* 250–300 micrograms/kg (maximum 10 mg) as a single dose.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Higher doses may be required for adequate response.

Adverse effects: Uncommon Hypersensitivity reactions including flushing, dyspnoea, bronchospasm, dizziness, hypotension and respiratory or circulatory collapse which may be due to polyethoxylated castor oil surfactant in some injection formulations, rather than due to phytomenadione.

Interactions with other medicines (* indicates severe):

* **Warfarin**: vitamin K antagonizes anticoagulant effect of warfarin.

Notes: In infants with cholestatic disease, vitamin K must be given either intramuscularly or intravenously because oral absorption is likely to be impaired.

Intravenous preparations can usually be given orally. Please check specific product information.

Tablets may be chewed.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Heparin sodium

ATC code: B01AB01

Injection: 1000 units/ml; 5000 units/ml in 1 ml ampoules

Special Notes: Also referred to as UFH (unfractionated heparin) or standard heparin.

Indications: Treatment and prophylaxis of deep-vein thrombosis and pulmonary embolism. Short-acting injectable anticoagulant.

Contraindications: Hypersensitivity to heparin; haemophilia and other haemorrhagic disorders; thrombocytopenia; peptic ulcer; recent cerebral haemorrhage; severe hypertension; severe liver or renal disease; after major trauma or recent surgery (especially to eye or nervous system); acute bacterial endocarditis.

Precautions: Hepatic impairment and renal failure; hypersensitivity to low molecular weight heparins; spinal or epidural anaesthesia (risk of spinal haematoma); diabetes mellitus; acidosis; concomitant potassium-sparing drugs (increased risk of hyperkalaemia).

Dose:

Treatment of deep-vein thrombosis and pulmonary embolism.

IV:

Neonate to **Child *1 year*** initially 75 units/kg (50 units/kg if < 35 weeks corrected age), then by continuous IV infusion, 25 units/kg/hour, adjusted according to activated partial thromboplastin time (APTT) or anti-Factor Xa;

1–12 years initially 75 units/kg, then by continuous IV infusion 20 units/kg/hour, adjusted according to APTT or anti-Factor Xa.

SC:

Child *1 month–12 years* 250 units/kg every 12 hours adjusted according to APTT or anti-Factor Xa.

Prophylaxis in general surgery.

SC:

Child *1 month–12 years* 100 units/kg (maximum 5000 units) twice daily, adjusted according to APTT or anti-Factor Xa.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Hepatic impairment with impaired haemostasis: increased risk of haemorrhage. Reduce dose in severe impairment.

Adverse effects: Common Hyperkalaemia, injection site reactions, haematoma if given IM.

Uncommon Haemorrhage, haematuria, thrombocytopenia.

Rare Immune-mediated thrombocytopenia usually developing 6–10 days after commencement of therapy (requires immediate withdrawal of heparin), skin necrosis, hypersensitivity reactions including urticaria, angioedema and anaphylaxis, osteoporosis after prolonged use, alopecia, rebound hyperlipidaemia after withdrawal, priapism.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: enhanced anticoagulant effect of heparin.

Enalapril: increased risk of hyperkalaemia.

* **Glyceryl trinitrate**: anticoagulant effects reduced by infusion of glyceryl trinitrate.

Ibuprofen: possibly increased risk of bleeding.

Notes: For continuous intravenous infusion, dilute with glucose 5% or sodium chloride 0.9%.

Laboratory monitoring of coagulation activity, preferably on a daily basis, involves determination of the APTT or of the anti-Factor Xa concentration. Local guidelines on recommended APTT for neonates and children should be followed.

If haemorrhage occurs, it is usually sufficient to withdraw heparin, but if rapid reversal of heparin effects is required, protamine sulfate is a specific antidote.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Protamine sulfate

ATC code: V03AB14

Injection: 10 mg/ml in 5 ml ampoule

Indications: Used to treat heparin overdose. If used in excess it has an anticoagulant effect.

Precautions: If used in excess, protamine has an anticoagulant effect; allergic reactions increased in persons at risk including previous treatment with protamine or protamine insulin; fish allergies; rapid administration or high dose.

Dose:

Heparin overdose by IV injection or IV infusion.

IV:

Child *1 month–12 years* 1 mg of protamine neutralizes approximately 100 units of heparin if less than 30 minutes has elapsed since overdose; 500–750 micrograms if 30–60 minutes has elapsed; 375–500 micrograms if 60–120 minutes has elapsed; 250–375 micrograms if over 120 minutes has elapsed. Maximum dose 50 mg. Do not exceed a rate of 5 mg/minute.

Heparin overdose by SC injection.

IV:

Child *1 month–12 years* 1 mg neutralizes approximately 100 units of heparin. Give 50–100% of the total dose by IV injection (rate not exceeding 5 mg/minute); then give any remainder of the dose by intravenous infusion over 8–16 hours. Maximum total dose 50 mg.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Nausea, vomiting, lassitude, flushing, hypotension/hypertension.

Rare Bradycardia, dyspnoea, allergic reactions (including angioedema, anaphylaxis), cardiovascular collapse, pulmonary vasoconstriction/hypertension.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: 1 mg neutralizes approximately 100 units of unfractionated heparin when given within 15 minutes; if longer time, less protamine is needed as heparin is rapidly excreted.

Monitor activated partial thromboplastin time (APTT) or other appropriate blood clotting parameters.

Do not administer at a rate exceeding 5 mg/minute.

May be diluted if necessary with sodium chloride 0.9%.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Warfarin

ATC code: B01AA03

Tablet: 0.5 mg; 1 mg; 2 mg; 5 mg (sodium salt)

Serious and potentially fatal bleeding may occur, especially during initiation of treatment and with higher doses.

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Prophylaxis of embolization in rheumatic heart disease and atrial fibrillation; prophylaxis after insertion of prosthetic heart valve; prophylaxis and treatment of venous thrombosis and pulmonary embolism; transient ischaemic attacks.

Contraindications: Pregnancy; peptic ulcer; severe hypertension; bacterial endocarditis.

Precautions: Hepatic impairment or renal failure; recent surgery; avoid cranberry juice (risk of potentiating anticoagulant effect).

Dose:

NOTE Wherever possible, the baseline prothrombin time should be determined before the initial dose is given, but the initial dose should not be delayed while awaiting the result.

Induction dose may need to be altered according to condition (e.g. hepatic impairment, cardiac failure), concomitant interacting drugs, and if baseline INR is above 1.3.

Prophylaxis and treatment of thromboembolic disorders.

Oral:

Neonate (under specialist advice) 200 micrograms/kg as a single dose on day 1, then 100 micrograms/kg once daily for following 3 days.
However, if INR is still below 1.4, continue to use 200 micrograms/kg once daily. If the INR is above 3, change to 50 micrograms/kg once daily, and if INR is above 3.5, omit dose. Adjust ongoing therapy in accordance with INR.
Usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily, especially if bottle fed; see Notes).

Child *1 month–12 years* 200 micrograms/kg (maximum 10 mg) as a single dose on day 1, then 100 micrograms/kg (maximum 5 mg) once daily for the following 3 days.
However, if INR is still below 1.4, continue to use 200 micrograms/kg (maximum 10 mg) once daily. If the INR is above 3, change to 50 micrograms/kg (maximum 2.5 mg) once daily, and if INR is above 3.5 omit dose. Adjust ongoing therapy in accordance with INR.
Usual maintenance 100–300 micrograms/kg once daily (may need up to 400 micrograms/kg once daily especially if bottle fed; see Notes).

Renal impairment: Use with caution; avoid in severe impairment.

Hepatic impairment: Avoid in severe impairment, especially if prothrombin time already prolonged.

Adverse effects: Common Haemorrhage.

Rare Hypersensitivity, rash, alopecia, diarrhoea, unexplained drop in haematocrit, systemic cholesterol microembolism ('purple toes syndrome'), skin necrosis, jaundice, hepatic dysfunction, nausea, vomiting, pancreatitis.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: increased risk of bleeding due to antiplatelet effect.
* **Alcohol**: enhanced anticoagulant effect with large amounts of alcohol; major changes in alcohol consumption may affect anticoagulant control.

Allopurinol: anticoagulant effect possibly enhanced.

* **Amitriptyline**: enhanced or reduced anticoagulant effect.

Amoxicillin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of amoxicillin.

Ampicillin: studies have failed to demonstrate an interaction, but common experience in anticoagulant clinics is that INR can be altered by a course of ampicillin.

* **Azathioprine**: anticoagulant effect possibly reduced.
* **Azithromycin**: possibly enhanced anticoagulant effect of warfarin.
* **Carbamazepine**: accelerated metabolism of warfarin (reduced anticoagulant effect).

Cefazolin: possibly enhanced anticoagulant effect.

* **Cefixime**: possibly enhanced anticoagulant effect.
* **Ceftazidime**: possibly enhanced anticoagulant effect.
* **Ceftriaxone**: possibly enhanced anticoagulant effect.
* **Chloramphenicol**: enhanced anticoagulant effect.
* **Ciprofloxacin**: enhanced anticoagulant effect.
* **Clomipramine**: enhanced or reduced anticoagulant effect.
* **Contraceptives, oral**: antagonism of anticoagulant effect by estrogens and progestogens.
* **Dexamethasone**: anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect).
* **Doxycycline**: anticoagulant effect possibly enhanced.
* **Erythromycin**: enhanced anticoagulant effect.
* **Etoposide**: possibly enhanced anticoagulant effect.
* **Fluconazole**: enhanced anticoagulant effect.
* **Fluorouracil**: anticoagulant effect possibly enhanced.
* **Fluoxetine**: anticoagulant effect possibly enhanced.
* **Glibenclamide**: possibly enhanced hypoglycaemic effects and changes to anticoagulant effect.
* **Griseofulvin**: reduced anticoagulant effect.
* **Hydrocortisone**: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).
* **Ibuprofen**: anticoagulant effect possibly enhanced.
* **Levamisole**: anticoagulant effect possibly enhanced.
* **Levofloxacin**: possibly enhanced anticoagulant effect.
* **Levonorgestrel**: antagonism of anticoagulant effect.

Levothyroxine: enhanced anticoagulant effect.

* **Medroxyprogesterone**: antagonism of anticoagulant effect.
* **Mercaptopurine**: anticoagulant effect possibly reduced.
* **Metronidazole**: enhanced anticoagulant effect.
* **Miconazole**: enhanced anticoagulant effect.
* **Nevirapine**: enhanced or reduced anticoagulant effect.
* **Norethisterone**: antagonism of anticoagulant effect.
* **Ofloxacin**: enhanced anticoagulant effect.

Paracetamol: prolonged regular use of paracetamol possibly enhances anticoagulant effect.

* **Phenobarbital**: metabolism of warfarin accelerated (reduced anticoagulant effect).
* **Phenytoin**: accelerated metabolism of warfarin (possibility of reduced anticoagulant effect, but enhancement also reported).
* **Phytomenadione**: antagonism of anticoagulant effect by phytomenadione.
* **Prednisolone**: anticoagulant effect enhanced or reduced (high-dose prednisolone enhances anticoagulant effect).

  Proguanil: isolated reports of enhanced anticoagulant effect.
* **Quinidine**: anticoagulant effect may be enhanced.
* **Rifampicin**: accelerated metabolism of warfarin (reduced anticoagulant effect).
* **Ritonavir**: plasma concentration possibly increased by ritonavir.

  Saquinavir: possibly enhanced anticoagulant effect.
* **Silver sulfadiazine**: enhanced anticoagulant effect.
* **Simvastatin**: enhanced anticoagulant effect.
* **Sulfadiazine**: enhanced anticoagulant effect.
* **Sulfadoxine + pyrimethamine**: enhanced anticoagulant effect.
* **Sulfamethoxazole + trimethoprim**: enhanced anticoagulant effect.
* **Tamoxifen**: enhanced anticoagulant effect.
* **Testosterone**: enhanced anticoagulant effect.

  Trimethoprim: possibly enhanced anticoagulant effect.

  Vaccine, influenza: effect of warfarin occasionally enhanced.

  Valproic acid: anticoagulant effect possibly enhanced.

  Cranberry juice and products: enhanced anticoagulant effect (cranberry flavonoids inhibit CYP2C9).

  High doses of vitamin A, E or C: altered prothrombin time.

Notes: MONITORING It is essential that the INR be determined daily or on alternate days in the early days of treatment, and then at longer intervals (depending on response), then up to every 12 weeks.

Infant formula is supplemented with vitamin K, which makes formula fed infants resistant to warfarin; they may need higher doses. Breast milk contains low concentrations of vitamin K and breastfed infants are more sensitive to warfarin.

Avoid switching warfarin brands once desired therapeutic response has been achieved.

Target INR range: generally 2–3 for most indications; 2.5–3.5 for prosthetic heart valves and antiphospholipid antibody syndrome associated with thrombosis.

OTHER CONSIDERATIONS Warfarin antagonizes the effects of vitamin K and takes at least 48–72 hours for the anticoagulant effect to develop fully; if an immediate effect is required, heparin must be given concomitantly.

Foods containing high amounts of vitamin K (such as beef liver, pork liver, green tea and green leafy vegetables) can reverse the anticoagulant effects of warfarin and affect therapeutic outcomes. A balanced diet is essential. Avoid large amounts of alfalfa, asparagus, broccoli, brussel sprouts, cabbage, cauliflower, green teas, kale, lettuce, spinach, turnip greens, watercress.

High doses of vitamin A, E or C may alter prothrombin time, use fish oils or omega 3 with caution and avoid large amounts of liver, avocado, soy protein, soybean, papain.

Avoid herbal teas or remedies (e.g. tonka beans, melilot, woodruff) as these contain natural coumarins and may increase the effect of warfarin.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

SECTION 11:
Blood products and plasma substitutes

11 Blood products and plasma substitutes

11.1 Plasma substitutes

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

11.2 Plasma fractions for specific use

Blood coagulation factors

Factor VIII is essential for blood clotting and the maintenance of effective haemostasis. Von Willebrand factor is a mediator in platelet aggregation and also acts as a carrier for factor VIII. Blood coagulation factors VII, IX and X are essential for the conversion of factor II (prothrombin) to thrombin clot.

Deficiency in any of these factors results in haemophilia, a group of X-linked bleeding disorders affecting 1 in 7000 males, most commonly presenting as bleeding into joints. Haemophilia A is factor VIII deficiency and haemophilia B is factor IX deficiency. Bleeding episodes in haemophilia require prompt treatment with replacement therapy.

Human normal immunoglobulin

Normal immunoglobulin solution is used as a source of antibody replacement in primary immunodeficiencies, and to modify the immune response in conditions such as Kawasaki disease.

Factor VIII concentrate

ATC code: B02BD02

Dried

Special Notes: Also known as antihaemophilic factor or Von Willebrand factor complex.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Control of haemorrhage in haemophilia A.

Contraindications: Previous anaphylactic reaction to factor VIII concentrate.

Precautions: Intravascular haemolysis after large or frequently repeated doses in patients with blood groups A, B or AB (less likely with high potency, highly purified concentrates).

Dose:

Haemophilia A.

Slow IV infusion:

Administer according to patient's needs and specific preparation used. For every 1 international unit per kg body weight of factor VIII activity administered, factor VIII level should increase by 2 international units/ml (or 2%); calculated dosage should be adjusted to the actual vial size. Calculation for units required, based on desired increase in factor VIII (% of normal). International units required = body weight (kg) x 0.5 x desired increase in factor VIII (international units/ml or % of normal).

NOTE This calculation assumes the patient's baseline factor VIII level is < 1%.

Renal impairment: Dose adjustment not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Allergic reactions including chills and fever, headache, urticaria.

Rare Pseudothrombocytopenia, elevated ALT.

Interactions with other medicines (* indicates severe):

Activated prothrombin complex concentrates.

Notes: IV compatibility: general advice is not to administer with any other drugs or IV fluids.

All plasma fractions should comply with the WHO requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (revised 1992). WHO Expert Committee on Biological Standardization forty-third report, WHO Technical Report Series, No. 840, 1994, Annex 2.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Factor IX complex (coagulation factors II, VII, IX, X) concentrate

ATC code: B02BD01

Dried

Special Notes: Both human and animal derived products are available.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Replacement therapy for factor IX deficiency in haemophilia B; bleeding due to deficiencies of factors II, VII or X.

Contraindications: Disseminated intravascular coagulation; hypersensitivity to mouse or hamster protein (if not the human form); fibrinolysis.

Precautions: Risk of thrombosis (probably less risk with highly purified preparations); because of this risk, use with caution in liver dysfunction, postoperative period, neonates or disseminated intravascular coagulation.

Dose:

Replacement therapy for factor IX deficiency in haemophilia B or bleeding due to deficiencies of factors II, VII or X as well as IX.
Slow IV infusion: administer according to patient's needs and specific preparation used.
Calculation for units required to raise blood level %.
Using Benefix.
Neonate, Infant or **Child** number of factor IX international units required = body weight (in kg) x desired factor IX level increase (% normal) x 1.4 international units/kg.
Using AlphaNine SD, Mononine.
Neonate, Infant or **Child** number of factor IX international units required = body weight (in kg) x desired factor IX level increase (% normal) x 1 international unit/kg.

GENERAL GUIDELINES

Minor spontaneous haemorrhage, prophylaxis.
Desired levels of factor IX for haemostasis: 15–25%.
Initial loading dose to achieve desired level: up to 20–30 international units/kg.
Frequency of dosing: every 12–24 hours.
Duration of treatment: 1–2 days.

Moderate haemorrhage.
Desired levels of factor IX for haemostasis: 25–50%.
Initial loading dose to achieve desired level: 25–50 international units/kg.
Frequency of dosing: every 12–24 hours.
Duration of treatment: 2–7 days.

Major haemorrhage.
Desired levels of factor IX for haemostasis: > 50%.
Initial loading dose to achieve desired level: 30–50 international units/kg.
Frequency of dosing: every 12–24 hours depending on half-life and measured factor IX levels (after 3–5 days, maintain at least 20% activity).
Duration of treatment: 7–10 days, depending upon nature of insult.

Surgery.
Desired levels of factor IX for haemostasis: 50–100%.
Initial loading dose to achieve desired level: 50–100 international units/kg.
Frequency of dosing: every 12–24 hours, depending on half-life and measured factor IX levels.
Duration of treatment: 7–10 days, depending upon nature of insult.

Renal impairment: Dose adjustment not necessary.

Hepatic impairment: Dose adjustment not necessary.

Adverse effects: Common Allergic reactions including chills and fever, flushing, headache, nausea, vomiting, urticaria.

Uncommon Disseminated intravascular coagulation, thrombosis following high doses in haemophilia B patients.

Notes: IV compatibility: general advice is not to administer with any other drugs or IV fluids.

All plasma fractions should comply with the WHO requirements for the collection, processing and quality control of blood, blood components and plasma derivatives (revised 1992). WHO Expert Committee on Biological Standardization forty-third report, WHO Technical Report Series, No. 840, 1994, Annex 2.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Human normal immunoglobulin

ATC code: J06BA02

Intramuscular administration: 16% protein solution*

Intravenous administration: 5%; 10% protein solution**

Subcutaneous administration: 15%; 16% protein solution*

Intravenous human normal immunoglobulin may very rarely induce thromboembolic events and should be used with caution in those with risk factors for arterial or venous thrombotic events and in obese individuals.

Normal immunoglobulin may interfere with the immune response to live virus vaccines which should therefore only be given at least 3 weeks before or 3 months after an injection of normal immunoglobulin (this does not apply to yellow fever vaccine since normal immunoglobulin does not contain antibody to this virus).

Special Notes: *Indicated for primary immune deficiency.

**Indicated for primary immune deficiency and Kawasaki disease.

NOTE Formulations from different manufacturers vary and should not be regarded as equivalent; consult individual manufacturer's product literature.

Indications: Replacement therapy in primary immunodeficiency; Kawasaki disease.

Contraindications: Hypersensitivity to immunoglobulin or blood products.

Precautions: IM PREPARATION Use with caution in patients with thrombocytopenia or coagulation disorders.

Dose:

Consult individual manufacturer's product literature for dose and administration recommendations for specific diseases; recommended doses may vary to those listed below.

Replacement therapy in primary immune deficiencies.
IV infusion:
Child *all ages* initial loading dose, administer until serum IgG level is > 6 g/l.
IV, IM or *SC* (depending on formulation):
Child *all ages* maintenance dose, normally 400–800 mg/kg/month, titrated according to intercurrent infections or trough serum IgG level. *IV* doses may be given at 1, 2, 3 or 4 week intervals. *SC* doses may be given at 1, 2, 3, 4 or 7 day intervals.

Kawasaki disease.
IV infusion:
Infant or **Child** 2 g/kg as a single dose, given over 10–12 hours; if signs and symptoms persist, re-treatment with a second 2 g/kg infusion should be considered. Must be used in combination with acetylsalicylic acid.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Nausea, vomiting, headache (may develop 24 hours after infusion), dizziness, dry mouth, chills, sweating, hypothermia, fever, eczema, rash, urticaria, hypotension, wheezing, anaphylactoid reactions.

Rare Immune haemolysis, aseptic meningism, increased plasma viscosity, hypercoagulopathy, renal impairment.

Interactions with other medicines (* indicates severe):

Live virus vaccines (measles, mumps, rubella): see Warnings.

Notes: IV compatibility: general advice is not to administer with any other drugs or IV fluids.

IV infusion over 2–12 hours.

ADMINISTRATION Infusion rates of < 8 g per hour are recommended. Immunoglobulin should be administered under the supervision of an immunologist or other experienced physician. In general, this should be in a hospital with adequate facilities for monitoring the infusion as well as the condition for which it is being administered, until the patient is stable, when treatment at home can be considered after formal training in an expert centre.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

SECTION 12:
Cardiovascular medicines

12 Cardiovascular medicines

12.1 Antianginal medicines

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

12.2 Antiarrhythmic medicines

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

12.3 Antihypertensive medicines

Hypertension

Blood pressure (BP) in children is classified according to centile charts according to age, gender and height. Hypertension in children is therefore defined as either systolic and/or diastolic BP ≥ 95th percentile measured on three or more separate occasions.

The goals of initial management of children with hypertension are to:

- establish whether it is secondary to an underlying cause which can be treated
- manage hypertensive emergencies
- determine if medication is required for blood pressure control
- assess and manage any associated cardiovascular risk factors (e.g. diabetes or obesity).

Specialist assessment and advice should be sought when possible.

Management

Hypertension which is severe (e.g. 5 mmHg greater than the 99th percentile) or symptomatic requires urgent pharmacological management. Symptoms suggestive of a hypertensive emergency include headache, seizures, altered conscious state, focal neurological symptoms or signs, visual disturbance or clinical features suggestive of cardiac failure (e.g. respiratory distress, chest pain). Controlled reduction in blood pressure should occur over a period of 72–96 hours, since rapid reduction can cause "end organ damage". Controlled reduction should therefore be undertaken in hospital with careful supervision and monitoring.

In hypertension which is mild to moderate and is not symptomatic, nonpharmacological measures (e.g. dietary measures such as salt restriction, management of obesity) should be considered. Pharmacological management may also be required, depending on duration of hypertension, any evidence of associated end organ damage (e.g. left ventricular hypertrophy or retinopathy), and associated conditions including other cardiovascular risk factors (e.g. diabetes mellitus).

Enalapril

ATC code: C09AA02

Tablet: 2.5 mg; 5 mg

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Hypertension; heart failure.

Contraindications: Hypersensitivity to angiotensin-converting enzyme (ACE) inhibitors (including angioedema); renovascular disease; pregnancy.

Precautions: Use with diuretics; hypotension with first doses, especially in patients on diuretics, on a low-sodium diet, on dialysis, if dehydrated, or with heart failure; peripheral vascular disease or generalized atherosclerosis (risk of clinically silent renovascular disease); use with great care in severe or symptomatic aortic stenosis; monitor renal function before and during treatment; renal impairment; hepatic impairment; possibly increased risk of agranulocytosis in collagen vascular disease; history of idiopathic or hereditary angioedema (use with care or avoid).

USE WITH DIURETICS Risk of very rapid falls in blood pressure in volume-depleted patients; treatment should therefore be initiated with very low doses. High-dose diuretic therapy should be discontinued, or dose significantly reduced, at least 24 hours before starting enalapril (may not be possible in heart failure; risk of pulmonary oedema). If high-dose diuretic cannot be stopped, medical supervision advised for at least 2 hours after administration or until blood pressure is stable.

ANAPHYLACTOID REACTIONS Avoid enalapril during dialysis with high-flux polyacrilonitrile membranes and during low-density lipoprotein apheresis with dextran sulfate; also withhold before desensitization with wasp or bee venom.

Dose:

Hypertension and heart failure.

Oral:

Neonate initially 10 micrograms/kg once daily, increased as necessary up to 500 micrograms/kg daily in 1–3 divided doses. Monitor blood pressure and urine output carefully for at least 2 hours following first dose and during dose escalation until blood pressure is stable.

Infant or **Child** initially 100 micrograms/kg once daily. Monitor blood pressure carefully for 1–2 hours, increased as necessary up to a maximum of 1 mg/kg daily in 1–2 divided doses.

Renal impairment: Use with caution in all degrees of impairment and monitor response. Start with a lower initial dose and adjust according to response. Hyperkalaemia and other adverse effects more common.

Hepatic impairment: Closely monitor liver function in patients with hepatic impairment.

Adverse effects: Common Hypotension, cough, hyperkalaemia, headache, dizziness, fatigue, nausea, renal impairment.

Uncommon Anaphylactoid reactions, angioedema (early or delayed onset), rash, itching, palpitations, chest pain, flushing, fever, taste disturbances, vomiting, anorexia, diarrhoea, constipation, stomatitis, dry mouth, sore throat, hoarseness, muscle cramps, elevated hepatic aminotransferases and bilirubin, abnormal dreams.

Rare Hepatitis (cholestatic or hepatocellular), pancreatitis, proteinuria, hyponatraemia, thrombocytopenia, neutropenia, aplastic anaemia, agranulocytosis, haemolytic anaemia, eosinophilia, myalgia, arthralgia, neuropathy, paraesthesia, photosensitivity, psoriasis, pemphigus, toxic epidermal necrolysis, gynaecomastia, visceral angioedema, Raynaud syndrome.

Interactions with other medicines (* indicates severe):

* **Acetazolamide**: enhanced hypotensive effect.

Acetylsalicylic acid: antagonism of hypotensive effect; risk of renal impairment when acetylsalicylic acid given in doses of over 300 mg daily.

Alcohol: enhanced hypotensive effect.

* **Amiloride**: enhanced hypotensive effect; increased risk of severe hyperkalaemia.

Amlodipine: enhanced hypotensive effect.

Antacids (aluminium hydroxide; magnesium hydroxide): absorption of enalapril reduced.

Atenolol: enhanced hypotensive effect.

Chlorpromazine: enhanced hypotensive effect.

* **Ciclosporin**: increased risk of hyperkalaemia.

Dexamethasone: antagonism of hypotensive effect.

Diazepam: enhanced hypotensive effect.

Fluphenazine: enhanced hypotensive effect.

* **Furosemide**: enhanced hypotensive effect.

Haloperidol: enhanced hypotensive effect.

Halothane: enhanced hypotensive effect.

Heparin: encreased risk of hyperkalaemia.

* **Hydrochlorothiazide**: enhanced hypotensive effect.

Hydrocortisone: antagonism of hypotensive effect.

Ibuprofen: antagonism of hypotensive effect, increased risk of renal impairment.

Insulins: hypoglycaemic effect possibly enhanced.

Ketamine: enhanced hypotensive effect.

* **Lithium**: enalapril reduces excretion of lithium (increased plasma lithium concentration).

Nitrous oxide: enhanced hypotensive effect.

* **Potassium salts**: increased risk of severe hyperkalaemia.

Prednisolone: antagonism of hypotensive effect.

Propranolol: enhanced hypotensive effect.

Sodium nitroprusside: enhanced hypotensive effect.

* **Spironolactone**: enhanced hypotensive effect; increased risk of severe hyperkalaemia (monitor plasma potassium concentration with low-dose spironolactone in heart failure).

Thiopental: enhanced hypotensive effect.

Notes: Tablets may be crushed and suspended in water immediately before use.

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.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

12.4 Medicines used in heart failure

Heart failure in children is less common than in adults, and can be due to left-to-right shunts (e.g. septal defects), valvular disease (e.g. in rheumatic heart disease), myocardial dysfunction or high-output heart failure (e.g. anaemia). Rheumatic heart disease remains a very large cause of heart failure in the developing world.

Digoxin

ATC code: C01AA05

Injection: 250 micrograms/ml in 2 ml ampoule

Oral liquid: 50 micrograms/ml

Tablet: 62.5 micrograms; 250 micrograms

Indications: Chronic heart failure.

Contraindications: Hypertrophic obstructive cardiomyopathy (unless also atrial fibrillation and heart failure); myocarditis; constrictive pericarditis; Wolff-Parkinson-White syndrome and atrial fibrillation concurrently; ventricular tachycardia or fibrillation; intermittent complete heart block; second-degree atrioventricular block.

Precautions: Recent myocardial infarction; sick sinus syndrome; severe pulmonary disease; thyroid disease; renal impairment; avoid hypokalaemia; avoid rapid intravenous administration (nausea and risk of arrhythmias).

Dose:

Chronic heart failure.

Oral:

Neonate *under 1.5 kg* initially 25 micrograms/kg in three divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses;
Neonate *1.5–2.5 kg* initially 30 micrograms/kg in three divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses;
Neonate *over 2.5 kg* or **Child *under 2 years*** initially 45 micrograms/kg in three divided doses for 24 hours then 10 micrograms/kg/day in 1–2 divided doses.
Child *2–5 years* initially 35 micrograms/kg in three divided doses for 24 hours then 10 micrograms/kg/day in 1–2 divided doses;
5–10 years initially 25 micrograms/kg (maximum 750 micrograms) in three divided doses for 24 hours then 6 micrograms/kg/day (maximum 250 micrograms daily) in 1–2 divided doses;
over 10 years initially 0.75–1.5 mg in three divided doses for 24 hours then 62.5–250 micrograms/daily in 1–2 divided doses (higher doses may be necessary).

Intravenous:

Neonate *under 1.5 kg* initially 20 micrograms/kg in three divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses;
Neonate *1.5–2.5 kg* initially 30 micrograms/kg in three divided doses for 24 hours then 4–6 micrograms/kg/day in 1–2 divided doses;
Neonate *over 2.5 kg* or **Child *under 5 years*** initially 35 micrograms/kg in three divided doses for 24 hours then 10 micrograms/kg/day in 1–2 divided doses.
Child *5–10 years* initially 25 micrograms/kg (maximum 500 micrograms) in three divided doses for 24 hours then 6 micrograms/kg/day (maximum 250 micrograms daily) in 1–2 divided doses;
over 10 years initially 0.5–1 mg in three divided doses for 24 hours then 62.5–250 micrograms daily in 1–2 divided doses (higher doses may be necessary).

Renal impairment: Reduce dose in all degrees of impairment; toxicity increased by electrolyte disturbances.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Anorexia, nausea, vomiting, diarrhoea, blurred vision, visual disturbances, confusion, drowsiness, dizziness, nightmares, agitation, depression.

Uncommon Acute psychosis, delirium, amnesia, shortened QRS complex, atrial or ventricular extrasystoles, paroxysmal atrial tachycardia with AV block, ventricular tachycardia or fibrillation, heart block, gynaecomastia (long-term use).

Rare Xanthopsia (yellow vision), rash, thrombocytopenia, seizures.

Interactions with other medicines (* indicates severe):

* **Acetazolamide**: hypokalaemia caused by acetazolamide increases cardiac toxicity of digoxin.
* **Amphotericin B**: hypokalaemia caused by amphotericin B increases cardiac toxicity of digoxin.

Antacids (aluminium hydroxide; magnesium hydroxide): possibly reduced absorption of digoxin.

Atenolol: increased risk of AV block and bradycardia.

Azithromycin: increased plasma concentration of digoxin (increased risk of toxicity).

Calcium salts: large intravenous doses of calcium salts can precipitate arrhythmias.

* **Chloroquine**: plasma digoxin concentration possibly increased.
* **Ciclosporin**: increased plasma concentration of digoxin (increased risk of toxicity).

Dexamethasone: increased risk of hypokalaemia.

Erythromycin: increased plasma concentration of digoxin (increased risk of toxicity).

* **Furosemide**: hypokalaemia caused by furosemide increases cardiac toxicity of digoxin.

Gentamicin: possibly increased plasma concentration of digoxin.

* **Hydrochlorothiazide**: hypokalaemia caused by hydrochlorothiazide increases cardiac toxicity of digoxin.

Hydrocortisone: increased risk of hypokalaemia.

Ibuprofen: possibly exacerbation of heart failure, reduced renal function, and increased plasma digoxin concentration.

Mefloquine: possibly increased risk of bradycardia.

* **Nifedipine**: possibly increased plasma concentration of digoxin.

Penicillamine: plasma concentration of digoxin possibly reduced.

Phenytoin: plasma concentration of digoxin possibly reduced.

Prednisolone: increased risk of hypokalaemia.

Propranolol: increased risk of AV block and bradycardia.

* **Quinidine**: plasma concentration of digoxin increased (halve dose of digoxin).
* **Quinine**: plasma concentration of digoxin increased.

Rifampicin: plasma concentration of digoxin possibly reduced.

Salbutamol: possibly reduced plasma concentration of digoxin.

* **Spironolactone**: plasma concentration of digoxin increased.

Sulfamethoxazole + trimethoprim: plasma concentration of digoxin possibly increased.

Sulfasalazine: absorption of digoxin possibly reduced.

Suxamethonium: risk of ventricular arrhythmias.

Timolol: increased AV block and bradycardia.

Trimethoprim: plasma concentration of digoxin possibly increased.

* **Verapamil**: increased plasma concentration of digoxin; increased AV block and bradycardia.

Notes: MONITORING For plasma digoxin concentration assay, blood should ideally be taken at least 6 hours after a dose, preferably prior to next dose, plasma digoxin concentration should be maintained in the range 0.8–2 micrograms/litre.

Unwanted effects depend both on the concentration of digoxin in the plasma and on 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 1.5–3 micrograms/litre for digoxin. Renal function is very important in determining digoxin dosage.

Signs of digoxin toxicity may include: anorexia, nausea, vomiting, dizziness, bradycardia and heart block. Patients at highest risk are those with renal impairment.

ADMINISTRATION For intravenous infusion, dilute with sodium chloride 0.9% or glucose 5% to a maximum concentration of 62.5 micrograms/ml; loading doses should be given over 30–60 minutes and maintenance doses over 10–20 minutes. Protect from light.

For oral administration, oral solution must not be diluted.

Doses may need to be reduced if digoxin (or another cardiac glycoside) has been given in the preceding 2 weeks. When changing 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 into account varying bioavailabilities.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Furosemide

ATC code: C03CA01

Injection: 10 mg/ml in 2 ml ampoule

Oral liquid: 4 mg/ml

Tablet: 40 mg

To avoid ototoxicity, intravenous doses should be given no faster than 0.5 mg/kg per minute (doses < 120 mg) or 4 mg/minute (doses ≥ 120 mg).

Special Notes: Also referred to as frusemide.

Indications: Oedema associated with heart failure.

Contraindications: Renal failure with anuria; precomatose states associated with liver cirrhosis.

Precautions: Monitor electrolytes particularly potassium and sodium; hypotension; renal impairment; hepatic impairment.

Dose:

Oedema in heart failure.

Oral:

Neonate 0.5–2 mg/kg every 12–24 hours (every 24 hours if corrected age under 31 weeks).

Infant or **Child** 0.5–2 mg/kg 2–3 times daily; higher doses may be required in resistant oedema; maximum 12 mg/kg (80 mg) daily.

IV:

Neonate 0.5–1 mg/kg every 12–24 hours (every 24 hours if corrected age under 31 weeks).

Infant or **Child** 0.5–1 mg/kg (maximum 4 mg/kg) repeated every 8 hours as necessary.

Renal impairment: Contraindicated in anuria.

Higher doses are usually required in impairment; renal function may worsen; monitor electrolytes and creatinine.

Treatment with nephrotoxic drugs increases risk of nephrotoxicity with loop diuretics; use combinations carefully, especially in renal impairment.

Hepatic impairment: Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this).

Adverse effects: Most adverse effects are dose related.

Common Hyponatraemia, hypokalaemia, hypomagnesaemia, dehydration, hyperuricaemia, gout, dizziness, orthostatic hypotension, syncope.

Uncommon Dyslipidaemia, increased creatinine concentration, hypocalcaemia, rash.

Rare Tinnitus, vertigo, deafness (especially with rapid intravenous administration), acute pancreatitis, jaundice, thrombocytopenia, haemolytic anaemia, agranulocytosis, interstitial nephritis, exfoliative dermatitis, Stevens-Johnson syndrome, bullous eruptions, allergic reactions.

Interactions with other medicines (* indicates severe):

* **Amikacin**: increased risk of ototoxicity.

Amitriptyline: increased risk of postural hypotension.

Amphotericin B: increased risk of hypokalaemia.

Carbamazepine: increased risk of hyponatraemia.

Chlorpromazine: enhanced hypotensive effect.

Cisplatin: increased risk of nephrotoxicity and ototoxicity.

Dexamethasone: antagonism of diuretic effect; increased risk of hypokalaemia.

Diazepam: enhanced hypotensive effect.

* **Digoxin**: hypokalaemia caused by furosemide increases cardiac toxicity of digoxin.

* **Enalapril**: enhanced hypotensive effect.

Ethanol: enhanced hypotensive effect.

* **Gentamicin**: increased risk of ototoxicity.

Halothane: enhanced hypotensive effect.

Hydrochlorothiazide: increased risk of hypokalaemia.

Hydrocortisone: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

Insulins: antagonism of hypoglycaemic effect.

Ketamine: enhanced hypotensive effect.

Lidocaine: action of lidocaine antagonized by hypokalaemia caused by furosemide (interaction less likely when lidocaine used topically).

* **Lithium**: reduced lithium excretion (increased plasma lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide.

Nitrous oxide: enhanced hypotensive effect.

Prednisolone: antagonism of diuretic effect; increased risk of hypokalaemia.

Propranolol: enhanced hypotensive effect.

* **Quinidine**: cardiac toxicity of quinidine increased by hypokalaemia caused by furosemide.

Salbutamol: increased risk of hypokalaemia with high doses of salbutamol.

* **Streptomycin**: increased risk of ototoxicity.

Thiopental: enhanced hypotensive effect.

* **Vancomycin**: increased risk of ototoxicity.

Notes: Advise patient or carer when taking furosemide twice daily, to take the first dose in the morning and the second dose before 18:00 to prevent overnight diuresis.

Monitor potassium during therapy. Consider the addition of potassium-sparing diuretics or potassium supplements.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Dopamine

ATC code: C01CA04

Injection: 40 mg/ml (hydrochloride) in 5 ml vial

Indications: Cardiac failure.

Contraindications: Tachyarrhythmia; phaeochromocytoma; manufacturer contraindicates treatment with halogenated hydrocarbon general anaesthetics or ergot alkaloids.

Precautions: Correct hypovolaemia before initiating treatment; maintain blood volume during treatment; correct hypoxia, hypercapnia and metabolic acidosis before or at same time as starting treatment; history of peripheral vascular disease (increased risk of ischaemia of extremities).

Dose:

Cardiac failure.

Continuous intravenous infusion:

Neonate initially 3 micrograms/kg/minute adjusted according to response to a maximum of 20 micrograms/kg/minute.

Infant or **Child** initially 5 micrograms/kg/minute adjusted according to response to a maximum of 20 micrograms/kg/minute.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Ectopic beats, nausea, vomiting, tachycardia, angina, palpitations, dyspnoea, headache, hypotension or hypertension.

Uncommon Abnormal ventricular conduction, bradycardia, piloerection, uraemia, mydriasis, vasoconstriction, extravasation (may cause necrosis and sloughing of surrounding tissue).

Rare Allergic reaction (if sodium metabisulfite in product).

Interactions with other medicines (* indicates severe):

Chlorpromazine: antagonism of hypertensive effect.

Ergometrine: increased risk of ergotism.

Fluphenazine: antagonism of hypertensive effect.

Haloperidol: antagonism of hypertensive effect.

Notes: For continuous intravenous infusion, dilute to a maximum 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 extravasation and fluid overload. Incompatible with bicarbonate and other alkaline solutions.

In neonates the response to inotropic sympathomimetics varies considerably, particularly in those born prematurely; careful dose titration and monitoring are necessary.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

12.5 Antithrombotic medicines

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

12.6 Lipid-lowering agents

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

SECTION 13:
Dermatological medicines (topical)

13 Dermatological medicines (topical)

13.1 Antifungal medicines

"Tinea" refers to a skin or nail infection with a dermatophyte (ringworm) fungus. Other fungi, such as *Candida*, can cause local skin infections as well as more serious systemic infections. Local treatments are often effective, and the choice of agent is often dictated by local availability and price. More severe infections may require systemic treatments.

Benzoic acid + Salicylic acid

ATC code: D01AE20

Cream or ointment: 6% + 3%

Special Notes: Also known as Whitfield's ointment.

Indications: Mild fungal skin infections, particularly localized tinea pedis and tinea corporis.

Precautions: Contact with eyes, mucous membranes, face and genitals; prolonged use; large areas.

Administration:

Fungal skin infections.
Topical:
Infant or **Child** apply twice daily until the infected skin is shed (usually at least 4 weeks).

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Uncommon Occasionally localized, mild inflammatory reaction.

Rare Skin ulceration, erosion, salicylate intoxication, systemic absorption.

Salicylate intoxication Although rare, topical use of salicylic acid has resulted in salicylate intoxication, particularly in babies and young children when applied in large amounts or when used under occlusion. Symptoms include confusion, dizziness, headaches, rapid breathing, tinnitus; deaths have occurred.

Interactions with other medicines (* indicates severe):

Warfarin: topical salicylates may be absorbed in sufficient amounts to cause an increase in INR, increasing risk of bleeding; avoid combinations.

Notes: Benzoic acid + salicylic acid are both mild irritants and can themselves cause dermatitis.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Miconazole

ATC code: D01AC02

Cream or ointment: 2% (nitrate)

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Fungal skin infections.

Administration:

Fungal skin infections.

Topical:

Child *all ages* apply twice daily to clean dry lesions, continuing for at least 10 days after the condition has cleared.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Uncommon Occasional local irritation and burning, stinging, itch, contact dermatitis; discontinue if sensitization occurs.

Rare Allergic reactions.

Interactions with other medicines (* indicates severe):

NOTE Drug interactions may occur rarely with miconazole as some absorption occurs from topical products.

Amphotericin B: possible antagonism of effects of amphotericin B.

Carbamazepine: plasma concentration of carbamazepine possibly increased.

* **Warfarin**: enhanced anticoagulant effect.

Notes: Continue using the treatment for 10 days after symptoms have gone.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Selenium sulfide

ATC code: D01AE13

Detergent based suspension: 2%

Indications: Pityriasis versicolor; seborrhoeic dermatitis.

Contraindications: Children under 5 years.

Precautions: Do not apply to damaged skin (risk of systemic toxicity); avoid contact with eyes; do not use within 48 hours of applying preparations for hair colouring, straightening or permanent waving.

Administration:

Pityriasis versicolor.

Topical:

Child *over 5 years* apply with a small amount of water to the entire affected area and leave for 30 minutes. Apply 2–7 times over 2 weeks; repeat course if necessary.

Seborrhoeic dermatitis.
Topical:
Child *over 5 years* massage 5–10 ml of suspension into wet hair and leave for 5–10 minutes before rinsing off thoroughly; repeat twice weekly for 2 weeks, then once weekly for 2 weeks and then as necessary.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Local irritation, skin discoloration (when applied topically for the treatment of tinea versicolor).

Uncommon Rebound oiliness of the scalp, hair discoloration (minimized by careful rinsing after treatment) or loss.

Rare Absorption may result in systemic toxicity including tremors, weakness, lethargy, loss of appetite, pain in lower abdomen, occasional vomiting (symptoms usually resolve within 10 days of discontinuing the medicine).

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: To minimize absorption, rinse hair thoroughly after use and remove all traces from skin (including nails).

Contact with eyes should be avoided; if contact occurs, the affected eye(s) should be rinsed thoroughly with water.

Patients should be advised to remove all jewellery before using the lotion, since selenium sulfide may damage it.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

13.2 Anti-infective medicines

Staphylococcal and streptococcal infections of the skin, such as impetigo, folliculitis, furunculosis, erysipelas and cellulitis, are very common.

Minor localized infections can often be treated with local treatments. Widespread superficial or deep-seated skin infections associated with fever require treatment with a **systemic antibiotic** (sections 6.2.1 and 6.2.2).

Methylrosanilinium chloride (gentian violet)

ATC code: D01AE02

Aqueous solution: 0.5%

Tincture: 0.5%

Special Notes: Also known as gentian violet or crystal violet.

Carcinogenic in animal studies and its use is restricted in some countries.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Fungal and bacterial skin infections.

Contraindications: Excoriated or ulcerated lesions, broken skin, mucous membranes; porphyria.

Administration:

Fungal and bacterial skin infections.
Topical:
Child apply two or three times daily for 3 days.

Renal impairment: No dose reduction required.

Hepatic impairment: No dose reduction required.

Adverse effects: Common Irritation and ulceration of mucous membranes if exposed to them, temporary skin staining.

Uncommon Severe irritation: discontinue treatment.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
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Neomycin sulfate + Bacitracin

ATC code: D06AX04

Ointment: 5 mg neomycin sulfate + 250 IU bacitracin zinc/g

Special Notes: BACITRACIN This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Bacterial skin infections.

Contraindications: Neonates.

Precautions: Avoid application to substantial areas of skin or to broken skin (risk of significant systemic absorption); occlusive dressings; overgrowth of resistant organisms on prolonged use.

LARGE AREAS If large areas of skin are being treated, ototoxicity may be a hazard in children, particularly in those with renal impairment.

Administration:

Bacterial skin infections.
Topical:
Infant or **Child** apply a thin layer three times daily (short-term use).

Renal impairment: Any systemic absorption in patients with renal impairment may cause increased side effects, particularly nephrotoxicity and ototoxicty.

Hepatic impairment: No dose reduction necessary.

Adverse effects: Common Hypersensitivity reactions (including contact dermatitis, burning, erythema, rash and urticaria).

Rare Anaphylactoid reactions, systemic absorption leading to nephrotoxicity and irreversible ototoxicity (particularly in renal impairment or in the presence of an occlusive dressing, including nappies).

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Topical neomycin is a contact sensitizer, especially when used for long periods of time. Sensitivity has been reported to occur in 5–15% of patients treated with the drug.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Potassium permanganate

ATC code: D08AX06

Aqueous solution: 1:10 000 (0.01%)

Indications: Assist healing of suppurating superficial wounds, tropical ulcers, tinea pedis, pemphigus and impetigo.

Contraindications: Avoid occlusive dressings.

Precautions: Irritant to mucous membranes.

Administration:

Suppurating superficial wounds and tropical ulcers.
Topical:
Child wet dressings of 1:10 000 (0.01%) solution, changed two or three times daily; tropical ulcers also require treatment for 2–4 weeks with procaine benzylpenicillin (section 6.2.1).

Tinea pedis.
Topical:
Child soak severe weeping lesions in 1:10 000 (0.01%) solution every 8 hours.

Impetigo and superficial crusts.
Topical:
Child crusts should be gently separated with a 1:10 000 (0.01%) solution.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Local irritation, skin and fabrics stained brown.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Potassium permanganate is sometimes supplied as an aqueous stock solution of 1 in 1000 (0.1%) for dilution before use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Silver sulfadiazine

ATC code: D06BA01

Cream: 1%

Use with caution if allergic to sulfonamides or the preservative agent used, e.g. chlorhexidine.

Owing to the association of sulfonamides with severe blood and skin disorders, treatment should be stopped immediately if blood disorders or rashes develop. Leukopenia 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).

Special Notes: WHO age/weight restriction: > 2 months.

Indications: Prophylaxis and treatment of infection in burns.

Contraindications: Hypersensitivity to sulfonamides; pregnancy; < 2 months age.

Precautions: Renal or hepatic impairment; large areas; G6PD deficiency.

Administration:

Prophylaxis and treatment of infection in burns.

Topical:

Child *over 2 months* apply using aseptic technique daily (more frequent if volume of exudate is large) while there is a possibility of infection, or until healing is complete.

Renal impairment: Use with caution in patients with impaired renal function, particularly those receiving treatment for extensive burns.

Hepatic impairment: Severe: use with caution.

Adverse effects: Common Pain, rash, burning, itching.

Rare Necrosis of skin, erythema multiforme, skin discoloration due to deposition of silver, transient neutropenia, transient leukopenia, development of bacterial resistance, hypersensitivity reactions, argyria and sulfonamide induced systemic toxicity.

Interactions with other medicines (* indicates severe):

When used over large areas of skin, plasma sulfadiazine concentrations may approach therapeutic levels and when this occurs the interactions below apply.

Sulfadiazine can cause nephrotoxicity; administration with other nephrotoxic drugs may result in additional renal adverse effects.

Sulfadiazine is a folate antagonist and will add to the effects on bone marrow of other folate antagonists, e.g. pyrimethamine.

Ciclosporin: sulfadiazine may decrease ciclosporin concentration and efficacy; monitor ciclosporin concentration and adjust dose as necessary.

Hexamine hippurate: hexamine requires low urine pH for effect; there is an increased risk of crystalluria with sulfonamides as they are poorly soluble at low pH; avoid combination.

Phenytoin: sulfadiazine inhibits metabolism of phenytoin, increasing its concentration and risk of adverse effects; monitor phenytoin concentration and for adverse effects; decrease phenytoin dose if necessary.

Notes: Some preparations may contain chlorhexidine 0.2%.

Apply with sterile gloved hands or spatula in a 3–5 mm layer.

Chlorhexidine (cation) is inactivated by anionic agents such as soap; do not use together.

Silver sulfadiazine may inactivate enzymatic debriding agents.

Plasma sulfadiazine concentrations may approach therapeutic levels with side-effects and interactions as for sulfonamides if large areas of skin are treated.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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13.3 Anti-inflammatory and antipruritic medicines

Eczema is a very common condition of infancy and childhood. Treatments include local application emollients, and, when needed, topical steroids. Topical steroids are available in a range of strengths and potencies. Treatment should be tailored to the degree of inflammation and dryness of the skin. Any associated infection should also be treated.

Betamethasone

ATC code: D07AC01

Cream or ointment: 0.1% (as valerate)

Special Notes: WHO age/weight restriction: hydrocortisone preferred in neonates.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Severe inflammatory skin conditions.

Contraindications: Untreated skin infections; broken skin; rosacea; acne; perioral dermatitis; viral skin lesions; widespread plaque psoriasis.

Precautions: Children (avoid prolonged use and use under specialist supervision); psoriasis (may precipitate severe pustular psoriasis on withdrawal); adrenal suppression if used on a large area of the body or for a long time, particularly with an occlusive dressing; use on the face or groin; secondary infection requires treatment with an appropriate antimicrobial.

Use of more than 100 g per week of 0.1% preparation likely to cause adrenal suppression.

Administration:

NOTE Use the smallest amount for the shortest period of time to avoid adverse effects. Reduce use once improvement occurs. Discontinue use once control is achieved. Reassess diagnosis if no improvement is seen within 2 weeks.

Severe inflammatory skin conditions.
Topical:
Child apply a small quantity to the affected area one to two times daily.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, dilatation of superficial blood vessels, formation of striae, purpura, depigmentation, telangiectasia, acneiform eruptions at site of application.

Uncommon Allergic contact dermatitis.

Rare Hyperaesthesia, subcutaneous tissue atrophy, hypertrichosis, systemic effects (growth retardation, hypothalamic-pituitary-adrenal axis suppression with prolonged or widespread use (particularly under occlusion), hyperglycaemia, Cushing syndrome, cataract, glaucoma).

Interactions with other medicines (* indicates severe):

Use of topical corticosteroids is less likely to result in drug interactions than systemic use, but interactions may occur rarely.

Acetylsalicylic acid: corticosteroids may decrease salicylate concentration when high-dose acetylsalicylic acid is used, e.g. in Kawasaki disease; monitor salicylate concentration and clinical effect; increase acetylsalicylic acid dose if necessary; be particularly careful to reduce the acetylsalicylic acid dose when withdrawing the corticosteroid.

NSAIMs: oral corticosteroids increase risk of gastric ulceration with NSAIMs; consider need for an NSAIM carefully; if an NSAIM cannot be avoided, use lowest effective dose for shortest period of time.

Rifampicin: increased metabolism of corticosteroid and may reduce activity; monitor clinical effect and increase corticosteroid dose if needed.

Warfarin: corticosteroids may increase warfarin's anticoagulant effect, increasing the risk of bleeding; monitor INR and decrease warfarin dose if necessary.

Notes: Occlusive, wet dressings (never plastic) may be used if condition is severe.

Tachyphylaxis may occur. Use minimum amount necessary to control symptoms. Intermittent use (i.e. 2 days on, 2 days off) may at times be appropriate.

Consider bone mineral density assessment for children receiving large and long-term doses of topical corticosteroids.

Dermatologist consultation advisable if using on the face.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Calamine lotion

ATC code: D04AX

Lotion

Indications: Mild pruritus.

Administration:

Mild pruritus.
Topical:
Child apply liberally 3–4 times daily.

Renal impairment: Dosage reduction not needed.

Hepatic impairment: Dosage reduction not needed.

Adverse effects: No adverse effects noted in literature.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Shake bottle well before use.

Avoid contact with eyes.

Do not use on open wounds or burns.

Calamine preparations are of little value for the treatment of insect stings or bites.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Hydrocortisone

ATC code: D07AA02

Cream or ointment: 1% (acetate)

Indications: Mild inflammatory skin disorders.

Contraindications: Untreated skin infections; broken skin; rosacea; acne; perioral dermatitis.

Precautions: Children (avoid prolonged use); occlusive dressings increase penetration into keratinized lesions; secondary infection requires treatment with an appropriate antimicrobial.

Administration:

Mild inflammatory skin disorders.

Topical:

Neonate, Infant or **Child** apply a small quantity to the affected area 1–2 times daily until improvement occurs, then less frequently.

Renal impairment: No dose reduction required.

Hepatic impairment: No dose reduction required.

Adverse effects: When used according to directions on small area of skin, adverse effects do not usually occur.

Common Folliculitis, steroid rosacea, perioral dermatitis, skin atrophy, delayed wound healing, dilatation of superficial blood vessels, formation of striae, purpura, depigmentation, telangiectasia, acneiform eruptions at site of application.

Uncommon Allergic contact dermatitis.

Rare Hyperaesthesia, subcutaneous tissue atrophy, hypertrichosis, systemic effects (growth retardation, hypothalamic-pituitary-adrenal axis suppression with prolonged or widespread use (particularly under occlusion), hyperglycaemia, Cushing syndrome, cataract, glaucoma).

Interactions with other medicines (* indicates severe):

NOTE Interactions do not generally apply to hydrocortisone used for topical application.

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

* **Carbamazepine**: accelerated metabolism of hydrocortisone (reduced effect).

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of hydrocortisone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.
* **Phenobarbital**: metabolism of hydrocortisone accelerated (reduced effect).
* **Phenytoin**: metabolism of hydrocortisone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of hydrocortisone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of hydrocortisone impair immune response.

* **Vaccine, live**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.
* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).

Notes: Tachyphylaxis to topical treatment may occur, therefore best used intermittently once control is achieved.

Consider bone mineral density assessment for children receiving large and long-term doses of topical corticosteroids or any child supplemented with oral corticosteroids.

Topically, hydrocortisone is a mild corticosteroid.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
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13.4 Astringent medicines

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

13.5 Medicines affecting skin differentiation and proliferation

Acne vulgaris

Acne typically first appears during puberty when androgenic stimulation triggers excessive production of sebum.

Mild acne usually responds to topical therapy alone and heals without scarring. In moderate acne, where there are more extensive pustules causing mild scarring, oral antibiotics such as a **tetracycline** or **erythromycin** (section 6.2.2) are commonly used. Severe acne is a distressing condition that may warrant further treatment with systemic medications under specialist supervision.

Psoriasis

Psoriasis can occur at any age. Various biological events may trigger psoriasis, such as streptococcal or viral infection, psychological stress or medication (e.g. beta-blockers, chloroquine, lithium and NSAIMs).

Management of psoriasis depends on the site and extent of the disease and the age of the child.

Warts

Warts are common, benign and self-limiting. When required, warts can often be effectively treated through application of a keratolytic agent such as salicylic acid, taking care to protect the surrounding skin. Podophyllum resin is an alternative agent.

Benzoyl peroxide

ATC code: D10AE01

Cream or lotion: 5%

Indications: Mild to moderate acne; adjunct to oral therapy in more severe cases.

Precautions: Avoid contact with eyes, mouth, and mucous membranes; avoid use of occlusive dressings; avoid excessive exposure to sunlight; may bleach fabrics, hair and skin.

Administration:

Acne.

Topical:

Child initially apply to clean skin on alternate days, increasing frequency to one to two times daily as tolerance to irritant effect develops.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Initial irritation but subsides with continued use (in some cases may need to reduce frequency or temporarily suspend use), skin dryness or peeling, feeling of warmth, mild stinging or erythema.

Rare Contact sensitivity occurs, occasionally even one application can cause severe irritation.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: If acne does not respond after 2 months then use of a topical antibacterial should be considered.

Cleanse skin before applying and gently pat dry.

Apply a thin layer to the affected area and rub in gently. Wash hands after application.

Avoid contact with eyes, lips and other sensitive areas.

Avoid contact with hair and coloured fabric as bleaching or discoloration may occur.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Coal tar

ATC code: D05AA

Solution: 5%

Special Notes: Preparations containing up to 6% coal tar may be used on children 1 month–2 years.

Preparations containing coal tar 10% may be used on children over 2 years with more severe psoriasis.

Indications: Psoriasis.

Contraindications: Inflamed, broken or infected skin; pustular psoriasis; presence of infection.

Precautions: Avoid eyes, mucosa, genital or rectal areas; skin protection possibly required to reduce photosensitivity reactions; may stain skin, hair (especially fair, bleached or grey hair) and clothing.

Administration:

Psoriasis.

Topical:

Child apply 1–3 times daily. A solution more dilute than 5% may be preferable to start.

Coal tar bath:

Child use 100 ml of solution in an adult-size bath of tepid water (proportionally less for a child's bath) and soak for 10–20 minutes; use once daily to once every 3 days for at least 10 baths.

Renal impairment: No dose reduction required.

Hepatic impairment: No dose reduction required.

Adverse effects: Common Mild stinging.

Rare Sterile folliculitis, irritant reactions, allergic reactions, photosensitivity, acne-like eruptions, hypersensitivity, skin, hair and fabrics discoloured.

CARCINOGENICITY Evidence is conflicting. Some epidemiological studies have raised the possibility of skin malignancies in patients with psoriasis with very high exposure to tar and/or ultraviolet radiation. Other studies have found no conclusive evidence of this.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Coal tar solutions are usually extemporaneous preparations and can be prepared in different strengths. Different strengths of solution should be available on request from compounding pharmacies.

Coal tar is often alternated with ultraviolet (UVB) rays, allowing at least 24 hours between exposure and treatment with coal tar.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Podophyllum resin

ATC code: D06BB04

Solution: 10% to 25%

Special Notes: Podophyllotoxin is the major active ingredient of podophyllum.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: External anogenital warts; plantar warts.

Contraindications: Pregnancy; breastfeeding; children under 2 years.

Precautions: Avoid use on large areas, mucous membranes; very irritant to eyes; keep away from face; avoid contact with normal skin and open wounds.

Administration:

NOTE Must be applied by a trained health-care professional.

External anogenital warts; plantar warts.

Topical:

Child *over 2 years* apply carefully to warts, avoiding contact with normal tissue; rinse off with soap and water after 6 hours; may be repeated at weekly intervals but no more than 4 times in all; only a few warts to be treated at any one time.

Renal impairment: No dose reduction required.

Hepatic impairment: No dose reduction required.

Adverse effects: Common Irritation, staining of skin.

Uncommon Burning, inflammation, pain, erosion.

Rare Systemic effects resulting from cutaneous absorption or after ingestion include nausea, vomiting, abdominal pain, diarrhoea, thrombocytopenia, leukopenia, renal failure, hepatotoxicity, CNS effects including acute psychotic reactions, hallucinations, confusion, dizziness, stupor, ataxia, hypotonia, seizures, coma, peripheral and autonomic neuropathies.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: An example of an application to treat warts. Various drugs can serve as alternatives.

Often causes considerable irritation to the treated area and is therefore only suitable for children who are able to cooperate with treatment.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Salicylic acid

ATC code: D01AE12

Solution: 5%

Salicylate toxicity may occur particularly with prolonged use, application to large areas or if used on neonatal skin.

Indications: Hyperkeratotic conditions.

Contraindications: Broken or inflamed skin; children under 2 years.

Precautions: Significant peripheral neuropathy; patients with diabetes at risk of neuropathic ulcers; avoid contact with eyes, mouth, anogenital region and mucous membranes; avoid application to large areas.

Administration:

Hyperkeratotic skin disorders.

Topical:

Child *over 2 years* apply once daily, starting with lower strength preparations; gradually increase strength until satisfactory response obtained.

Renal impairment: Dosage reduction not required.

Hepatic impairment: Dosage reduction not required.

Adverse effects: Common Local irritation, dermatitis, salicylism on excessive application or treatment of large areas.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Protect surrounding skin and avoid broken skin.

For use on warts, soak area in warm water for 5 minutes, dry area thoroughly and then apply solution.

Salicyclic acid preparations are usually prepared extemporaneously using salicyclic acid powder. Different strength preparations can be requested from compounding pharmacies.

Salicylic acid for the treatment of warts is usually prepared extemporaneously in an ointment using powdered salicyclic acid; different strengths can be prepared as required.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Urea

ATC code: D02AE01

Cream or ointment: 10%

Special Notes: Also known as carbamide.

Indications: Hydrating agent and keratolytic for dry, scaling and itching skin conditions.

Precautions: Avoid application to face or broken skin; avoid contact with eyes.

Administration:

Dry, scaling and itching skin conditions.
Topical:
Child apply twice daily, preferably while skin is still moist after washing or bathing.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Transient stinging and local irritation.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

13.6 Scabicides and pediculicides

Scabies

Scabies is caused by a mite, *Sarcoptes scabiei*, that burrows into the skin. It is readily transmitted from person to person, and therefore the entire household must be treated at the same time to prevent re-infection. Although it is not necessary to take a bath before treatment with an acaricide, all clothing and bedding should be washed to prevent reinfection.

Pediculosis (lice)

Pediculosis of the head and body is caused by *Pediculus humanus capitis* and *Pediculus humanus corporis*, respectively. Pubic lice (crab lice) infestations are caused by *Pthirus pubis*, which may also affect the eyelashes and brows. All are transmitted by person-to-person contact, and may also contaminate clothing and bedding. All members of the affected household (and sexual contacts) must be treated at the same time, and clothing and bedding should be washed or exposed to the air; in head lice infestations, hair brushes and combs should also be disinfected.

Benzyl benzoate

ATC code: P03AX01

Lotion: 25%

Special Notes: WHO age/weight restriction: > 2 years.

Not the treatment of choice for scabies. Permethrin is preferred.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Scabies; head, body and pubic lice.

Precautions: Do not use on inflamed or broken skin; avoid contact with eyes and mucous membranes.

Administration:

Scabies.

Topical:

Child *over 2 years* apply over whole body with a brush (except for face and head); repeat without bathing on the following day and wash off 24 hours later. A third application may be needed in some cases.

Head, body and pubic lice.

Topical:

Child *over 2 years* apply to affected area and wash off 24 hours later. Further applications are possibly needed after 7 and 14 days.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Local irritation, particularly in children.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Can be irritant, especially in patients with eczema, so perform a 10 minute patch test prior to body application.

Bathing in hot water prior to application is no longer recommended as it may increase absorption and toxicity.

Scabies itch is often worse in first 24 hours.

Avoid eye contact.

Thoroughly clean all clothing and bed linen.

Exclude treated patients from contact with hairy toys.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Sansom L, ed. *Australian pharmaceutical formulary and handbook. 20th ed.* Curtin, Pharmaceutical Society of Australia, 2006.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Permethrin

ATC code: P03AC04

Cream: 5%

Lotion: 1%

Indications: Scabies; head and body lice.

Precautions: Do not use on inflamed or broken skin; avoid contact with eyes; do not use on secondarily infected skin.

Administration:

Scabies and body lice.

Topical:

Child *over 2 months* apply cream 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, treat again. Repeat application after 7 days. Pay particular attention to the areas between the fingers and toes, wrists, axillae, genital area and buttocks.

Head lice.

Topical:

Child *over 2 months* apply lotion to clean damp hair and rinse off after 10 minutes. Rinse completely, then remove eggs and dead lice from hair with a fine comb, preferably made of metal. Repeat in 7–10 days if necessary.

Renal impairment: No dosage reduction required.

Hepatic impairment: No dosage reduction required.

Adverse effects: Common Local irritation, pruritus, erythema, stinging.

Rare Rashes and oedema.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Avoid mucous membranes.

Thoroughly clean all clothing and bed linen.

Exclude treated patients from contact with hairy toys.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
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SECTION 14:
Diagnostic agents

14 Diagnostic agents

14.1 Ophthalmic medicines

For general information on the use of eye drops, see section 21.

Fluorescein is used in ocular diagnostic procedures and for locating damaged areas of the cornea due to injury or disease.

Tropicamide is a short-acting, relatively weak mydriatic that dilates the pupil and paralyses the ciliary muscle for up to 4–6 hours. It facilitates examination of the fundus of the eye. It carries the potential to cause CNS disturbances in children in rare cases.

Fluorescein

ATC code: S01JA01

Eye drops: 1% (sodium salt)

Indications: Diagnosis of corneal abrasions, ulcers and foreign bodies.

Contraindications: Avoid use with soft contact lenses.

Precautions: SKILLED TASKS Transient blurring of vision, warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for several hours.

Dose:

Diagnosis of corneal abrasions, ulcers and foreign bodies.
Ocular instillation (into the eye):
Child *all ages* instil sufficient solution dropwise to stain damaged area.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Temporarily stains skin, urine, tears and nasal secretions yellow, may permanently stain soft contact lenses and clothing.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Tropicamide

ATC code: S01FA06

Eye drops: 0.5%

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Short-acting mydriatic which facilitates the examination of the fundus for diagnostic ophthalmic procedures.

Contraindications: Glaucoma; adhesions between the iris and the lens.

Precautions: Hypermetropic (long-sighted) (may precipitate acute angle-closure glaucoma); darkly pigmented iris (more resistant to pupillary dilatation; exercise caution to avoid overdosage).

SKILLED TASKS Transient blurring of vision; warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery, for several hours.

Dose:

Dilatation of pupil to examine the fundus.
Ocular instillation:
Child *all ages* 1 drop, 15–20 minutes before examination of eye.

Renal impairment: No dose reduction necessary.

Hepatic impairment: No dose reduction necessary.

Adverse effects: Common Intolerance to bright light (glare), stinging on instillation, blurred vision (especially near vision), transient intraocular pressure elevation (especially in pre-existing ocular hypertension).

Uncommon Persistent ocular irritation (mucus discharge, severe watering discharge, superficial punctate keratopathy and characteristically no itch, punctal stenosis with prolonged use (years), insomnia, drowsiness.

Rare Systemic toxicity, e.g. dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Neonates are at increased risk of systemic toxicity.

To minimize systemic absorption, apply finger pressure on the lacrimal sac for 1–2 minutes following instillation of the ophthalmic solution.

Avoid contact of bottle tip with skin or eye.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

14.2 Radiocontrast media

Radiographic contrast media are needed for defining soft tissue structures such as blood vessels, stomach, bowel loops and body cavities that are not otherwise visualized by standard X-ray examination. Radiocontrast media should only be used in specialized facilities under the supervision of radiologists.

Barium sulfate

ATC code: V08BA01

Aqueous suspension

Indications: Radiographic examination of gastrointestinal tract.

Contraindications: Intestinal obstruction; intestinal perforation.

Precautions: Conditions which predispose to intestinal obstruction such as pyloric stenosis or lesions; conditions with risk of perforation such as acute ulcerative colitis, diverticulitis, or after rectal or colonic biopsy, sigmoidoscopy or radiotherapy; hereditary fructose intolerance (some preparations may contain fructose).

Dose:

Radiographic examination of gastrointestinal tract.

Child *all ages* route and dosage depend on procedure and preparation used (consult manufacturer's literature and/or specialist physician/radiographer).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Constipation or diarrhoea.

Rare Gastrointestinal obstruction, appendicitis, abdominal cramps and bleeding, perforation of bowel resulting in peritonitis, adhesions, granulomas, electrocardiographic changes with rectal administration, pneumonitis or granuloma formation may occur following accidental aspiration into lungs.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Ensure adequate hydration after procedure to prevent severe constipation.

Monitor electrolytes as some preparations contain sodium and potassium.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Polibar Product Information. E–Z–EM, 2009 (http://emc.medicines.org.uk/medicine/22332/SPC/Polibar/, accessed 10 February 2010).

SECTION 15:
Disinfectants and antiseptics

15 Disinfectants and antiseptics

Although disinfectants and antiseptics are not medicines, their use remains important for minimizing transmission of infections within hospitals (nosocomial infections). Adequate sterilization of equipment and medical care surfaces; washing of hands between patients; adequate antiseptic care of surgical sites; antiseptic care during invasive procedures; and topical umbilical cord care all contribute to control of nosocomial infection spread.

15.1 Antiseptics

An antiseptic is a disinfectant that destroys or inhibits growth of microorganisms on living tissues without causing harm when applied to surfaces of the body or to exposed tissues.

Chlorhexidine

ATC code: D08AC02

Solution: 5% (digluconate) for dilution

Solution: 20% (digluconate) (needs to be diluted prior to use for cord care)

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Antiseptic; disinfection of clean instruments.

Precautions: Aqueous solutions are susceptible to microbial contamination, use sterilized preparation or freshly prepared solution and avoid contamination during storage or dilution; instruments with cemented glass components (avoid preparations containing surface active agents); irritant (avoid contact with middle ear, eyes, brain and meninges); not for use in body cavities; alcoholic solutions not suitable before diathermy; syringes and needles treated with chlorhexidine (rinse thoroughly with sterile water or saline before use); inactivated by cork (use glass, plastic or rubber closures); ethanol-based solutions are flammable.

Administration:

Antiseptic (pre-operative skin disinfection and hand hygiene).
Topical:
Child *all ages* use 0.5% solution in ethanol (70%) or 2 or 4% detergent solution.

Antiseptic (wounds, burns and other skin damage).
Topical:
Child *all ages* apply 0.05% aqueous solution.

Disinfection of clean instruments.
Immerse for at least 30 minutes in 0.05% solution. The addition of 0.1% sodium nitrate minimizes metal corrosion.

Emergency disinfection of clean instruments.
Immerse for 2 minutes in 0.5% solution in ethanol (70%).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Skin sensitivity and irritation.

Rare Corneal damage due to contact, hypersensitivity reactions.

Interactions with other medicines (* indicates severe):

Inactivated by soaps and other anionic materials. Activity may be reduced in the presence of suspending agents, insoluble powders or compounds. Insoluble salts may form in hard water. Chlorhexidine is inactivated by cork.

Notes: Most active against Gram-positive bacteria, with some Gram-negative activity. Spores and hydrophilic viruses are resistant. Chlorhexidine gluconate may be mixed with quaternary ammonium compounds (QAC) for broader antimicrobial activity.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Ethanol

ATC code: D08AX08

Solution: 70% (denatured)

Special Notes: Also known as alcohol.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Disinfection of skin prior to injection, venepuncture or aseptic procedures.

Precautions: Avoid broken skin; when used as a surgical skin prep, avoid pooling under patient and allow to dry before using diathermy.

Administration:

Disinfection of skin prior to injection, venepuncture or surgical procedures.
Topical:
Child *all ages* apply 70% solution.
Do not use absolute ethanol as it is a less effective antimicrobial agent. Allow to dry completely for maximum effectiveness.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Skin dryness and irritation with frequent application. Absolute (undiluted) ethanol will produce greater skin irritation.

Notes: Ethanol is a flammable liquid and should be kept cool and away from any heat source.

Alternative alcohol products such as isopropanol are also effective agents. Ethanol alone is a short-acting antimicrobial agent. May be used in combination with other active agents such as 0.5% chlorhexidine or iodine. Ethanol is less effective on non-enveloped viruses (such as hepatitis A virus) and is not effective on fungal or bacterial spores.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Polyvidone iodine

ATC code: D08AG02

Solution: 10%

Povidone iodine solutions (i.e. surgical scrub, skin cleanser) should not be warmed or heated before use unless specific manufacturer labeling states otherwise. Upon heating, iodine can interact with dissolved oxygen causing a decrease in iodine concentration, or water evaporation may occur resulting in an increase in iodine concentration.

Special Notes: Also known as povidone iodine.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Antiseptic; skin disinfection.

Contraindications: Avoid regular or prolonged use in patients with thyroid disorders or those taking lithium; avoid regular use in neonates and avoid in very low birth weight infants due to iodine absorption.

Precautions: Broken skin or to severe burns (see below); renal impairment.

LARGE OPEN WOUNDS The application of polyvidone iodine to large wounds or severe burns may produce systemic adverse effects such as metabolic acidosis, hypernatraemia and impairment of renal function.

Administration:

Pre and post-operative skin disinfection.
Topical:
Child ***all ages*** apply undiluted.

Antiseptic for minor wounds and burns.
Topical:
Child ***all ages*** apply undiluted twice daily.

Renal impairment: Severe: avoid regular application to inflamed or broken mucosa.

Hepatic impairment: Avoid in hepatic impairment.

Adverse effects: Uncommon Irritation of skin and mucous membranes.

Rare May interfere with thyroid function tests; systemic effects (see under Precautions), hypersensitivity reactions.

Notes: Inactivated by organic material. Polyvidone iodine has broad antimicrobial activity, including against spores and viruses.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
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15.2 Disinfectants

A disinfectant is a chemical agent that does not necessarily kill all microorganisms present, but reduces them to a level which does not harm health or the quality of perishable goods.

Disinfection of water can be either physical (boiling, filtration, UV irradiation) or chemical. Chemical methods include the use of **chlorine-based compounds**, such as sodium hypochlorite, tosylchloramide sodium (chloramine), halazone or sodium dichloroisocyanurate. Chlorine is a hazardous substance, being highly corrosive in concentrated solution, and splashes can cause burns and can damage the eyes. Appropriate precautions must be taken when concentrated chlorine solutions or powders are handled.

Chlorine base compound

ATC code: D08AX

Powder: (0.1% available chlorine) for solution

Special Notes: Concentrations ranging from 0.01% (100 parts per million (ppm)) to 1% (10 000 ppm) free chlorine depending on use.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Disinfection of surfaces, equipment and water.

Contraindications: Avoid exposure of product to flame.

Precautions: Hypochlorite solutions may delay wound healing.

Administration:

Surface disinfection (minor contamination).
Apply solutions containing 500–1000 ppm (0.05–0.1%) to clean surfaces.
5000 ppm (0.5%) for blood spills.

Instrument disinfection.
Soak in solution containing 1000 ppm (0.1%) for a minimum of 15 minutes; to avoid corrosion, do not soak for more than 30 minutes; rinse with sterile water.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Irritation and burning sensation on skin.

Interactions with other medicines (* indicates severe):

The antimicrobial activity of chlorine base compounds is rapidly reduced in the presence of organic material; it is also pH dependent. Avoid mixing with solutions of strong acids or ammonia; the subsequent reactions can release toxic gases.

Notes: Broad-spectrum antimicrobial with sporicidal activity (at optimum pH 7.6). Corrosive to metals with repeated application. Deteriorates with exposure to light and heat. Shelf life of diluted ingredients < 7 days.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
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Chloroxylenol

ATC code: D08AE05

Solution: 4.8%

Special Notes: Also known as 4-chloro-3,4-dimethylphenol; a chlorinated phenolic disinfectant.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Antiseptic; disinfection of instruments and surfaces, the active ingredient in some commercial antibacterial soaps and lotions.

Precautions: Aqueous solutions should be freshly prepared; appropriate measures required to prevent contamination during storage or dilution.

Administration:

Antiseptic (wounds and other skin damage).
Topical:
Child *all ages* apply a 1 in 20 dilution of 4.8% concentrate in water.

Disinfection of instruments.
Immerse in a 1 in 20 dilution of 4.8% concentrate in ethanol (70%).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Mild skin and mucous membrane irritant. Harmful if swallowed.

Interactions with other medicines (* indicates severe):

Inactivated by hard water.

Notes: Broad spectrum antimicrobial activity but more active against Gram-positive bacteria than Gram-negative organisms such as *Pseudomonas* spp. Not active against hydrophilic viruses or spores. Not readily inactivated by organic matter.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
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Glutaral

ATC code: V07AV

Solution: 2%

Special Notes: Also know as glutaraldehyde.

Store at a temperature not exceeding 15 °C. Protect from light.

Indications: Disinfection and sterilization of instruments (particularly those which are heat sensitive) and surfaces.

Precautions: Minimize occupational exposure. Handle with gloves, aprons and safety glasses in an area with adequate ventilation to avoid inhalation of vapour.

Administration:

Disinfection of clean instruments.

Completely immerse in undiluted 2% solution for 20 minutes at 20 °C.

Up to 3 hours may be required for certain instruments (e.g. bronchoscopes with possible mycobacterial contamination).

Rinse with sterile water or ethanol after disinfection and allow to dry completely.

For endoscopes, ensure that all channels are cleaned. Immersion in 2% glutaral for 20 minutes at 20 °C will provide high-level disinfection.

Sterilization of clean instruments.

Immerse in undiluted solution for up to 10 hours; rinse with sterile water or ethanol after disinfection.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Skin sensitizer and toxic if inhaled or has direct contact with skin, eyes or mucous membranes. May cause nausea, headache, airway obstruction, asthma, rhinitis, eye irritation and dermatitis and skin discoloration.

Risk of occupational exposure to glutaral vapour may be higher in warm climates.

Notes: Thorough rinsing of endoscopes is required to prevent mucous membrane irritation and colitis.

Orthophthalaldehyde (OPA) may be used as an alternative agent with lower toxicity.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.

WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

SECTION 16:
Diuretics

16 Diuretics

Diuretics increase urinary excretion of water and electrolytes, and are used to relieve oedema associated with heart failure, pulmonary oedema, glomerulonephritis and hepatic cirrhosis. Some diuretics are used at lower doses to reduce raised blood pressure. Osmotic diuretics are used to treat cerebral oedema and to lower raised intraocular pressure. Care is advised with use of diuretics in children, given the difficulty of fluid and electrolyte maintenance, particularly in neonates, whose renal function may be immature.

Furosemide

ATC code: C03CA01

Injection: 10 mg/ml in 2 ml ampoule

Oral liquid: 4 mg/ml

Tablet: 40 mg

To avoid ototoxicity, intravenous doses should be given no faster than 0.5 mg/kg per minute (doses < 120 mg) or 4 mg/minute (doses ≥ 120 mg).

Special Notes: Also referred to as frusemide.

Indications: Oedema; oliguric renal failure.

Contraindications: Renal failure with anuria; precomatose states associated with liver cirrhosis.

Precautions: Monitor electrolytes, particularly potassium and sodium; hypotension; renal impairment; hepatic impairment.

Dose:

Oedema in heart failure.

Oral:

Neonate 0.5–2 mg/kg every 12–24 hours (every 24 hours if corrected age under 31 weeks).

Infant or **Child** 0.5–2 mg/kg 2–3 times daily; higher doses may be required in resistant oedema, maximum 12 mg/kg (80 mg) daily.

IV:

Neonate 0.5–1 mg/kg every 12–24 hours (every 24 hours if corrected age under 31 weeks).

Infant or **Child** 0.5–1 mg/kg (maximum 4 mg/kg) repeated every 8 hours as necessary.

Oliguric renal failure.

IV injection:

Infant or **Child** 2–5 mg/kg (maximum 250 mg) up to four times daily.

Renal impairment: Contraindicated in anuria.

Higher doses are usually required in impairment; renal function may worsen; monitor electrolytes and creatinine. Risk of ototoxicity increased.

Treatment with nephrotoxic drugs increases risk of nephrotoxicity with loop diuretics; use combinations carefully, especially in renal impairment.

Hepatic impairment: Hypokalaemia may precipitate coma (use potassium-sparing diuretic to prevent this).

Adverse effects: Most adverse effects are dose-related.

Common Hyponatraemia, hypokalaemia, hypomagnesaemia, dehydration, hyperuricaemia, gout, dizziness, orthostatic hypotension, syncope.

Uncommon Dyslipidaemia, increased creatinine concentration, hypocalcaemia, rash.

Rare Tinnitus, vertigo, deafness (especially with rapid intravenous administration), acute pancreatitis, jaundice, thrombocytopenia, haemolytic anaemia, agranulocytosis, interstitial nephritis, exfoliative dermatitis, Stevens-Johnson syndrome, bullous eruptions, allergic reactions.

Interactions with other medicines (* indicates severe):

* **Amikacin**: increased risk of ototoxicity.

Amitriptyline: increased risk of postural hypotension.

Amphotericin B: increased risk of hypokalaemia.

Carbamazepine: increased risk of hyponatraemia.

Chlorpromazine: enhanced hypotensive effect.

Cisplatin: increased risk of nephrotoxicity and ototoxicity.

Dexamethasone: antagonism of diuretic effect; increased risk of hypokalaemia.

Diazepam: enhanced hypotensive effect.

* **Digoxin**: hypokalaemia caused by furosemide increases cardiac toxicity of digoxin.
* **Enalapril**: enhanced hypotensive effect.

Ethanol: enhanced hypotensive effect.

* **Gentamicin**: increased risk of ototoxicity.

Halothane: enhanced hypotensive effect.

Hydrochlorothiazide: increased risk of hypokalaemia.

Hydrocortisone: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

Insulins: antagonism of hypoglycaemic effect.

Ketamine: enhanced hypotensive effect.

Lidocaine: action of lidocaine antagonized by hypokalaemia caused by furosemide (interaction less likely when lidocaine used topically).

* **Lithium**: reduced lithium excretion (increased plasma lithium concentration and risk of toxicity); furosemide safer than hydrochlorothiazide.

Nitrous oxide: enhanced hypotensive effect.

Prednisolone: antagonism of diuretic effect; increased risk of hypokalaemia.

Propranolol: enhanced hypotensive effect.

* **Quinidine**: cardiac toxicity of quinidine increased by hypokalaemia caused by furosemide.

Salbutamol: increased risk of hypokalaemia with high doses of salbutamol.

* **Streptomycin**: increased risk of ototoxicity.

Thiopental: enhanced hypotensive effect.

* **Vancomycin**: increased risk of ototoxicity.

Notes: Advise patient or carer that if taking furosemide twice daily, take the first dose in the morning and the second dose before 18:00 to prevent overnight diuresis.

Monitor potassium during therapy. Consider the addition of potassium-sparing diuretics or potassium supplements.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Hydrochlorothiazide

ATC code: C03AA03

Tablet (scored): 25 mg

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Oedema; hypertension.

Contraindications: Severe renal impairment; severe hepatic impairment; hyponatraemia; hypercalcaemia; refractory hypokalaemia; symptomatic hyperuricaemia; Addison disease.

Precautions: Renal impairment; hepatic impairment; electrolytes may need to be monitored with high doses or in renal impairment; may aggravate diabetes mellitus and gout; may exacerbate systemic lupus erythematosus; porphyria.

Dose:

Oedema.

Oral:

Infant *under 6 months* 2–3.3 mg/kg daily in two divided doses. Maximum dose 37.5 mg daily;
Child *over 6 months* 2 mg/kg daily in two divided doses. Maximum dose 200 mg daily.

Hypertension.

Oral:

Child *all ages* initially 1 mg/kg once daily. May increase to a maximum 3 mg/kg daily (maximum 50 mg daily).

Renal impairment: Moderate to severe impairment: hydrochlorothiazide may be ineffective.

Hepatic impairment: Severe impairment; hypokalaemia may precipitate coma (potassium-sparing diuretic can prevent this); increased risk of hypomagnesaemia in alcoholic cirrhosis.

Adverse effects: Common Dizziness, weakness, muscle cramps, polyuria, orthostatic hypotension, hyponatraemia, hypokalaemia, hyperuricaemia, hypochloraemic alkalosis, hypomagnesaemia.

Uncommon Rash, hyperglycaemia, hypercalcaemia, blurred vision, dyslipidaemia (increased total cholesterol, LDL and triglyceride concentrations and reduced HDL concentration), photosensitivity.

Rare Nausea, vomiting, constipation, diarrhoea, paraesthesia, intrahepatic cholestatic jaundice, cholecystitis, pancreatitis, agranulocytosis, aplastic anaemia, haemolytic anaemia, thrombocytopenia, dermatitis, urticaria, toxic epidermal necrolysis, purpura, necrotizing vasculitis.

Interactions with other medicines (* indicates severe):

Allopurinol: increased risk of hypersensitivity, especially in renal impairment.

Amitriptyline: increased risk of postural hypotension.

Amphotericin B: increased risk of hypokalaemia.

Calcium salts: increased risk of hypercalcaemia.

Carbamazepine: increased risk of hyponatraemia.

Chlorpromazine: enhanced hypotensive effect.

Ciclosporin: increased risk of nephrotoxicity and possibly hypermagnesaemia.

Dexamethasone: antagonism of diuretic effect; increased risk of hypokalaemia.

Diazepam: enhanced hypotensive effect.

* **Digoxin**: hypokalaemia caused by hydrochlorothiazide increases cardiac toxicity of digoxin.

* **Enalapril**: enhanced hypotensive effect.

Ergocalciferol: increased risk of hypercalcaemia.

Fluconazole: plasma concentration of fluconazole increased.

Furosemide: increased risk of hypokalaemia.

Halothane: enhanced hypotensive effect.

Hydrocortisone: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

Insulins: antagonism of hypoglycaemic effect.

Ketamine: enhanced hypotensive effect.

* **Lidocaine**: action of lidocaine antagonized by hypokalaemia caused by hydrochlorothiazide (interaction less likely when lidocaine used topically).

Metformin: antagonism of hypoglycaemic effect.

Nitrous oxide: enhanced hypotensive effect.

Prednisolone: antagonism of diuretic effect; increased risk of hypokalaemia.

Propranolol: enhanced hypotensive effect.

Salbutamol: increased risk of hypokalaemia with high doses of salbutamol.

Thiopental: enhanced hypotensive effect.

Notes: Can be easily confused with chlorothiazide.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Mannitol

ATC code: B05BC01

Injectable solution: 10%; 20%

Indications: Assessment of renal function; cerebral oedema; raised intraocular pressure (emergency treatment or before surgery).

Contraindications: Pulmonary oedema; intracranial bleeding (except during craniotomy); severe congestive heart failure; metabolic oedema with abnormal capillary fragility; severe dehydration; renal failure (unless test dose produces diuresis).

Precautions: Monitor fluid and electrolyte balance; monitor renal function.

Dose:

Test dose (to assess adequate renal function).

IV:

Child *all ages* 200 mg/kg (maximum dose 12.5 g) given over 3–5 minutes to produce urine flow of at least 1 ml/kg/hour for 1–3 hours.

Cerebral oedema; raised intraocular pressure.

IV infusion:

Infant or **Child *1 month–12 years*** 0.25–1.5 g/kg given over 30–60 minutes, repeated if necessary 1–2 times after 4–8 hours.

Renal impairment: All degrees of impairment: avoid unless test dose produces a diuretic response.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Fluid and electrolyte imbalance, circulatory overload, acidosis.

Uncommon Dry mouth, thirst, nausea, vomiting, oedema, raised intracranial pressure, arrhythmia, hypotension, pulmonary oedema, chest pain, headache, seizures, dizziness, chills, fever, pulmonary oedema (particularly in diminished cardiac reserve), chest pain, visual disturbances, hypotension or hypertension, urticaria, hypersensitivity reactions, extravasation may cause oedema, skin necrosis, thrombophlebitis.

Rare Acute renal failure (large doses), congestive heart failure.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Solutions containing more than mannitol 15% may crystallize during storage, crystals must be redissolved by warming solution before use and solution must not be used if any crystals remain; intravenous administration sets must have a filter; mannitol should not be administered with whole blood or passed through the same transfusion set as blood.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Spironolactone

ATC code: C03DA01

Tablet: 25 mg

Oral liquid: 1 mg/ml; 2 mg/ml and 5 mg/ml

Indications: Diuresis in congestive heart failure, ascites, oedema and nephrotic syndrome; reduction of hypokalaemia induced by other diuretics or amphotericin; primary hyperaldosteronism.

Contraindications: Hyperkalaemia; hyponatraemia; moderate or worse renal impairment; Addison disease.

Precautions: Monitor blood urea nitrogen and plasma electrolytes (discontinue if hyperkalaemia); diabetes mellitus; renal impairment; hepatic impairment; porphyria.

Dose:

Diuresis in congestive heart failure, ascites, oedema and nephrotic syndrome; reduction of hypokalaemia induced by other diuretics or amphotericin.
Oral:
Neonate 1–2 mg/kg daily in 1–2 divided doses.
Infant or **Child** ***1 month–12 years*** 1–3 mg/kg daily in 1–2 divided doses (maximum 100 mg daily).

Primary hyperaldosteronism; resistant ascites.
Oral:
Neonate up to a maximum of 7 mg/kg daily may be used.
Infant or **Child** ***1 month–12 years*** up to a maximum of 9 mg/kg daily (total maximum 400 mg daily) may be used.

Renal impairment: Mild impairment: high risk of hyperkalaemia, therefore monitor plasma potassium.

Moderate to severe impairment: avoid.

Hepatic impairment: Use with caution; rarely hepatotoxic.

Adverse effects: Common Hyperkalaemia, hyponatraemia, hypochloraemia (especially when combined with thiazide diuretics), weakness, headache, nausea, vomiting, mastalgia.

Uncommon Gastrointestinal cramps, diarrhoea, ataxia, drowsiness, confusion, impotence, gynaecomastia, menstrual irregularities, mild acidosis, renal impairment.

Rare Agranulocytosis, hepatotoxicity, rash, lichen planus, lupus-like syndrome, cutaneous vasculitis, urticaria, alopecia, chloasma, osteomalacia.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: antagonism of diuretic effect.

Amitriptyline: increased risk of postural hypotension.

Carbamazepine: increased risk of hyponatraemia.

Chlorpromazine: enhanced hypotensive effect.

* **Ciclosporin**: increased risk of hyperkalaemia.

Cisplatin: increased risk of nephrotoxicity and ototoxicity.

Dexamethasone: antagonism of diuretic effect.

Diazepam: enhanced hypotensive effect.

* **Digoxin**: plasma concentration of digoxin increased.

* **Enalapril**: enhanced hypotensive effect; increased risk of severe hyperkalaemia (monitor plasma potassium concentration with low-dose spironolactone in heart failure).

Halothane: enhanced hypotensive effect.

Hydrocortisone: antagonism of diuretic effect.

Ibuprofen: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia.

Ketamine: enhanced hypotensive effect.

Nitrous oxide: enhanced hypotensive effect.

* **Potassium salts**: risk of hyperkalaemia.

Prednisolone: antagonism of diuretic effect.

Propranolol: enhanced hypotensive effect.

Thiopental: enhanced hypotensive effect.

Notes: Advise patient and/or carer not to take potassium supplements while taking this medication.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

SECTION 17:
Gastrointestinal medicines

17 Gastrointestinal medicines

Pancreatic enzymes

Pancreatic enzymes are combinations of enzymes (proteases, lipases and amylases), in varying proportions, which aid the digestion of food products. They are taken orally with food, as replacement for natural pancreatic enzymes when they are deficient. Deficiency can occur in diseases such as cystic fibrosis or after removal of the pancreas. Specialist advice is recommended when considering the use of these medicines.

Gastro-oesophageal reflux disease

Gastro-oesophageal reflux disease (GORD) is associated with symptoms which include heartburn, acid regurgitation and sometimes difficulty in swallowing (dysphagia); ulceration and stricture formation may occur. The management of GORD is age-dependent. Most symptoms in infants resolve without treatment, but for older children, management involves lifestyle changes (see above), and medications as necessary.

Pancreatic enzymes

ATC code: A09AA; A09AA02

Age-appropriate formulations and doses including lipase, protease and amylase

Indications: Reduced or absent exocrine secretion in cystic fibrosis, following pancreatectomy, total gastrectomy or chronic pancreatitis.

Contraindications: Acute pancreatitis; acute exacerbations of chronic pancreatic disease.

Precautions: Higher strength preparations have been associated with the development of large bowel strictures (fibrosing colonopathy); hyperuricaemia and hyperuricosuria have been associated with very high doses; history of fibrosing colonopathy; history of or pre-existing intestinal blockage; hyperuricaemia.

Dose:

Dose must be individualized and is guided by stool quality and quantity. Specialist supervision is recommended.
Daily dose should not exceed 10 000 lipase units per kg body weight per day.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, abdominal pain.

Uncommon Irritation of skin around mouth and anus.

Rare Hyperuricaemia, hyperuricuria, fibrosing colonopathy (bowel stricture) in children with cystic fibrosis taking high doses.

Interactions with other medicines (* indicates severe):

Avoid placing contents of opened capsules on alkaline foods (pH > 5.5) such as dairy products (milk, custard or ice cream).

There are no known drug interactions where it is recommended to avoid concomitant use.

Notes: Pancreatic enzymes are essential for fat, carbohydrate and protein digestion. Supplements aim to correct enzymatic deficiency.

All products are of porcine origin.

Pancreatic enzymes are inactivated by gastric acid. It is best to administer with food (or immediately before or after food).

Do not crush or chew the capsule or granules.

It is best to swallow capsule whole with a glass of water.

If the capsules are opened the enteric-coated granules should be mixed (do not crush) with slightly acidic cool soft food or liquid such as apple sauce or puree, mashed fruits or rice cereal. Mixture should be administered immediately. Do not prepare ahead of time.

Pancreatic enzymes are inactivated by heat: excessive heat should be avoided if preparations are mixed with liquids or food.

Pancreatic enzymes can irritate the perioral skin and buccal mucosa if retained in the mouth and excessive doses can cause perianal irritation.

If any patient on pancreatic enzyme supplementation develops new abdominal symptoms (or change in existing abdominal symptoms) the patient should be reviewed to exclude the possibility of colonic damage.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

17.1 Antacids and other antiulcer medicines

Antacids often relieve symptoms in ulcer dyspepsia and GORD. H_2-receptor antagonists heal gastric and duodenal ulceration and relieve GORD by reducing the secretion of gastric acid through histamine H_2-receptor blockade. Proton-pump inhibitors inhibit gastric acid secretion by blocking the hydrogen–potassium ATP enzyme system (proton pump) of the gastric parietal cell.

Aluminium hydroxide

ATC code: A02AB01

Oral liquid: 64 mg/ml

Tablet: 500 mg

Indications: Ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux; hyperphosphataemia.

Contraindications: Hypophosphataemia; undiagnosed gastrointestinal or rectal bleeding; appendicitis; porphyria; neonates and infants.

Precautions: Impaired renal function; renal dialysis; hepatic impairment; constipation; dehydration; fluid restriction; gastrointestinal disorders associated with decreased bowel motility or obstruction.

Dose:

Dyspepsia; gastro-oesophageal reflux.
Oral:
Child *6–12 years* 5 ml (= 320 mg) up to three times daily.

Hyperphosphataemia.
Oral:
Child *5–12 years* 500–1000 mg of aluminium hydroxide three times daily adjusted as necessary; or
over 5 years 30 mg/kg/day in divided doses three or four times/day, maximum daily dose 3000 mg/day.

Renal impairment: Severe: aluminium is absorbed and may accumulate.

NOTE Absorption of aluminium from aluminium salts is increased by citrates which are contained in many effervescent preparations (such as effervescent analgesics).

In moderate to severe renal impairment monitor plasma aluminium concentrations at baseline and every 3 months.

Hepatic impairment: Use with caution. Side effect of constipation may precipitate hepatic encephalopathy and coma.

Adverse effects: Common Constipation.

Uncommon Hypophosphataemia.

Rare Intestinal obstruction, hypercalciuria, hyperaluminaemia, osteomalacia, proximal myopathy, encephalopathy, anaemia, dementia.

Interactions with other medicines (* indicates severe):

NOTE Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.

Acetylsalicylic acid: excretion of acetylsalicylic acid increased by alkaline urine.

Azithromycin: reduced absorption of azithromycin.

Chloroquine: reduced absorption of chloroquine.

Chlorpromazine: reduced absorption of chlorpromazine.

Ciprofloxacin: reduced absorption of ciprofloxacin.

Digoxin: possibly reduced absorption of digoxin.

Doxycycline: reduced absorption of doxycycline.

Enalapril: reduced absorption of enalapril.

Isoniazid: reduced absorption of isoniazid.

Ofloxacin: reduced absorption of ofloxacin.

Penicillamine: reduced absorption of penicillamine.

Phenytoin: reduced absorption of phenytoin.

Rifampicin: reduced absorption of rifampicin.

Notes: Advise patient or carer not to take other medicines within 2–4 hours of aluminium hydroxide preparations.

May be taken with water to reduce constipating adverse effects.

Relatively slow onset of action as an antacid, optimum antacid effect is achieved if taken 1–3 hours after meals.

Commonly combined with magnesium to prevent constipating effects.

Liquid products are more effective, but less convenient, than solid products.

To decrease phosphate, administer within 20 minutes of a meal.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Magnesium hydroxide

ATC code: A02AA04

Oral liquid: equivalent to 80 mg magnesium hydroxide/ml (Mg 1.37 mmol/ml)

Special Notes: Also referred to as milk of magnesia, MOM and magnesia magma.

Indications: Ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux.

Contraindications: Severe renal impairment.

Precautions: Renal impairment; hepatic impairment.

Dose:

Ulcer and non-ulcer dyspepsia; gastro-oesophageal reflux.

Oral:

Infant or **Child *under 2 years*** 0.5 ml/kg per dose up to four times daily when required for symptomatic relief;

2–6 years 5–15 ml per day once before bedtime or in up to four divided doses;

6–12 years 15–30 ml per day once before bedtime or in up to four divided doses.

Renal impairment: Moderate: avoid or reduce dose; increased risk of toxicity.

Severe: avoid as toxicity from magnesium accumulation may occur.

Hepatic impairment: Avoid in hepatic coma if risk of renal failure.

Adverse effects: Common Diarrhoea.

Rare Hypermagnesaemia (more common in renal impairment; see below).

HYPERMAGNESAEMIA Hypermagnesaemia can result in loss of deep tendon reflexes and respiratory depression, with other symptoms including nausea, vomiting, flushing of skin, thirst, hypotension, drowsiness, confusion, muscle weakness, bradycardia, coma and cardiac arrest.

Interactions with other medicines (* indicates severe):

NOTE Antacids should preferably not be taken at the same time as other drugs since they may impair absorption.

Acetylsalicylic acid: excretion of acetylsalicylic acid increased by alkaline urine.

Azithromycin: reduced absorption of azithromycin.

Chloroquine: reduced absorption of chloroquine.

Chlorpromazine: reduced absorption of chlorpromazine.

Ciprofloxacin: reduced absorption of ciprofloxacin.

Digoxin: possibly reduced absorption of digoxin.

Doxycycline: reduced absorption of doxycycline.

Enalapril: reduced absorption of enalapril.

Isoniazid: reduced absorption of isoniazid.

Ofloxacin: reduced absorption of ofloxacin.

Penicillamine: reduced absorption of penicillamine.

Phenytoin: reduced absorption of phenytoin.

Rifampicin: reduced absorption of rifampicin.

Notes: Magnesium hydroxide oral liquid should be vigorously shaken before use.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Omeprazole

ATC code: A02BC01

Powder for oral liquid: 20 mg; 40 mg sachets

Solid oral dosage form: 10 mg; 20 mg; 40 mg

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Gastro-oesophageal reflux disease; acid-related dyspepsia; treatment of benign gastric ulcer including those complicating non-steroidal anti-inflammatory medicine (NSAIM) therapy; Zollinger-Ellison syndrome; prophylaxis of acid aspiration; fat malabsorption despite pancreatic enzyme replacement therapy in cystic fibrosis; *Helicobacter pylori* eradication.

Precautions: Gastric carcinoma; hepatic impairment; patients of Asian descent (bioavailability may be increased).

Dose:

Conditions requiring reduced gastric acid production.

Oral:

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.

Infant or **Child** ***1 month–2 years*** 700 micrograms/kg once daily, increased if necessary to 3 mg/kg (maximum 20 mg) once daily;

2–12 years 1 mg/kg once or twice daily (maximum 40 mg/day).

H. pylori eradication (in combination with antibacterials).

Oral:

Child 1–2 mg/kg (maximum 40 mg) once daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: No more than 700 micrograms/kg (maximum 20 mg) once daily.

Adverse effects: Common Headache, nausea, vomiting, diarrhoea, abdominal pain, constipation, flatulence.

Uncommon Rash, itch, dizziness, fatigue, drowsiness, insomnia, dry mouth, decreased absorption of cyanocobalamin (vitamin B_{12}) with long-term use, paraesthesia.

Rare Gynaecomastia, myalgia, myopathy, arthralgia, blurred vision, taste disturbance, interstitial nephritis, peripheral oedema, raised liver enzymes, hepatitis, jaundice, thrombocytopenia, leukopenia, skin reactions (including Stevens-Johnson syndrome, toxic epidermal necrolysis, photosensitivity), hypersensitivity reactions, alopecia, confusion, haemolytic anaemia.

Interactions with other medicines (* indicates severe):

Ciclosporin: may increase levels and effect of ciclosporin.

* **Methotrexate**: may increase concentration and toxicity of methotrexate.

Phenytoin: may increase levels and effect of phenytoin.

Saquinavir: may increase concentration and toxicity of saquinavir.

* **Tacrolimus**: may increase concentration and toxicity of tacrolimus.

* **Warfarin**: may increase INR and anticoagulant effects.

Notes: Standard preparations: swallow tablet or capsule whole; do not crush or chew.

Alternatively, some dispersible preparations are available and these may be dispersed in water, orange juice or yoghurt; take within 30 minutes of mixing.

PATIENT/CARER ADVICE Tell your doctor if you develop symptoms such as black stools or coffee-coloured vomit.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Ranitidine

ATC code: A02BA02

Injection: 25 mg/ml in 2 ml ampoule

Tablet: 150 mg (as hydrochloride)

Oral liquid: 15 mg/ml

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Benign gastric and duodenal ulceration; gastro-oesophageal reflux; Zollinger-Ellison syndrome; prophylaxis of stress ulceration; other conditions where gastric acid reduction is beneficial.

Contraindications: Acute porphyria.

Precautions: Hepatic impairment; renal impairment; phenylketonuria (oral products may contain aspartame).

Dose:

Conditions requiring reduced gastric acid production.

Oral:

Neonate 2 mg/kg three times daily. Absorption is unreliable. A maximum of 3 mg/kg three times daily may be used.

Infant ***1–6 months*** 1 mg/kg three times daily. A maximum of 3 mg/kg three times daily may be used.

Infant or **Child** ***6 months–3 years*** 2–4 mg/kg twice daily;
3–12 years 2–4 mg/kg (maximum 150 mg) twice daily. Dose may be increased up to 5 mg/kg (maximum 300 mg) twice daily in severe gastro-oesophageal reflux disease.

IV:

Neonate 0.5–1 mg/kg 3–4 times daily.

Infant or **Child** 1 mg/kg (maximum 50 mg) 3–4 times daily.

Zollinger-Ellison syndrome.

Oral:

Child 2–4 mg/kg (maximum 150 mg) 2–3 times daily. Doses of up to 6 g daily in divided doses have been used for severe Zollinger-Ellison syndrome.

Renal impairment: Mild to moderate impairment: reduce dose to 50% of dose recommended for indication.

Severe impairment: reduce dose to 25% of dose recommended for indication.

Hepatic impairment: Increased risk of confusion; reduce dose.

Adverse effects: Uncommon Hypotension, bradyarrhythmia (following rapid intravenous administration).

Rare Headache, tiredness, dizziness, confusion, diarrhoea, constipation, rash, hepatitis, vasculitis, interstitial nephritis, involuntary movement disorder (reversible), acute pancreatitis, bradycardia, AV block, confusion, depression, hallucinations, hypersensitivity reactions (including fever, arthralgia, myalgia, anaphylaxis), blood disorders (including agranulocytosis, leukopenia, pancytopenia, thrombocytopenia), alopecia, visual disturbances, Stevens-Johnson syndrome.

Interactions with other medicines (* indicates severe):

Atazanavir: may decrease absorption of atazanavir and its therapeutic effect. If used in combination, give ranitidine at least 2 hours before or 10 hours after atazanavir.

Iron salts: decreased absorption of iron.

* **Itraconazole**: decreased antifungal effect.

* **Ketoconazole**: decreased antifungal effect.

* **Warfarin**: increased anticoagulant effect and/or toxicity.

Saquinavir: increased effect/toxicity of saquinavir.

Notes: For intravenous administration: dilute in sodium chloride 0.9% and give over not less than 5 minutes or preferably, infuse over 15–30 minutes or more.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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17.2 Antiemetic medicines

Antiemetic medications should only be used when the cause of the vomiting is known. Antiemetics are unnecessary and sometimes harmful when the cause can be treated, such as in diabetic ketoacidosis.

Gastroenteritis

The current body of evidence is insufficient to recommend the routine use of dopamine antagonists, antihistamines or serotonin 5-HT_3 antagonists in the management of children with gastroenteritis.

Dexamethasone

ATC code: H02AB02

Injection: 4 mg/ml in 1 ml ampoule

Oral liquid: 0.1 mg/ml; 0.4 mg/ml

Solid oral dosage form: 0.5 mg; 0.75 mg; 1.5 mg; 4 mg

Indications: Chemotherapy-induced nausea and vomiting.

Contraindications: Untreated systemic infection (unless condition life threatening); administration of live virus vaccines.

Precautions: Increased susceptibility to and severity of infection; activation or exacerbation of tuberculosis; amoebiasis; strongyloidiasis; risk of severe chickenpox in non-immune patients (varicella zoster immunoglobulin required if exposed to chickenpox); avoid exposure to measles (normal immunoglobulin possibly required if exposed); diabetes mellitus; peptic ulcer; hypertension; corneal perforation; osteoporosis; myasthenia gravis.

Dose:

Chemotherapy-induced nausea and vomiting.
Oral or *IV:*
Child *all ages* 0.2 mg/kg (maximum 8 mg) then 0.1 mg/kg/dose (maxiumum 4 mg) every 6 hours, in conjunction with a $5HT_3$-antagonist.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Incidence of adverse effects is related to dose and duration of treatment. Short courses of high-dose systemic treatment cause fewer adverse effects than prolonged courses of lower doses.

Common Nausea, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, increased appetite, dyspepsia, delayed wound healing, bruising, acne, psychiatric effects (see below).

INTRAVENOUS Transient itching, burning or tingling in perineal area (after intravenous bolus).

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions including anaphylaxis.

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium and psychosis are less common.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; dexamethasone reduces plasma salicylate concentration.

Albendazole: plasma albendazole concentration possibly increased.

Amphotericin B: increased risk of hypokalaemia.

* **Carbamazepine**: accelerated metabolism of dexamethasone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of dexamethasone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: erythromycin possibly inhibits metabolism of dexamethasone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

* **Lopinavir**: possibly reduced plasma lopinavir concentration.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

Phenobarbital: metabolism of dexamethasone accelerated (reduced effect).

Phenytoin: metabolism of dexamethasone accelerated (reduced effect).

Praziquantel: plasma praziquantel concentration reduced.

Propranolol: antagonism of hypotensive effect.

Rifampicin: accelerated metabolism of dexamethasone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Saquinavir: possibly reduced plasma saquinavir concentration.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of dexamethasone impair immune response.

* **Vaccine, live**: high doses of dexamethasone impair immune response; avoid use of live vaccines while taking dexamethasone courses longer than 2 weeks.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose dexamethasone enhances anticoagulant effect).

Notes: When used in a syringe driver, special care is needed in preparation to avoid precipitation.

To be given/taken in the morning to avoid causing insomnia. If divided doses are required 08:00 and 12:00 are recommended.

Tablets can be dissolved in water prior to administration.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Metoclopramide

ATC code: A03FA01

Injection: 5 mg (hydrochloride)/ml in 2 ml ampoule

Tablet: 10 mg (hydrochloride)

Special Notes: WHO age/weight restriction: not for use in neonates.

Indications: Nausea and vomiting in gastrointestinal disorders; nausea and vomiting associated with radiotherapy and cytotoxic chemotherapy; gastro-oesophageal reflux; gastroparesis; pre- and postoperatively; aid to gastrointestinal intubation; nausea and vomiting in migraine.

Contraindications: Gastrointestinal obstruction, haemorrhage or perforation; 3–4 days after gastrointestinal surgery; convulsive disorders; phaeochromocytoma; previous extrapyramidal reaction.

Precautions: Hepatic impairment; renal impairment; may mask underlying disorders such as cerebral irritation; epilepsy; depression; porphyria.

Dose:

Nausea and vomiting in gastrointestinal disorders; vomiting associated with radiotherapy and cytotoxic chemotherapy; aid to gastrointestinal intubation; gastro-oesophageal reflux; gastroparesis; nausea and vomiting in migraine.
Oral or *IM* or *slow IV* (over 15 minutes):
Infant *(up to 10 kg)* 100 micrograms/kg (maximum 1 mg) twice daily.
Child *1–3 years (10–14 kg)* 1 mg 2–3 times daily;
3–5 years (15–19 kg) 2 mg 2–3 times daily;
5–9 years (20–29 kg) 2.5 mg three times daily;
9–12 years (30 kg and over) 5 mg three times daily (usual maximum 500 micrograms/kg daily).

Pre- and postoperatively.
Oral or *IM* or *slow IV* (over 15 minutes):
Child *all ages* 0.1–0.2 mg/kg per dose 3–4 times daily as needed.

Renal impairment: Mild impairment: reduce dose to 75% of dose recommended for indication.

Moderate impairment: reduce dose to 50% of dose recommended for indication.

Severe impairment: reduce dose to 25–50% of dose recommended for indication.

Hepatic impairment: Reduce dose.

Adverse effects: Common Akathisia, drowsiness, dizziness, headache.

Uncommon Depression, extrapyramidal symptoms including tardive dyskinesia, hypertension, hypotension, hyperprolactinaemia leading to galactorrhoea, diarrhoea, constipation.

Rare Neuroleptic malignant syndrome, rash, pruritus, oedema, cardiac conduction abnormalities following intravenous administration, methaemoglobinaemia (more severe in G6PD deficiency), agranulocytosis, hyperaldosteronism.

Interactions with other medicines (* indicates severe):

Absorption of some drugs may be altered due to increased gastric motility caused by metoclopramide.

Acetylsalicylic acid: enhanced effect of acetylsalicylic acid (increased rate of absorption).

Atropine: antagonism of effect of metoclopramide on gastrointestinal activity.

Chlorpromazine: increased risk of extrapyramidal effects.

* **Ciclosporin**: plasma ciclosporin concentration increased.

Codeine: antagonism of effect of metoclopramide on gastrointestinal activity.

Haloperidol: increased risk of extrapyramidal effects.

Methadone: antagonism of effect of metoclopramide on gastrointestinal activity.

Morphine: antagonism of effect of metoclopramide on gastrointestinal activity.

Paracetamol: increased absorption of paracetamol.

Suxamethonium: enhanced effects of suxamethonium.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

Ondansetron

ATC code: A04AA01

Injection: 2 mg base/ml in 2 ml ampoule (as hydrochloride)

Oral liquid: 0.8 mg base/ml

Solid oral dosage form: 4 mg; 8 mg

Special Notes: WHO age/weight restriction: > 1 month.

Indications: Prevention and treatment of nausea and vomiting caused by cytotoxic chemotherapy or radiotherapy and postoperatively.

Precautions: Phenylketonuria (some dosage forms (wafers or tablets) contain aspartame); hepatic impairment; prolonged QT interval or risk factors for prolonged QT interval.

Dose:

Prevention and treatment of chemotherapy and radiotherapy-induced nausea and vomiting.
Slow IV injection or *IV infusion:*
Infant or **Child** ***6 months–12 years*** 5 mg/m^2 (maximum 8 mg) immediately before chemotherapy or 1–2 hours before radiotherapy, then repeat every 8 hours during chemotherapy and for at least 24 hours afterwards, or follow with oral administration.
Oral following IV administration:
Child 4 mg every 8–12 hours for up to 5 days.

Treatment and prevention of postoperative nausea and vomiting.
Oral or by *slow IV injection:*
Child ***2–12 years*** 100 micrograms/kg (maximum 4 mg) as a single dose either before, during or after induction of anaesthesia.

Renal impairment: No dose reduction required.

Hepatic impairment: Moderate and severe impairment: reduce dose.

Adverse effects: Common Constipation, headache, transient rise in hepatic aminotransferases.

Uncommon Hiccups, hypotension, chest pain, diarrhoea.

Rare Hypersensitivity reactions (including anaphylaxis), arrhythmias, ECG changes, extrapyramidal effects, seizures, transient visual disturbances, e.g. blurred vision (with rapid IV administration).

Interactions with other medicines (* indicates severe):

Rifampicin: may increase metabolism of ondansetron, increase dose if necessary.

Notes: 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%; give over at least 15 minutes.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

17.3 Anti-inflammatory medicines

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

17.4 Laxatives

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

17.5 Medicines used in diarrhoea

Diarrhoea remains a leading cause of death among infants and young children, particularly in developing countries. It is estimated that more than three quarters of all deaths from diarrhoea could be prevented with universal availability and utilization of oral rehydration solution (ORS) and zinc.

17.5.1 Oral rehydration

Acute diarrhoea in children should always be treated with ORS, according to their degree of dehydration, following one of three management plans (see Oral rehydration solution monograph).

Oral rehydration salts

ATC code: A07CA

Powder for dilution in 200 ml; 500 ml; 1 litre

Contains: glucose 13.5 g/l, sodium chloride 2.6 g/l, potassium chloride 1.5 g/l, trisodium citrate dihydrate 2.9 g/l

Provides: glucose 75 mmol/l, sodium 75 mEq or mmol/l, chloride 65 mEq or mmol/l, potassium 20 mEq or mmol/l, citrate 10 mmol/l, osmolarity 245 mOsm/l

Special Notes: Oral rehydration salts are also referred to as ORS.

Known by the brand names Gastrolyte and Dioralyte.

Indications: Oral rehydration salts replace fluid and salts lost in acute diarrhoea.

Precautions: Renal impairment.

Dose:

WHO Recommends Plans A, B and C; see below.

PLAN A: NO DEHYDRATION Nutritional advice, increased fluid intake (e.g. unsalted soup, unsalted rice water, yoghurt or plain water), at least one fluid that normally contains salt (e.g. ORS solution, salted drinks including salted rice water and vegetable or chicken soup with salt) and zinc supplementation (section 17.5.2) at home are usually sufficient. The aim is to give as much nutrient-rich food as the child will accept. Breastfeeding should always be continued to reduce the risk of diminishing supply. Give as much fluid as the child wants until diarrhoea stops and, as a guide, after each loose stool give:
Child *under 2 years* 50–100 ml (a quarter to half a large cup) of fluid;
2–10 years 100–200 ml (a half to one large cup);
older than 10 years as much fluid as the child wants.
Parents should be advised about circumstances in which they should seek further advice.

PLAN B: MODERATE DEHYDRATION Whatever the child's age, a 4 hour treatment plan is applied to avoid short-term problems. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution over a 4 hour period, and it is suggested that parents should be watched to see how they cope at the beginning of the treatment. A larger amount of solution (up to 20 ml/kg/hour and maximum 750 ml/hour) can be given if the child continues to have frequent stools or if the child wants more than the estimated amount of ORS solution, and there are no signs of overhydration (e.g. oedematous eyelids). In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate. In younger children, breastfeeding should be continued on demand and the mother should be encouraged to do so; older children should receive milk and nutritious food as normal after completing the 4 hours of oral rehydration. The child's status must be reassessed after 4 hours to decide on the most appropriate subsequent treatment. If signs of dehydration worsen, shift to treatment plan C; and if the child develops signs of severe dehydration, intravenous rehydration should be started as per treatment plan C. Zinc supplementation (section 17.5.2) should begin as soon as the child can eat and has completed 4 hours of rehydration. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea.

PLAN C: SEVERE DEHYDRATION Hospitalization is necessary, but the most urgent priority is to start rehydration. The preferred treatment for children with severe dehydration is rapid intravenous rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution should be given during the intravenous rehydration (20 ml/kg/hour by mouth before infusion, then 5 ml/kg/hour by mouth during intravenous rehydration). For intravenous rehydration, it is recommended that compound solution of sodium lactate (or, if this is unavailable, sodium chloride 0.9% intravenous infusion) (see section 26.2) is administered at a rate adapted to the child's age.

Intravenous rehydration using compound sodium lactate solution or sodium chloride 0.9% infusion

IV:

Infant 30 ml/kg over 1 hour, then 14 ml/kg/hour for 5 hours.

Child 30 ml/kg over 30 minutes, then 28 ml/kg/hour for 2.5 hours.

If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution.

Nasogastric rehydration using oral rehydration solution

Nasogastric tube:

Infant or **Child** 20 ml/kg/hour for 6 hours (total 120 ml/kg).

If the child vomits, the rate of administration of the oral solution should be reduced. Reassess the child's status after 3 hours (6 hours for infants) and continue treatment as appropriate with plan A, B or C.

Renal impairment: Dose reduction may be necessary; monitor electrolytes carefully.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common or uncommon Vomiting may indicate too rapid administration, hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

Glucose salt solution:

sodium chloride 2.6 g/l of clean water

sodium citrate (dihydrate) 2.9 g/l of clean water

potassium chloride 1.5 g/l of clean water

glucose (anhydrous) 13.5 g/l of clean water.

When glucose and sodium citrate are not available, they may be replaced by:

sucrose (common sugar) 27 g/l of clean water

sodium bicarbonate 2.5 g/l of clean water.

NOTE The solution may be prepared either from prepackaged sugar/salt mixtures or from bulk substances and water. Solutions must be freshly prepared, preferably with recently boiled and cooled water. Accurate weighing and thorough mixing and dissolution of ingredients in the correct volume of clean water is important. Administration of more concentrated solutions can result in hypernatraemia.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

The treatment of diarrhoea, a manual for physicians and other senior health workers. Geneva, World Health Organization, 2005.

17.5.2 Medicines for diarrhoea in children

Zinc supplementation is used in combination with ORS for the management of acute diarrhoea in children. When given during an acute episode, zinc supplements reduce the severity and duration of the episode, as well as reducing the incidence of new episodes of diarrhoea in the 2–3 months following treatment.

Zinc sulfate

ATC code: A12CB01

Oral liquid: in 10 mg per unit dosage forms

Tablet: in 10 mg per unit dosage forms

Indications: Adjunct to oral rehydration therapy in acute diarrhoea.

Precautions: Acute renal failure (may accumulate).

Dose:

Adjunct to oral rehydration therapy in acute diarrhoea.
Oral:
Infant *under 6 months* 10 mg (elemental zinc) daily for 10–14 days.
Infant or **Child *over 6 months*** 20 mg (elemental zinc) daily for 10–14 days.

Renal impairment: May accumulate in acute renal failure.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Abdominal pain, dyspepsia, nausea, vomiting, diarrhoea, gastric irritation, gastritis, irritability, headache, lethargy.

Interactions with other medicines (* indicates severe):

Calcium salts: reduced absorption of zinc sulfate.

Ciprofloxacin: reduced absorption of ciprofloxacin.

Ferrous salts: absorption of zinc and of oral ferrous salts reduced.

Ofloxacin: reduced absorption of ofloxacin.

Penicillamine: absorption of both drugs reduced.

Notes: Zinc sulfate tablets may be dispersed in breast milk, in oral rehydration solution or in water on a small spoon; older children may chew tablets or swallow them with water.

Administer with food if gastrointestinal upset occurs.

References:

Clinical management of acute diarrhoea. Geneva, World Health Organization, 2004 (http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/Acute_Diarrhoea.pdf).
Diarrhoea treatment guidelines including new recommendations for the use of ORS and zinc supplementation for clinic-based healthcare workers. Geneva, World Health Organization, 2005 (available from http://www.who.int/child-adolescent-health/New_Publications/CHILD_HEALTH/Diarrhoea_guidelines.pdf).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

SECTION 18:
Hormones, other endocrine medicines and contraceptives

18 Hormones, other endocrine medicines and contraceptives

18.1 Adrenal hormones and synthetic substitutes

Corticosteroids include hormones secreted by the adrenal cortex (hydrocortisone and aldosterone) and synthetic analogues of these hormones. In physiological (low) doses, corticosteroids replace deficient endogenous hormones. In pharmacological (high) doses, glucocorticoids decrease inflammation and suppress the immune response. Side-effects of systemic glucocorticoids are dose and duration dependent, therefore patients should be given treatment for the shortest period at the lowest dose that is clinically necessary. After prolonged therapy, or if there is uncertainty about adrenal suppression, withdrawal should be gradual to enable the adrenal gland to recover. Patients should be advised not to stop taking glucocorticoids abruptly unless permitted by their doctor.

Fludrocortisone

ATC code: H02AA02

Tablet: 100 micrograms

Indications: Mineralocorticoid replacement in adrenocortical insufficiency.

Contraindications: Congestive cardiac failure; systemic fungal infections.

Precautions: Dosage should be tapered gradually if therapy is discontinued; use with caution in patients with hypertension, oedema or renal impairment.

Dose:

Mineralocorticoid replacement in adrenocortical insufficiency.

Oral:

Neonate initially 100 micrograms once daily. Maintenance dose 50–300 micrograms daily. Adjust dose according to response.

Infant or **Child** initially 50–100 micrograms once daily. Maintenance dose 50–300 micrograms once daily. Adjust dose according to response.

Renal impairment: Use with caution. Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: When used as mineralocorticoid replacement, adverse effects usually indicate that the dose (and/or salt intake) is too high.

Common Sodium and water retention, oedema, hypokalaemia, hypertension.

Rare Hypokalaemic alkalosis, heart failure.

Interactions with other medicines (* indicates severe):

Systemic corticosteroids (such as fludrocortisone) reduce potassium concentration and increase risk of hypokalaemia. Administration with other drugs which also reduce potassium concentration may increase this risk; monitor potassium concentration and give supplements if necessary.

Phenytoin: increases metabolism of fludrocortisone and may reduce its activity; monitor clinical effect and increase corticosteroid dose if necessary (large increases may be needed). Metabolism of phenytoin may be affected.

Rifampicin: increases metabolism of fludrocortisone and may reduce its activity; monitor clinical effect and increase corticosteroid dose if needed (may need to double dose).

Warfarin: fludrocortisone may increase warfarin's anticoagulant effect, increasing the risk of bleeding; monitor INR and decrease warfarin dose if necessary.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Hydrocortisone

ATC code: H02AB09

Tablet: 5 mg; 10 mg; 20 mg

Hypothalamic-pituitary-adrenal (HPA) axis suppression may occur, acute adrenal insufficiency (adrenal crisis) may occur with abrupt withdrawal after long-term therapy (longer than 3 weeks) or with stress; withdrawal and discontinuation of steroids should be performed carefully; patients with HPA axis suppression may require doses of systemic glucocorticosteroids prior to, during and after unusual stress (e.g. surgery). Immunosuppression may occur; patients may be more susceptible to infections; avoid exposure to chickenpox and measles. Corticosteroids may activate latent opportunistic infections or exacerbate systemic fungal infections. May cause osteoporosis (at any age) or inhibition of bone growth in paediatric patients. Acute myopathy may occur with high doses, elevated intraocular pressure may occur (especially with prolonged use), and CNS effects (ranging from euphoria to psychosis) may occur.

Indications: Congenital adrenal hyperplasia; Addison disease; adrenal hypoplasia; chronic maintenance or replacement therapy.

Contraindications: Systemic infection (unless specific therapy given); avoid live virus vaccines in patients receiving immunosuppressive doses.

Precautions: Avoid using higher than recommended dose; titrate to lowest effective dose; adrenal suppression; abrupt withdrawal; peptic ulcer disease; psychiatric disorders; glaucoma; osteoporosis; myasthenia gravis; infection; growth restriction; hypertension; congestive heart failure; hepatic impairment; renal impairment; diabetes mellitus; ocular herpes simplex; epilepsy; hypothyroidism; history of steroid myopathy; ulcerative colitis; diverticulitis; recent intestinal anastomoses; thromboembolic disorders; latent tuberculosis.

When used in the treatment of adrenal insufficiency, these precautions may not apply; seek specialist advice.

Dose:

Congenital adrenal hyperplasia.
Oral:
Neonate 6–7 mg/m^2 every 8 hours, adjusted according to response.
Infant or **Child** 5–6.5 mg/m^2 every 8 hours, adjusted according to response. Usual maintenance dose is 4–5 mg/m^2 every 8 hours but higher doses may be needed.

NOTE Administer morning doses as early as possible.

Addison disease, adrenal hypoplasia, chronic maintenance or replacement therapy.
Oral:
Neonate, Infant or **Child** usual dose 4–5 mg/m^2 every 8 hours. Higher doses may be needed.

NOTE Give larger doses in the morning and smaller doses in the evening.

Renal impairment: Use with caution. Dose reduction not necessary.

Hepatic impairment: Adverse effects are more common.

Adverse effects: When used as mineralocorticoid replacement, adverse effects usually indicate that the dose (and/or salt intake) is too high.

Common Adrenal suppression, increased susceptibility to infection, masking of signs of infection, sodium and water retention, oedema, hypertension, hypokalaemia, hyperglycaemia, dyslipidaemia, osteoporosis, fractures, increased appetite, dyspepsia, delayed wound healing, skin atrophy, bruising, acne, hirsutism, growth retardation in children, myopathy, muscle weakness and wasting, fat redistribution (producing cushingoid appearance), weight gain, amenorrhoea, psychiatric effects (see below).

Uncommon Osteonecrosis, particularly of the femoral and humeral heads.

Rare Peptic ulceration, posterior subcapsular cataracts, glaucoma, hypersensitivity reactions, tendon rupture (especially of the Achilles tendon).

PSYCHIATRIC EFFECTS Include euphoria, hypomania, depression, disturbances of mood, cognition, sleep and behaviour. Delirium or psychosis are less common.

Interactions with other medicines (* indicates severe):

Acetylsalicylic acid: increased risk of gastrointestinal bleeding and ulceration; hydrocortisone reduces plasma salicylate concentration.

Amiloride: antagonism of diuretic effect.

* **Amphotericin B**: increased risk of hypokalaemia (avoid concomitant use unless hydrocortisone needed to control reactions).

Atenolol: antagonism of hypotensive effect.

Calcium salts: reduced absorption of calcium salts.

* **Carbamazepine**: accelerated metabolism of hydrocortisone (reduced effect).

Contraceptives, oral: oral contraceptives containing estrogens increase plasma concentration of hydrocortisone.

Digoxin: increased risk of hypokalaemia.

Enalapril: antagonism of hypotensive effect.

Erythromycin: inhibits metabolism of hydrocortisone.

Furosemide: antagonism of diuretic effect; increased risk of hypokalaemia.

Glibenclamide: antagonism of hypoglycaemic effect.

Glyceryl trinitrate: antagonism of hypotensive effect.

Hydralazine: antagonism of hypotensive effect.

Hydrochlorothiazide: antagonism of diuretic effect; increased risk of hypokalaemia.

Ibuprofen: increased risk of gastrointestinal bleeding and ulceration.

Insulins: antagonism of hypoglycaemic effect.

Metformin: antagonism of hypoglycaemic effect.

* **Methotrexate**: increased risk of haematological toxicity.

Nifedipine: antagonism of hypotensive effect.

* **Phenobarbital**: metabolism of hydrocortisone accelerated (reduced effect).

* **Phenytoin**: metabolism of hydrocortisone accelerated (reduced effect).

Propranolol: antagonism of hypotensive effect.

* **Rifampicin**: accelerated metabolism of hydrocortisone (reduced effect).

Ritonavir: plasma concentration possibly increased by ritonavir.

Salbutamol: increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Sodium nitroprusside: antagonism of hypotensive effect.

Spironolactone: antagonism of diuretic effect.

Vaccine, influenza: high doses of hydrocortisone impair immune response.

* **Vaccine, live**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

* **Warfarin**: anticoagulant effect possibly enhanced or reduced (high-dose hydrocortisone enhances anticoagulant effect).

Notes: Administer with food or milk to decrease gastrointestinal upset.

In adrenal replacement therapy, the dose may need to be increased at time of stress or infection; seek specialist advice.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

18.2 Androgens

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

18.3 Contraceptives

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

18.4 Estrogens

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

18.5 Insulins and other antidiabetic agents

Type 1 (insulin-dependent) diabetes mellitus is due to a deficiency of insulin caused by autoimmune destruction of pancreatic beta cells. Patients require lifelong administration of insulin. Type 1 diabetes mellitus forms the majority of cases of diabetes in children.

Type 2 (non-insulin dependent) diabetes mellitus is due to reduced secretion of, or peripheral resistance to the action of, insulin. Sometimes patients may be managed with diet and exercise alone, although treatment may also be required. The aim of treatment is to achieve the best possible control of blood glucose concentration without causing hypoglycaemia, as well as preventing or minimizing long-term complications.

Insulin

Appropriate insulin regimens should be worked out for each patient. Insulin requirements and plasma glucose concentrations may be affected by variations in lifestyle (diet and exercise). The duration of action of different insulin preparations varies considerably from one patient to another, and this needs to be assessed for every individual. Guidelines for management of diabetes should be consulted, and possible complications of treatment should be considered.

Insulin injection (soluble)

ATC code: A10AB

Injection: 100 IU/ml in 10 ml vial

Indications: Diabetes mellitus; diabetic emergencies and at surgery; diabetic ketoacidosis or coma.

Precautions: Acute trauma or illness: insulin requirement may increase.

Surgery: monitor blood glucose and urine ketones perioperatively; insulin infusion may be required in complex or prolonged surgery.

Dose:

Hyperglycaemia, surgery in children with diabetes.
IV infusion:
Neonate 0.01–0.1 units/kg/hour, adjusted according to blood glucose concentration. Start at lower rate and monitor closely; neonates are very sensitive to insulin.
Infant or **Child** 0.025–0.1 units/kg/hour, adjusted according to blood glucose concentration.

Diabetes mellitus.
SC:
Neonate, Infant or **Child** according to requirements.

Diabetic ketoacidosis or coma.
IV infusion:
Infant or **Child** 0.05–0.1 units/kg/hour (maximum 0.2 units/kg/hour) depending on the rate of reduction of serum glucose (decreasing the serum glucose level too rapidly may lead to cerebral oedema), until acidosis is corrected and patient is resumed on subcutaneous insulin.

Renal impairment: May need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Hypoglycaemia (see below), weight gain, hypokalaemia when given without potassium in the treatment of diabetic ketoacidosis.

Uncommon Allergic reactions, local reactions including erythema, itching, lipodystrophy, lipoatrophy.

HYPOGLYCAEMIA The most frequent and serious adverse effect of insulin therapy; may occur with excessive dosage, delayed or insufficient food, increased physical activity. Warning symptoms include sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance and altered mood.

Interactions with other medicines (* indicates severe):

Dexamethasone: antagonism of hypoglycaemic effect.

Enalapril: hypoglycaemic effect possibly enhanced.

Ethanol: enhanced hypoglycaemic effect.

Furosemide: antagonism of hypoglycaemic effect.

Hydrochlorothiazide: antagonism of hypoglycaemic effect.

Hydrocortisone: antagonism of hypoglycaemic effect.

Prednisolone: antagonism of hypoglycaemic effect.

Propranolol: enhanced hypoglycaemic effect; propranolol may mask warning signs of hypoglycaemia such as tremor.

Notes: For maintenance regimes it is usual to inject 15–30 minutes before meals.

When injected subcutaneously, soluble insulin has a rapid onset of action (30–60 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.

If changing from intravenous to subcutaneous insulin, do not stop the intravenous infusion until 30–60 minutes after the subcutaneous dose (to allow time for effect).

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.

Patients need to be instructed to rotate the subcutaneous injection site to avoid fat necrosis (lipoatrophy) and erratic absorption. Can be a particular problem in children because lipoatrophic area less painful to inject into than normal areas.

Refrigerate unopened vials of insulin at 2–8 °C. Once opened vials may be stored in refrigerator or at room temperature for up to 28 days. Only use soluble insulin if it is clear and not cloudy.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Intermediate-acting insulin

ATC code: A10AC

Injection: 100 IU/ml in 10 ml vial (as compound insulin zinc suspension or isophane insulin)

Indications: Diabetes mellitus.

Contraindications: Intravenous administration.

Precautions: Acute trauma or illness: insulin requirement may increase.

Surgery: monitor blood glucose and urine ketones perioperatively; soluble insulin infusion may be required in complex or prolonged surgery.

Dose:

Diabetes mellitus.
SC:
Neonate, Infant or **Child** according to requirements.

Renal impairment: May need dose reduction; insulin requirements fall; compensatory response to hypoglycaemia is impaired.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Hypoglycaemia (see below), weight gain.

Uncommon Allergic reactions, local reactions including erythema, itching, lipodystrophy, lipoatrophy.

HYPOGLYCAEMIA The most frequent and serious adverse effect; may occur with excessive dosage, delayed or insufficient food, increased physical activity. Warning symptoms include sweating, hunger, faintness, palpitations, tremor, headache, visual disturbance and altered mood.

Interactions with other medicines (* indicates severe):

Dexamethasone: antagonism of hypoglycaemic effect.

Enalapril: hypoglycaemic effect possibly enhanced.

Ethanol: enhanced hypoglycaemic effect.

Furosemide: antagonism of hypoglycaemic effect.

Hydrochlorothiazide: antagonism of hypoglycaemic effect.

Hydrocortisone: antagonism of hypoglycaemic effect.

Prednisolone: antagonism of hypoglycaemic effect.

Propranolol: enhanced hypoglycaemic effect; propranolol may mask warning signs of hypoglycaemia such as tremor.

Notes: When given by subcutaneous injection, intermediate 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 action (soluble) insulin and others are given once daily. Soluble insulin can be mixed with intermediate insulins.

Patients need to be instructed to rotate the subcutaneous injection site to avoid fat necrosis (lipoatrophy) and erratic absorption. Can be a particular problem in children because lipoatrophic area less painful to inject into than normal areas.

Isophane insulin is a suspension of insulin with protamine; it is of particular value for initiation of twice daily insulin regimes. Isophane can be mixed with soluble insulin before injection.

Insulin zinc suspension (30% amorphous, 70% crystalline) has a more prolonged duration of action.

Refrigerate unopened vials of insulin at 2–8 °C. Once opened vials may be stored in refrigerator or at room temperature for up to 28 days.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Metformin

ATC code: A10BA02

Tablet: 500 mg (as hydrochloride)

Special Notes: Determine renal function before treatment and once or twice annually during treatment.

Should only be used under specialist supervision.

Indications: Non-insulin-dependent diabetes mellitus (type 2).

Contraindications: Acidosis, including diabetic ketoacidosis; use of iodine-containing X-ray contrast media; general anaesthesia; severe renal impairment.

Precautions: Hepatic impairment; renal impairment (determine renal function before treatment and once or twice annually); substitute insulin during severe infection, trauma or surgery; dehydration.

Dose:

Diabetes mellitus.

Oral:

Child *8–10 years* initially 200 mg once daily adjusted according to response at intervals of at least a week. Maximum 2 g daily in 2–3 divided doses;

over 10 years initially 500 mg once daily adjusted according to response at intervals of at least a week. Maximum 2 g daily in 2–3 divided doses.

Renal impairment: Metformin should be used cautiously in renal impairment because of the increased risk of lactic acidosis; it is contraindicated 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.

Hepatic impairment: Avoid use in hepatic impairment; risk of lactic acidosis.

Adverse effects: Common Malabsorption of vitamin B_{12}, nausea, vomiting, anorexia, diarrhoea.

Uncommon Rash.

Rare Lactic acidosis (see below), acute hepatitis, hypoglycaemia.

LACTIC ACIDOSIS Rare, but often fatal; may be associated with metformin accumulation when precautions or high-risk situations are overlooked. Early symptoms include anorexia, nausea, vomiting, abdominal pain, cramps, malaise and weight loss.

Interactions with other medicines (* indicates severe):

Dexamethasone: antagonism of hypoglycaemic effect.

Enalapril: hypoglycaemic effect possibly enhanced.

Ethanol: enhanced hypoglycaemic effect; increased risk of lactic acidosis.

Furosemide: antagonism of hypoglycaemic effect.

Hydrochlorothiazide: antagonism of hypoglycaemic effect.

Hydrocortisone: antagonism of hypoglycaemic effect.

* **Iodinated radiocontrast media**: increased risk of lactic acidosis and acute renal failure; contraindicated.

Prednisolone: antagonism of hypoglycaemic effect.

Propranolol: propranolol may mask warning signs of hypoglycaemia such as tremor.

Notes: Doses should be administered with a meal.

Gastrointestinal 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.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

18.6 Ovulation inducers

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

18.7 Progestogens

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

18.8 Thyroid hormones and antithyroid medicines

Thyroid hormones

Thyroid agents are natural or synthetic agents containing **levothyroxine** (thyroxine) or liothyronine (tri-iodothyronine). They increase the metabolic rate and exert a cardiostimulatory effect. Neonatal hypothyroidism requires prompt treatment for normal development. Dosage should be titrated according to clinical response, growth assessment and measurement of plasma thyroxine and thyroid-stimulating hormone.

Levothyroxine

ATC code: H03AA01

Tablet: 25 micrograms; 50 micrograms; 100 micrograms (sodium salt)

Special Notes: Also known as thyroxine sodium, thyroxine and T4.

Indications: Hypothyroidism.

Contraindications: Thyrotoxicosis; uncorrected adrenal insufficiency.

Precautions: 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 diabetic drugs including insulin may need to be increased).

Dose:

Hypothyroidism.

Oral:

Neonate initially 10–15 micrograms/kg (maximum 50 micrograms) once daily. Adjust in steps of 5 micrograms/kg every 2 weeks or as necessary. Usual maintenance dose 20–50 micrograms daily.

Infant or **Child** ***1 month–2 years*** initially 5 micrograms/kg (maximum 50 micrograms) once daily. Adjust in steps of 10–25 micrograms daily every 2–4 weeks. 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 normalized; usual dose 75–100 micrograms daily.

NOTE In cardiac disease reduce dose by 50% and increase more slowly.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Usually associated with excessive dosage and correspond to symptoms of hyperthyroidism.

Common (when used in excess doses) Tachycardia, arrhythmia, excitability, insomnia, flushing, sweating, diarrhoea and excessive weight loss.

Uncommon Worsening ischaemic symptoms may occur in those with ischaemic heart disease, even at reduced doses.

Rare Benign intracranial hypertension with headache, vomiting and papilloedema has been reported in children in the first few weeks of treatment, craniosynostosis and advancement of bone age may develop in infants treated with excessive doses, pruritus, oedema.

Interactions with other medicines (* indicates severe):

Amitriptyline: enhanced effects of amitriptyline.

Calcium salts: reduced absorption of levothyroxine.

Carbamazepine: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

Ferrous salts: absorption of levothyroxine reduced by oral ferrous salts (give at least 2 hours apart).

Phenobarbital: metabolism of levothyroxine accelerated (may increase levothyroxine requirements in hypothyroidism).

Phenytoin: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism); plasma concentration of phenytoin possibly increased.

Rifampicin: accelerated metabolism of levothyroxine (may increase levothyroxine requirements in hypothyroidism).

* **Warfarin**: enhanced anticoagulant effect.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Lugol's solution

ATC code: D08AG

Oral liquid: approximately 130 mg of total iodine/ml

Special Notes: Lugol's solution: iodine 5%, potassium iodide 10% in freshly boiled and cooled purified water.

Also known as strong iodine solution.

Easily confused with potassium iodide.

Indications: Thyrotoxicosis; thyrotoxic crisis.

Contraindications: Breastfeeding (possibly concentrated in milk; risk of neonatal goitre and hypothyroidism); pregnancy (risk of neonatal hypothyroidism); surgery for toxic nodular goitre (may worsen hyperthyroidism); pulmonary oedema; hyperthyroidism; severe renal impairment.

Precautions: Long-term use; cystic fibrosis; myotonia congenita; Addison disease; tuberculosis; acute bronchitis; treatment may worsen acne; cardiac disease.

Dose:

Neonatal thyrotoxicosis.
Oral:
Neonate 0.05–0.1 ml three times daily.

Thyrotoxicosis (preoperative).
Oral:
Neonate 0.1–0.3 ml three times daily.
Infant or **Child** 0.1–0.3 ml three times daily.

Thyrotoxic crisis.
Oral:
Infant 0.2–0.3 ml three times daily.
Child 1 ml three times daily.

Renal impairment: Use with caution.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Gastrointestinal intolerance including nausea, vomiting, diarrhoea and metallic taste.

Uncommon or rare Hypersensitivity reactions, including corzya-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes, on prolonged treatment, insomnia and depression, cardiac arrhythmias.

Interactions with other medicines (* indicates severe):

Sodium iodide (iodine-131): decreased effect.

Enalapril: increased effect/toxicity.

Notes: ADMINISTRATION Dilute well with milk or water.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Potassium iodide

ATC code: H03CA

Tablet: 60 mg

Special Notes: Can be confused with Lugol's solution which is potassium iodide and iodine.

Indications: Thyrotoxic crisis; preoperative thyroidectomy.

Contraindications: Hyperkalaemia; pulmonary oedema; iodine-induced goitre; dermatitis herpetiformis; hypocomplementemic vasculitis; breastfeeding.

Precautions: Cystic fibrosis; myotonia congenita; cardiac disease; Addison disease; tuberculosis; acute bronchitis; treatment may worsen acne; renal impairment; hyperthyroidism.

Dose:

Preoperative thyroidectomy.
Oral:
Child *all ages* 60–240 mg three times daily.

Thyrotoxic crisis.
Oral:
Infant 150–240 mg three times daily.
Child 300–480 mg three times daily.

NOTE Doses may need to be rounded to the nearest 30 mg (half a tablet).

Renal impairment: Use with caution.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Hypothyroidism, hyperthyroidism, metallic taste, increased salivation, coryza-like symptoms, irritation and swelling of the eyes, lacrimation, conjunctivitis, gastrointestinal disturbances, diarrhoea, skin reactions including acneiform.

Uncommon Pulmonary oedema, bronchitis, depression, insomnia, headache, laryngitis, goitre.

Rare Pain or inflammation of salivary glands, hypersensitivity reactions, Jod-Basedow phenomenon or iodine-induced thyrotoxicosis.

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: increased risk of hyperkalaemia.
* **Enalapril**: increased risk of severe hyperkalaemia.
* **Spironolactone**: risk of hyperkalaemia.

Sodium iodide (iodine-131): decreased effect.

Notes: ADMINISTRATION Give after meals with food or milk. Tablets may be crushed and dispersed in water, fruit juice, milk or formula.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Propylthiouracil

ATC code: H03BA02

Tablet: 50 mg

Rare severe hepatic reactions including hepatic necrosis and hepatitis may occur. Children appear to be at higher risk of propylthiouracil-induced liver injury than adults.

Special Notes: Where possible, carbimazole (not on the essential medicines list for children) should be used in place of propylthiouracil because of its preferable side-effect profile.

Indications: Treatment of hyperthyroidism; thyrotoxic crisis; thyrotoxicosis.

Precautions: Hepatic impairment; renal impairment; large goitre; concomitant myelosuppresive drugs.

Dose:

Hyperthyroidism (including Graves disease), thyrotoxic crisis, thyrotoxicosis.

Adjust dosage to maintain T3, T4 and TSH in normal range; elevated T3 may be sole indicator of inadequate treatment. Elevated TSH indicates excessive antithyroid treatment.

Oral:

Neonate initially 2.5–5 mg/kg twice daily until euthyroid. Adjusted as necessary; higher doses occasionally required, particularly in thyrotoxic crisis.

Infant initially 2.5 mg/kg three times daily until euthyroid. Adjusted as necessary; higher doses occasionally required, particularly in thyrotoxic crisis.

Child *1–5 years* initially 25 mg three times daily until euthyroid. Adjusted as necessary; higher doses occasionally required, particularly in thyrotoxic crisis;

5–12 years initially 50 mg three times daily until euthyroid. Adjusted as necessary; higher doses occasionally required, particularly in thyrotoxic crisis.

NOTE Maintenance dosage to maintain euthyroid state is commonly 30–60% of the initial dose.

Renal impairment: Mild to moderate: use 75% of the normal dose.

Severe: use 50% of the normal dose.

Hepatic impairment: Withdraw treatment if hepatic function deteriorates (fatal reactions reported).

Adverse effects: Occur most often during the first 8 weeks of treatment. Itching and mild rashes may respond to antihistamines while continuing treatment.

Common Itching, rash, mild leukopenia, nausea, vomiting, gastric discomfort, headache, arthralgia.

Rare Agranulocytosis (see below), hypoprothrombinaemia and bleeding, myositis, hepatotoxicity (see below), vasculitis, lupus-like syndrome.

AGRANULOCYTOSIS Most likely in first 3 months of treatment; its rapid onset means regular monitoring is of questionable value.

HEPATOTOXICITY Asymptomatic increases in serum aminotransferases may occur commonly during the first 2 months of propylthiouracil treatment, but resolve with continued treatment. Serious hepatotoxic reactions (usually hepatocellular hepatitis) occur rarely with propylthiouracil and may be immune-based.

Interactions with other medicines (* indicates severe):

Sodium iodide (iodine-131): avoid combination.

* **Warfarin**: decreased anticoagulant effect.

Notes: PATIENT ADVICE Warn patient or carer to tell doctor immediately if sore throat, mouth ulcers, bruising, fever, malaise or non-specific illness occur.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

SECTION 19:
Immunologicals

19 Immunologicals

Immunity

Active immunity is acquired by administration of microorganisms or their products to induce antibodies. Active immunity can be acquired by natural disease or by vaccination. *Passive immunity* is conferred by preparations made from the plasma of immune individuals.

19.1 Diagnostic agents

The tuberculin skin test (**tuberculin, purified protein derivative**) is a subcutaneous injection of purified tuberculin derivative used to identify exposure to mycobacteria, particularly *Mycobacterium tuberculosis*. The local skin reaction is 'read' at 72 hours post-inoculation. It is limited in its efficacy, given that it does not distinguish between *Mycobacterium* species, active and quiescent disease, or acquired infection and seroconversion from BCG vaccination.

Tuberculin, purified protein derivative

ATC code: V04CF01

Injection

Special Notes: Tuberculin purified protein derivative PPD is a sterile isotonic solution of tuberculin. It is obtained from a human strain of *Mycobacterium tuberculosis* grown on a protein-free synthetic medium.

Tuberculin PPD is indicated as a diagnostic aid in the detection of *Mycobacterium tuberculosis* infection (Mantoux test).

Indications: Test for hypersensitivity to tuberculoprotein.

Contraindications: Should not be used within 4 weeks of receiving a live viral vaccine.

Precautions: Malnutrition; viral or bacterial infections (including HIV and severe tuberculosis); malignant disease; corticosteroid or immunosuppressant therapy: diminished sensitivity to tuberculin; avoid contact with open cuts, abraded or diseased skin, eyes or mouth.

Response to tuberculin may be suppressed by live viral vaccines, viral infection, sarcoidosis.

Dose:

NOTE National recommendations may vary.

Test for hypersensitivity to tuberculoprotein.

Intradermal:

Child *all ages* 5 or 10 units (1 unit may be used in hypersensitive patients or if tuberculosis is suspected). See Notes for method of administration.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Nausea, headache, malaise, rash, immediate local reactions (more common in atopic patients).

Rare Vesicular or ulcerating local reactions, regional adenopathy and fever.

Interactions with other medicines (* indicates severe):

Systemic steroids: may suppress the reaction to the test.

Live vaccines: may suppress the reaction to the test and should either be administered on the same day as the test or 4 weeks after.

Notes: Not for intravenous or intramuscular injection.

Administration of the Mantoux test consists of an intradermal injection of 5 or 10 tuberculin units into the flexor or dorsal surface of the forearm (about 4 inches below the bend of the elbow). A tuberculin syringe with a ½ inch 26 or 27 gauge needle should be used to administer the test material. The bevel of the needle should be pointing upward and inserted into the most superficial layers of the skin. As the PPD is injected, a pale bleb (6–10 mm) will rise over the point of the needle; the bleb will disappear in minutes. If the bleb does not form, repeat the test at least 2 inches from the original injection site. No dressing is required.

All tuberculins should comply with the Requirements for Tuberculins (Revised 1985) WHO Expert Committee on Biological Standardization Thirty-sixth report (WHO Technical Report Series, No. 745, 1987, Annex 1).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

19.2 Sera and immunoglobulins

Antibodies of human origin are usually termed **immunoglobulins**. Material prepared from animals is called **antiserum**. Due to 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.

Contraindications, precautions and adverse reactions

Anaphylaxis, although rare, can occur and epinephrine (adrenaline) must always be available. *Intramuscular injection* of sera and immunoglobulins may cause local reactions including pain and tenderness. Live virus vaccines should be given either 3 weeks before or 3 months after immunoglobulin.

Antitetanus immunoglobulin (human)

ATC code: J06BB02

Injection: 500 IU in vial

Special Notes: Also referred to as tetanus immunoglobulin.

Indications: Passive immunization against tetanus as part of the management of tetanus-prone wounds; treatment of tetanus.

Contraindications: Thrombocytopenia (IM injection contraindicated).

Precautions: Anaphylaxis, although rare, may occur; concomitant or recent use of live virus vaccines (see below).

LIVE VIRUS VACCINES Immunoglobulins may interfere with the immune response to live virus vaccines, which should be administered 3 weeks before or 3 months after immunoglobulin.

Dose:

NOTE National recommendations may vary.

Passive immunization against tetanus as part of the management of tetanus-prone wounds.

IM:

Child *all ages* 250 units, increase to 500 units if wound older than 24 hours or there is risk of heavy contamination or following burns.

Treatment of tetanus.

IV:

Child *all ages* consult specialist protocols.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Local reactions including pain and tenderness may occur at the site of IM injection. Systemic reactions following IV injection including fever, chills, facial flushing, headache and nausea.

Rare Hypersensitivity including anaphylaxis.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect.

Notes: Antitetanus immunoglobulin of human origin is a preparation containing immunoglobulins derived from the plasma of adults immunized with tetanus toxoid. It is used for the management of tetanus-prone wounds in addition to wound toilet and if appropriate antibacterial prophylaxis and adsorbed tetanus vaccine.

Adrenaline should be available to treat anaphylaxis should it occur.

TETANUS VACCINE If clinical situation requires tetanus vaccine and antitetanus immunoglobulin to be administered at the same time, they should be administered using separate syringes and separate sites.

Plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Technical Report Series No. 840, 1994, Annex 2.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).

Antivenom immunoglobulin

ATC code: J06AA03

Injection

Indications: Acute envenomation following snake or spider bite.

Contraindications: There are no absolute contraindications to antivenom treatment in significant systemic envenoming; treatment can be life saving.

A number of antivenoms are derived from rabbit, equine or ovine sources and should be used in caution in patients allergic to these animals, but do not withhold treatment in severe or potentially severe envenomation.

Precautions: Anaphylaxis, although rare, may occur; concomitant or recent use of live virus vaccines (see below); resuscitation facilities should be immediately available.

LIVE VIRUS VACCINES Immunoglobulins may interfere with the immune response to live virus vaccines which should be administered 3 weeks before or 3 months after immunoglobulin.

Dose:

Depends on the specific antivenom used, consult local protocol and manufacturers' literature.

Children are at greater risk of severe envenoming because of smaller body mass and likelihood of physical activity immediately following a bite. Children require the same doses of antivenom as adults and should not be given weight-adjusted doses, which may grossly underestimate antivenom requirement; the amount of antivenom required depends on the amount of venom to be neutralized, not the weight of the patient.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Rash (transient), headache, hypotension, fever, anaphylaxis or anaphylactoid reactions (immediate or early onset), serum sickness (delayed onset, risk increases with volume of antivenom).

Uncommon Abdominal pain, vomiting, arthralgia, myalgia, pain at infusion site.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect.

Notes: All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization Forty-third report, WHO Technical Report Series, No. 840, 1994, Annex 2.

Acute envenomation from snakes or spiders is common in many parts of the world. The bite may cause local and systemic effects.

Local effects include pain, swelling, bruising and tender enlargement of regional lymph nodes. Wounds should be cleaned and pain may be relieved by analgesics.

If significant amounts of toxin are absorbed after a snake bite, this may result in early anaphylactoid symptoms such as transient hypotension, angioedema, abdominal colic, diarrhoea and vomiting, followed by persistent or recurrent hypotension and ECG abnormalities. Spontaneous systemic bleeding, coagulopathy, respiratory distress syndrome and acute renal failure may occur. Early anaphylactoid symptoms may be treated with adrenaline. Snake antivenom immunoglobulins are the only specific treatment available but they can produce severe adverse reactions. They are generally only used if there is a clear indication of systemic involvement, severe local involvement or, in regions where supplies are not limited, in patients at high risk of systemic or severe local involvement.

There are many antivenom immunoglobulins each containing specific venom-neutralizing globulins. It is important that the specific antivenom immunoglobulin suitable for the species causing the envenomation is administered.

In countries where there are a number of venomous snake species (e.g. Australia), a polyvalent immunoglobulin is also available to be used. This is used when the snake species is not known, the specific antivenom is not available or is not available in sufficient quantity to treat the envenomation.

Risk of anaphylactoid reaction can be reduced by adequate dilution of antivenom before infusion.

Spider bites may cause either necrotic or neurotoxic syndromes depending on the species involved. Supportive and symptomatic treatment is required and in the case of necrotic syndrome, surgical repair may be necessary. Spider antivenom immunoglobulin, suitable for the species involved, may prevent symptoms if administered as soon as possible after envenomation.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Diphtheria antitoxin

ATC code: J06AA01

Injection: 10 000 IU; 20 000 IU in vial

Indications: Passive immunization in suspected cases of diphtheria without waiting for bacterial confirmation.

Contraindications: Not to be used for primary prophylaxis of diphtheria.

Precautions: In patients allergic to horses, antitoxin should be used with caution but not withheld.

Initial test dose should be given to exclude hypersensitivity; anaphylaxis, although rare, may occur; observation required after full dose (epinephrine and resuscitation facilities should be available); concomitant or recent use of live virus vaccines (see below).

LIVE VIRUS VACCINES Immunoglobulins may interfere with the immune response to live virus vaccines which should be administered 3 weeks before or 3 months after immunoglobulin.

Dose:

NOTE National recommendations may vary.

Passive immunization in suspected diphtheria.

IM:

Child *all ages* 10 000–30 000 units in mild to moderate cases; 40 000–100 000 units in severe cases (for doses of more than 40 000 units, a portion should be given by intramuscular injection followed by the bulk of the dose intravenously after an interval of 0.5–2 hours).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Hypersensitivity, anaphylaxis with urticaria, hypotension, dyspnoea and shock, serum sickness up to 12 days after injection.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect.

Notes: All plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (Revised 1992). WHO Expert Committee on Biological Standardization Forty-third report, WHO Technical Report Series, No. 840, 1994, Annex 2.

Antitoxin will only neutralize circulating toxin that is not yet bound to tissue. If diphtheria is strongly suspected, treatment with diphtheria antitoxin should be given immediately after bacteriological specimens are taken, without waiting for laboratory results.

To eradicate diphtheria infection antibiotic therapy using an appropriate agent such as erythromycin or penicillin should be given in addition to diphtheria antitoxin.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Rabies immunoglobulin

ATC code: J06BB05

Injection: 150 IU/ml in vial

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Also referred to as RIG (rabies immune globulin) or HRIG (human rabies immune globulin).

Human and equine forms are available dependent on country. There are two forms of equine RIG; purified equine immunoglobulin (ERIG) and F(ab')2.

The indication for post-exposure prophylaxis with or without RIG depends on the type of contact with the suspected rabid animal:

Category I: touching or feeding animals, licks on intact skin (i.e. no exposure);

Category II: nibbling of uncovered skin, minor scratches or abrasions without bleeding, licks on broken skin;

Category III: single or multiple transdermal bites or scratches, contamination of mucous membrane with saliva from licks, exposures to bats.

For category I exposures, no prophylaxis is required; whereas for category II, immediate vaccination, and for category III, immediate vaccination and administration of RIG are recommended.

RIG should be administered in all category III exposures and in category II exposures involving immunodeficient individuals (for exposure categories, see WHO position below).

Given its relatively slow clearance (half-life about 21 days), human rabies immunoglobulin (HRIG) is the preferred product, particularly in cases of multiple severe exposures. However, HRIG is in short supply and available mainly in industrialized countries. Where HRIG is not available or affordable, purified equine immunoglobulin (ERIG) or F(ab′)2 products of ERIG should be used. Most of the new ERIG preparations are potent, highly purified, safe and considerably less expensive than HRIG. However, they are of heterologous origin and carry a small risk of hypersensitivity reactions. There are no scientific grounds for performing a skin test prior to administration of ERIG because testing does not predict reactions, and ERIG should be given whatever the result of the test.

RIG for passive immunization should not be injected later than 7 days after the initiation of post-exposure vaccination. The dose for HRIG is 20 units/body weight, and for ERIG and F(ab′)2 products 40 units/kg body weight. All of the RIG, or as much as anatomically possible (cave compartment syndrome), should be administered into or around the wound site(s). Remaining RIG if any should be injected intramuscularly at a site distant from the site of vaccine administration. RIG can be diluted if necessary to ensure infiltration of all wounds at a volume determined by the capacity of the site and sound clinical judgement.

Indications: Post-exposure (or suspected exposure) prophylaxis against rabies.

Precautions: Anaphylaxis, although rare, may occur; concomitant or recent use of live virus vaccines (see below).

LIVE VIRUS VACCINES Immunoglobulins may interfere with the immune response to live virus vaccines, which should be administered 3 weeks before or 3 months after immunoglobulin.

Dose:

Dose refers to human rabies immunoglobulin. Refer to Special notes for dosing of other rabies immunoglobulins.

NOTE National recommendations may vary.

Post-exposure (or suspected exposure) prophylaxis against rabies.

Child *all ages* 20 units/kg single dose by *infiltration* in and around the cleansed wound as soon as possible after exposure; if wound not visible or healed or if *infiltration* of whole volume not possible, give remainder by *intramuscular injection* into anterolateral thigh. Give with the first dose of rabies vaccine.

Renal impairment: Dose reductions not necessary.

Hepatic impairment: Dose reductions not necessary.

Adverse effects: Uncommon Local reactions including pain and tenderness may occur at the site of intramuscular injection, systemic reactions following intravenous injection including fever, chills, facial flushing, headache and nausea.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect.

Notes: For children with a small muscle mass, it may be necessary to administer immunoglobulin at multiple sites.

In the case of multiple wounds in which the volume of immunoglobulin is insufficient for infiltration, dilution in saline solution to an adequate volume has been recommended to ensure all wound areas receive infiltrate.

Rabies immunoglobulin is a preparation containing immunoglobulins derived from the plasma of adults immunized with rabies vaccine. It is used as part of the management of potential rabies following exposure of an unimmunized individual to an animal in or from a high-risk country. It should be administered as soon as possible after exposure, without waiting for confirmation that the animal is rabid. The site of the bite should be washed with soapy water and the rabies immunoglobulin should be infiltrated in and around the site of the bite. In addition, rabies vaccine should be administered at a different site.

Plasma fractions should comply with the WHO Requirements for the Collection, Processing and Quality Control of Blood, Blood Components and Plasma Derivatives (revised 1992). WHO Technical Report Series No 840, 1994, Annex 2.

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

19.3 Vaccines

Selection of vaccines from the *2nd WHO Model List of Essential Medicines for Children* for individual countries should be determined after consideration of international recommendations, epidemiology and national priorities.

Adverse effects

Vaccines are generally both effective and safe. Reactions are usually mild. Injection site reactions may occur and some vaccines may cause a very mild form of the disease. Serious reactions are rare. If a serious adverse event occurs following a dose of a vaccine, subsequent doses should **not** be given.

Vaccines are contraindicated in individuals with known severe hypersensitivity to any component.

HIV infection

The likelihood of successful immunization is reduced in some HIV-infected individuals, but the risk of serious adverse effects remains low, except for BCG (see BCG monograph). Most vaccines are safe in HIV-positive individuals, although live vaccines should be avoided if the CD4 count is very low. See under individual vaccine monographs.

Live vaccines

When two live virus vaccines are required they should either be given simultaneously at different sites, or with an interval of at least 4 weeks between them.

Contraindications

There are very few absolute contraindications to immunization. These include encephalopathy within 7 days of a previous dose, anaphylaxis to a previous dose or known component, and live vaccines in immunocompromised individuals (see above).

BCG vaccine

ATC code: J07AN01; L03AX03

Powder for injection

Special Notes: Also referred to as bacillus Calmette-Guérin.

Tuberculosis (TB) is a bacterial infection caused by *Mycobacterium tuberculosis,* transmitted from person to person through respiratory contact. Where tuberculosis remains highly prevalent, routine immunization of infants within the first year of life with BCG vaccine, derived from bacillus Calmette-Guérin (an attenuated strain of *Mycobacterium bovis)* reduces the incidence of meningeal and miliary tuberculosis in early childhood. The efficacy against pulmonary tuberculosis is doubtful; the mainstay of the tuberculosis control programme is case-finding and treatment.

WHO recommends that all infants in highly endemic countries should receive a single dose of BCG vaccine as soon as possible after birth. In low-endemic countries, BCG vaccine can be given to infants and children at high risk of tuberculosis exposure. Infants known to be HIV-infected (with or without symptoms) should not receive BCG vaccination. Infants born to known HIV-infected mothers should only be immunized if no signs or symptoms suggestive of HIV infection are present and after taking into consideration the likelihood of the infant being infected with HIV, and the potential risk of exposure to tuberculosis. If HIV infection status can be established with early virological testing, BCG vaccine can be administered once HIV infection has been ruled out.

Infants exposed to smear-positive pulmonary tuberculosis shortly after birth should not receive BCG vaccination until completion of 6 months of prophylactic isoniazid treatment.

BCG vaccine may be given simultaneously with other live vaccines, but if not given at the same time they should be given 4 weeks apart. When BCG vaccine is given to infants, there is no need to delay routine primary immunizations.

Indications: Active immunization against tuberculosis.

Contraindications: HIV infection; immunodeficiency; patients receiving immunosuppressive therapy; generalized septic skin conditions; current isoniazid treatment; history of anaphylaxis to any component of the vaccine; pregnancy; bone marrow or lymphoid malignancy.

Precautions: Eczema or skin infection (vaccine site must be lesion-free); concomitant administration of other vaccines (either administer concurrently with other vaccines or separate by 4 weeks).

Dose:

Active immunization against tuberculosis.
Intradermal:
Neonate or **Infant** 0.05 ml.
Child 0.1 ml.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Ulcer at injection site (2–6 weeks after vaccination), enlargement of regional lymph nodes, transient injection site reactions (pain, redness, itching, swelling or burning).

Uncommon Transient fever, fainting.

Rare Abscess, keloid formation, disseminated infection, lymphadenitis, local ulceration, disseminated BCG infection in immunodeficient individuals, osteitis, anaphylactoid reactions.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

* **Isoniazid**: conconcurrent treatment with isoniazid can inactivate the vaccine.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
World Health Organization. BCG vaccine: WHO position paper. *Weekly epidemiological record,* 2004, 79(4):27–38 (http://www.who.int/immunization/wer7904BCG_Jan04_position_paper.pdf, accessed 13 April 2010).

Cholera vaccine

ATC code: J07AE01

Oral suspension

Special Notes: Two types of oral cholera vaccines are available: (i) Dukoral and (ii) Shanchol and mORCVAX. Shanchol and mORCVAX are identical vaccines in terms of strains but formulated by different manufacturers using different methods.

Dukoral is also referred to as WC-rBS.

Cholera is caused by *Vibrio cholerae* and is closely associated with poor sanitation. It is transmitted by faecal contamination of water and food; person-to-person transmission is uncommon.

Cholera control should be a priority in areas where the disease is endemic. Given the availability of two oral cholera vaccines and data on their efficacy, field effectiveness, feasibility and acceptance in cholera-affected populations, immunization with these vaccines should be used in conjunction with other prevention and control strategies in areas where the disease is endemic and should be considered in areas at risk for outbreaks.

Vaccination should not disrupt the provision of other high-priority health interventions to control or prevent cholera outbreaks. Vaccines provide a short-term effect that can be implemented to bring about an immediate response while the longer-term interventions of improving water and sanitation, which involve large investments, are put into place.

Although all age groups are vulnerable to cholera, where resources are limited immunization should be targeted at high-risk children aged ≥ 1 year (Shanchol or mORCVAX) or ≥ 2 years (Dukoral). (For vaccine schedules and administration, see recommendations made by the manufacturers.)

Immunization for travellers is only recommended for individuals at increased risk of exposure, particularly emergency relief and health-care workers in refugee situations or individuals at particular risk of complications of diarrhoeal disease including those with inflammatory bowel disease, poorly controlled diabetes, cardiovascular disease or immune suppression.

Injectable cholera vaccine is not recommended by WHO because it provides unreliable protection and does not prevent transmission of infection.

Indications: Active immunization against cholera.

Contraindications: Anaphylaxis to the vaccine or any component of the vaccine.

Dose:

DUKORAL (WC-RBS)

Primary immunization against *V. cholerae.*

Oral:

Child *2–5 years* three doses given > 7 days apart (but < 6 weeks apart);
6–12 years two doses given > 7 days apart (but < 6 weeks apart).
NOTE If the interval between the primary immunization doses is delayed for > 6 weeks, primary immunization should be restarted.

Continued risk of *V. cholerae* infection.

Oral:

Child *2–5 years* one booster dose every 6 months. If the interval between the primary immunization series and the booster immunization is > 6 months, primary immunization must be repeated;
6–12 years one booster dose after 2 years. If the interval between the primary immunization series and booster immunization is > 2 years, primary immunization must be repeated.

SHANCHOL

Immunization against *V. cholerae.*

Oral:

Child *all ages* two doses given 14 days apart. A booster dose is recommended after 2 years.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Abdominal discomfort, diarrhoea, headache.

Rare Allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).
* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Oral typhoid vaccine: inactivated vaccine buffer may affect transit time; allow at least 8 hours between the administration of cholera and typhoid vaccines.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

Dukoral: intake of food and drink should be avoided for 1 hour before and after vaccination.

The sodium hydrogen carbonate buffer is supplied as effervescent granules, which should be dissolved in a glass of water (approximately 150 ml).

Dukoral should be mixed with the sodium hydrogen carbonate solution and drunk.

Protection may be expected about 1 week after the last scheduled dose.

Dukoral has been shown to cross-protect against enterotoxigenic *Escherichia coli* (ETEC).

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
World Health Organization. Cholera vaccines: WHO position paper. *Weekly epidemiological record,* 2010, 85(13):117–128 (http://www.who.int/wer/2010/wer8513.pdf, accessed April 11 2010).

Diphtheria vaccine

ATC code: J07AJ51; J07AM51

Injection: form will vary depending on other vaccines combined with diphtheria. Diphtheria and tetanus toxoids are adsorbed onto a mineral carrier.

Special Notes: In regards to diphtheria toxoid containing coformulations, "D" refers to the paediatric formulation and "d" refers to the adult formulation.

Children under 7 years should use high-dose diphtheria ("D") vaccines.

Please be aware that formulations designed for adult immunization or booster doses in children who have received the full schedule of childhood vaccines may not contain as much diphtheria toxoid as those designed for primary immunization and may not provide adequate immunity.

In most cases, diphtheria toxoid is administered in fixed combination with other vaccines. Currently, diphtheria toxoid is almost exclusively available in combination with tetanus toxoid (T) as DT, or with tetanus and pertussis vaccine as DTP (the origin of the pertussis component often specified as whole cell (wP) or acellular (aP). Diphtheria toxoid may also be combined with additional vaccine antigens, such as hepatitis B and *Haemophilus influenzae* type b.

DIPHTHERIA Diphtheria is a bacterial infection caused by *Corynebacterium diphtheriae* and is transmitted from person to person through close physical and respiratory contact. Diphtheria vaccine is a formaldehyde-inactivated preparation of diphtheria toxin, adsorbed onto a mineral carrier to increase its antigenicity and reduce adverse reactions.

Diphtheria vaccine is given as part of primary immunization schedule in fixed combinations with tetanus, or tetanus and pertussis vaccines. Combinations with other antigens such as *Haemophilus influenzae* type b, poliomyelitis and hepatitis B vaccines are available in some countries. Immunization against diphtheria should be considered for health-care workers who are at risk of occupational exposure to *Corynebacterium diphtheriae.*

For primary immunization in infants, a three-dose schedule of a three-component preparation of diphtheria vaccine in combination with pertussis and tetanus vaccines is recommended.

A two-component diphtheria vaccine with tetanus exists in two forms. The form containing a low dose of diphtheria toxoid is associated with less frequent local reactions in adults and older children than the standard dose diphtheria preparation. Low-dose diphtheria with tetanus should be used for adults and children 7 years of age and older. When tetanus prophylaxis is needed following tetanus injuries, combined diphtheria and tetanus preparations should be used rather than tetanus alone to promote immunity against diphtheria. These lower-dose vaccines should not be used for primary vaccination of children under 7 as the decreased amount of diphtheria toxoid may not provide adequate immunity.

Indications: Active immunization against diphtheria, in addition to tetanus and/or pertussis.

Contraindications: Anaphylaxis to the vaccine or any component or the vaccine; acute febrile illness (defer vaccination until recovery).

Precautions: Coagulation disorders including thrombocytopenia.

Dose:

Primary immunization of children against diphtheria, tetanus and pertussis.

IM injection:

Infant *over 6 weeks* three doses each of 0.5 ml with an interval of not less than 4 weeks between each dose.

NOTE Where resources permit, additional doses can be given after the completion of the primary series. In non-endemic countries, at least one booster dose should be given after completion of the primary series. Many national immunization programmes offer 1–2 booster doses, for example one at 2 years of age and a second at age 4–7 years.

Child *1–7 years* (previously unimmunized children) two doses each of 0.5 ml separated by an interval of 2 months, followed by a third dose after 6–12 months.

Primary immunization of children against diphtheria and tetanus.

IM injection:

Child *1–7 years* three doses each of 0.5 ml with an interval of not less than 4 weeks between each dose;

7–12 years using diphtheria (low dose) and tetanus toxoid combination (dT), two doses each of 0.5 ml separated by an interval of 2 months, followed by a third dose after 6–12 months.

Reinforcing immunization of children against diphtheria and tetanus.

IM injection:

Child *1–10 years* 0.5 ml at least 3 years after completion of primary course of diphtheria, pertussis and tetanus vaccine, or diphtheria and tetanus vaccine;

10–12 years using diphtheria (low dose) and tetanus toxoid combination (dT), 0.5 ml 10 years after previous booster dose and subsequently every 10 years throughout life.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Crying, irritability, drowsiness, restlessness, limb swelling (booster vaccination (fourth dose) has caused extensive swelling of the arm or thigh (usually with redness and pain) in approximately 2% of patients. Swelling subsides spontaneously and completely (usually within 2 days but may take seven)).

Uncommon Lethargy, myalgia, malaise.

Rare Urticaria, headache, peripheral neuropathy, seizures, allergic (including anaphylactoid) reactions occur with vaccines containing DTP, and collapse and hypotonic-hyporesponsiveness episodes with vaccines containing pertussis.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
World Health Organization. Diptheria vaccine: WHO position paper. *Weekly epidemiological record,* 2006, 81(3):24–32 (http://www.who.int/immunization/wer8103Diphtheria_Jan06_position_paper.pdf, accessed 11 April 2010).

Haemophilus influenzae type b vaccine

ATC code: J07AG01; J07CA06; J07CA09; J07CA11; J07CA08; J07CA04

Injection, capsular polysaccharide of Haemophilus influenzae type b conjugated to a protein carrier

Special Notes: There are a number of combination products that are available (often denoted by abbreviations) and these vary depending on country.

Haemophilus influenzae type b (Hib) causes serious infection such as bacterial pneumonia and meningitis, especially in young children. The bacteria are transmitted from person to person by droplets from nasopharyngeal secretions. WHO recommends the inclusion of *Haemophilus influenzae* type b vaccine in all routine infant immunization programmes. The risk of infection decreases in older children and therefore Hib vaccine is not generally offered to children over 2 years of age. However, older children and adults at an increased risk of Hib infection should be vaccinated, including individuals with HIV or immunoglobulin deficiency, stem cell transplant recipients, patients with malignant neoplasms receiving chemotherapy, and those with asplenia (for example, due to sickle-cell disease or splenectomy).

For primary immunization, a three-dose series is generally given at the same time as the primary series of diphtheria-tetanus-pertussis vaccine. Combination preparations containing *Haemophilus influenzae* type b vaccine with either diphtheria-tetanus-pertussis, hepatitis B or poliomyelitis vaccines are available.

NOTE Risk of infection reduces rapidly in older children and the vaccine is generally not required in children over 10 years of age.

Indications: Active immunization against *Haemophilus influenzae* type b.

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness (postpone all vaccinations until patient is well).

Dose:

Primary immunization against *Haemophilus influenzae* type b.

IM:

Infant *6 weeks–1 year* three doses of 0.5 ml, each separated by 4–8 weeks (generally given at the same time as the primary series of diphtheria-tetanus-pertussis vaccine). A booster dose of 0.5 ml may be given between 12 and 18 months of age.

Not previously immunized against *Haemophilus influenzae* type b.

IM:

Child *1–10 years* 0.5 ml as a single dose.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Irritability, drowsiness, prolonged crying, vomiting, appetite loss, nausea, malaise, rash, myalgia, arthralgia, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Uncommon Itching, urticaria, dizziness.

Rare Lymphadenopathy, peripheral neuropathy, delayed hypersensitivity reactions.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.
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World Health Organization. WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. *Weekly epidemiological record,* 2006, 81(47):445–451 (http://www.who.int/immunization/REH_47_8_pages.pdf, accessed 13 April 2010).

Hepatitis A vaccine

ATC code: J07BC02

Injection, inactivated hepatitis A virus

Special Notes: There are a number of combination products that are available (often denoted by abbreviations) and these vary depending on country.

Hepatitis A is caused by hepatitis A virus. It is transmitted via the faecal-oral route from person to person through close physical contact and ingestion of contaminated food and water. Those at increased risk of infection include parenteral drug abusers, individuals who change sexual partners frequently, individuals exposed to untreated sewage, those living in closed communities, travellers to endemic countries, laboratory staff working with the virus, patients with haemophilia treated with plasma-derived clotting factors, and individuals who work with primates. Patients with chronic liver disease including chronic hepatitis B or chronic hepatitis C are at risk of severe liver disease if infected with hepatitis A.

In highly endemic countries, exposure is almost universal before 10 years of age and large-scale immunization programmes should not be undertaken. In areas of intermediate endemicity with periodic outbreaks, control of hepatitis A may be achieved through widespread vaccination programmes, but is most successful in small, self-contained communities. In countries with low endemicity, vaccination for high-risk populations may be recommended.

Several vaccines are available, which provide long-lasting protection, but none are licensed for use in children under 1 year of age; the dose of the vaccine and vaccination schedule varies between manufacturers. A single dose of vaccine provides a protective antibody response within a month; the manufacturers recommend a second dose 6–18 months later to ensure long-term protection.

Indications: Active immunization against hepatitis A.

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Serious active infection; cardiovascular disease; pulmonary disorders; previous unexplained hepatitis or jaundice; previous hepatitis A infection; previous confirmed hepatitis A injection (likely to confer immunity: vaccine not needed).

Dose:

Active immunization against hepatitis A.

IM:

Child The vaccines are given parenterally, as a two-dose series, 6–18 months apart. The dose of vaccine, vaccination schedule, ages for which the vaccine is licensed, and whether there is a paediatric and adult formulation varies from manufacturer to manufacturer.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Headache, malaise, fatigue, nausea, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Uncommon Urticaria, rash, myalgia.

Rare Encephalopathy, allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

References:

American Academy of Pediatrics. *Red Book: 2009 report of the committee on infectious diseases. 28th ed.* Elk Grove Village, American Academy of Pediatrics, 2009.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

World Health Organization. Hepatitis A vaccines: WHO position paper. *Weekly epidemiological record,* 2000, 75(5):38–43 (http://www.who.int/immunization/wer7505Hepatitis%20A_Feb00_position_paper.pdf, accessed 13 April 2010).

Hepatitis B vaccine

ATC code: J07BC01

Injection, inactivated hepatitis B surface antigen adsorbed onto a mineral carrier

Special Notes: Hepatitis B is caused by hepatitis B virus. It is transmitted in blood and blood products, by sexual contact and by contact with infectious body fluids. Persons at increased risk of infection because of their lifestyle, occupation or other factors include dialysis patients and haemophiliacs. Also at risk are babies born to mothers who are hepatitis B virus surface antigen-positive (HbsAg-positive), those having medical or dental procedures in countries with high prevalence and travellers to endemic countries.

WHO recommends hepatitis B vaccine is given as part of the national infant immunization programme. Catch-up immunization should be considered for older age groups, or high-risk individuals who have not been previously immunized in countries with intermediate or low hepatitis B endemicity. High-risk groups may include but are not limited to: household or sexual contacts of known carriers, haemodialysis patients, HIV-positive, immunosuppressed, injecting drug users, chronic liver disease, regular blood product recipients.

Two types of hepatitis B vaccines are available: plasma-derived and recombinant vaccines. Both types are highly effective but the recombinant vaccine is most commonly used. Hepatitis B vaccine is available as a monovalent or a fixed-combination vaccine with other antigens such as *Haemophilus influenzae* type b, poliomyelitis, diphtheria, pertussis and tetanus. The monovalent vaccine should be used when immunizing infants at birth. Recommended schedules vary considerably between

countries, but the minimum recommended interval between doses is 4 weeks. In countries where a high proportion of hepatitis B infections are acquired perinatally, a three-dose or four-dose schedule is recommended with the first dose given within 24 hours of birth. The other doses are usually given at the same time as diphtheria-tetanus-pertussis (DTP) or other vaccines.

Also referred to as adsorbed recombinant DNA hepatitis B surface antigen.

Indications: Active immunization against hepatitis B; post-exposure prophylaxis.

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness (postpone all vaccinations until patient is well).

A reduced immunogenicity of the vaccine may occur in individuals with immunodeficiency including advanced HIV infection, diabetes, chronic liver disease or chronic renal failure.

Dose:

NOTE The actual dose used depends on the formulation available.

Primary immunization of children against hepatitis B.

IM:

Neonate, Infant or **Child** ***from birth*** one monovalent dose at birth, then two or three subsequent doses of monovalent or combined hepatitis B vaccine administered according to schedules of national routine immunization programmes. Generally subsequent doses after birth dose are given at 2, 4 and 6 or 12 months of age depending on the vaccine used.

NOTE Combination hepatitis B vaccines should not be used for the birth dose. This dose should be provided using the monovalent hepatitis B vaccine.

Alternatively if birth dose is missed (three-dose schedule).

IM:

Neonate, Infant or **Child** ***over 8 days*** three doses with 1 month duration between the first and second dose and the third dose to be given 5 months after the second dose (or at a minimum at least 2 months after the second dose).

Hepatitis B prophylaxis for infants born to hepatitis B surface antigen-positive mother.

IM:

Neonate one dose of vaccine with hepatitis B immunoglobulin (in the opposite thigh) within 12 hours of birth (yet preferably immediately after birth); then three subsequent doses as per primary immunization (as above).

Post-exposure prophylaxis (other than at birth).

IM:

Child ***all ages*** administer vaccine at age appropriate dose, with the second dose given at 1 month and the third dose given at 2 months after the initial dose. For those at continued risk, a fourth dose should be given 12 months after the first dose.

Hepatitis B immunoglobulin should also be administered with the first dose.

Percutaneous/ ocular/ mucous membrane exposure.

IM:

Child ***all ages*** administer first dose of vaccine within 7 days and hepatitis B immunoglobulin within 72 hours.

Sexual exposure.

IM:

Child ***all ages*** administer first dose of vaccine and hepatitis B immunoglobulin within 14 days.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common or uncommon Transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Malaise, myalgia, arthralgia, lymphadenopathy, peripheral neuropathy, delayed hypersensitivity reactions, allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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Influenza vaccine

ATC code: J07BB

Injection: inactivated influenza virus, types A and B

Special Notes: Influenza viruses type A and B are common causes of respiratory illnesses and are transmitted from person to person via droplets or respiratory secretions; their antigenic structure is constantly changing. WHO monitors these changes each year and makes recommendations for inclusion of strains in the influenza vaccines for the following season.

There are various forms of inactivated influenza vaccine available, and live vaccines are licensed for use in some countries. Some vaccines are grown on chick embryos and are therefore contraindicated in individuals hypersensitive to eggs. Split virus vaccines and subunit vaccines show reduced systemic reactogenicity compared with whole virus preparations.

Annual immunization with inactivated vaccine is recommended in patients of any age with diabetes mellitus, chronic heart disease, chronic liver disease, chronic renal disease, chronic respiratory disease including asthma, or immunosuppression due to disease or drug treatment. Vaccination with inactivated vaccine can be considered for contacts of high-risk people, children between 6–23 months of age, health-care workers or other key workers, on the basis of national risk.

Indications: Active immunization against influenza in individuals at risk.

Contraindications: Hypersensitivity to influenza virus vaccine or any component; allergy to egg or egg products, chicken, chicken feathers or chicken dander; presence of acute respiratory disease or other active infections or illnesses (delay immunization); influenza vaccines from previous seasons must not be used.

Precautions: History of febrile convulsions or Guillain-Barré syndrome; children < 5 years (adverse effects may be more severe); acute febrile illness (postpone all vaccinations until patient is well).

Dose:

Active immunization against influenza in individuals at risk.
IM:
Infant or **Child *6 months–3 years*** 0.25 ml (one or two doses);
Child *over 3 years* 0.5 ml (one or two doses).

NOTE A second dose after at least 4 weeks is recommended in previously unvaccinated children 6 months to 9 years of age.

Renal impairment: No dose reduction necessary.

Hepatic impairment: No dose reduction necessary.

Adverse effects: Common Fever, malaise, myalgia, headache (these reactions may last 1–2 days), transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Allergic reactions (hives, angioedema, asthma, anaphylaxis).

Interactions with other medicines (* indicates severe):

In most countries the inactivated vaccine is used but live vaccines are available in some countries. Please check which is available and whether interactions are applicable to the form being used.

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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Japanese encephalitis vaccine

ATC code: J07BA02

Injection, inactivated mouse brain-derived vaccine, or inactivated cell culture-derived vaccine, or live attenuated cell culture-derived SA 14-14-2 vaccine

Special Notes: Japanese encephalitis is the leading cause of viral encephalitis in Asia. It is transmitted to humans by mosquitoes from animal hosts (often pigs and water birds) found mostly in rural areas where flooding irrigation is practised. Vaccination against Japanese encephalitis should be considered for endemic populations where it presents a public health problem; the most effective strategy is an immunization catch-up campaign, followed by incorporation of the Japanese encephalitis vaccine into the routine immunization programme. Vaccination is also recommended for travellers to endemic areas.

Three types of vaccine are available: inactivated mouse brain-derived vaccine based on the Nakayama or Beijing strains, inactivated cell culture-derived vaccine based on the Beijing P-3 strain, and live attenuated cell culture-derived SA 14-14-2 vaccine; all are suitable for use in children. The recommended immunization schedule varies between vaccines and is dependent on local epidemiology; individual product information should be consulted.

Indications: Active immunization against Japanese encephalitis.

Contraindications: Anaphylaxis to the vaccine or any component of the vaccine; hypersensitivity to proteins of rodent or neural origin; live vaccine contraindicated in immunosuppression and pregnancy.

Precautions: Acute illness (postpone all vaccinations until patient is well).

Dose:

NOTE Formulations, doses and immunization schedules vary between products and manufacturers; consult product literature carefully before administration.

Active immunization against Japanese encephalitis.

SC using inactivated mouse brain-derived vaccine:
Child *1–3 years* 0.5 ml dose given on days 0, 7 and 28 (total of three doses), followed by a booster after 1 year and then every 3 years;
over 3 years 1 ml dose given on days 0, 7 and 28 (total of three doses), followed by a booster after 1 year and then every 3 years.

SC using inactivated cell culture-derived vaccine:
Child *1–3 years* two doses each given at intervals of 4 weeks followed by a booster dose after 1 year.

SC using live attenuated cell culture-derived vaccine:
Child one dose followed by a single booster dose after 1 year.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Headache, myalgia, gastrointestinal disturbances, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Uncommon Delayed hypersensitivity reactions including generalized urticaria or angioedema usually within 2 weeks of administration.

Rare Potentially fatal acute disseminated encephalomyelitis reported with inactivated mouse brain-derived vaccine, allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: The inactivated mouse brain-derived vaccine is no longer being manufactured so stock may be difficult to obtain.

All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Measles vaccine

ATC code: J07BD52; J07BD01

Injection (powder for solution), live, attenuated measles virus

Injection, live, attenuated measles virus, mumps virus and rubella virus

Special Notes: Measles is an acute viral infection transmitted by close respiratory contact. Immunization against measles is recommended for all infants and young children, and also for adolescents and adults who are susceptible or at high risk of exposure. Immunization should be considered for individuals with early signs of HIV-induced immunosuppression in endemic areas or during outbreaks.

To limit the impact of measles outbreaks, WHO encourages surveillance for early detection, thorough assessment of the risk of spread and of severe disease outcomes, and rapid responses, including expanded use of the measles vaccine.

Immunization of high-risk individuals within 2 days of exposure with a measles-containing vaccine may improve the clinical course of measles. A single dose of measles vaccine is recommended as part of the primary immunization programme. A second opportunity for measles immunization either through routine or periodic immunization services is also recommended.

Because of the risk of early and severe measles infection, HIV-infected infants (unless severely immunocompromised) should be given the measles vaccine at 6 months of age, followed by two additional doses according to the national immunization schedule (generally at 9–12 months and again before 6 years).

The measles vaccine is a live, attenuated vaccine, available either as a single-antigen vaccine or combined with either rubella (MR), or mumps and rubella (MMR) vaccines; the combined vaccines are usually given as part of the primary immunization schedule.

Multiple international studies have found no evidence for an alleged association between measles or MMR immunization and serious developmental disorders including autism, or chronic bowel disease.

Indications: Active immunization against measles.

Contraindications: Pregnancy (pregnancy should be avoided for 28 days after vaccination with MMR due to the theoretical risk of transmission of the rubella component of the vaccine to a susceptible fetus); immunosuppression (measles as a live vaccine is contraindicated in congenital or acquired impaired immunity. An exception is HIV-positive individuals where MMR may be given unless they have advanced AIDS with severely impaired immunity).

Precautions: Acute illness (postpone all vaccinations until patient is well); treatment with immunoglobulins or whole blood normal immunoglobulin (see note below); whole blood transfusion (see note below).

WHOLE BLOOD TRANSFUSION Whole blood transfusion may reduce antibody response to vaccine; test for antibodies after 8 weeks; revaccinate if necessary.

IMMUNOGLOBULINS Treatment with immunoglobulins or whole blood normal immunoglobulin may interfere with the immune response to some live virus vaccines. Do not give rubella vaccine for 3 months after IM immunoglobulin or 9 months after IV immunoglobulin.

Dose:

Primary immunization of children against measles.

IM or *SC:*

Infant *9–12 months* 0.5 ml dose. A second dose of 0.5 ml is recommended for patients up to 6 years of age, but not within 4 weeks of the first dose.

Immunization of HIV-infected children against measles (unless severely immunocompromised).
IM or *SC:*
Infant or **Child** first dose of 0.5 ml as early as 6 months followed by two additional doses according to the national immunization schedule (generally 0.5 ml dose at 9–12 months and another given up to 6 years of age but not within 4 weeks).

Prophylaxis in susceptible individuals after exposure to measles (within 48 hours of contact).
IM or *SC:*
Infant or **Child** ***over 9 months*** 0.5 ml.

Primary immunization of children against measles, mumps and rubella.
IM or *SC:*
Child ***12–15 months*** 0.5 ml dose. A second dose of 0.5 ml can be given 2–5 years after the primary dose.

Prophylaxis in susceptible children after exposure to measles using combined MMR vaccine (within 48 hours of contact).
IM or *SC:*
Child 0.5 ml dose.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Sore throat, lymphadenopathy, rash, fever (5–12 days after vaccination), parotid swelling, headache.

Uncommon Febrile seizures, arthritis, arthralgia.

Rare Encephalitis, chronic joint symptoms, thrombocytopenia.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Meningococcal meningitis vaccine

ATC code: J07AH

Injection: capsular polysaccharide antigen of Neisseria meningitidis serogroup C conjugated to a protein carrier and adsorbed onto a mineral carrier; and the same for serogroups A and C or groups A, C, W135 and Y

Special Notes: *N. meningitidis* causes meningococcal disease including meningitis and septicaemia and primarily affects young children. The bacteria are transmitted from person to person via respiratory secretions. Immunization against meningococcal disease is recommended as part of the routine childhood immunization programme, for outbreak situations, for individuals at high risk including those in military camps and boarding schools, travellers to endemic areas, and for those with a predisposition to meningococcal disease (such as asplenia and inherited immune deficiencies).

Meningococcal vaccines are available as combinations of capsular polysaccharide antigens (serogroups A and C, or A, C, W135 and Y) or as a polysaccharide of serogroup C conjugated to a protein carrier. There is also a polysaccharide of serogroups A, C, Y and W135 conjugated to a protein carrier. Other variants of the vaccine are available in some countries.

Group C conjugate vaccine is recommended for national childhood immunization programmes; for children 2–12 months of age, three doses are given at intervals of 4 weeks. A booster at 12 months is recommended.

A single dose of group C conjugate vaccine is sufficient in children over 12 months of age. However, individuals with asplenia or splenic dysfunction should be given two doses each 2 months apart; immunized individuals who develop splenic dysfunction should be given one additional dose.

A single dose of either A and C, or A, C, W135 and Y polysaccharide vaccine is recommended to control outbreaks and for at-risk individuals including travellers to endemic areas. Groups A and C, and A, C, W135 and Y unconjugated vaccines elicit a suboptimal response in infants under 2 years of age and are not recommended for routine immunization; however, they may be given in emergency outbreak situations.

Meningococcal C conjugate vaccines also known as MenCCV.

Meningococcal polysaccharide vaccines (groups A, C, Y and W135) also known as 4vMenPV.

Meningococcal conjugate vaccine (groups A, C, Y and W135) also known as MCV4.

Indications: Active immunization against meningitis and septicaemia caused by *Neisseria meningitidis* serogroup C, serogroups A and C, or serogroups A, C, W135 and Y.

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute illness: postpone all vaccinations until patient is well.

Dose:

Primary immunization against *N. meningitidis* serogroup C.

IM:

Infant *2–12 months* three doses of 0.5 ml each given at intervals of 4 weeks (e.g. at 6, 10 and 14 weeks) or 2, 4 and 6 months. A booster at 12 months is recommended;

Child 0.5 ml as a single dose.

Immunization against infection by *N. meningitidis* serogroups A and C, or A, C, W135 and Y.

SC:

Child *all ages* 0.5 ml as a single dose.

NOTE The polysaccharide versions of this vaccine are recommended to control outbreaks and for at-risk individuals including travellers to endemic areas. The unconjugated versions of this vaccine elicit a suboptimal response in infants under 2 years of age and are not recommended for routine immunization; however, they may be given in emergency outbreak situations.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Meningococcal C vaccine: irritability, anorexia, headache.

Uncommon Both vaccines: transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Mumps vaccine

ATC code: J07BD52; J07BE01

Injection (powder for solution), live attenuated strain of mumps virus

Special Notes: Mumps is a mostly mild childhood disease, but it can also affect adults, in whom complications such as meningitis and orchitis are more common. The mumps virus is transmitted from person to person via airborne droplets. Mumps vaccine is a live, attenuated vaccine and is available as a single-antigen vaccine or in combination with measles and rubella vaccines. For countries seeking to immunize against mumps, WHO recommends the use of the combined measles, mumps and rubella vaccine (MMR) as part of the national infant immunization programme. Two doses of mumps vaccine are required for long-term protection; the first dose should be given at 12–18 months of age; the second dose at least 4 weeks later up to 6 years of age (usually school entry age).

Indications: Active immunization against mumps.

Contraindications: Immunosuppression (mumps as a live vaccine is contraindicated in congenital or acquired impaired immunity. An exception is HIV-positive individuals where measles, mumps, rubella (MMR) vaccine may be given unless they have severely impaired immunity); pregnancy (pregnancy should be avoided for 28 days after vaccination with MMR due to theoretical risk of transmission of the rubella component of the vaccine to a susceptible fetus); history of anaphylaxis to any component of the vaccine.

Precautions: Acute illness (postpone all vaccinations until patient is well); treatment with immunoglobulins or whole blood normal immunoglobulin (see note below); whole blood transfusion (see note below).

WHOLE BLOOD TRANSFUSION Whole blood transfusion may reduce antibody response to vaccine; test for antibodies after 8 weeks; revaccinate if necessary.

IMMUNOGLOBULINS Treatment with immunoglobulins or whole blood normal immunoglobulin may interfere with the immune response to some live virus vaccines. Do not give rubella vaccine for 3 months after IM immunoglobulin or 9 months after IV immunoglobulin.

Dose:

Active immunization against mumps (usually as combined measles, mumps, rubella (MMR) vaccine).
SC or *IM:*
Child *12–18 months* 0.5 ml. Follow with a second dose of 0.5 ml at least 4 weeks later, and up to 6 years of age.

Renal impairment: No dose reduction required.

Hepatic impairment: No dose reduction required.

Adverse effects: Uncommon Parotid swelling, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Orchitis, sensorineural deafness, aseptic meningitis (higher risk with some specific strains), allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

* **Immunoglobulin, anti-D**: avoid use of live virus vaccines during 4 weeks before or during 3 months after injection of anti-D immunoglobulin (impairment of immune response).

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: Monovalent mumps vaccine is not available in some countries.

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Pertussis vaccine

ATC code: J07AJ51; J07AJ02; J07AJ01

Injection, acellular or whole cell vaccine usually combined with diphtheria and tetanus toxoids

Special Notes: Two types of pertussis vaccine are available, acellular pertussis (aP) and whole-cell pertussis (wP).

Pertussis (whooping cough) is a bacterial respiratory infection caused by *Bordetella pertussis* and is transmitted through droplets. Pertussis vaccine is usually administered in fixed-dose combinations with diphtheria, tetanus and other vaccines as part of the primary immunization programme. WHO recommends three doses, each to be given at 6, 10 and 14 weeks of age. Booster doses are recommended 1–6 years after the primary series in countries where the incidence of pertussis has been reduced by immunization. Single component pertussis vaccines are available in some countries.

Whole-cell vaccine composed is frequently associated with minor adverse reactions such as local redness and swelling, fever and agitation. Prolonged crying and seizures are less common. Local administration site reactions tend to increase with age and number of injections and so whole-cell pertussis vaccine is not recommended for adolescents and adults. An acellular form of the vaccine is also available and can be used for immunization of older children and adults; it has fewer local and systemic effects compared with whole-cell pertussis vaccine (see under Diphtheria).

Indications: Active immunization against pertussis.

Contraindications: Anaphylaxis to vaccine or any component of the vaccine.

Precautions: Acute illness (postpone all vaccinations until patient is well).

Dose:

Immunization against pertussis.

IM:

Infant three doses, each separated by at least 4 weeks (for example at 6, 10, and 14 weeks of age or at 2, 4 and 6 months of age).

Booster doses are recommended 1–6 years after the primary series in countries where the incidence of pertussis has been reduced by immunization. Some countries are now recommending a booster dose in adolescence or early adulthood due to waning immunity of the vaccine in childhood.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Side-effects are less common with the use of the acellular vaccine than they are with the whole-cell vaccine.

Common Local redness and swelling, fever, agitation.

Uncommon Prolonged crying, febrile seizures.

Rare Seizures, hypotonic hyporesponsive episodes.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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Pneumococcal vaccine

ATC code: J07AL02

Injection, capsular polysaccharides of Streptococcus pneumoniae conjugated to a protein carrier, adsorbed onto a mineral carrier

Special Notes: There are three variants of the conjugated vaccine:

7-valent conjugate vaccine known as PCV-7 or 7vPCV;

10-valent conjugate vaccine known as PCV-10 or 10vPCV;

13-valent conjugate vaccine known as PCV-13 or 13vPCV.

There is also a 23-valent unconjugated pneumococcal polysaccharide vaccine known as 23vPPV.

Streptococcus pneumoniae causes serious infection such as pneumonia and meningitis, especially in young children under 2 years of age, the elderly and individuals with immunodeficiency. The bacteria are transmitted via respiratory secretions. WHO recommends that pneumococcal conjugate vaccine should be included in national routine childhood immunization programmes. The 7-valent conjugate vaccine (PCV-7) provides effective protection in young children; the primary schedule usually consists of three doses, each administered at intervals of at least 4 weeks;

other three-dose schedules have been shown to be effective and are in use in some countries. A booster dose given after 12 months of age may improve the immune response. Immunization should be initiated before 6 months of age and may start as early as 6 weeks of age. The vaccine can be given to HIV-infected individuals.

A single dose of PCV-7 can be given to children aged 12–24 months of age who have not been previously vaccinated and children 2–5 years of age at high risk of pneumococcal disease.

A 23-valent (unconjugated) polysaccharide vaccine is also available for adults and children over 2 years of age at risk of pneumococcal infection (it provides a suboptimal response in infants).

Indications: Active immunization against *Streptococcus pneumoniae.*

Contraindications: History of anaphylaxis to any component of the vaccine.

Precautions: Acute febrile illness: postpone all vaccinations until patient is well.

23-valent (unconjugated) polysaccharide vaccine is not recommended for children under 2 years.

Dose:

Primary immunization against *Streptococcus pneumoniae.*

IM injection using pneumococcal polysaccharide conjugated vaccine (7vPCV):
Infant three doses of 0.5 ml, each a minimum of 4 weeks apart, e.g. at 6, 10 and 14 weeks of age or 2, 4 and 6 months of age.
A booster dose can be given at 12 months of age.
Infant presenting late for vaccination, two doses of 0.5 ml at least 4 weeks apart followed by a third dose at 13 months.
Child *1–5 years* previously not vaccinated or not completed primary course, 0.5 ml as a single dose or 0.5 ml separated by 2 months in the immunocompromised or those with asplenia or splenic dysfunction.

Revaccination of children who are at increased risk of pneumococcal disease and its complications due to underlying health conditions.

SC or *IM injection* using 23-valent pneumococcal polysaccharide vaccine (23vPPV):
Child *over 2 years* 0.5 ml as a single dose and subsequently every 5 years.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Uncommon Myalgia, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Cellulitis, seizures, angioedema, allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Poliomyelitis vaccine

ATC code: J07BF01; J07BF02; J07BF03

Oral suspension, live, attenuated poliomyelitis virus, types 1, 2 and 3

Injection, inactivated poliomyelitis virus, types 1, 2 and 3

Special Notes: Poliomyelitis is an acute viral infection, which causes paralysis of varying degrees. It is transmitted from person to person via the oral-oral or faecal-oral route. Poliomyelitis vaccine should be included in national routine childhood immunization programmes.

There are two types of vaccines. Oral poliomyelitis vaccine (OPV) contains three types of live attenuated poliomyelitis viruses; monovalent live oral vaccines are also available. Injectable inactivated poliomyelitis vaccine (IPV) contains three types of inactivated strains.

For primary immunization using oral poliomyelitis vaccine, a three-dose schedule is used. The vaccine may need to be repeated in patients with diarrhoea or vomiting. HIV-infected individuals can receive the live oral vaccine, but it must not be used for those with primary immunodeficiency, those who are immunosuppressed or their close contacts. The need for strict personal hygiene must be stressed as the vaccine virus is excreted in the faeces; the contacts of a recently vaccinated baby should be advised of the need to wash their hands after changing the baby's nappies. Reinforcing doses can be given after primary immunization.

Inactivated poliomyelitis vaccine is used in some countries for routine immunization; routine schedules vary widely, but in industrialized countries usually include 2–3 doses in the first year of life and at least one booster dose 6–12 months after the last dose of the primary series. Sequential schedules using IPV followed by OPV are also used in some countries to decrease the risk of vaccine-associated poliomyelitis, which occurs rarely with OPV; usually 1–3 doses of IPV are followed by 2–3 doses of OPV. The inactivated vaccine is available as a monovalent vaccine or in fixed combinations with other antigens.

Countries considering a change from OPV to IPV use should conduct a thorough evaluation of the epidemiological, financial and operational implications before finalizing a change in policy.

Indications: Active immunization against poliomyelitis.

Contraindications: Anaphylaxis to previous dose of the vaccine or following any component of the vaccine; primary immunodeficiency or immunosuppressed patients or their close contacts (avoid live oral vaccine).

Precautions: HIV-infected individuals (may receive the live oral vaccine); stringent hand-washing required (oral polio vaccine may be excreted in the stools).

Dose:

Primary immunization of children against poliomyelitis.

Oral:

Neonate or **Infant** 3 drops at birth and 3 drops at 6, 10 and 14 weeks of age.

IM:

Child three doses of 0.5 ml, each separated by at least 4 weeks (e.g. at 6, 10 and 14 weeks of age or at 2, 4 and 6 months of age).

Reinforcing immunization of children against poliomyelitis.

Oral:

Child 3 drops at least 3 years after completion of primary course and a further 3 drops at 15–19 years of age.

IM:

Infant or **Child** 0.5 ml 6–12 months after primary immunization. Further reinforcing doses are given in some countries (e.g. at 4–6 years; consult national schedule).

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: INJECTABLE VACCINE **Uncommon** Diarrhoea, headache, myalgia, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Allergic reactions including anaphylaxis.

ORAL VACCINE **Rare** Vaccine-associated poliomyelitis in recipients of vaccine and contacts of recipients.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Rabies vaccine

ATC code: J07BG01

Injection, inactivated rabies virus prepared in cell culture

Special Notes: Rabies is a virus transmitted to humans by rabid animals via a bite or scratch. It is invariably fatal once signs of disease occur. WHO recommends pre-exposure immunization of individuals at increased risk of contracting rabies either due to occupational exposure such as laboratory workers, veterinary surgeons, animal handlers and health workers or people living or travelling to enzootic areas; in such areas children aged 5–15 years are at particular risk of exposure. Cell-derived vaccines are used for both pre-exposure and post-exposure protection. Vaccines of nerve cell tissue origin should not be used because they are less potent and are frequently associated with adverse events.

Rabies vaccine is used as part of the post-exposure treatment to prevent rabies in patients who have been bitten by rabid animals or animals suspected of being rabid. The bite wound or scratch should be thoroughly cleansed. Treatment is dependent upon the individual's immune status and upon the level of risk of rabies in the country concerned (consult national immunization schedule).

In certain circumstances, such as patients with incomplete prophylaxis or unimmunized individuals, passive immunization with rabies immunoglobulin can be given (see rabies immunoglobulin, section 19.2). Rabies has occurred in people who have received post-exposure rabies vaccine without rabies immunoglobulin being infiltrated in and around the wound. Therefore, post-exposure treatment, in those who have not completed pre-exposure prophylaxis, should include infiltration of human rabies immunogobulin (HRIG) in and around wound(s) at the same time as the first dose of the rabies vaccine.

Post-exposure treatment with rabies vaccine and rabies immunoglobulin is necessary for individuals who are immunocompromised, HIV-positive, taking malaria chemoprophylaxis or under anaesthesia; antibody response should be monitored.

Indications: Pre-exposure immunization against rabies; post-exposure prophylaxis against rabies.

Contraindications: There are no contraindications to post-exposure prophylaxis following high-risk exposure. For pre-exposure immunization, previous severe reaction to any of the vaccine components is a contraindication to further use of the same vaccine.

Precautions: Concomitant chloroquine use (reduced response to intradermal route; use IM route); concomitant rabies immunoglobulin (administer using different sites and different syringes).

Dose:

Pre-exposure immunization against rabies.

IM:

Child *all ages* 1 ml on days 0, 7 and 28 (day 28 preferable, but administration may be advanced towards day 21 if time is limited).

Intradermal:

Child *all ages* 0.1 ml on days 0, 7 and 28 (administration may be advanced towards day 21 if time is limited).

BOOSTER DOSES Periodic booster doses are recommended only for individuals whose environment puts them at continuous or frequent risk of rabies exposure. In such cases, a booster dose should be given at intervals dictated by regular testing for rabies antibodies (virus neutralizing antibodies of at least 0.5 IU/ml indicate protection). Where serological testing is unavailable, booster vaccination every 5 years may be an acceptable alternative.

Post-exposure prophylaxis against rabies in unimmunized individuals.
IM:
Child *all ages* 1 ml on days 0, 3, 7, 14 and 28 (five-dose regimen). Alternatively, a four-dose regimen may be used with two doses of 1 ml on day 0 (one in each of the two deltoid or thigh regions) followed by one dose each on days 7 and 21.
Intradermal:
Child *all ages* (eight-site regimen) 0.1 ml administered at eight separate sites on day 0 (one in each upper arm, one in each lateral thigh, one on each side of the suprascapular region, and one on each side of the lower quadrant region of the abdomen); on day 7, 0.1 ml in each upper arm and each lateral thigh; on days 30 and 90, 0.1 ml in one upper arm. The one dose on day 90 may be replaced by two intradermal injections on day 30.
Alternatively (two-site regimen) 0.1 ml at two sites on days 0, 3, 7 and 28.

Post-exposure treatment against rabies in fully immunized individuals.
IM or *intradermal:*
Child *all ages* two doses (1 ml IM or 0.1 ml intradermal) on days 0 and 3.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Headache, dizziness, malaise, myalgia, nausea, serum sickness-like reaction (after booster dose), weakness, rash, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting, mild gastrointestinal disturbances.

Uncommon Angioedema.

Rare Neuroparalytic events, allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: WHO recommends the intradermal route of administration for rabies pre- and post-exposure prophylaxis. Refer to manufacturer literature for product specific advice.

Intradermal administration is technically more demanding and requires appropriate staff training and qualified supervision.

All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Rotavirus vaccine

ATC code: J07BH01; J07BH02

Oral suspension, live, attenuated rotavirus

Special Notes: Two oral, live, attenuated rotavirus vaccines, Rotarix® and RotaTeq®, are available internationally; both vaccines are considered safe and effective in preventing gastrointestinal disease caused by rotaviruses.

The dose, schedule and preparation varies between products. Ensure correct product is selected.

Rotaviruses are the most common cause of severe diarrhoea in infants and young children. The virus is transmitted via the faecal-oral route from person to person in close contact or via contaminated fomites.

WHO recommends that rotavirus vaccine for infants should be included in all national immunization programmes. In countries where diarrhoeal deaths account for ≥ 10% of mortality among children aged < 5 years, the introduction of the vaccine is strongly recommended.

Taking into account new evidence, WHO now recommends that infants worldwide be vaccinated against rotavirus.

Indications: Active immunization against rotavirus infection.

Contraindications: Anaphylaxis to previous dose of rotavirus vaccine or vaccine component.

Precautions: Diarrhoea or vomiting (postpone immunization); immunosuppressed close contacts (see note below); acute illness (postpone immunization); history of intussusception.

IMMUNOSUPPRESSED CONTACTS The rotavirus vaccine virus is excreted in the faeces and may be transmitted to close contacts; the vaccine should be used with caution in those with immunosuppressed close contacts. Carers should be advised of the need for careful hand-washing techniques.

Dose:

Immunization of infants against rotavirus infection.

Oral using Rotarix®:

Infant *6–24 weeks* two-dose schedule, 1 ml dose given at 2 and 4 months of age.

NOTE Initial dose should be administered from 6 weeks through 14 weeks and 6 days of age; the first and second dose should be separated by at least 4 weeks. The two-dose schedule should be completed by 24 weeks of age.

Oral using RotaTeq®:

Infant *6–32 weeks* three-dose schedule, 2 ml dose given at 2, 4 and 6 months of age.

NOTE Initial dose should be administered from 6 weeks through 14 weeks and 6 days of age; the doses should be separated by at least 4 weeks. The three-dose schedule should be completed by 8 months (32 weeks) of age.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Irritability, loss of appetite, diarrhoea, vomiting.

Rare Allergic reactions including anaphylaxis.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

* **Immunoglobulin, anti-D**: avoid use of live virus vaccines during 4 weeks before or during 3 months after injection of anti-D immunoglobulin (impairment of immune response).

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: Initial dose should be given by 14 weeks and 6 days of age.

Subsequent booster doses after the primary schedule are not recommended.

All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Rubella vaccine

ATC code: J07BJ01; J07BD52; J07BD53

Injection (powder for solution for injection), live attenuated rubella virus

Special Notes: Rubella is normally a mild childhood disease, which is transmitted from person to person via the respiratory route. The primary purpose of rubella vaccination is to prevent rubella infection during pregnancy, which can lead to fetal death and congenital rubella syndrome (characterized by multiple birth defects including mental retardation, hearing and visual impairment). WHO recommends either universal immunization of infants and children through the national immunization programme to eliminate rubella and congenital rubella syndrome, or prevention of congenital rubella syndrome through immunization of women of childbearing age. Countries seeking to eliminate rubella should ensure that women of childbearing age and over 80% of children are immunized.

There are a number of rubella vaccines available, either as single antigen vaccines or combined with measles and mumps vaccine (MMR), or measles vaccine (MR). In most countries, the vaccine is given as MMR or MR as part of the childhood immunization programme. Most vaccines are based on the live, attenuated RA 27/3 strain of rubella virus. Rubella vaccine is usually given to infants together with measles vaccine (see MMR vaccine).

Indications: Active immunization against rubella.

Contraindications: Untreated active tuberculosis; pregnancy (avoid pregnancy for 28 days after vaccination with rubella vaccine or MMR due to the theoretical risk of transmission of the rubella component of the vaccine to a susceptible fetus); history of anaphylaxis to any component of the vaccine; advanced immunodeficiency (asymptomatic HIV-positive patients may be given rubella vaccine).

Precautions: Acute illness (postpone all vaccinations until patient is well); treatment with immunoglobulins or whole blood normal immunoglobulin (see note below); whole blood transfusion (see note below).

WHOLE BLOOD TRANSFUSION Whole blood transfusion may reduce antibody response to vaccine; test for antibodies after 8 weeks; revaccinate if necessary.

IMMUNOGLOBULINS Treatment with immunoglobulins or whole blood normal immunoglobulin may interfere with the immune response to some live virus vaccines. Do not give rubella vaccine for 3 months after IM immunoglobulin or 9 months after IV immunoglobulin.

Dose:

Immunization against rubella.

SC:

Child *all ages* 0.5 ml as a single dose.

See measles vaccine for combined measles, mumps and rubella (MMR) doses.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Sore throat, lymphadenopathy, rash.

Uncommon Arthritis, arthralgia.

Rare Chronic joint symptoms, thrombocytopenia.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

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Tetanus vaccine

ATC code: J07AJ52; J07AJ51; J07AM51

Injection, tetanus toxoid adsorbed onto a mineral carrier

Special Notes: Tetanus toxoid vaccines are available as single toxoid (TT), combined with diphtheria toxoid (DT) or low-dose diphtheria toxoid (dT) and in combination with diphtheria and pertussis vaccines (DTwP, DTaP, dTaP or dTaP). Vaccines containing DT are used for children aged under 7 years and dT-containing vaccines for individuals aged 7 years and over. Tetanus toxoid is also available in combination with vaccines against hepatitis B, *Haemophilus influenzae* type b and poliomyelitis.

As a rule, vaccine combinations containing diphtheria toxoid (D or d) and tetanus toxoid, rather than tetanus toxoid alone, should be used when immunization against tetanus is indicated.

Tetanus is caused by the action of a neurotoxin of *Clostridium tetani* in necrosed tissues such as occur in dirty wounds. Tetanus vaccines are based on tetanus toxoid, which is adsorbed on aluminium or calcium salts to increase immunogenicity. Tetanus toxoid is available both as single antigen and in vaccine combinations.

Neonatal tetanus due to infection of the baby's umbilical stump during unclean delivery is the cause of many deaths of newborn infants. Control of neonatal tetanus may be achieved by ensuring adequate hygiene during delivery and by ensuring protective immunity of mothers in late pregnancy. Alternatively, women of childbearing age may be immunized.

For clean wounds, fully immunized individuals (those who have received a total of five doses of tetanus vaccine at appropriate intervals) and those whose primary immunization is complete (with boosters up to date) do not require tetanus vaccine; individuals whose primary immunization is incomplete or whose boosters are not up to date require a reinforcing dose of tetanus vaccine (followed by further doses as required to complete the schedule); non-immunized individuals (or those whose immunization status is not known or who have been immunized but are now immunocompromised) should be given a dose of the vaccine immediately (followed by completion of the full course of the vaccine if records confirm the need).

Wounds are considered to be tetanus-prone if they are sustained either more than 6 hours before surgical treatment of the wound or at any interval after injury and show one or more of the following: a puncture-type wound, a compound fracture, a wound containing foreign bodies, a significant degree of devitalized tissue, clinical evidence of sepsis, contamination with soil/manure likely to contain tetanus organisms. All wounds should receive thorough cleansing. Antibacterial prophylaxis may also be required for tetanus-prone wounds. For tetanus-prone wounds, management is as for clean wounds with the addition of a dose of antitetanus immunoglobulin (section 19.2) given at a different site; in fully immunized individuals and those whose primary immunization is complete (see above) the immunoglobulin is needed only if the risk of infection is especially high (for example, contamination with manure). Antibacterial prophylaxis (with benzylpenicillin, or amoxicillin with clavulanic acid, or metronidazole) may also be required for tetanus-prone wounds.

Indications: Active immunization against tetanus; wound management (tetanus-prone wounds and clean wounds).

Contraindications: Hypersensitivity to tetanus toxoid or any component of the vaccine.

Precautions: Acute febrile illness (postpone immunization, unless a tetanus-prone wound).

Dose:

WHO recommends a childhood tetanus immunization schedule of five doses; the primary series of three doses should be given during the first year of life as combined diphtheria, tetanus and pertussis vaccine (DTP). The fourth booster dose with a tetanus toxoid-containing vaccine should be given at 4–7 years and the fifth dose during adolescence at 12–15 years. A sixth dose can be given in early adulthood for lifelong protection. When tetanus prophylaxis is needed following tetanus injuries, combined diphtheria and tetanus preparations should be used rather than tetanus alone to promote immunity against diphtheria.

Renal impairment: No dose reduction necessary.

Hepatic impairment: No dose reduction necessary.

Adverse effects: Common or uncommon Lethargy, myalgia, transient injection site reactions (pain, redness, itching, swelling or burning, small hard lump which may persist for some weeks), transient fever, fainting.

Rare Urticaria, malaise, headache, peripheral neuropathy, allergic reactions including anaphylaxis.

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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Typhoid vaccine

ATC code: J07AP01; J07AP03

Capsules or suspension, live attenuated strain of Salmonella typhi (Ty21a)

Injection, Vi capsular polysaccharide typhoid 25 micrograms/0.5 ml

Special Notes: Typhoid fever is caused by *Salmonella typhi.* It is transmitted via the faecal-oral route and associated with poor hygiene and sanitation. Immunization against typhoid fever is recommended for children of school age and adults in endemic areas, travellers to endemic areas and laboratory workers handling specimens from suspected cases. The vaccines do not provide complete protection and should not replace hygiene precautions.

A single dose of parenteral Vi capsular polysaccharide vaccine is recommended for adults and children over 2 years of age, followed by booster doses every 3 years on continued exposure.

A live oral typhoid vaccine containing an attenuated strain of *S. typhi* (Ty21a) is available either as enteric-coated capsules, or as a liquid suspension. The capsules are licensed for individuals over 5 years of age and are given as four doses, each 2 days apart; the suspension can be administered to children over 2 years of age and is given as three doses, each 2 days apart. Protection is achieved 7 days after the last dose. In endemic areas, a booster dose of the live oral vaccine is recommended every 3 years; for travellers to endemic areas from non-endemic areas, an annual booster is recommended.

Inactivated whole cell typhoid vaccines may still be available in some countries; children over 5 years of age are given two doses separated by an interval of 4 weeks, with a booster dose every 3 years. However, inactivated whole cell vaccines are associated with frequent adverse effects and WHO recommends that these vaccines should be replaced with either the Vi-based polysaccharide vaccine or live oral vaccines.

Indications: Active immunization against typhoid.

Contraindications: Anaphylaxis following previous typhoid vaccine or history of anaphylaxis to one of the vaccine components; acute gastrointestinal illness (oral vaccine).

Precautions: Acute illness (postpone vaccination until well); HIV-positive patients (see below); immunosuppressed patients (see below); treatment with anti-infectives active against *S. typhi* (see below).

HIV AND IMMUNOSUPPRESSED PATIENTS Asymptomatic HIV-positive individuals can be given the vaccine if CD4 counts are over 200 cells/mm^3. It is recommended to use the Vi-based polysaccharide parenteral vaccine rather than the oral vaccine in individuals with impaired immunity.

ANTIBACTERIALS Oral typhoid vaccine is inactivated by concomitant administration of antibacterials; if possible, antibacterials should be avoided 3 days before and 3 days after.

Dose:

For immunization against *S. typhi* fever.

IM or *SC* using Vi-based polysaccharide parenteral vaccine:
Child *2 years and over* a single dose of parenteral Vi capsular polysaccharide vaccine is recommended followed by booster doses every 3 years on continued exposure.
Oral using live oral typhoid vaccine:

Child *over 2 years* the suspension is given as three doses, each 2 days apart;
over 5 years the capsules are given as four doses, each 2 days apart.

Protection is achieved 7 days after the last dose. In endemic areas, a booster dose of the live oral vaccine is recommended every 3 years. Travellers to endemic areas from non-endemic areas should receive an annual vaccine.

Renal impairment: No dose reduction required.

Hepatic impairment: No dose reduction required.

Adverse effects: Common IM vaccine: headache, nausea, malaise, myalgia.

Uncommon Oral vaccine: diarrhoea, constipation, nausea, vomiting, anorexia.

Rare Allergic reaction.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mefloquine: recommend a 12 hour interval between mefloquine and doses of oral typhoid vaccine; vaccination should be completed at least 3 days before the first dose of mefloquine.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Proguanil: unless combined with atovaquone, start proguanil at least 10 days after the last oral typhoid vaccine dose (or use IM vaccine).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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Varicella vaccine

ATC code: J07BK01

Injection, live, attenuated varicella-zoster virus

Special Notes: Varicella-zoster (chickenpox) is a highly contagious disease caused by varicella-zoster virus. Transmission is via droplets, aerosol or direct person to person contact. Various formulations of the live attenuated vaccine based on the Okastrain are available. Varicella-zoster vaccine may be used as part of a national childhood immunization programme. The vaccine may also be used in adolescents or adults without a history of varicella and who are at increased risk of infection.

A single dose of vaccine is effective in children aged 1–12 years (the optimal age is 12–24 months).

Rarely, the varicella-zoster vaccine virus has been transmitted from vaccinated individuals to close contacts; if a vaccine-related rash develops within 4–6 weeks, contact with varicella-susceptible pregnant women and individuals at high risk of severe varicella infection, including patients with immunodeficiency or receiving immunosuppressive therapy, should be avoided.

Indications: Active immunization against varicella-zoster.

Contraindications: Pregnancy (avoid pregnancy for 3 months after vaccination); immunodeficiency; patients receiving immunosuppressive therapy; untreated active tuberculosis; history of anaphylaxis to any component of the vaccine.

Precautions: Acute illness (postpone all vaccinations until patient is well); treatment with immunoglobulins or whole blood normal immunoglobulin (see below); whole blood transfusion (see below); family history of congenital immune disorders; post-vaccination close contact with susceptible individuals.

WHOLE BLOOD TRANSFUSION Whole blood transfusion may reduce antibody response to vaccine; test for antibodies after 8 weeks; revaccinate if necessary.

IMMUNOGLOBULINS Treatment with immunoglobulins or whole blood normal immunoglobulin may interfere with the immune response to some live virus vaccines. Do not give varicella-zoster vaccines for 3 months after IM immunoglobulin or 9 months after IV immunoglobulin.

Dose:

Immunization against varicella infection.
SC:
Child *1–12 years* 0.5 ml as a single dose.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Fever, mild papular-vesicular rash (usually within 5–26 days).

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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Yellow fever vaccine

ATC code: J07BL01

Powder for injection live, attenuated yellow fever virus

Special Notes: Also referred to as yellow fever 17D.

Yellow fever is a viral haemorrhagic fever endemic in tropical regions of Africa and South America. The disease is transmitted by Haemagogus and Aedes mosquito bites. Yellow fever 17D vaccine is a live attenuated vaccine, which offers protection from 10 days after vaccination, for at least 10 years.

WHO recommends that all countries with endemic yellow fever should incorporate yellow fever vaccine into their national immunization programme; the vaccine should be given to infants 9–12 months of age and can be given at the same time as the measles vaccine. Yellow fever vaccine is also recommended for people at high risk of yellow fever exposure, people living in or travelling to endemic areas. During epidemics, mass vaccination campaigns should be initiated as early as possible.

Immunization is not recommended for infants 6–8 months of age or during pregnancy, except during an epidemic when the risk of transmission may be very high. Yellow fever vaccine is contraindicated in individuals with severe immunodeficiency or severe egg allergy (HIV-infected individuals may be vaccinated if CD4 cell counts are over 200 cells/mm^3).

Indications: Active immunization against yellow fever.

Contraindications: Hypersensitivity to the vaccine, egg or chick embryo protein, or any component; immunosuppressed patients; children less than 6 months of age.

Precautions: Patients with thymic disorders including myasthenia gravis, thymoma or prior thymectomy; concomitant administration of other live vaccines.

Dose:

Active immunization against yellow fever.

Deep SC or *IM:*

Child *over 9 months* 0.5 ml single dose. Repeat same dosage every 10 years if at continued risk of exposure.

NOTE Dose should be given at least 10 days before travel to yellow fever endemic area.

Renal impairment: Dose reduction not required.

Hepatic impairment: Dose reduction not required.

Adverse effects: Common Headache, myalgia, weakness, nausea, diarrhoea.

Uncommon Abdominal pain, vomiting, malaise, influenza-like symptoms, arthralgia.

Rare Allergic reactions (rash, urticaria, asthma, anaphylactoid reaction), yellow fever vaccine-associated neurotropic disease or viscerotropic disease (see below).

YELLOW FEVER VACCINE-ASSOCIATED NEUROTROPIC DISEASE (YELAND) Occurs within 30 days of vaccination and may be fatal; symptoms include high fever, headache, confusion, encephalopathy, meningitis and seizures.

YELLOW FEVER VACCINE-ASSOCIATED VISCEROTROPIC DISEASE (YELAVD) Occurs within 10 days of vaccination and may be fatal; symptoms include fever, myalgia, headache, liver and muscle cytolysis, thrombocytopenia, acute renal failure and respiratory failure.

Interactions with other medicines (* indicates severe):

Asparaginase: avoid use of live vaccines with asparaginase (impairment of immune response).

* **Azathioprine**: avoid use of live vaccines with azathioprine (impairment of immune response).

Bleomycin: avoid use of live vaccines with bleomycin (impairment of immune response).

Chlorambucil: avoid use of live vaccines with chlorambucil (impairment of immune response).

* **Ciclosporin**: avoid use of live vaccines with ciclosporin (impairment of immune response).

Cyclophosphamide: avoid use of live vaccines with cyclophosphamide (impairment of immune response).

Cytarabine: avoid use of live vaccines with cytarabine (impairment of immune response).

Dacarbazine: avoid use of live vaccines with dacarbazine (impairment of immune response).

Dactinomycin: avoid use of live vaccines with dactinomycin (impairment of immune response).

Daunorubicin: avoid use of live vaccines with daunorubicin (impairment of immune response).

* **Dexamethasone**: high doses of dexamethasone impair immune response; avoid use of live vaccines.

Doxorubicin: avoid use of live vaccines with doxorubicin (impairment of immune response).

Etoposide: avoid use of live vaccines with etoposide (impairment of immune response).

Fluorouracil: avoid use of live vaccines with fluorouracil (impairment of immune response).

* **Hydrocortisone**: high doses of hydrocortisone impair immune response; avoid use of live vaccines.

Mercaptopurine: avoid use of live vaccines with mercaptopurine (impairment of immune response).

Methotrexate: avoid use of live vaccines with methotrexate (impairment of immune response).

* **Prednisolone**: high doses of prednisolone impair immune response; avoid use of live vaccines.

Procarbazine: avoid use of live vaccines with procarbazine (impairment of immune response).

Vinblastine: avoid use of live vaccines with vinblastine (impairment of immune response).

Vincristine: avoid use of live vaccines with vincristine (impairment of immune response).

Notes: All vaccines should comply with the WHO Recommendations for Production, Control and Evaluation of Vaccines and Other Biological Substances; these recommendations provide guidance for national regulatory authorities and for vaccine manufacturers.

www.who.int/biologicals/publications/trs/areas/en/index.html

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SECTION 20:
Muscle relaxants (peripherally-acting) and cholinesterase inhibitors

20 Muscle relaxants (peripherally-acting) and cholinesterase inhibitors

Muscle relaxants

Muscle relaxants used in surgery are classified, according to their mode of action, as either depolarizing or non-depolarizing neuromuscular blocking drugs. Their use allows abdominal surgery to be carried out under light anaesthesia. They should never be given until it is certain that general anaesthesia has been established, and ventilation must be mechanically assisted until they have been completely inactivated.

Cholinesterase inhibitors

Reversal of block

Cholinesterase inhibitors, such as **neostigmine,** are used at the end of surgery as the preferred agent to reverse the muscle paralysis produced by non-depolarizing blocking drugs such as **vecuronium**. **Neostigmine** must NOT be used with depolarizing blocking drugs such as **suxamethonium**, since **neostigmine** will prolong the muscle paralysis.

Myasthenia gravis

Cholinesterase inhibitors such as **neostigmine** and **pyridostigmine** are also used in the symptomatic treatment of myasthenia gravis. They enhance neuromuscular transmission by inhibiting acetylcholinesterase, thereby prolonging the action of acetylcholine. This produces at least a partial improvement in most myasthenic patients, but complete restoration of muscle strength is rare.

In a myasthenic crisis, if the patient has difficulty in breathing and in swallowing, cholinesterase inhibitors must be given by intramuscular or subcutaneous injection.

Neostigmine

ATC code: N07AA01

Injection: 500 micrograms in 1 ml ampoule; 2.5 mg (metilsulfate) in 1 ml ampoule

Tablet: 15 mg (bromide)

Indications: Treatment of myasthenia gravis; reversal of non-depolarizing muscle block.

Contraindications: Recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

Precautions: Asthma; urinary tract infection; cardiovascular disease including arrhythmias, bradycardia, vagotonia, recent myocardial infarction or atrioventricular block; hyperthyroidism; hypotension; peptic ulcer; epilepsy; renal impairment.

Dose:

Treatment of myasthenia gravis (using neostigmine bromide).

Oral:

Neonate initially 1–2 mg, then 1–5 mg every 4 hours, 30 minutes before feeds.

Infant or **Child** ***less than 6 years*** initially 7.5 mg, repeated at suitable intervals throughout the day. Total daily dose usually 15–90 mg;

6–12 years initially 15 mg, repeated at suitable intervals throughout the day. Total daily dose usually 15–90 mg.

Treatment of myasthenia gravis (using neostigmine metilsulfate).
SC or *IM:*
Neonate 150 micrograms/kg every 6–8 hours, 30 minutes before feeds, increased to a maximum of 300 micrograms/kg every 4 hours, if necessary.
Infant or **Child** 200–500 micrograms repeated at suitable intervals throughout the day.

Reversal of non-depolarizing muscle block (using neostigmine metilsulfate).
IV over 1 minute:
Neonate 50–80 micrograms/kg, after or with atropine.
Infant or **Child** 50–80 micrograms/kg (maximum 2.5 mg) after or with atropine.

Renal impairment: Mild to moderate impairment: administer 50% of normal dose.

Severe impairment: administer 25% of normal dose.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Increased salivation, nausea, vomiting, abdominal cramps, diarrhoea, bradycardia.

Uncommon Thrombophlebitis, rash associated with bromide salt, signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis.

Interactions with other medicines (* indicates severe):

Amikacin: antagonism of effects of neostigmine.

Atropine: antagonism of effects of neostigmine.

Chloroquine: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of neostigmine.

Clindamycin: antagonism of effects of neostigmine.

Gentamicin: antagonism of effect of neostigmine.

Paromomycin: possible antagonism.

Propranolol: antagonism of effect of neostigmine.

Streptomycin: antagonism of effect of neostigmine.

Suxamethonium: effect of suxamethonium enhanced.

Vecuronium: antagonism of muscle relaxant effect.

Notes: Simultaneous administration of an antimuscarinic drug such as atropine may be required to reduce the muscarinic side-effects of neostigmine; however it is not used routinely in treatment of myasthenia gravis as it can mask the signs of overdose.

ADMINISTRATION For intravenous injection, give undiluted or dilute with glucose 5% or sodium chloride 0.9% or water for injections.

For treatment of myasthenia gravis, oral doses can be divided so that the patient receives the larger doses at the times of greatest fatigue.

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Suxamethonium

ATC code: M03AB01

Injection: 50 mg (chloride)/ml in 2 ml ampoule

Powder for injection (chloride) in vial

Special Notes: Also referred to as succinylcholine.

NOTE Powder formulation recommended; liquid requires refrigerated storage.

Indications: Skeletal muscle relaxation in procedures of short duration such as endotracheal intubation or endoscopy.

Contraindications: Inability to maintain clear airway; personal or family history of malignant hyperthermia; neurological disease involving acute wasting of major muscle; skeletal myopathies; prolonged immobilisation; personal or family history of congenital myotonic disease, Duchenne muscular dystrophy or low plasma cholinesterase activity (including severe liver disease); myasthenia gravis; glaucoma; ocular surgery; penetrating eye injury; liver disease; burns; personal or family history of prolonged paralysis or apnoea with the use of depolarizing muscle relaxants; recent multiple trauma or spinal cord injury.

Precautions: Digitalis toxicity or recent digitalization; cardiac, respiratory or neuromuscular disease; paraplegia; severe sepsis; prolonged apnoea on repeated injection (infusion preferred for long surgical procedures); hyperkalaemia; renal impairment.

Dose:

Muscle relaxation (neuromuscular blockade) in procedures of short duration.

IM:

Neonate or **Infant** up to 4–5 mg/kg produces a 10–30 minute paralysis (after 2–3 minute delay).

Child up to 4 mg/kg produces a 10–30 minute paralysis (after 2–3 minute delay). Maximum dose 150 mg.

IV:

Neonate 2 mg/kg produces 5–10 minute paralysis, 3 mg/kg results in full neuromuscular block.

Infant initially 2 mg/kg, maintenance is usually 1–2 mg/kg at 5–10 minute intervals as necessary.

Child initially 1 mg/kg, then 0.5–1 mg/kg repeated every 5–10 minutes as necessary.

Renal impairment: Severe: dose reduction not required yet use with caution.

Hepatic impairment: Avoid use in severe hepatic impairment. Prolonged apnoea may occur in liver disease due to reduced hepatic synthesis of pseudocholinesterase.

Adverse effects: Common Postoperative muscle pain, muscle fasciculations prior to paralysis, increased salivary, bronchial and gastric secretions, transient rise in intragastric pressure, increased intraocular pressure, bradycardia (particularly with repeated dosing).

Uncommon Hypotension, arrhythmias, hyperkalaemia.

Rare Myoglobinuria, myoglobinaemia, hypersensitivity reactions (including flushing, rash, urticaria, bronchospasm and shock), malignant hyperthermia (may be fatal).

Interactions with other medicines (* indicates severe):

* **Amikacin**: enhanced effects of suxamethonium.

* **Capreomycin**: enhanced effects of suxamethonium.

Cyclophosphamide: enhanced effect of suxamethonium.

Digoxin: risk of ventricular arrhythmias.

* **Gentamicin**: enhanced muscle relaxant effect.

Halothane: enhanced effects of suxamethonium.

Lidocaine: neuromuscular blockade enhanced and prolonged (interaction less likely when lidocaine used topically).

Lithium: enhanced muscle relaxant effect.

Magnesium (parenteral): enhanced muscle relaxant effect.

Metoclopramide: enhanced effects of suxamethonium.

Neostigmine: effect of suxamethonium enhanced.

* **Paromomycin**: possibly enhanced effects of suxamethonium.

Procainamide: enhanced muscle relaxant effect.

Propranolol: enhanced muscle relaxant effect.

Pyridostigmine: effect of suxamethonium enhanced.

* **Quinine**: possibly enhanced effects of suxamethonium.

* **Streptomycin**: enhanced muscle relaxant effect.

Notes: Suxamethonium is usually administered after anaesthetic induction.

Neonates and young infants are less sensitive to suxamethonium and higher doses may be required.

ADMINISTRATION For intravenous injection, give undiluted, or dilute with glucose 5% or sodium chloride 0.9%.

Premedication with atropine reduces bradycardia and excessive salivation.

Refrigerate solution form of injection; room temperature stability is product specific. Check with the manufacturer.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010 (http://www.thomsonhc.com, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Vecuronium

ATC code: M03AC03

Powder for injection: 10 mg (bromide) in vial

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Muscle relaxation during surgery.

Precautions: Hepatic impairment; possibly increase dose in patient with burns; electrolyte disturbances; possibly decrease dose in respiratory acidosis, hypokalaemia and hypothermia; history of asthma; severe obesity (maintenance of adequate airway and ventilation support); neuromuscular disease; myasthenia gravis; renal impairment.

Dose:

Muscle relaxation during surgery.

IV:

Neonate initially 80–100 micrograms/kg, then 30–50 micrograms/kg adjusted according to response.

Infant or **Child** initially 80–100 micrograms/kg; then either by *IV injection* 20–30 micrograms/kg repeated as required, or by *IV infusion* 50–80 micrograms/kg per hour, adjusted according to response.

NOTE To avoid excessive dosage in obese patients, dose should be calculated on the basis of ideal body weight.

Renal impairment: Dose reduction not necessary yet duration of action may be prolonged in renal impairment; use cautiously.

Hepatic impairment: Dose reductions are necessary in patients with cirrhosis or cholestasis. Impairment decreases clearance resulting in prolonged duration of action.

Adverse effects: Rare Hypersensitivity reactions including bronchospasm, hypotension, tachycardia, oedema, erythema, pruritus.

Interactions with other medicines (* indicates severe):

* **Amikacin**: enhanced effects of vecuronium.

  Carbamazepine: antagonism of muscle relaxant effect (recovery from neuromuscular blockade accelerated).

* **Capreomycin**: enhanced effects of vecuronium.

* **Clindamycin**: enhanced muscle relaxant effect.

* **Gentamicin**: enhanced muscle relaxant effect.

  Halothane: enhanced effects of vecuronium.

  Neostigmine: antagonism of muscle relaxant effect.

  Phenytoin: antagonism of muscle relaxant effect (accelerated recovery from neuromuscular blockade).

* **Procainamide**: enhanced muscle relaxant effect.

  Propranolol: enhanced muscle relaxant effect.

  Pyridostigmine: antagonism of muscle relaxant effect.

* **Quinidine**: enhanced muscle relaxant effect.

* **Streptomycin**: enhanced muscle relaxant effect.

Notes: Vecuronium may be supplied with diluent containing benzyl alcohol. Use sterile water for injections to reconstitute for neonates.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Pyridostigmine

ATC code: N07AA02

Injection: 1 mg in 1 ml ampoule

Tablet: 60 mg (bromide)

Indications: Treatment of myasthenia gravis; reversal of non-depolarizing muscle block.

Contraindications: Recent intestinal or bladder surgery; mechanical intestinal or urinary tract obstruction; after suxamethonium; pneumonia; peritonitis.

Precautions: Asthma; urinary tract infection; cardiovascular disease including arrhythmias, bradycardia, vagotonia, recent myocardial infarction or atrioventricular block; hyperthyroidism; hypotension; peptic ulcer; epilepsy; renal impairment.

Dose:

Treatment of myasthenia gravis.

Oral:

Neonate initially 1–1.5 mg/kg, increased gradually to maximum of 10 mg, every 4–6 hours. Give dose 30–60 minutes before feeds.

Infant or **Child** initially 1–1.5 mg/kg daily increased gradually to 7 mg/kg daily in six divided doses. Usual total daily dose is 30–360 mg.

IM or *IV:*

Neonate, Infant or **Child** 50–150 micrograms/kg per dose. Maximum 10 mg per dose.

Reversal of non-depolarizing muscle block.

IV:

Child *all ages* 100–250 micrograms/kg per dose (maximum 20 mg per dose), preceded by atropine.

Renal impairment: Use with caution. Dosage reduction may be required.

Hepatic impairment: Dosage adjustment considered unnecessary.

Adverse effects: Muscarinic effects generally weaker than with neostigmine.

Common Increased salivation, nausea, vomiting, abdominal cramps, diarrhoea, bradycardia.

Uncommon Thrombophlebitis, rash associated with bromide salt; signs of overdosage include bronchoconstriction, increased bronchial secretions, lacrimation, excessive sweating, involuntary defecation and micturition, miosis, nystagmus, heart block, arrhythmias, hypotension, agitation, excessive dreaming, weakness eventually leading to fasciculation and paralysis.

Interactions with other medicines (* indicates severe):

* **Amikacin**: antagonism of effect of pyridostigmine.

Atropine: antagonism of effect of pyridostigmine.

Chloroquine: chloroquine has potential to increase symptoms of myasthenia gravis and thus diminish effect of pyridostigmine.

Clindamycin: antagonism of effects of pyridostigmine.

* **Gentamicin**: antagonism of effect of pyridostigmine.

* **Paromomycin**: possible antagonism.

Propranolol: antagonism of effect of pyridostigmine.

* **Streptomycin**: antagonism of effect of pyridostigmine.

Suxamethonium: effect of suxamethonium enhanced.

Vecuronium: antagonism of muscle relaxant effect.

Notes: For treatment of myasthenia gravis, oral doses can be divided so that the patient receives the larger doses at the times of greatest fatigue.

Give 30–60 minutes before feeds in babies to improve suckling, but give after food or milk in older children/adults to reduce abdominal cramping.

ADMINISTRATION For IV injections, administer slowly over 2–4 minutes; patients receiving large parenteral doses should be pretreated with atropine. The patient must be closely observed for cholinergic reactions.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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SECTION 21:
Ophthalmological preparations

21 Ophthalmological preparations

Administration of eye preparations

Preparations for the eye should be sterile when issued. Use of single application containers is preferable.

Eye drops are generally instilled into the lower conjunctival sac, which is accessed by gently pulling down the lower eyelid to form a pocket into which one drop is instilled. The eye should be kept closed for as long as possible after application, preferably 1–2 minutes. A small amount of eye ointment is applied similarly; the ointment melts rapidly and blinking helps to spread it. When two different eye drops are required at the same time, an interval of at least 5 minutes should be allowed between the two applications. Drops and ointment may both cause transient blurred vision. Systemic absorption can be minimized by using the finger to compress the lacrimal sac at the medial canthus (nasal aspect of the eye) for at least 1 minute after instillation of the drops.

21.1 Anti-infective agents

Acute infective bacterial conjunctivitis is treated with antibacterial eye drops by day and eye ointment applied at night. A poor response may indicate viral or allergic conjunctivitis. Corneal ulcer, keratitis and endophthalmitis require immediate specialist treatment.

Aciclovir

ATC code: S01AD03

Ointment: 3% w/w

Indications: Keratitis caused by herpes simplex.

Precautions: Avoid wearing contact lenses when using aciclovir ophthalmic ointment.

Dose:

Herpes simplex keratitis.

Eye:

Infant or **Child** 1 cm of ointment five times daily. Continue for at least 3 days after healing is complete.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Local irritation including transient mild stinging, inflammation.

Uncommon Superficial punctate keratopathy.

Rare Blepharitis, hypersensitivity reactions including angioedema.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Avoid contaminating the tip of the ointment tube.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Gentamicin

ATC code: S01AA11

Solution (eye drops): 0.3% (sulfate)

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Blepharitis; bacterial conjunctivitis.

Contraindications: Hypersensitivity to aminoglycoside group of antibiotics.

Precautions: Prolonged use may lead to skin sensitization and emergence of resistant organisms including fungi; discontinue if purulent discharge, inflammation or exacerbation of pain.

Dose:

Mild to moderate infection.

Eye:

Infant or **Child** 1 drop every 2 hours, reducing frequency as infection is controlled to 1 drop four times daily, and then continued for 48 hours after healing is complete.

Severe infection.

Eye:

Infant or **Child** 1 drop every hour reducing frequency as infection is controlled to 1 drop four times daily, and then continued for 48 hours after healing is complete.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Burning, stinging, itching, dermatitis, redness, lacrimation, superficial punctate keratitis.

Uncommon Delayed corneal epithelial wound healing, retinal toxicity (if there is leakage through corneoscleral wound).

Rare Hypersensitivity reactions.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Avoid contaminating the tip of the solution bottle. Apply finger pressure to the lacrimal sac during and for 1–2 minutes after instillation to decrease risk of absorption and systemic effects.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
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Tetracycline

ATC code: S01AA09

Eye ointment: 1% (hydrochloride)

Discontinue if periocular rash develops.

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Superficial bacterial infection of the eye; mass treatment of trachoma in endemic areas; prophylaxis of neonatal conjunctivitis (ophthalmia neonatorum) due to *Neisseria gonorrhoea* or *Chlamydia trachomatis*.

Contraindications: Hypersensitivity to tetracycline group of antibiotics; photodermatosis.

Precautions: Prolonged use may lead to overgrowth of non-susceptible organisms; intensive exposure to the sun or ultraviolet radiation should be avoided during treatment since photodermatosis has been observed in isolated cases in hypersensitive patients.

Dose:

Superficial bacterial infection.

Eye:

Infant or **Child** one application of ointment 3–4 times daily.

Prophylaxis of neonatal conjunctivitis.

Eye:

Neonate *at birth* as soon as possible after delivery after cleansing eyes with sterile gauze, one application of ointment into each eye; close eyelids and massage gently to aid spread of ointment.

Trachoma, intermittent treatment.

Eye:

Infant or **Child** one application of ointment into each eye either twice daily for 5 days or once daily for 10 days, every month for 6 consecutive months each year, repeated as necessary.

Trachoma, continuous intensive treatment.

Eye:

Infant or **Child** one application of ointment into each eye twice daily for at least 6 weeks.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Rare Rash, stinging, burning, allergic reaction, photodermatosis.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Avoid contaminating the tip of the ointment tube.

When treating bacterial conjunctivitis, it is advisable to continue therapy for a further 2–3 days after regression of the symptoms.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
MIMS Online. Sydney, UBM Medica, 2009 (http://www.mimsonline.com.au/Search/Search.aspx, accessed 10 February 2010).
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

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21.2 Anti-inflammatory agents

Ophthalmic corticosteroids such as **prednisolone** should only be used under supervision of an ophthalmologist, as inappropriate use is potentially blinding.

Before administration of an ophthalmic corticosteroid, the possibility of bacterial, viral or fungal infection should be excluded.

Prednisolone

ATC code: S01BA04

Solution (eye drops): 0.5% (sodium phosphate)

Use increases risk of ocular hypertension and cataract.

Inappropriate use is potentially blinding.

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Short-term local treatment of inflammation of the eye, including severe allergic conjunctivitis, iritis, uveitis and following intraocular surgery.

Contraindications: Undiagnosed 'red eye' caused by herpetic keratitis; glaucoma.

Precautions: Cataract; corneal thinning; corneal or conjunctival infection; discontinue treatment if no improvement within 7 days; risk of adrenal suppression after prolonged use in infants; allergy to sodium bisulfite which may be contained in ophthalmic solution.

Dose:

NOTE Use only under the supervision of an ophthalmologist.

Inflammation of the eye.

Eye:

Neonate, Infant or **Child** 1 drop every 1–2 hours, reducing frequency as inflammation is controlled.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Ocular hypertension (usually reversible) proportional to dose, potency, penetration and duration of treatment, retarded corneal healing due to corneal thinning, rebound inflammation.

Uncommon Secondary ocular infection, mydriasis, epithelial punctuate keratitis.

Rare Transient stinging, burning or local irritation, refractive changes, ptosis, chemosis, lid swelling, exophthalmos (slowly, incompletely reversible), with prolonged use: optic nerve damage, defects in visual acuity and field of vision, open-angle glaucoma and cataracts (see below).

CATARACTS Posterior subcapsular cataracts may occur with long-term (> 1 year) high-dose use; mostly asymptomatic and partially reversible.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Avoid contaminating the tip of the solution bottle. Apply finger pressure to the lacrimal sac during and for 1–2 minutes after instillation to decrease risk of absorption and systemic effects.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.
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21.3 Local anaesthetics

Topical local anaesthetics are employed for simple ophthalmological procedures and for short operative procedures involving the cornea and conjunctiva. **Tetracaine** provides a rapid local anaesthesia which lasts for 15 minutes or more. Prolonged or unsupervised use of tetracaine is not recommended.

Tetracaine

ATC code: S01HA03

Solution (eye drops): 0.5% (hydrochloride)

Prolonged use impairs corneal epithelial healing, prevents reflex ocular protection and masks progression of keratopathy; use only for short procedures (< 20 minutes).

Special Notes: WHO age/weight restriction: not in preterm neonates.

Also referred to as amethocaine.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Short-acting local anaesthesia of cornea and conjunctiva.

Contraindications: Hypersensitivity to ester-type local anaesthetics; eye inflammation or infection.

Precautions: Avoid prolonged use (cause of severe keratitis, permanent corneal opacification, scarring, delayed corneal healing); protect eye from dust and bacterial contamination until sensation fully restored; corneal scrapings: use preservative-free drops (preservative may affect microbiological culture).

Dose:

Local anaesthesia.

Eye:

Neonate, Infant or **Child** 1 drop repeated in 5 minutes if necessary to a maximum of 1 drop every 5 minutes for five doses.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Burning, stinging on initial instillation, redness, punctate epithelial damage of cornea (do not use long term because of epithelial toxicity, i.e. acute corneal ulceration).

Rare Allergy.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Anaesthetic effect occurs within 3 minutes and lasts for 15 minutes or more.

Close eyes after instillation and dab away tears without rubbing eyes.

These eye drops may sting at first.

Never prescribe for home use.

Topical anaesthetics increase corneal permeability and intraocular bioavailability of other topical drugs; they also reduce the initial stinging of other topical drugs and should be instilled first.

Single-use drops are useful if infection is suspected, otherwise avoid contaminating the tip of the solution bottle.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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21.4 Miotics and antiglaucoma medicines

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

21.5 Mydriatics

These paralyse the pupillary constrictor muscles, causing dilation of the pupil (mydriasis), and paralyse the ciliary muscles, resulting in paralysis of accommodation (cycloplegia).

Atropine

ATC code: S01FA01

Solution (eye drops): 0.1%; 0.5%; 1% (sulfate)

Special Notes: WHO age/weight restriction: > 3 months.

WHO Essential Medicines for Children's list indicates that atropine is one alternative for use; other options are homatropine or cyclopentolate.

Indications: Iritis; uveitis; cycloplegic refraction procedures.

Contraindications: Closed angle glaucoma.

Precautions: May precipitate acute attack of closed angle glaucoma; significant head injury (use only short-acting agents with care; always make a note that pupils were dilated intentionally).

Use with extreme caution, if at all, in children with spastic paralysis or brain damage (increased susceptibility to systemic reactions). 1 drop of 0.5% atropine can cause systemic effects in infants. In young children, long-term cycloplegia may induce amblyopia.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery. Blurred vision may persist for up to 14 days after administration.

Dose:

Cycloplegic refraction.

Eye:

Infant *3 months–1 year* 1 drop (0.1%) twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure.

Child *1–5 years* 1 drop (0.1–0.5%) twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure;

over 5 years 1 drop (0.5–1%) twice daily for 1–3 days before procedure with a further dose given 1 hour before procedure.

Iritis, uveitis.

Eye:

Infant *over 3 months* 1 drop (0.5 or 1%) up to three times daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Intolerance to bright light (glare), stinging on instillation, blurred vision (especially near vision), transient intraocular pressure elevation.

Uncommon Conjunctivitis, contact allergic blepharitis, persistent ocular irritation (mucus discharge, severe watering discharge, superficial punctate keratopathy and characteristically no itch), punctal stenosis with prolonged use (years), insomnia.

Rare Systemic toxicity (may be more frequent in children), e.g. dryness of skin and mouth, fever, facial flushing, tachycardia, irritability, disorientation, ataxia, visual hallucinations, incoherent speech, delirium, psychosis, seizures, hyperactivity.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Avoid contaminating the tip of the solution bottle. Apply finger pressure to the lacrimal sac during and for 1–2 minutes after instillation to decrease risk of absorption and systemic effects.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Epinephrine (Adrenaline)

ATC code: S01EA01

Solution (eye drops): 2% (as hydrochloride)

Special Notes: Also referred to as adrenaline.

Indications: Chronic open-angle glaucoma; ocular hypertension.

Contraindications: Closed-angle glaucoma, unless an iridectomy has been performed.

Precautions: Hypertension; heart disease; aneurysm; arrhythmia; tachycardia; hyperthyroidism; cerebral arteriosclerosis; diabetes mellitus.

Dose:

Chronic open-angle glaucoma.
Eye:
No paediatric dose available.
Adult 1 drop (0.5% or 1%) 1–2 times daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Stinging, blurred vision, photophobia, eye pain.

Uncommon Conjunctival hyperaemia, headache or browache.

Rare Conjunctival sensitization, local skin reactions, after prolonged use, conjunctival pigmentation and macular oedema in aphakia, systemic adverse reactions (see below).

SYSTEMIC ADVERSE REACTIONS are rare following topical use at normal dosage but tachycardia, hypertension, arrhythmia, dizziness, sweating may occur.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Avoid contaminating the tip of the solution bottle. Apply finger pressure to the lacrimal sac during and for 1–2 minutes after instillation to decrease risk of absorption and systemic effects.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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SECTION 22:
Oxytocics and antioxytocics

22 Oxytocics and antioxytocics

This section has been deleted from the *2nd WHO Model List of Essential Medicines for Children*.

SECTION 23:
Peritoneal dialysis solution

23 Peritoneal dialysis solution

Solutions for peritoneal dialysis are preparations for intraperitoneal use that contain electrolytes in a similar concentration to that in plasma, and also contain glucose or another suitable osmotic agent. Peritoneal dialysis is often preferred over haemodialysis in children, and is generally used in acute rather than chronic dialysis. It is unsuitable for patients who have had significant abdominal surgery.

In peritoneal dialysis, the solution is infused into the peritoneal cavity using the peritoneal membrane as an osmotic membrane. There are two forms of peritoneal dialysis:

- *continuous ambulatory peritoneal dialysis* (CAPD), in which dialysis is performed manually by the patient several times each day
- *automated peritoneal dialysis* (APD), in which dialysis is performed by machine overnight.

The main complication of peritoneal dialysis is peritonitis, which often results from poor exchange technique; infections of the catheter exit site may also occur. With long-term dialysis, progressive structural changes to the peritoneal membrane occur, ultimately resulting in dialysis failure.

Intraperitoneal dialysis solution (of appropriate composition)

ATC code: B05DA

Indications: To correct electrolyte imbalance, fluid overload and to remove metabolites in renal failure.

Contraindications: Abdominal sepsis; severe inflammatory bowel disease.

Precautions: Previous abdominal surgery; care required with technique to reduce risk of infection; some drugs may be removed by dialysis.

Dose:

Individualized according to clinical condition and based on blood results.

Initial dialysis ideally delayed for 2 weeks after insertion of catheter. Start with low volumes, e.g. 10 ml/kg and gradually increase to maximum 50 ml/kg (1100 ml/m^2) to avoid creating leak at catheter exit site.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Infection (including peritonitis), hernia, haemoperitoneum, hyperglycaemia, protein malnutrition, blocked catheter, pain on filling (related to acidic pH of some dialysis solutions), hypokalaemia with aggressive dialysis.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Warm dialysis solution to body temperature before use.

Increasing concentrations of glucose allow increasing efficiency of fluid removal (e.g. 1.5%, 2.3%, 4.5%). Lower concentrations (e.g. 1.5%) are gentler and appropriate for maintenance. High osmolality solutions (e.g. 4.25%) can be used intermittently for severe fluid overload.

Solutions containing 1.5% of glucose may be used in the management of acute renal failure, uncontrolled hyperkalemia or oliguria in the presence of a rapid catabolic rate.

Solutions containing decreased sodium concentration are used to prevent post-dialysis hypernatraemia.

Solutions containing acetate are used in patients with impaired lactate metabolism and also in patients with hepatic dysfunction or impaired tissue perfusion.

Solutions containing decreased magnesium concentrations (i.e. 0.5 mEq/l) are used for patients with hypermagnesaemia or in patients in whom increased oral magnesium intake is desirable.

Commercially available solutions do not usually contain potassium as the solutions are frequently used for removing potassium in patients with hyperkalaemia. Potassium may be added to the dialysis solution and used cautiously when necessary.

For further information, specialized references on peritoneal dialysis and the manufacturer's product information (where available) should be consulted.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

McEvoy GK, ed. *AHFS drug information.* Bethesda, American Society of Health-System Pharmacists, 2009.

WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

SECTION 24:
Psychotherapeutic medicines

24 Psychotherapeutic medicines

24.1 Medicines used in psychotic disorders

Antipsychotic drugs (neuroleptics) generally tranquillize without impairing consciousness or causing paradoxical excitement. In the short term, they are used to manage children with severe violent, threatening, aggressive or self-injurious behaviour that is not adequately controlled by other strategies. Treatment of chronic psychotic disorders (e.g. schizophrenia) involves both pharmacological and psychosocial interventions. The lowest possible dose of antipsychotic drug that will prevent major exacerbations of florid symptoms is used for long-term management.

Withdrawal of antipsychotics after long-term therapy should be gradual and closely monitored, to avoid the risk of acute withdrawal syndromes or rapid relapse. Relapse may be delayed for several weeks.

Chlorpromazine

ATC code: N05AA01

Injection: 25 mg (as hydrochloride)/ml in 2 ml ampoule

Oral liquid: 5 mg (as hydrochloride)/ml

Tablet: 10 mg, 25 mg, 50 mg and 100 mg (hydrochloride)

Owing to the risk of contact sensitization, pharmacists, nurses and other health workers should avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care.

Indications: Schizophrenia; autism; psychomotor agitation and violent behaviour; adjunct in severe anxiety; other psychotic disorders.

Contraindications: Impaired consciousness due to CNS depression; phaeochromocytoma; narrow angle glaucoma; bone marrow suppression; severe liver or cardiac disease; hypersensitivity to chlorpromazine (cross-sensitivity with other phenothiazines may exist); breastfeeding.

Precautions: Cardiovascular and cerebrovascular disorders; respiratory disease; parkinsonism; epilepsy; acute infections; renal and hepatic impairment (avoid if severe); history of jaundice; leukopenia (monitor blood counts if unexplained fever or infection); hypothyroidism; myasthenia gravis; prostatic hypertrophy; avoid abrupt withdrawal; patients should remain supine and the blood pressure monitored for 30 minutes after intramuscular injection.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

Dose:

Childhood schizophrenia, autism, severe anxiety and other psychoses.

Oral:

Child *1–6 years* 500 micrograms/kg every 4–6 hours adjusted according to response (maximum 40 mg daily);

6–12 years 10 mg three times daily, adjusted according to response (maximum 75 mg daily).

Relief of acute symptoms of psychoses (including psychomotor agitation and violent behaviour).

Deep IM:

Child *1–6 years* 500 micrograms/kg every 6–8 hours (maximum 40 mg daily).

Renal impairment: Start with small doses; increased cerebral sensitivity.

Hepatic impairment: Can precipitate coma; hepatotoxic.

Adverse effects: Common Sedation, anxiety, agitation, extrapyramidal side-effects (see below), orthostatic hypotension, tachycardia, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility), photosensitivity, phototoxicity and hyperpigmentation.

Uncommon or rare Cholestatic jaundice, allergic reactions (including urticaria, Stevens-Johnson syndrome), corneal and lens opacities, syndrome of inappropriate antidiuretic hormone (SIADH) secretion, hyperthermia, hypothermia, neuroleptic malignant syndrome (see below), anaemia, thrombocytopenia, agranulocytosis, venous thromboembolism, ECG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, priapism, systemic lupus erythematosus, seizures, increased blood glucose (see Metabolic effects below), dysarthria, dysphagia.

EXTRAPYRAMIDAL SIDE-EFFECTS **Dystonias** Torticollis, carpopedal spasm, trismus, perioral spasm and oculogyric crisis, as well as medical emergencies, such as laryngeal spasm and opisthotonos, may occur. Dystonias are more common in children and young adults and more likely with high doses. They often occur within 24–48 hours of starting treatment or increasing dose and respond rapidly to anticholinergics. In some cases, treatment with a benzodiazepine may also prove helpful. It may be possible to reintroduce the drug at a lower dose or consider an alternative.

Akathisia A feeling of motor restlessness; usually occurs 2–3 days (up to several weeks) after starting treatment and may subside spontaneously. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased; agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced.

Parkinsonism Characterized by features such as tremor, rigidity or bradykinesia; usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short-term use of an anticholinergic may be helpful. If parkinsonism persists, consider reducing antipsychotic dose or switching to an alternative antipsychotic.

Tardive dyskinesia (TD) Characterized by involuntary movements of the face, mouth or tongue, and sometimes head and neck, trunk or limbs. TD may appear after medium to long-term treatment, or even after stopping the antipsychotic (particularly after suddenly stopping). Up to a third of people treated for 10 years with conventional antipsychotics will develop TD. There may be a slow improvement after the drug is withdrawn, particularly in young patients or early in the syndrome.

NEUROLEPTIC MALIGNANT SYNDROME (NMS) A potentially fatal condition characterized by fever, marked muscle rigidity, altered consciousness and autonomic instability. The syndrome usually progresses rapidly over 24–72 hours. Elevation of serum creatine kinase concentration (skeletal muscle origin) and leukocytosis often occur. Not all typical signs need to be present for diagnosis. The incidence of NMS is greatest in young men. It does not always occur immediately after starting antipsychotic treatment, and may be seen after many months or years. Treatment involves ceasing the antipsychotic, general supportive care such as cooling, volume replacement and treatment of hyperkalaemia. Paralysis and mechanical ventilation may also be required.

METABOLIC EFFECTS People with schizophrenia are at increased cardiovascular risk. Antipsychotic agents have been associated with increased blood glucose, weight gain and dyslipidaemia. Increases risk of type 2 diabetes.

Interactions with other medicines (* indicates severe):

* **Amitriptyline**: increased risk of antimuscarinic adverse effects; increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias.

  Amodiaquine: plasma concentration of chlorpromazine increased (consider reducing chlorpromazine dose).

  Antacids (aluminium hydroxide; magnesium hydroxide): reduced absorption of chlorpromazine.

* **Artemether + lumefantrine**: manufacturer of artemether with lumefantrine advises to avoid concomitant use.

  Atropine: increased antimuscarinic adverse effects (but reduced plasma chlorpromazine concentration).

* **Carbamazepine**: antagonism of anticonvulsant effect (convulsive threshold lowered).

* **Clomipramine**: increased antimuscarinic adverse effects; increased plasma clomipramine concentration; possibly increased risk of ventricular arrhythmias.

  Codeine: enhanced sedative and hypotensive effect.

  Diazepam: enhanced sedative effect.

  Dopamine: antagonism of hypertensive effect.

  Enalapril: enhanced hypotensive effect.

  Epinephrine: antagonism of hypertensive effect.

  Ethanol: enhanced sedative effect.

* **Ethosuximide**: antagonism of anticonvulsant effect (convulsive threshold lowered).

* **Erythromycin**: increased risk of cardiotoxicity.

* **Fluoxetine**: increased risk of cardiotoxicity.

  Furosemide: enhanced hypotensive effect.

* **Halothane**: enhanced hypotensive effect.

  Hydrochlorothiazide: enhanced hypotensive effect.

* **Ketamine**: enhanced hypotensive effect.

* **Metoclopramide**: increased risk of extrapyramidal effects.

  Morphine: enhanced sedative and hypotensive effect.

  Nifedipine: enhanced hypotensive effect.

  Nitrous oxide: enhanced hypotensive effect.

* **Phenobarbital**: antagonism of anticonvulsant effect (convulsive threshold lowered).

* **Phenytoin**: antagonism of anticonvulsant effect (convulsive threshold lowered).

* **Procainamide**: increased risk of ventricular arrhythmias.

* **Propranolol**: concomitant administration may increase plasma concentration of both drugs; enhanced hypotensive effect.

* **Ritonavir**: plasma concentration possibly increased by ritonavir.

  Spironolactone: enhanced hypotensive effect.

* **Thiopental**: enhanced hypotensive effect.

* **Valproic acid**: antagonism of anticonvulsant effect (convulsive threshold lowered).

Notes: Not recommended for rapid tranquillization as locally irritant if given intramuscularly, can alter QTc interval and cause hypotension when given at high dose.

Deep intramuscular injection is very painful, particularly in children.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Haloperidol

ATC code: N05AD01

Injection: 5 mg in 1 ml ampoule

Oral liquid: 2 mg/ml

Solid oral dosage form: 0.5 mg; 2 mg; 5 mg

Indications: Schizophrenia and other psychotic disorders; short-term adjunctive management of psychomotor agitation, excitement; violent, dangerous or impulsive behaviour and severe anxiety; motor tics (including Tourette syndrome).

Contraindications: Impaired consciousness due to CNS depression; bone marrow depression; phaeochromocytoma; porphyria; basal ganglia disease; severe liver or cardiac disease.

Precautions: Cardiovascular and cerebrovascular disorders; respiratory disease; parkinsonism; epilepsy; acute infections; renal and hepatic impairment (avoid if severe); history of jaundice; leukopenia (blood count required if unexplained fever or infection); hypothyroidism; myasthenia gravis; prostatic hypertrophy; closed-angle glaucoma; subarachnoid haemorrhage; metabolic disturbances such as hypokalaemia, hypocalcaemia or hypomagnesaemia; avoid abrupt withdrawal; patients should remain supine and have their blood pressure monitored for 30 minutes after intramuscular injection.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

Dose:

Schizophrenia and other psychoses; short-term adjunctive management of psychomotor agitation; excitement and violent or dangerous impulsive behaviour; severe anxiety.
Oral:
Child *3–12 years* initially 0.125–0.25 mg twice daily, increase by 0.25–0.5 mg/day every 5–7 days. Maximum 0.15 mg/kg daily. Usual maintenance 0.025–0.05 mg/kg three times daily.
IM (when rapid effect required):
Child *6–12 years* 1–3 mg per dose every 4–8 hours to a maximum of 0.15 mg/kg daily. Change to oral therapy as soon as possible.

Motor tics (including Tourette syndrome).
Oral:
Child *5–12 years* 0.0125–0.025 mg/kg twice daily, adjusted according to response up to 10 mg daily.

Renal impairment: Severe: start with small doses; increased cerebral sensitivity.

Hepatic impairment: Can precipitate coma, consider dose reduction. Avoid use in severe impairment.

Adverse effects: Common Sedation, anxiety, agitation, extrapyramidal side-effects (EPSE, see below), orthostatic hypotension, tachycardia, blurred vision, mydriasis, constipation, nausea, dry mouth, urinary retention, weight gain, hyperprolactinaemia (may result in galactorrhoea, gynaecomastia, amenorrhoea or infertility).

Uncommon or rare Allergic reactions, including urticaria, Stevens-Johnson syndrome, corneal and lens opacities, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hyperthermia, hypothermia, neuroleptic malignant syndrome (see below), anaemia, thrombocytopenia, agranulocytosis, venous thromboembolism, ECG changes (reversible, broadened QT interval), arrhythmias, cardiac arrest, sudden death, hepatic fibrosis, priapism, systemic lupus erythematosus, seizures, increased blood glucose (see Metabolic effects below), dysarthria, dysphagia, weight loss, hypoglycaemia.

EXTRAPYRAMIDAL SIDE EFFECTS Reduce antipsychotic dose to avoid recurrent EPSE when possible.

Dystonias Torticollis, carpopedal spasm, trismus, perioral spasm and oculogyric crisis, as well as medical emergencies, such as laryngeal spasm and opisthotonos, may occur. Dystonias are more common in children and young adults, and more likely with high doses. They often occur within 24–48 hours of starting treatment or increasing dose, and respond rapidly to anticholinergics. In some cases, treatment with a benzodiazepine may also prove helpful. It may be possible to reintroduce the drug at a lower dose, or consider an alternative.

Akathisia A feeling of motor restlessness; usually occurs 2–3 days (up to several weeks) after starting treatment and may subside spontaneously. It is important to differentiate between akathisia and agitation secondary to psychosis. Akathisia tends to improve with dose reduction and deteriorate when the dose is increased; agitation due to psychosis tends to improve if the dose is increased and deteriorate if it is reduced. Children may not complain of the sensation of akathisia in the same way as adults; monitor closely. Sedating agents such as haloperidol are more likely to impair cognition and therefore learning at school.

Parkinsonism Characterized by features such as tremor, rigidity or bradykinesia; usually develops after weeks or months. Although usually reversible, symptomatic treatment is sometimes necessary. Short-term use of an anticholinergic may be helpful. If parkinsonism persists, consider reducing antipsychotic dose or switching to an alternative antipsychotic (possibly an atypical agent).

Tardive dyskinesia (TD) Characterized by involuntary movements of the face, mouth or tongue, and sometimes head and neck, trunk or limbs. TD may appear after medium to long-term treatment, or even after stopping the antipsychotic (particularly after suddenly stopping). Diabetics and those with affective disorders appear to be at increased risk. Up to a third of people treated for 10 years with conventional antipsychotics will develop TD. There may be a slow improvement after the drug is withdrawn, particularly in young patients or early in the syndrome.

NEUROLEPTIC MALIGNANT SYNDROME (NMS) All antipsychotics can cause NMS, a potentially fatal condition characterized by fever, marked muscle rigidity, altered consciousness and autonomic instability. The syndrome usually progresses rapidly over 24–72 hours. Elevation of serum creatine kinase concentration (skeletal muscle origin) and leukocytosis often occur. Not all typical signs need to be present for diagnosis. The incidence of NMS is greatest in young men. It does not always occur immediately after starting antipsychotic treatment, and may be seen after many months or years. Treatment involves ceasing the antipsychotic, general supportive care such as cooling, volume replacement and treatment of hyperkalaemia. Paralysis and mechanical ventilation may also be required.

METABOLIC EFFECTS People with schizophrenia are at increased cardiovascular risk. Antipsychotic agents have been associated with increased blood glucose, weight gain, dyslipidaemia and an increased risk of type 2 diabetes.

Interactions with other medicines (* indicates severe):

* **Amitriptyline**: increased plasma amitriptyline concentration; possibly increased risk of ventricular arrhythmias.
* **Artemether + lumefantrine**: maufacturer of artemether with lumefantrine advises avoidance of concomitant use.

  Atropine: possible reduced effects of haloperidol.
* **Carbamazepine**: antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration).
* **Clomipramine**: increased plasma clomipramine concentration; possible increased risk of ventricular arrhythmias.

  Codeine: enhanced sedative and hypotensive effect.

  Diazepam: enhanced sedative effect.

  Dopamine: antagonism of hypertensive effect.

  Enalapril: enhanced hypotensive effect.

  Epinephrine: antagonism of hypertensive effect.
* **Erythromycin**: increased risk of cardiotoxicity.

  Ethanol: enhanced sedative effect.
* **Ethosuximide**: antagonism of anticonvulsant effect (convulsive threshold lowered).

* **Fluoxetine**: plasma concentration of haloperidol increased.
* **Halothane**: enhanced hypotensive effect.
* **Ketamine**: enhanced hypotensive effect.
* **Metoclopramide**: increased risk of extrapyramidal effects.

  Morphine: enhanced sedative and hypotensive effect.

  Nifedipine: enhanced hypotensive effect.
* **Nitrous oxide**: enhanced hypotensive effect.
* **Phenobarbital**: antagonism of anticonvulsant effect (convulsive threshold lowered); metabolism of haloperidol accelerated (reduced plasma concentration).
* **Phenytoin**: antagonism of anticonvulsant effect (convulsive threshold lowered).
* **Procainamide**: increased risk of ventricular arrhythmias.
* **Quinidine**: increased risk of ventricular arrhythmias.
* **Rifampicin**: accelerated metabolism of haloperidol (reduced plasma haloperidol concentration).
* **Ritonavir**: plasma concentration possibly increased by ritonavir.
* **Thiopental**: enhanced hypotensive effect.
* **Valproic acid**: antagonism of anticonvulsant effect (convulsive threshold lowered).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

24.2 Medicines used in mood disorders

Mood disorders can be classified as depression and mania; alternating episodes of mania and depression (manic depression) are termed bipolar disorder.

24.2.1 Medicines used in depressive disorders

The response to antidepressant therapy is usually delayed, with a lag period of up to 2 weeks, and at least 6 weeks before maximum improvement occurs.

There is some concern that selective serotonin reuptake inhibitors (SSRIs), including **fluoxetine**, may increase suicidal ideation, especially in at-risk children and adolescents.

Fluoxetine

ATC code: N06AB03

Solid oral dosage form: 20 mg (present as hydrochloride)

Clinical worsening of depression or suicidal ideation may occur.

Special Notes: WHO age restriction: > 8 years.

Indications: Major depression.

Contraindications: Use of monoamine oxidase inhibitors (MAOIs) such as phenelzine within 14 days of starting fluoxetine (potentially fatal reactions may occur), do not use MAOIs for at least 5 weeks after fluoxetine has been discontinued.

Precautions: Epilepsy; cardiac disease; bleeding disorders; diabetes mellitus; susceptibility to closed-angle glaucoma; history of mania (discontinue if patient entering manic phase); concurrent electroconvulsive therapy (prolonged seizures reported); hepatic impairment; avoid abrupt withdrawal (see below); increased risk of suicidal thinking and behaviour in children and adolescents, risk should be considered when prescribing; may cause decreased growth possibly by suppression of growth hormone secretion.

SKILLED TASKS Warn patient or carer about the risk of undertaking tasks requiring attention or coordination, for example riding a bike or operating machinery.

WITHDRAWAL Dizziness, nausea, anxiety, headaches, paraesthesia, sleep disturbances, fatigue, agitation, tremor and sweating may occur if withdrawn abruptly.

Dose:

Major Depression.

Oral:

Child *8–12 years* 10 mg once daily increased after 1–2 weeks if necessary to a maximum of 20 mg once daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Reduce dose or administer on alternate days.

Avoid in severe impairment.

Adverse effects: Common Nausea, agitation, insomnia, drowsiness, tremor, dry mouth, diarrhoea, dizziness, headache, sweating, weakness, anxiety, weight gain or loss, sexual dysfunction, rhinitis, myalgia, rash, chills, euphoria, yawning.

Uncommon Extrapyramidal reactions (including tardive dyskinesia and dystonia), sedation, confusion, palpitations, tachycardia, hypotension, hyponatraemia (as part of syndrome of inappropriate antidiuretic hormone secretion), abnormal platelet aggregation/haemorrhagic complications (e.g. bruising, epistaxis, gastrointestinal and vaginal bleeding), alopecia, changes in blood sugar, serotonin syndrome.

Rare Elevated liver enzymes, hepatitis, hepatic failure, galactorrhoea, blood dyscrasias, seizures, akathisia, paraesthesia, taste disturbance, toxic epidermal necrolysis and neuroleptic malignant syndrome.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: increased risk of bleeding.
* **Artemether + lumefantrine**: avoid concomitant use.
* **Carbamazepine**: plasma concentration of carbamazepine increased.
* **Erythromycin**: increased risk of cardiotoxicity.

  Ethanol: possible increased sedation.
* **Haloperidol**: plasma concentration of haloperidol increased.
* **Ibuprofen**: increased risk of bleeding.
* **Lithium**: increased risk of CNS effects (lithium toxicity reported).
* **MAOIs (monoamine oxidase inhibitors)**: the cumulative effects on serotonin metabolism can cause serotonin toxicity; combination contraindicated. Fatal reactions have occurred.
* **Metoclopramide**: increased risk of extrapyramidal side-effects and neuroleptic malignant syndrome.

  Phenobarbital: antagonism of anticonvulsive effect (convulsive threshold lowered).
* **Phenytoin**: plasma concentration of phenytoin increased.
* **Phenelzine**: concurrent use contraindicated; potentially fatal interaction.

* **Ritonavir**: plasma concentration of fluoxetine possibly increased.
* **Tranylcypromine**: concurrent use contraindicated; potentially fatal interaction.
* **Warfarin**: anticoagulant effect possibly enhanced.

Notes: Consider the long duration of action of fluoxetine when adjusting dosage.

Family members and carers of children or adolescents prescribed fluoxetine for depression should be warned to observe for signs of clinical worsening of depression and suicidality, particularly in the first few months of therapy.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

24.2.2 Medicines used in bipolar disorders

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

24.3 Medicines used in generalized anxiety

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

24.4 Medicines used for obsessive compulsive disorders and panic attacks

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

24.5 Medicines used in substance dependence programmes

There are currently no medicines in this section of the *2nd WHO Model List of Essential Medicines for Children*.

SECTION 25:
Medicines acting on the respiratory tract

25 Medicines acting on the respiratory tract

25.1 Antiasthmatic medicines

Asthma is a chronic inflammatory disease characterized by episodes of reversible airways obstruction due to bronchial hyper-responsiveness. It generally presents as recurrent episodes of wheeze, cough, shortness of breath and/or chest tightness that responds to bronchodilators and anti-inflammatory drugs.

Classification based on severity is important when decisions have to be made about management. Acute exacerbations are divided into mild, moderate, severe or life threatening (critical). Chronic asthma can be divided by severity into infrequent episodic, frequent episodic or persistent (mild, moderate or severe).

Routes of delivery

Inhalation of medicines allows high concentrations to be delivered more effectively and rapidly to the airways, with systemic adverse effects being avoided or minimized. It is important that patients receive careful instruction in the use of pressurized (aerosol) inhalation using a metered-dose inhaler (MDI) with spacer device to obtain optimum results. For smaller children, a face mask will also enhance the delivery of inhaled medicines. It is important to check that patients continue to use their inhalers correctly. Solutions for nebulization are available for use in acute severe asthma.

Management of acute exacerbations of asthma

Severe asthma can be fatal and **must** be treated promptly and energetically. Acute severe asthma attacks require hospital admission where resuscitation facilities are immediately available.

Management of chronic asthma

The management of chronic asthma is undertaken in a stepwise fashion, using the least possible medications for adequate control. Monitoring control requires assessment of the number of acute attacks, the presence of interval symptoms, limitation to normal daily activities and the frequency of use of beta-agonists for acute relief. Medications may then be reduced or increased in a stepwise fashion as required.

Budesonide

ATC code: R03BA02

Inhalation (aerosol): 100 micrograms per dose; 200 micrograms per dose

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Prophylaxis of asthma.

Precautions: Systemic corticosteriod therapy may be required during periods of stress, such as severe infections or when airways obstruction or mucus prevent drug access to smaller airways.

Dose:

Prophylaxis of asthma.
Inhalation:
Child *under 12 years* 100–400 micrograms twice a day, adjusted as necessary.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Dysphonia (hoarse voice), oropharyngeal candidiasis (risk reduced by using a spacer device; rinsing the mouth with water or cleaning the child's teeth after inhalation), bruising.

Rare Allergic reactions, including bronchospasm, rash, urticaria and angioedema.

Occurrence of systemic adverse effects depends on systemic absorption which is influenced by dosage, duration of treatment and the delivery system. Delivery direct to the lower respiratory tract is approximately 70% greater with the use of a spacer, and systemic adverse effects can be further reduced by rinsing mouth with water, gargling and spitting out after the use of the inhaler with spacer.

Interactions with other medicines (* indicates severe):

Interactions listed relate to systemically absorbed drug; consider relevance when using inhaled drug.

Ritonavir: ritonavir inhibits CYP3A4 and as such may increase the concentration of budesonide by inhibiting its metabolism. Cases of Cushing syndrome reported with concurrent use of fluticasone and ritonavir.

Notes: PATIENT ADVICE After using this medicine rinse your mouth with water, gargle and spit out.

Do not use this medicine for immediate relief of symptoms.

Use this medicine every day even if you are feeling better; do not reduce dosage or stop this medicine unless instructed by your doctor.

References:

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.
eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hansten PD, Horn JH. *Drug interactions analysis and management.* St Louis, Wolters Kluwer Health, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
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Epinephrine (Adrenaline)

ATC code: C01CA24

Injection: 1 mg (as hydrochloride or hydrogen tartrate) in 1 ml ampoule

Intravenous epinephrine should be used with extreme care by specialists only.

Special Notes: Also known as adrenaline.

Indications: Used in the treatment of acute asthma, as rescue therapy where B_2 agonist not available or no response to maximal B_2 agonist doses.

Contraindications: Hypertension; cardiac arrhythmias; closed-angle glaucoma; psychoneurosis; use during halothane or cyclopropane anaesthesia.

Precautions: Hyperthyroidism; diabetes mellitus; heart disease; cerebrovascular disease; phaeochromocytoma; susceptibility to closed-angle glaucoma.

Dose:

Treatment of acute asthma.

SC:

Child *all ages* 0.01 ml/kg of 1:1000 solution up to a maximum of 0.5 ml by subcutaneous injection. The dose may be repeated every 20 minutes for up to three doses.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea, vomiting, anxiety, headache, fear, palpitations, tachycardia, restlessness, tremor, dizziness, dyspnoea, weakness, sweating, pallor, hyperglycaemia.

Uncommon Excessive increase in blood pressure, ventricular arrhythmias, pulmonary oedema (on excessive dosage or extreme sensitivity), angina, cold extremities, peripheral ischaemia and necrosis (at infusion site).

Rare Allergic reaction (sodium metabisulfite in some products).

OVERDOSE OR RAPID INTRAVENOUS ADMINISTRATION Arrhythmias (ventricular and supraventricular), severe hypertension, cerebral haemorrhage, pulmonary oedema.

Interactions with other medicines (* indicates severe):

Amitriptyline: increased effect or toxicity of epinephrine.

* **Cyclopropane**: may precipitate ventricular arrhythmias.

* **Ergot derivatives**: may precipitate hypertensive crisis.

Fluoxetine: increased effect or toxicity of epinephrine.

* **Halothane**: may precipitate ventricular arrhythmias.

Propranolol: hypertension, bradycardia, resistance to epinephrine effect.

Notes: 1 mg/ml = 1:1000 or 0.1%.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Salbutamol

ATC code: R03AC02

Injection: 50 micrograms (as sulfate)/ml in 5 ml ampoule

Metered dose inhaler (aerosol): 100 micrograms (as sulfate) per dose

Oral liquid: 0.4 mg/ml

Respirator solution for use in nebulizers: 5 mg (as sulfate)/ml

Tablet: 2 mg; 4 mg (as sulfate)

Special Notes: Also referred to as albuterol.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Prophylaxis and treatment of asthma.

Precautions: Hyperthyroidism; myocardial insufficiency; arrhythmias; susceptibility to QT interval prolongation; hypertension; diabetes mellitus, especially intravenous administration (monitor blood glucose, ketoacidosis reported).

Dose:

Acute asthma.

Inhaler:

Infant or **Child** ***less than 6 years*** 4–6 puffs (400–600 micrograms) via small volume spacer and face mask; repeat dose as above. Give up to three doses in first hour if moderate or severe attack, then every 1–4 hours as required;

over 6 years 8–12 puffs (800–1200 micrograms) via large volume spacer; repeat every 20 minutes according to response. Give up to three doses in first hour if moderate or severe attack, then every 1–4 hours as required.

Nebulizer:

Infant or **Child** 0.15 mg/kg (minimum dose 2.5 mg) every 20 minutes for three doses then 0.15–0.3 mg/kg (maximum 10 mg) every 1–4 hours as needed or 0.5 mg/kg/hour by continuous nebulization.

IV (over 5 minutes):

Infant or **Child** ***1 month–2 years*** 5 micrograms/kg as a single dose;

2–12 years 15 micrograms/kg (maximum 250 micrograms) as a single dose.

Continuous IV infusion:

Infant or **Child** 1–2 micrograms/kg/minute (maximum 5 micrograms/kg/minute) adjusted according to response and heart rate.

Doses above 2 micrograms/kg/minute should be given in an intensive care setting.

Exacerbations of reversible airways obstruction (including nocturnal asthma) and acute prevention of allergen or exercise induced bronchospasm.

Inhaler:

Infant or **Child** 100–200 micrograms (1–2 puffs) up to four times daily for persistent symptoms.

Nebulizer:

Infant or **Child** ***less than 2 years*** 0.1 mg/kg up to a maximum of 2.5 mg up to four times daily for persistent symptoms;

over 2 years 2.5–5 mg up to four times daily for persistent symptoms.

Oral:

Infant or **Child** ***1 month–2 years*** 100 micrograms/kg (maximum 2 mg) up to four times daily for persistent symptoms;

2–6 years 1–2 mg up to four times daily for persistent symptoms;

6–12 years 2 mg up to four times daily for persistent symptoms.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Fine tremor (usually hands), palpitations, headache.

Uncommon Hyperglycaemia (high dose), tachycardia, muscle cramps, agitation, behavioural disturbances including hyperactivity in children, insomnia.

Rare Paradoxical bronchospasm, allergic reactions including urticaria, angioedema and anaphylaxis, hypokalaemia after high doses of salbutamol or beta$_2$-agonists (may be worsened by theophylline, corticosteroids, diuretics and hypoxia), lactic acidosis (see below).

LACTIC ACIDOSIS There are reports with high-dose intravenous and nebulized salbutamol. Respiratory compensation (increased respiratory rate and effort) due to increased lactate levels may be mistaken for worsening asthma.

Interactions with other medicines (* indicates severe):

Dexamethasone: increased risk of hypokalaemia if high doses of salbutamol given with dexamethasone.

Digoxin: possible reduced plasma concentration of digoxin.

Furosemide: increased risk of hypokalaemia with high doses of salbutamol.

Hydrochlorothiazide: increased risk of hypokalaemia with high doses of salbutamol.

Hydrocortisone: increased risk of hypokalaemia if high doses of salbutamol given with hydrocortisone.

Prednisolone: increased risk of hypokalaemia if high doses of salbutamol given with prednisolone.

Notes: Reserve nebulizer solution for life-threatening acute asthma.

Intravenous administration may be necessary in acute severe asthma, but has a higher risk of adverse effects than when inhaled (intramuscular and subcutaneous injection are rarely indicated). For intravenous administration, dilute to a concentration of 200 micrograms/ml with glucose 5%, sodium chloride 0.9% or water for injection.

For nebulization, dilute respirator solution with a suitable volume of sterile sodium chloride 0.9% according to the directions for the nebulizer being used.

Oral salbutamol treatment should only be considered when inhaled asthma therapy is not feasible. Oral administration is rarely used now due to systemic adverse effects.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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SECTION 26:
Solutions correcting water, electrolyte and acid-base disturbances

26 Solutions correcting water, electrolyte and acid-base disturbances

26.1 Oral

Oral rehydration salts are detailed elsewhere (see section 17.5.1), and potassium chloride is recommended as a powder for solution (see below).

Oral rehydration salts

ATC code: A07CA

Powder for dilution in 200 ml; 500 ml; 1 litre

Contains: glucose 13.5 g/l, sodium chloride 2.6 g/l, potassium chloride 1.5 g/l, trisodium citrate dihydrate 2.9 g/l

Provides: glucose 75 mmol/l, sodium 75 mEq or mmol/l, chloride 65 mEq or mmol/l, potassium 20 mEq or mmol/l, citrate 10 mmol/l, osmolarity 245 mOsm/l

Special Notes: Oral rehydration salts are also referred to as ORS.

Known by the brand names Gastrolyte and Dioralyte.

Indications: Oral rehydration salts replace fluid and salts lost in acute diarrhoea.

Precautions: Renal impairment.

Dose:

WHO recommends Plans A, B and C; see below.

PLAN A: NO DEHYDRATION Nutritional advice, increased fluid intake (e.g. unsalted soup, unsalted rice water, yoghurt or plain water), at least one fluid that normally contains salt (e.g. ORS solution, salted drinks including salted rice water and vegetable or chicken soup with salt) and zinc supplementation (section 17.5.2) at home are usually sufficient. The aim is to give as much nutrient-rich food as the child will accept. Breastfeeding should always be continued to reduce the risk of diminishing supply. Give as much fluid as the child wants until diarrhoea stops and, as a guide, after each loose stool give:
Child *under 2 years* 50–100 mL (a quarter to half a large cup) of fluid;
2–10 years 100–200 ml (a half to one large cup);
older than 10 years as much fluid as the child wants.
Parents should be advised about circumstances in which they should seek further advice.

PLAN B: MODERATE DEHYDRATION Whatever the child's age, a 4 hour treatment plan is applied to avoid short-term problems. It is recommended that parents are shown how to give approximately 75 ml/kg of oral rehydration solution over a 4 hour period, and it is suggested that parents should be watched to see how they cope at the beginning of the treatment. A larger amount of solution (up to 20 ml/kg/hour and maximum 750 ml/hour) can be given if the child continues to have frequent stools or if the child wants more than the estimated amount of ORS solution, and there are no signs of overhydration (e.g. oedematous eyelids). In case of vomiting, rehydration must be discontinued for 10 minutes and then resumed at a slower rate. In younger children, breastfeeding should be continued on demand and the mother should be encouraged to do so; older children should receive milk and nutritious food as normal after completing the 4 hours of oral rehydration. The child's status must be reassessed after 4 hours to decide on the most appropriate subsequent treatment. If signs of dehydration worsen, shift to treatment plan C; and if the child develops signs of severe dehydration, intravenous rehydration should be started as per treatment plan C. Zinc supplementation (section 17.5.2) should begin as soon as the child can eat and has completed 4 hours of rehydration. Oral rehydration solution should continue to be offered once dehydration has been controlled, for as long as the child continues to have diarrhoea.

PLAN C: SEVERE DEHYDRATION Hospitalization is necessary, but the most urgent priority is to start rehydration. The preferred treatment for children with severe dehydration is rapid intravenous rehydration. In hospital (or elsewhere), if the child can drink, oral rehydration solution should be given during intravenous rehydration (20 ml/kg/hour by mouth before infusion, then 5 ml/kg/hour by mouth during intravenous rehydration). For intravenous rehydration, it is recommended that compound solution of sodium lactate (or, if this is unavailable, sodium chloride 0.9% intravenous infusion) (see section 26.2) is administered at a rate adapted to the child's age.

Intravenous rehydration using compound sodium lactate solution or sodium chloride 0.9% infusion

IV:

Infant 30 ml/kg over 1 hour, then 14 ml/kg/hour for 5 hours.

Child 30 ml/kg over 30 minutes, then 28 ml/kg/hour for 2.5 hours.

If the intravenous route is unavailable, a nasogastric tube is also suitable for administering oral rehydration solution.

Nasogastric rehydration using oral rehydration solution

Nasogastric tube:

Infant or **Child** 20 ml/kg/hour for 6 hours (total 120 ml/kg).

If the child vomits, the rate of administration of the oral solution should be reduced. Reassess the child's status after 3 hours (6 hours for infants) and continue treatment as appropriate with plan A, B or C.

Renal impairment: Dose reduction may be necessary. Monitor electrolytes carefully.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common or uncommon Vomiting may indicate too rapid administration, hypernatraemia and hyperkalaemia may result from overdose in renal impairment or administration of too concentrated a solution.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Trisodium citrate dihydrate may be replaced by sodium hydrogen carbonate (sodium bicarbonate) 2.5 g/l. However, as the stability of this latter formulation is very poor under tropical conditions, it is only recommended when manufactured for immediate use.

Glucose salt solution:

sodium chloride 2.6 g/l of clean water

sodium citrate (dihydrate) 2.9 g/l of clean water

potassium chloride 1.5 g/l of clean water

glucose (anhydrous) 13.5 g/l of clean water.

When glucose and sodium citrate are not available, they may be replaced by:

sucrose (common sugar) 27 g/l of clean water

sodium bicarbonate 2.5 g/l of clean water.

NOTE The solution may be prepared either from prepackaged sugar/salt mixtures or from bulk substances and water. Solutions must be freshly prepared, preferably with recently boiled and cooled water. Accurate weighing and thorough mixing and dissolution of ingredients in the correct volume of clean water is important. Administration of more concentrated solutions can result in hypernatraemia.

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Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.
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Potassium chloride

ATC code: A12BA01

Powder for solution

Indications: Prevention and treatment of hypokalaemia.

Contraindications: Severe renal impairment; plasma potassium concentration above 5 mmol/l.

Precautions: Mild to moderate renal impairment (close monitoring required); history of peptic ulcer; intestinal stricture.

IMPORTANT Special hazard if given with drugs liable to raise plasma potassium concentration such as potassium-sparing diuretics, ACE inhibitors or ciclosporin.

Dose:

Mild hypokalaemia.

Oral:

Neonate, Infant or **Child** 2–5 mmol/kg/day in 3–4 divided doses.

Renal impairment: Moderate to severe: avoid routine use; high risk of hyperkalaemia.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Nausea and vomiting (severe symptoms may indicate obstruction), gastrointestinal irritation.

Uncommon Oesophageal and small bowel obstruction.

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: increased risk of hyperkalaemia.
* **Enalapril**: increased risk of severe hyperkalaemia.
* **Spironolactone**: risk of hyperkalaemia.

Notes: Give oral preparations after food.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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26.2 Parenteral

Solutions of electrolytes are given intravenously to meet normal fluid and electrolyte requirements, or to replenish substantial deficits or continuing losses, when a child is nauseated or vomiting and is unable to take adequate amounts orally or via nasogastric tube. Administration of both acute and ongoing intravenous fluids should be regularly reassessed by both clinical examination and, when appropriate (and available), biochemical monitoring. Parenteral solutions should not be administered orally or via nasogastric tube.

Glucose

ATC code: B05BA03

Injectable solution: 5% (isotonic); 10% (hypertonic); 50% (hypertonic)

Increased risk of thrombophlebitis with hypertonic solutions (> 10%) infused via peripheral veins. A central line should be considered.

Special Notes: Also referred to as dextrose.

Indications: Fluid replacement without significant electrolyte deficit; treatment of hypoglycaemia.

Contraindications: Hypersensitivity to corn or corn products; diabetic coma with hyperglycaemia; hypertonic solutions in patients with intracranial or intraspinal haemorrhage; patients with delirium tremens and dehydration; patients with anuria; hepatic coma; galactose malabsorption syndrome.

Precautions: Diabetes mellitus (may require additional insulin).

Dose:

Fluid replacement.

IV infusion:

Neonate, Infant or **Child** determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Neonatal hypoglycaemia.

IV:

Neonate initial dose of 2.5 ml/kg of glucose 10% over 5 minutes; then 5 ml/kg/hour of glucose 10%. Recheck glucose after initial dose.

Hypoglycaemia.

IV doses should be given into a large vein because of risk of superficial thrombophlebitis and through a large gauge needle.

IV:

Infant or **Child** 5 ml/kg of glucose 10% as a bolus.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Most adverse effects are associated with excessive dosage or rate of infusion.

Common or uncommon Hypertonic solutions may cause venous irritation and thrombophlebitis, fluid and electrolyte disturbances (particularly hyponatraemia which may lead to cerebral oedema), oedema or water intoxication (on prolonged administration or rapid infusion of large volumes), hyperglycaemia.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Glucose intravenous infusion of 50% is not recommended as it is very viscous and hypertonic.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Glucose with sodium chloride

ATC code: B05BB02

Injectable solution: 5% glucose, 0.9% sodium chloride (equivalent to 150 mmol/l Na^+ and 150 mmol/l Cl^-); 5% glucose, 0.45% sodium chloride (equivalent to 75 mmol/l Na^+ and 75 mmol/l Cl^-)

Indications: Fluid and electrolyte replacement.

Precautions: Hyponatraemia; hypernatraemia; restrict intake in impaired renal function; cardiac failure; hypertension; peripheral and pulmonary oedema; meningitis; head injury.

Dose:

Fluid and electrolyte replacement.
IV infusion:
Neonate, Infant or **Child** determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Renal impairment: Restrict intake dependent on renal function and fluid requirements or restrictions.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Dilutional hyponatraemia especially in children when using 0.45% sodium chloride (rapid decrease in serum sodium may result in cerebral oedema), administration of large doses may give rise to oedema.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Indicated when there is combined sodium and water depletion. It is preferable to use 5% glucose with 0.9% sodium chloride to avoid rapid changes in sodium.

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Potassium chloride

ATC code: B05XA01

Solution: 7.5% (equivalent to K^+ 1 mmol/ml and Cl^- 1 mmol/ml); 15% (equivalent to K^+ 2 mmol/ml and Cl^- 2 mmol/ml)

Extreme caution is necessary when giving potassium chloride infusions as an overdose can cause fatal cardiac arrest.

Never give a bolus of fluids containing potassium chloride.

Never flush after potassium chloride infusions.

Ready-mixed infusion solutions containing potassium should be used when available.

If potassium chloride concentrate is used for preparing an infusion, the infusion solution should be thoroughly mixed by inverting the fluid bag at least ten times.

Do not add potassium to a bag that is already hanging.

Local policies on avoiding inadvertent use of potassium chloride concentrate should be followed.

Indications: Electrolyte imbalance; see also oral potassium (section 26.1).

Contraindications: Plasma potassium concentration above 5 mmol/l.

Precautions: Specialist advice and ECG monitoring; renal impairment; cardiac disease; patients receiving potassium-sparing drugs.

Dose:

Maintenance.

IV:

Neonate, Infant or **Child** 1–2 mmol/kg/day.

Acute deficiency.

IV:

Neonate, Infant or **Child** 0.2–0.4 mmol/kg/hour for 4–6 hours via a central line in an ICU setting with ECG monitoring only. Monitor serum potassium after 3 hours and adjust dose accordingly. Dilute to 120 mmol/l or weaker.

Renal impairment: Moderate to severe: avoid routine use; high risk of hyperkalaemia.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: WITH RAPID INTRAVENOUS ADMINISTRATION Hyperkalaemia, arrhythmias and cardiac arrest, heart block, hypotension.

Common Hyperkalaemia (see below).

Uncommon Nausea, vomiting, pain at site of injection, phlebitis.

Rare Mental confusion, diarrhoea, abdominal pain, gastrointestinal lesions, flatulence, muscle weakness, paraesthesia, flaccid paralysis.

SYMPTOMS OF HYPERKALAEMIA Paraesthesia of extremities, listlessness, confusion, weakness, flaccid paralysis, hypotension, cardiac arrhythmias, cardiac arrest, heart block. ECG changes: peaking of T waves, shortening of P wave, shortening of ST segment and prolongation of QT interval.

Interactions with other medicines (* indicates severe):

* **Ciclosporin**: increased risk of hyperkalaemia.
* **Enalapril**: increased risk of severe hyperkalaemia.
* **Spironolactone**: risk of hyperkalaemia.

Notes: Consider special storage requirements for intravenous potassium salts given that administration errors may lead to fatal outcomes.

ADMINISTRATION Peripheral and central line: dilute to 40 mmol/l or weaker (preferably use a pre-mixed solution) and infuse at a maximum rate of 0.2 mmol/kg/hour.

If central line access is available and in an ICU setting with ECG monitoring only: dilute to 120 mmol/l or weaker and infuse at a maximum rate of 0.4 mmol/kg/hour.

MONITORING DURING ADMINISTRATION Hourly: check IV site for signs of extravasation and document volume infused.

Monitor serum potassium and pulse, respiratory rate, blood pressure, urine output and other electrolytes every 4–6 hours until stable, then daily; repeat sample if haemolysed as this can result in a falsely elevated potassium result.

If potassium level is high: ensure blood sample was not haemolysed, was actually a venous sample and was not taken from the line where potassium was being infused. Repeat potassium measurement every 30–60 minutes. Hyperkalaemia may require treatment with calcium gluconate, insulin and glucose, salbutamol, calcium resonium, furosemide and sodium bicarbonate or other measures.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Sodium chloride

ATC code: B05XA03

Injectable solution: 0.9% isotonic (equivalent to Na^+ 154 mmol/l, Cl^- 154 mmol/l)

Special Notes: Also known as normal saline; this term should not be used to describe sodium chloride intravenous infusion 0.9%, as error may occur.

Indications: Electrolyte and fluid replacement.

Precautions: Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, toxaemia of pregnancy, cardiorespiratory disease, hepatic cirrhosis and in children receiving glucocorticoids.

Dose:

Fluid and electrolyte replacement.
IV infusion:
Neonate, Infant or **Child** determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Administration of large doses may give rise to sodium accumulation and oedema.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

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Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Sodium hydrogen carbonate

ATC code: B05XA02

Injectable solution: 1.4% isotonic (equivalent to Na^+ 167 mmol/l, HCO_3^- 167 mmol/l)

Solution: 8.4% in 10 ml ampoule (equivalent to Na^+ 1000 mmol/l, HCO_3^- 1000 mmol/l)

Avoid extravasation; may cause cellulitis and tissue necrosis due to the hypertonicity of sodium hydrogen carbonate. Preferably administer into a large vein.

Special Notes: Also known as sodium bicarbonate, sodium acid carbonate and $NaHCO_3$.

Indications: Severe metabolic acidosis.

Contraindications: Metabolic or respiratory alkalosis; hypocalcaemia; hypochlorhydria; hypernatraemia; unknown abdominal pain; inadequate ventilation during cardiopulmonary resuscitation; excessive chloride losses. Not for intra-arterial or intra-osseous injection.

Precautions: Restrict intake in impaired renal function, congestive heart failure, hypertension, peripheral and pulmonary oedema; other sodium-retaining conditions.

Caution should be taken when administering to patients under 2 years as hypernatraemia due to rapid injection may occur. Maximum rate in children under 2 should be 10 mmol/minute.

Dose:

Severe metabolic acidosis.

IV (by continuous infusion with 1.4% solution co-infused with isotonic sodium chloride, or by *slow infusion* of 8.4% solution):

Neonate, Infant or **Child** mmol of HCO_3 = 0.5 x weight (kg) x (24 - serum mmol of HCO_3/l).

Half the required volume of sodium hydrogen carbonate solution should be infused and the patient's clinical progress and serum HCO_3 should be monitored before giving the remaining half.

1.4% solution contains, per 1 ml, 0.167 mmol of Na and 0.167 mmol of HCO_3.

8.4% solution contains, per 1 ml, 1 mmol of Na and 1 mmol of HCO_3.

If acid-base status not available.

IV infusion:

Child *over 2 years* 1–5 mmol/kg; subsequent doses should be based on patient's acid-base status. Extreme care should be taken when administering to patients without confirmed metabolic acidosis.

Renal impairment: Severe: avoid; specialized role in some forms of renal disease.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Excessive administration may cause hypokalaemia and metabolic alkalosis, especially in renal impairment; large doses may give rise to sodium accumulation and oedema.

Extravasation may lead to tissue necrosis or ulceration.

Interactions with other medicines (* indicates severe):

Epinephrine: physically incompatible; do not infuse together with sodium hydrogen carbonate.

* **Flecainide**: can decrease renal excretion of flecainide and lead to flecainide toxicity.

Quinine: sodium hydrogen carbonate may increase the levels/effect of quinine.

Notes: Monitor for hypokalaemia and hyperkalaemia. Na^+ content = 1 mmol/ml (8.4%) and HCO_3^- 1 mmol/ml (8.4%).

0.18 mmol/ml ≈ 1.5% ≈ isotonic.

Rapid injection (10 ml/minute) of sodium hydrogen carbonate solutions in children up to 2 years of age may produce hypernatraemia, decreased cerebrospinal fluid pressure and possible intracranial haemorrhage.

Avoid extravasation; tissue necrosis can occur due to the hypertonicity of sodium hydrogen carbonate.

References:

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
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Sodium lactate, compound solution

ATC code: B05BB01

Injectable solution

Special Notes: Also known as Hartmann's Solution.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Preoperative and perioperative fluid and electrolyte replacement; hypovolaemic shock.

Contraindications: Hypercalcaemia or hypochlorhydria; hypernatraemia; lactic acidosis; severe acidosis requiring immediate repletion of plasma bicarbonate; concomitant treatment with ceftriaxone (ceftriaxone should not be used in neonates less than 28 days of age if they are receiving (or are expected to receive) calcium-containing intravenous products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid).

Precautions: Restrict intake in impaired renal function, cardiac failure, hypertension, peripheral and pulmonary oedema, concurrent corticosteroids; conditions impairing lactate utilization; metabolic or respiratory alkalosis.

Dose:

Fluid and electrolyte replacement or hypovolaemic shock.
IV infusion:
Neonate, Infant or **Child** determined on the basis of clinical and, whenever possible, electrolyte monitoring.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Uncommon Excessive administration may cause metabolic alkalosis; excessive administration may cause hyperkalaemia; administration of large doses may give rise to oedema.

Interactions with other medicines (* indicates severe):

* **Ceftriaxone**: contraindicated; see notes in Contraindications section.

Notes: Composition: sodium chloride 0.6%, sodium lactate 0.32%, potassium chloride 0.04%, calcium chloride 0.027% (containing Na^+ 131 mmol/l, K^+ 5 mmol/l, Ca^{2+} 2 mmol/l, HCO_3^- (as lactate) 29 mmol/l, Cl^- 111 mmol/l).

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Royal College of Paediatrics and Child Health. *Medicines for Children. 2nd ed.* London, RCPCH Publications, 2003.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

26.3 Miscellaneous

Water for injection

ATC code: V07AB

2 ml; 5 ml; 10 ml ampoules

Indications: In preparations intended for parenteral administration and in other sterile preparations.

Precautions: Should not be administered in large quantities as excessive water can lead to water intoxication with disturbances of the electrolyte balance.

Dose:

For dissolving or diluting agents for parenteral administration.

The dosage for water for injections is that required to dissolve or dilute other agents. Aseptic technique should be followed when preparing solutions for parenteral administration. Check the product information of any substance, preparation or drug before use to ensure appropriate solubility, dilution or compatibility with other additives.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: No adverse effects documented except in overdose (see Notes).

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Care should be exercised that solutions prepared with water for injection are isotonic before use. If large volumes of water for injection are inadvertently injected without first ensuring isotonicity, the hypotonic effects may include local cell damage or haemolysis. Electrolyte abnormalities are possible.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
WHO expert committee on the selection and use of essential medicines. The selection and use of essential medicines: report of the WHO expert committee, October 2007 (including the model list of essential medicines for children). *WHO Technical Report Series,* 2008, 950 (http://www.who.int/medicines/publications/essentialmeds_committeereports/TRS_950.pdf).

SECTION 27:
Vitamins and minerals

27 Vitamins and minerals

Vitamins and minerals

Vitamins and minerals are used for prevention and treatment of specific deficiency states, or when the diet is known to be inadequate. Most are comparatively non-toxic; however, prolonged administration of high doses of **retinol** (vitamin A), **ergocalciferol** (vitamin D), **pyridoxine** (vitamin B) and **sodium fluoride** may have severe adverse effects.

Ascorbic acid

ATC code: A11GA01

Tablet: 50 mg

Special Notes: Also referred to as vitamin C.

Indications: Treatment and prophylaxis of scurvy.

Contraindications: Hyperoxaluria.

Dose:

Treatment of scurvy.

Oral:

Child not less than 250 mg daily in 1–2 divided doses until clinical signs of scurvy disappear.

Prophylaxis of scurvy.

Oral:

Child 25–75 mg daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Side-effects only occur in very large doses.

Rare Nausea, diarrhoea, headache, fatigue, hyperoxaluria.

Interactions with other medicines (* indicates severe):

Aluminium hydroxide: ascorbic acid may increase the level/effect.

Deferoxamine: ascorbic acid may increase the level/effect.

Notes: Ascorbic acid also has antioxidant effects.

Tablets may be crushed and mixed with a small amount of food or water and given immediately.

Ascorbic acid is quickly oxidized when in solution.

RECOMMENDED DAILY INTAKE

Infant 0–6 months, 25 mg/day;

7–12 months, 30 mg/day.

Child 1–8 years, 35 mg/day;

> 9 years, 40 mg/day.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Nutrient reference values for Australia and New Zealand including recommended dietary intakes. Australian National Health and Medical Research Council, 2006 (http://www.nrv.gov.au/resources/_files/n35-vitamind.pdf, accessed 10 February 2010).

Colecalciferol

ATC code: A11CC05

Oral liquid: 400 IU/ml

Solid oral dosage form: 400 IU; 1000 IU

Special Notes: Also known as vitamin D or vitamin D_3.

Ergocalciferol is vitamin D_2 and can be used as an alternative.

1000 units = 25 micrograms ergocalciferol = 25 micrograms colecalciferol.

Indications: Prevention and treatment of vitamin D deficiency; treatment of vitamin D deficiency caused by malabsorption or chronic liver disease; hypocalcaemia associated with hypoparathyroidism; treatment of vitamin D deficiency rickets.

Contraindications: Hypercalcaemia; malabsorption syndrome; evidence of vitamin D toxicity; metastatic calcification.

Precautions: Coronary artery disease; renal stones; impaired renal function.

Dose:

Prevention of vitamin D deficiency.
Oral:
Neonate 10 micrograms (400 units) daily.
Infant or **Child** 10–15 micrograms (400–600 units) daily.

Treatment of vitamin D deficiency; treatment of vitamin D deficiency rickets.
Oral:
Infant ***under 6 months*** 75 micrograms (3000 units) daily, adjusted as necessary.
Infant ***over 6 months*** or **Child** 150 micrograms (6000 units) daily, adjusted as necessary.

Hypocalcaemia associated with hypoparathyroidism.
Oral:
Child 1.25–5 mg (50 000–200 000 units) daily with calcium supplements.

Treatment of vitamin D deficiency caused by intestinal malabsorption or chronic liver disease.
Oral:
Child 250–625 micrograms (10 000–25 000 units) daily, adjusted as necessary.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Adverse effects usually only occur in overdose.

Uncommon Anorexia, lassitude, nausea and vomiting, diarrhoea, constipation, weight loss, polyuria, sweating, headache, thirst, vertigo, and raised concentrations of calcium and phosphate in plasma and urine.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Patients receiving pharmacological doses of colecalciferol should have their plasma calcium concentration checked at regular intervals and whenever nausea or vomiting occur.

Adequate calcium intake is necessary for a clinical response to vitamin D.

RECOMMENDED DAILY INTAKE FOR PREVENTING VITAMIN D DEFICIENCY

Oral:

Infant 0–12 months, 5 micrograms/day.

Child 1–8 years, 5 micrograms/day;

9–14 years, 5 micrograms/day.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
Nutrient reference values for Australia and New Zealand including recommended dietary intakes. Australian National Health and Medical Research Council, 2006 (http://www.nrv.gov.au/resources/_files/n35-vitamind.pdf, accessed 10 February 2010).

Iodine

ATC code: H03CA

Capsule: 200 mg

Iodized oil: 1 ml (480 mg iodine); 0.5 ml (240 mg iodine) in ampoule (oral or injectable); 0.57 ml (308 mg iodine) in dispenser bottle

Indications: Prevention and treatment of iodine deficiency.

Contraindications: Breastfeeding (may cause neonatal hypothyroidism).

Precautions: May interfere with thyroid function tests.

Dose:

Iodine deficiency.
IM (provides up to 3 years protection):
Infant 190 mg as a single dose.
Child 380 mg as a single dose.
Oral:
Infant single dose of 100 mg once a year.
Child *1–5 years* 200 mg once a year;
over 6 years 400 mg once a year.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Rare Hypersensitivity reactions including coryza-like symptoms, headache, lacrimation, conjunctivitis, pain in salivary glands, laryngitis, bronchitis, rashes, goitre and hypothyroidism, hyperthyroidism. With prolonged treatment, insomnia and depression.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Iodized oil may also be given by mouth.

Iodine is among the body's essential trace elements.

Deficiency causes goitre and cretinism (characterized by deaf-mutism, intellectual deficit, spasticity and sometimes hypothyroidism) and impaired mental function.

Control of iodine deficiency largely depends upon salt iodization (with potassium iodide or potassium iodate) and dietary diversification.

RECOMMENDED DAILY INTAKE

Infant, 50 micrograms daily.

Child 1–6 years, 90 micrograms daily;

7–12 years, 120 micrograms daily.

References:
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Pyridoxine

ATC code: A11HA02

Tablet: 25 mg (hydrochloride)

Special Notes: Also referred to as vitamin B_6.

Indications: Treatment of pyridoxine deficiency due to metabolic disorders; treatment and prevention of isoniazid neuropathy; sideroblastic anaemia.

Dose:

Metabolic disorders responsive to pyridoxine, sideroblastic anaemia.
Oral:
Neonate 50–100 mg 1–2 times daily.
Infant or **Child** 50–250 mg 1–2 times daily.

Treatment of isoniazid-induced neuropathy.
Oral:
Neonate 5–10 mg daily.
Infant or **Child** 10–20 mg 2–3 times daily.

Prevention of isoniazid-induced neuropathy.
Oral:
Neonate 5 mg daily.
Infant or **Child** 5–10 mg daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Generally well tolerated, but chronic administration of high doses may cause peripheral neuropathies and headache.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: RECOMMENDED DAILY INTAKE

Oral:

Infant < 6 months, 0.01 mg/kg;

6–12 months, 0.03 mg/kg.

Child 1–3 years, 0.5 mg;

4–8 years, 0.6 mg;

9–12 years, 1 mg.

References:

Ashley C, Currie A, eds. *The renal drug handbook. 3rd ed.* Oxford, Radcliffe Publishing, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Retinol

ATC code: A11CA01; S01XA02

Capsule: 100 000 IU; 200 000 IU (as palmitate)

Oral oily solution: 100 000 IU (as palmitate)/ml in multidose dispenser

Tablet (sugar coated): 10 000 IU (as palmitate)

Water-miscible injection: 50 000 IU (as palmitate)/ml in 2 ml ampoule

Indications: Prevention and treatment of vitamin A deficiency; prevention of complications of measles.

Contraindications: Pregnancy (teratogenic).

Dose:

Prevention of vitamin A deficiency (universal or targeted distribution programmes).

Oral:

Infant *under 6 months* 50 000 units single dose;
6–12 months 100 000 units every 4–6 months.
Child 200 000 units every 4–6 months.

A dose should preferably be administered with measles vaccination.

Treatment of xerophthalmia caused by vitamin A deficiency.

Oral:

Infant *under 6 months* 50 000 units on diagnosis, repeated the next day and then after 2 weeks;
6–12 months 100 000 units immediately on diagnosis, repeated next day and then after 2 weeks.
Child 200 000 units on diagnosis, repeated next day and then after 2 weeks.

Measles (unless the child has already had adequate treatment with retinol for measles).

Oral:

Infant *under 6 months* 50 000 units daily for 2 days;
6–11 months 100 000 units daily for 2 days.
Infant or **Child *11 months–5 years*** 200 000 units daily for 2 days.

If the child shows any eye signs of vitamin A deficiency or is severely malnourished, a third dose must be given 2–4 weeks after the second dose.

Prevention of deficiency in complete biliary obstruction.

IM:

Neonate or **Infant** 50 000 units once per month.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Supplementation may be required in children with liver disease, particularly cholestatic liver disease, due to malabsorption of fat soluble vitamins. In those with complete biliary obstruction, intramuscular dosing may be appropriate.

Adverse effects: No serious or irreversible adverse effects are seen in recommended doses.

High intake may cause birth defects (if taken during pregnancy), transient increased intracranial pressure in adults and older children or a tense and bulging fontanelle in infants (with high dosage), massive overdose can cause rough skin, dry hair, enlarged liver, raised erythrocyte sedimentation rate, raised serum calcium and raised serum alkaline phosphatase concentrations.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Oral vitamin A preparations are preferred for the prevention and treatment of vitamin A deficiency. However, in situations where patients have severe anorexia or vomiting or are suffering from malabsorption, a water-miscible injection preparation may be administered intramuscularly.

Dietary vitamin A is derived from two sources, preformed retinoids from animal sources such as liver, kidney, dairy produce and eggs (fish liver oils are the most concentrated natural source) and provitamin carotenoids which can be obtained from many plants; the latter are converted to retinol in the body but are less effectively utilized. Betacarotene is the most plentiful in food and can be found in carrots and dark green or yellow vegetables.

RECOMMENDED DAILY INTAKE TO PREVENT VITAMIN A DEFICIENCY

Infant, 630 units.

Child 1–6 years, 670 units;

7–10 years, 830 units;

> 10 years, 1100–3330 units.

1 international unit (IU) vitamin A = 0.3 micrograms retinol.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Nutrient reference values for Australia and New Zealand including recommended dietary intakes. Australian National Health and Medical Research Council, 2006 (http://www.nrv.gov.au/resources/_files/n35-vitamind.pdf, accessed 10 February 2010).
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources. Geneva, World Health Organization, 2005.
Sweetman SC, ed. *Martindale: the complete drug reference. 34th ed.* London, Pharmaceutical Press, 2005.
Vitamin and mineral requirements in human nutrition: report of a joint FAO/WHO expert consultation. Geneva, World Health Organization, 2004 (http://whqlibdoc.who.int/publications/2004/9241546123_chap2.pdf, accessed 9 April 2010).

Riboflavin

ATC code: A11HA04

Tablet: 5 mg

Special Notes: Also known as vitamin B_2 or riboflavine.

Indications: Vitamin B_2 deficiency.

Dose:

Treatment of vitamin B_2 deficiency.
Oral:
Child 3–10 mg daily in divided doses.

Prophylaxis of vitamin B_2 deficiency.
Oral:
Child up to 1–2 mg daily. See recommended dietary intake in Notes.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Bright yellow urine.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Take with food.

Also used in metabolic diseases such as glutaric aciduria and mitochondrial respiratory chain disorders in doses of 50–300 mg/day in 1–2 doses.

RECOMMENDED DIETARY INTAKE

Infant, 0.04 mg/kg.

Child 1–3 years, 0.5 mg;

4–8 years, 0.6 mg;

9–12 years, 0.9 mg.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Sodium fluoride

ATC code: A01AA01

In any appropriate topical formulation

Indications: Prevention of dental caries.

Contraindications: Not for areas where drinking water is fluoridated or where fluorine content is naturally high.

Precautions: Mouthwash solutions are not to be swallowed and caution should be used to ensure children do not swallow any excess.

Dose:

Prevention of dental caries.
Oral rinse:
Child *over 6 years* 10 ml of a 0.05% solution daily or 10 ml of a 0.2% solution weekly.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: In recommended doses toxicity is unlikely.

Uncommon Occasional white flecks (fluorosis) on teeth at recommended doses.

Rare Yellowish-brown discoloration of teeth if recommended doses are exceeded. Excessive intake may lead to osteosclerosis and bone deformities.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Fluoridated toothpastes are also a convenient source of fluoride for prophylaxis of dental caries where drinking water is not fluoridated.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Thiamine

ATC code: A11DA01

Tablet: 50 mg (hydrochloride)

Special Notes: Also known as vitamin B_1.

Indications: For the prevention and treatment of vitamin B_1 deficiency or beri-beri.

Dose:

Prevention of thiamine deficiency.
Oral:
Infant 0.3–0.5 mg/day.
Child 0.5–1 mg/day.

Treatment of thiamine deficiency (beri-beri).
Oral:
Child 10–50 mg/dose daily for 2 weeks, then 5–10 mg/dose daily for 1 month.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: For smaller doses the tablet may be dispersed in a small amount, e.g. 5 ml of clean water to produce a solution (10 mg/ml) that then allows the appropriate volume to be given. Discard any remaining solution and use a new tablet for each dose.

RECOMMENDED DIETARY INTAKE

Infant, 0.03 mg/kg.

Child 1–3 years, 0.5 mg;

4–8 years, 0.6 mg;

9–12 years, 0.9 mg.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Calcium gluconate

ATC code: A12AA03

Injection: 100 mg/ml in 10 ml ampoule

Do not administer with intravenous ceftriaxone.

Indications: Hypocalcaemia; hypocalcaemic tetany.

Contraindications: Conditions associated with hypercalcaemia and hypercalciuria (for example some forms of malignant disease); renal calculi; ventricular fibrillation.

Precautions: Sarcoidosis; respiratory failure; acidosis; renal or cardiac disease; avoid extravasation (do not give subcutaneous or intramuscular injection as it will cause tissue necrosis); digitalised patients.

Dose:

NOTE Doses expressed in mg of calcium gluconate.

Hypocalcaemia (dose depends on clinical condition and serum calcium level).

IV:

Neonate 200–800 mg/kg/day as a continuous infusion, or in four divided doses.

Infant or **Child** 200–500 mg/kg/day as a continuous infusion, or in four divided doses.

Treatment of tetany.

IV:

Neonate, Infant or **Child** 100–200 mg/kg/dose, over 5–10 minutes, may repeat after 6 hours or follow with an infusion with a maximum dose of 500 mg/kg/day.

Renal impairment: Moderate and severe: may require dose adjustment depending upon serum calcium level. Risk of hypercalcaemia and renal calculi.

Hepatic impairment: Dose reduction not required.

Adverse effects: Uncommon Bradycardia, arrhythmia, injection site reactions, peripheral vasodilation, fall in blood pressure, tissue necrosis (if extravasation occurs).

Interactions with other medicines (* indicates severe):

* **Ceftriaxone**: should not be used in neonates less than 28 days of age if they are receiving (or are expected to receive) calcium-containing intravenous products. In patients > 28 days of age, ceftriaxone and calcium-containing products may be administered sequentially, provided the infusion lines are thoroughly flushed between infusions with a compatible fluid.

* **Digoxin**: large intravenous doses of calcium salts can precipitate arrhythmias.

Hydrochlorothiazide: increased risk of hypercalcaemia.

Notes: Monitor serum calcium for duration of treatment.

For direct intravenous injection, give over 5–10 minutes (maximum 50–100 mg calcium gluconate per minute).

For intravenous infusion: dilute to 50 mg/ml and infuse at 120–240 mg/kg over 1 hour.

Do not give calcium gluconate by subcutaneous or intramuscular injection as extravasation, severe necrosis and sloughing may occur.

100 mg/ml (10%) calcium gluconate provides 0.22 mmol Ca^{2+} per ml.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

SECTION 28:
Ear, nose and throat conditions in children

28 Ear, nose and throat conditions in children

Ear conditions

Pathology within the middle ear is categorized as acute otitis media (AOM), otitis media with effusion (OME) and chronic suppurative otitis media (CSOM). AOM is diagnosed by an acute (< 2 weeks) history of ear pain or pus draining from the ear and examination showing a red, inflamed, bulging, opaque ear drum or perforation with discharge. Treatment involves analgesia and oral antibiotics. Decongestants and antihistamines have no proven benefit in AOM management.

Mastoiditis, a complication of ear infections presenting with high fever and an often tender swelling behind the ear, should not be missed. Antibiotic treatment as well as a surgical opinion is usually warranted.

Nasal conditions

Conditions resulting in nasal congestion include allergic rhinitis, seasonal rhinitis and perennial rhinitis; sinusitis may also present with symptoms of nasal congestion and headaches.

Epistaxis is another common condition in children. If local pressure applied with the thumb and first finger over both sides of the nose is not sufficient to resolve the bleeding, other treatments may involve nasal creams, drops and jellies. Nasal packing or local cauterization may be required in difficult cases.

Throat conditions

Sore throat is a common presenting symptom in children, with most cases due to viral infections that do not need specific treatment other than oral fluids and simple oral analgesia (see section 2.1). Streptococcal pharyngitis ("strep throat"), caused by group A streptococci, is common in children 5–15 years of age. It should be treated with a course of oral **penicillin** (see section 6.2) to minimize complications such as scarlet fever, glomerulonephritis and rheumatic heart disease.

Croup (laryngotracheobronchitis) is a viral infection of the upper airway. Management involves minimal handling of the child and the use of an oral **steroid**, while for severe symptoms nebulized epinephrine (**adrenaline**) may be needed.

Epiglottitis is a bacterial infection of the epiglottis, usually caused by *Haemophilus influenzae* type B (HiB). Rates of epiglottitis have declined dramatically since the introduction of HiB vaccinations in many regions. Epiglottitis presents with an unwell, febrile child, often sitting forwards and drooling. Medical personnel should **never** use a tongue depressor for oral examination as respiratory arrest may occur. Management is with parenteral antibiotics (see Section 6.2) in hospital, with protection of the airway when required. Bacterial tracheitis is a differential diagnosis of epiglottitis and requires parenteral antibiotics and, often, surgical drainage.

Acetic acid

ATC code: S02AA10

Topical: 2%, in alcohol

Indications: Prevention of otitis externa after exposure to water; otitis externa; suppurative otitis media.

Contraindications: Perforated eardrum; tympanostomy tube.

Precautions: Inflamed or broken skin (may cause irritation and pain); transient stinging or burning may be noted when solution is first instilled into acutely inflamed ears.

Dose:

Prevention of otitis externa after exposure to water.
Instil into ear:
Child *all ages* 5 drops into each ear once after swimming or bathing.

Otitis externa; suppurative otitis media.
Instil into ear:
Child *all ages* 5 drops into each ear 2–3 times daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Stinging on instillation.

Uncommon Irritation of skin.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Budesonide

ATC code: R01AD05

Nasal spray: 32 micrograms per dose, 64 micrograms per dose

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Allergic rhinitis; nasal polyps.

Contraindications: Severe nasal infection.

Precautions: Bleeding disorders as intranasal corticosteroids may cause nose bleeding; recent nasal surgery or trauma as intranasal corticosteroids may delay healing.

Dose:

Allergic rhinitis; nasal polyps.
Nasal inhalation:
Child *over 6 years* initially 128 micrograms into each nostril once daily or 64 micrograms into each nostril twice daily.
Maintenance dose 32–64 micrograms into each nostril daily.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Systemic adverse effects are rare with nasal products used at recommended doses.

Common Nasal stinging, itching, sneezing, sore throat, dry mouth, cough.

Uncommon Nose bleed.

Rare Nasal septal perforation, glaucoma, cataract, allergic reactions (urticaria, angioedema, bronchospasm, rash), raised intraocular pressure and other systemic effects.

Interactions with other medicines (* indicates severe):

There are no known interactions where it is recommended to avoid concomitant use.

Notes: Onset of action within 3–7 hours; effective on an as-needed basis; optimum effect after several days of regular use. Patients transferred from oral to intranasal corticosteroids may have impaired adrenal function; intranasal corticosteroids have little systemic effect.

Shake the canister gently before use and prime by actuating eight times prior to initial use. If not used for two consecutive days, re-prime until a fine mist appears. If not used for 14 days, rinse the applicator and re-prime until a fine mist appears.

References:

eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Kemp CA, McDowell JM. *Paediatric pharmacopoeia. 13th ed.* Melbourne, Royal Children's Hospital, 2002.
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Ciprofloxacin

ATC code: S02AA15

Topical: 0.3% drops

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Chronic suppurative otitis media.

Contraindications: Hypersensitivity to quinolones including nalidixic acid.

Dose:

Chronic suppurative otitis media.
Topical instillation into ear:
Infant or **Child** 5 drops twice daily for 9 days.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Local discomfort, bitter taste, fungal infection.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: To avoid dizziness, which may be associated with instillation of a cold solution into the ear, if the solution is cold, it should be warmed by holding the bottle in the hand for 1 or 2 minutes before instillation.

Patients or carers should be advised to avoid contamination of the dispensing tip.

References:

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Klasco RK, ed. *Drugdex system.* Greenwood Village, Thomson Micromedex, 2010. (http://www.thomsonhc.com, accessed 10 February 2010).
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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Xylometazoline

ATC code: R01AA07

Nasal spray: 0.05%

Do not use this medicine more than recommended or for more than 5 days at a time as it can worsen your symptoms when treatment is stopped.

Special Notes: WHO age/weight restriction: not in children less than 3 months of age.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Relief of nasal congestion associated with acute and chronic rhinitis, common cold, sinusitis; to facilitate intranasal examination.

Contraindications: Should not be used with, or within 3 weeks of, the non-selective monoamine oxidase inhibitors (MAOIs) phenelzine and tranylcypromine, due to the risk of a hypertensive reaction; rhinitis sicca.

Dose:

Nasal congestion; to facilitate intranasal examination.

Nasal inhalation:

Infant or **Child** ***3 months–6 years*** 1 spray into each nostril up to three times daily for a maximum of 5 days;

6–12 years 2 or 3 sprays into each nostril up to three times daily for a maximum of 5 days.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Systemic side-effects are rare with intranasal use but children may be more susceptible to them.

Common Transient burning, stinging, increased nasal discharge, rebound congestion with prolonged use (> 5 days).

Rare Hypertension, nausea, nervousness, dizziness, insomnia, headache.

Interactions with other medicines (* indicates severe):

* **MAOIs (monoamine oxidase inhibitors)**: concurrent use contraindicated; risk of hypertensive crisis.
* **Phenelzine**: concurrent use contraindicated; risk of hypertensive crisis.
* **Tranylcypromine**: concurrent use contraindicated; risk of hypertensive crisis.

Notes: Do not use in infants less than 3 months of age. If nasal congestion impairs feeding, use sodium chloride 0.9% (nose drops, irrigation or spray) to loosen and liquefy mucous secretions in preference to an intranasal sympathomimetic.

References:

Baxter K, ed. *Stockley's drug interactions. 8th ed.* London, Pharmaceutical Press, 2008.
eTG complete. Melbourne, Therapeutic Guidelines Limited, 2009 (http://etg.tg.org.au/ip/, accessed 10 February 2010).
Hansten PD, Horn JH. *Drug interactions analysis and management.* St Louis, Wolters Kluwer Health, 2009.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
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Section 29
Specific medicines for neonatal care

29 Specific medicines for neonatal care

Quality evidence for safety and efficacy of medicines in this population is lacking. The medicines listed in this section are for exclusive use in the neonatal age group. Other medicines listed in previous sections may be suitable for neonatal use; following local guidelines or using specialist supervision is always advised.

Respiratory

Apnoea of prematurity is a common phenomenon in those < 35 weeks gestation. Before consideration of treatment, other causes of apnoea must be excluded, including infection, respiratory disease, seizures and gastro-oesophageal reflux disease.

Surfactant is normally produced by the lungs to reduce surface tension in alveoli, thereby preventing atelectasis (lung collapse). A deficiency of natural surfactant is common in premature infants < 32 weeks gestation, thus treatment or prophylaxis of primary respiratory distress syndrome with **surfactant** (animal or synthetic), administered down the endotracheal tube, can be considered in this population. It may also be used in secondary surfactant deficiency in infants.

Cardiology (ductus arteriosus)

The ductus arteriosus, a fetal communication between the pulmonary artery and aorta, is required for adequate fetal circulation. In duct-dependent congenital cardiac lesions, closure of the ductus arteriosus (due to prostaglandin blockade) results in absence of adequate circulation. **Prostaglandin E**, a powerful vasodilator, is used to maintain or re-obtain a patent ductus arteriosus (PDA) until cardiac surgery is undertaken.

Premature infants are at an increased risk of PDA given the lack of natural prostaglandin blockade. An ongoing PDA, in a patient with otherwise normal cardiac anatomy, may lead to pulmonary congestion and heart failure, along with other complications. Ibuprofen, an NSAIM that blocks prostaglandin synthesis, is used to close a clinically significant PDA.

Caffeine citrate

ATC code: N06BC01

Injection: 20 mg/ml (equivalent to 10 mg caffeine base/ml)

Oral liquid: 20 mg/ml (equivalent to 10 mg caffeine base/ml)

Special Notes: Caffeine citrate, a respiratory stimulant, is used for neonatal apnoea in preterm infants (born less than 35 weeks gestational age and under 2 kg). It is preferred over theophylline, as caffeine has a better safety profile and does not require routine drug level monitoring. Other causes of neonatal apnoea should be sought and treated before treatment with caffeine is started (e.g. sepsis, hypothermia, hypoglycaemia, hypoxaemia, anaemia, seizures).

Indications: Neonatal apnoea in preterm infants.

Contraindications: Hypersensitivity to caffeine or citrate.

Precautions: Cardiovascular disorders; gastro-oesophageal reflux; seizure disorders.

Dose:

NOTE All doses expressed as caffeine citrate.

Neonatal apnoea.

Oral or *IV:*

Neonate 20 mg/kg as a loading dose, then 5 mg/kg once daily starting 24 hours after loading dose. Maintenance dose may be increased by 5 mg/kg every 24 hours to a maximum of 20 mg/kg/day, unless side-effects develop. Continue 4–5 days after cessation of apnoea.

NOTE Caffeine citrate 2 mg = caffeine base 1 mg.

Renal impairment: Dose reduction not necessary.

Hepatic impairment: Dose reduction not necessary.

Adverse effects: Common Gastric irritation (oral administration) including nausea and vomiting, feeding intolerance, irritability, agitation, hyperglycaemia or hypoglycaemia, tachycardia, diuresis.

Uncommon Lethargy (physical sign of withdrawal), excessive central nervous system stimulation.

Rare Acidosis, necrotizing enterocolitis.

Interactions with other medicines (* indicates severe):

Ciprofloxacin: reduces metabolism of caffeine, increased toxicity.

Theophylline: theophylline is metabolized to caffeine in neonates; do not use concurrently.

Notes: Oral liquid may be given without regard to feeds.

Injectable formulation (caffeine citrate) may be given orally if necessary.

ADMINISTRATION For intravenous administration, infuse loading dose over at least 30 minutes and maintenance dose over at least 10 minutes. May be given undiluted or diluted with 5% dextrose to caffeine citrate 10 mg/ml.

Discoloured or cloudy solutions for injection should not be used.

The pharmacological actions of caffeine in apnoea includes stimulation of the medullary respiratory centre, increased sensitivity to carbon dioxide and enhanced diaphragmatic contractility.

References:

Fary R, Smith R, eds. *RWH Neonatal Pharmacopoeia. 2nd ed.* Melbourne, Pharmacy Department, The Royal Women's Hospital, 2005.
Hey E. *Neonatal formulary. 4th ed.* Oxford, Blackwell Publishing, 2007.
Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.
Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.
Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.
Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Ibuprofen

ATC code: C01EB16

Solution for injection: 5 mg/ml

Special Notes: This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Closure of ductus arteriosus.

Contraindications: Life-threatening infection; active bleeding especially intracranial or gastrointestinal; thrombocytopenia or coagulation defects; marked unconjugated hyperbilirubinaemia; known or suspected necrotizing enterocolitis; pulmonary hypertension; severe renal failure, hepatic failure or cardiac failure.

Precautions: May mask symptoms of infection; monitor for bleeding; monitor gastrointestinal function; cardiac disease; volume depletion; dehydration; coagulation defects; allergic disorders; renal impairment; deterioration in renal function possibly leading to renal failure may occur; hepatic impairment.

Dose:

Closure of ductus arteriosus.

IV:

Neonate 10 mg/kg as a single dose, followed by two doses of 5 mg/kg after 24 and 48 hours. Course may be repeated after 48 hours if necessary.

Renal impairment: Use lowest effective dose and monitor renal function. Sodium and water retention may occur. Deterioration in renal function possibly leading to renal failure may occur. Avoid if possible in severe impairment.

Hepatic impairment: Avoid in severe liver disease.

Adverse effects: Common Gastro-oesophageal reflux, gastritis, hypoglycaemia, hypocalcaemia, elevated creatinine, anaemia, apnoea, sepsis.

Uncommon Rash, urticaria, photosensitivity, renal impairment, ileus, feeding problems, gastrointestinal perforation, necrotizing enterocolitis.

Rare Angioedema, bronchospasm, hepatic damage, alveolitis, pulmonary eosinophilia, pancreatitis, visual disturbances, erythema multiforme (Stevens-Johnson syndrome), toxic epidermal necrolysis (Lyell syndrome), colitis, aseptic meningitis.

Interactions with other medicines (* indicates severe):

* **Acetylsalicylic acid**: avoid concomitant use (increased adverse effects).
* **Ciclosporin**: increased risk of nephrotoxicity.
* **Ciprofloxacin**: possibly increased risk of seizures.

Dexamethasone: increased risk of gastrointestinal bleeding and ulceration.

Digoxin: possible exacerbation of heart failure, reduced renal function and increased plasma digoxin concentration.

Enalapril: antagonism of hypotensive effect, increased risk of renal impairment.

Furosemide: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect.

Heparin: possibly increased risk of bleeding.

Hydrocortisone: increased risk of gastrointestinal bleeding and ulceration.

* **Levofloxacin**: possibly increased risk of seizures.
* **Methotrexate**: excretion of methotrexate reduced (increased risk of toxicity).
* **Ofloxacin**: possible increased risk of seizures.

Penicillamine: possible increased risk of nephrotoxicity.

* **Phenytoin**: effect of phenytoin possibly enhanced.

Prednisolone: increased risk of gastrointestinal bleeding and ulceration.

Propranolol: antagonism of hypotensive effect.

Ritonavir: plasma concentration possibly increased by ritonavir.

Spironolactone: risk of nephrotoxicity of ibuprofen increased; antagonism of diuretic effect; possibly increased risk of hyperkalaemia.

* **Warfarin**: anticoagulant effect possibly enhanced.

Zidovudine: increased risk of haematological toxicity.

Notes: ADMINISTRATION By slow intravenous injection over 15 minutes, preferably undiluted.

May be diluted with glucose 5% or sodium chloride 0.9%.

References:

Fary R, Smith R, eds. *RWH Neonatal Pharmacopoeia. 2nd ed.* Melbourne, Pharmacy Department, The Royal Women's Hospital, 2005.

Hill SR, Kouimtzi M, Stuart MC, eds. *WHO model formulary.* Geneva, World Health Organization, 2008.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

Paediatric Formulary Committee. *British national formulary for children 2009.* London, BMJ Group RBS Publishing, 2009.

Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Prostaglandin E

ATC code: C01EA01

Solution for injection

Prostaglandin E_1: 0.5 mg/ml in alcohol

Prostaglandin E_2: 1 mg/ml

Special Notes: Prostaglandin E_1 is also referred to as alprostadil. Prostaglandin E_2 is also referred to as dinoprostone.

This medicine is listed as a representative of its pharmacological class. Other medicines in the same class may have similar clinical performance and may be selected for local formularies based on availability and price. The information in this monograph only applies to the medicine listed here.

Indications: Temporary maintenance of patency of the ductus arteriosus in infants with congenital heart malformation dependent on ductal shunting for oxygenation/perfusion.

Contraindications: PROSTAGLANDIN E_1 Respiratory distress syndrome; infants with total anomalous pulmonary venous return with obstruction.

PROSTAGLANDIN E_2 Hepatic impairment; renal impairment.

Precautions: PROSTAGLANDIN E_1 History of bleeding tendencies or haemorrhage; persistent fetal circulation; 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.

PROSTAGLANDIN E_2 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.

Dose:

PROSTAGLANDIN E_1

Maintaining patency of the ductus arteriosus.

Continuous IV infusion:

Neonate initially 5–10 nanograms/kg/minute, adjusted according to response in steps of 5–10 nanograms/kg/minute. Maximum dose 100 nanograms/kg/minute (but associated with increased adverse effects).

To open a closed ductus arteriosus.

IV infusion:

Neonate 100 nanograms/kg/minute for a maximum of 30 minutes. Doses greater than this are rarely more effective and may cause serious adverse effects.

PROSTAGLANDIN E_2

Maintaining patency of the ductus arteriosus.

Continuous IV infusion:

Neonate initially 5–10 nanograms/kg/minute, adjusted according to response in 5 nanograms/kg/minute increments to 20 nanograms/kg/minute. Doses up to 100 nanograms/kg/minute have been used but are associated with increased side-effects.

Oral:

Neonate 20–25 micrograms/kg every 1–2 hours. Dose may be doubled if necessary. If treatment continues for more than 1 week, gradually reduce the dose.

Renal impairment: PROSTAGLANDIN E_1 No dosage adjustment necessary.

PROSTAGLANDIN E_2 Manufacturer advises to avoid in renal impairment.

Hepatic impairment: PROSTAGLANDIN E_1 No dosage adjustment necessary.

PROSTAGLANDIN E_2 Manufacturer advises to avoid in hepatic impairment.

Adverse effects: PROSTAGLANDIN E_1 **Common** Apnoea (particularly in neonates under 2 kg), flushing, bradycardia, hypotension, tachycardia, cardiac arrest, oedema, fever, seizures, decreased platelet aggregation, thrombocytopenia.

Uncommon Diarrhoea, disseminated intravascular coagulation, sepsis, hypokalaemia, congestive heart failure, hyperaemia, pneumopericardium, second-degree heart block, shock, spasm of the right ventricle infundibulum, supraventricular tachycardia, ventricular fibrillation, ventricular hypertrophy, tachyphylaxis, cerebral bleeding (with recorded fatalities), hyperextension of the neck, hyperirritability, hypothermia, jitteriness, lethargy, stiffness, bradypnoea, bronchial wheezing, hypercapnia, pneumothorax, respiratory depression, respiratory distress and tachypnoea.

Rare Following prolonged use, cortical proliferation of long bones, weakening of the wall of the ductus arteriosus and pulmonary artery have been reported.

PROSTAGLANDIN E_2 **Common** Nausea, vomiting, diarrhoea, flushing, bradycardia, hypotension, cardiac arrest, respiratory depression and apnoea (particularly with high doses and in low-birth-weight neonates).

Uncommon Bronchospasm, fever, raised white blood cell count, shivering, local reactions, erythema.

Rare Following prolonged use (greater than 5 days), gastric outlet obstruction and cortical hyperostosis have been reported.

Interactions with other medicines (* indicates severe):

Prostaglandin E_1: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Prostaglandin E_2: There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: PROSTAGLANDIN E_1 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 a final volume.

The solution may turn hazy if the undiluted solution comes into contact with the plastic syringe barrel. Discard the solution if it turns hazy.

Prepare a fresh solution every 24 hours.

Should be administered via a dedicated line and not mixed with other medications either via infusion or bolus.

PROSTAGLANDIN E_2 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.

References:

Fary R, Smith R, eds. *RWH Neonatal Pharmacopoeia. 2nd ed.* Melbourne, Pharmacy Department, The Royal Women's Hospital, 2005.

Hey E. *Neonatal formulary. 4th ed.* Oxford, Blackwell Publishing, 2007.

Hodding JH, Kraus DM, Taketomo CK. *Pediatric dosage handbook. 16th ed.* Hudson, Lexi-Comp, 2009.

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Rossi S, ed. *Australian medicines handbook.* Adelaide, Australian Medicines Handbook, 2009.

Surfactant

ATC code: R07AA02

Suspension for intratracheal instillation: 25 mg/ml or 80 mg/ml

Special Notes: Surfactant is available as beractant (bovine lung surfactant providing phospholipid 25 mg/ml) and poractant alfa (porcine lung surfactant providing phospholipid 80 mg/ml).

Indications: Treatment and prophylaxis of respiratory distress syndrome (hyaline membrane disease) in preterm neonates.

Contraindications: There are no contraindications to the use of surfactant in preterm neonates.

Precautions: Continuous monitoring is required to avoid hyperoxaemia caused by rapid improvement in arterial oxygen concentration.

Dose:

BERACTANT

Treatment of respiratory distress syndrome (hyaline membrane disease) in preterm neonates.
Endotracheal tube:
Neonate 100 mg/kg (equivalent to a volume of 4 ml/kg) preferably within 8 hours of birth. Dose may be repeated within 48 hours at intervals of at least 6 hours for up to four doses. Administer dose of beractant in four 1 ml/kg aliquots with infant in different position for each aliquot. Ventilator support or inspired oxygen may need to be temporarily increased.

Prophylaxis of respiratory distress syndrome (hyaline membrane disease) in preterm neonates.
Endotracheal tube:
Neonate 100 mg/kg as soon as possible after birth. Up to four doses may be administered in the first 48 hours of life, not more frequently than 6 hours apart.
Administer dose of beractant in four 1 ml/kg aliquots with infant in different position for each aliquot. Ventilator support or inspired oxygen may need to be temporarily increased.

PORACTANT ALFA

Treatment of respiratory distress syndrome (hyaline membrane disease) in preterm neonates.
Endotracheal tube:
Neonate 100–200 mg/kg (equivalent to a volume of 1.25–2.5 ml/kg). If still intubated, two further doses of 100 mg/kg may be given at 12 hour intervals. Maximum total dose is 400 mg/kg.

Prophylaxis of respiratory distress syndrome (hyaline membrane disease) in preterm neonates.
Endotracheal tube:
Neonate 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 a further 12 hours if still intubated. Maximum total dose is 400 mg/kg.
Administer dose of poractant in two aliquots with infant in different position for each aliquot to ensure delivery to the two main bronchi. Ventilator support or inspired oxygen may need to be temporarily increased.

Renal impairment: No dosage adjustment necessary.

Hepatic impairment: No dosage adjustment necessary.

Adverse effects: Rare Pulmonary haemorrhage has been rarely associated with pulmonary surfactants, especially in more preterm neonates. Obstruction of the endotracheal tube by mucus secretions has been reported.

Interactions with other medicines (* indicates severe):

There are no known interactions involving a significant change in effect or where it is recommended to avoid concomitant use.

Notes: Beractant and poractant alfa are not the same product. Consult product information for more details on administration.

Refrigerate and protect from light.

Do not shake. Gently swirl to ensure complete mixing of suspension.

Prior to administration, warm by standing at room temperature for 20 minutes or hold in hand for 8 minutes. Artificial warming methods should not be used. Do not use or return vials to the refrigerator if they have been at room temperature for 8 hours or more (beractant) or 24 hours or more (poractant alfa). Vials may only be returned to the refrigerator once after having reached room temperature.

Suction infant prior to administration.

Continuous monitoring of heart rate and transcutaneous oxygen saturation should be performed during administration.

Pneumothorax has occurred due to sudden changes in pulmonary compliance if ventilator settings are not appropriately adjusted.

Avoid suctioning the endotracheal tube for 2 hours post-administration unless there are clear signs of airway obstruction.

References:

Fary R, Smith R, eds. *RWH Neonatal Pharmacopoeia. 2nd ed.* Melbourne, Pharmacy Department, The Royal Women's Hospital, 2005.

Hey E. *Neonatal formulary. 4th ed.* Oxford, Blackwell Publishing, 2007.

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